RS general・RS strategy consultation

Develop your innovative medical product in Japan and Bring it to the world

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* The electronic version (PDF file) of this pamphlet is available on the PMDA website "RS general consultation/RS strategy consultation" (http://www.pmda.go.jp/operations/shonin/info/consult/yakujisenryaku/file/pamphlet.pdf).
* The URL, etc. described as general information are as of the end of March 2023.
* This pamphlet is basically English translation of original one which is aimed at Japanese stakeholders.

1. Why are breakthrough research results not linked to innovative drugs, medical devices, and regenerative medical products?

1-1 Current status and issues

In Japan, approximately 100 new drugs and approximately 30 new medical devices have been newly approved for marketing each year under the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (PMD Act) (including approval for partial changes such as additional indications). These products provide new treatment methods and options, and have helped improve the level of medical care in Japan. However, it does not necessarily mean that the existing drugs, medical devices, and regenerative medical products have provided satisfactory therapeutic effects and sufficiently solve medical issues. For example, the current treatment methods for Alzheimer's disease and many cancers do not provide sufficient satisfaction, and the development of innovative drugs, medical devices, and regenerative medical products is awaited. In the future, Japan will enter an aging society unprecedented in the world, and it is required to develop and deliver new treatment methods, particularly not symptomatic treatment methods, and disease modifying treatment methods for patients with many diseases.

In order to develop innovative products and deliver them to patients, Japan's development capability need to be high. From this point of view, a recent survey on drugs reported that Japan was the fourth country to create new drugs, following the US, Switzerland, and the UK*. In addition, as can be seen from the fact that many papers have been published from Japan to some of the world's leading academic journals on basic research, the level of basic research in Japan is recognized globally†. However, the drugs, medical devices, and regenerative medical products approved in Japan were not always approved first in the world.

In recent years, the drug lag has tended to be shortened, because the review lag (delay in the regulatory review time compared to Europe and the US) has been shortened. As for the regulatory review time after the approval application, approval can be obtained for almost the same period as in Europe and the US. On the other hand, development lag (delay in the date of the approval application compared to the US and Europe due to delay in clinical development, etc.) still exists and is one of the major factors causing drug lag. If the basic research capabilities are high, it is expected that the subsequent development will be smoothly conducted, the approval application will be made earlier, and there will be no development lag. However, under the current situation in Japan, there is a development lag even though the basic research capabilities are high. There are two main factors in this background. The first factor is the gap between basic research and development, the so-called "valley of death," which means that the outcomes of basic research have not been successfully linked to practical application (Figure 1). The second factor is that even if the development is proceeded, it is conducted overseas, not in Japan.

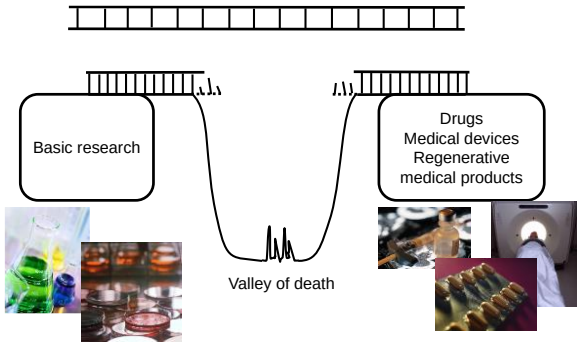


Figure 1 Gap between basic research and development (existence of valley of death)

Elimination of these factors will lead to approval of innovative products and delivery of them to patients. In addition to issues related to cost for improvement of the clinical study (clinical trial) environment and development costs, etc., there are two main factors to be considered: scientific and regulatory. The former is that scientific evaluation methods to predict the efficacy and safety in humans have not been fully established generally based on the results of basic research such as non-clinical studies.

*:Akira Nakao: Nationality of a company that created top pharmaceutical products in the world: Trend in 2021. *Office of Pharmaceutical Industry Research, OPIR News* 67,119-127 (2022).
†: Satoshi Kaneko: International comparison of the number of publications in major basic and clinical medical journals. *Office of Pharmaceutical Industry Research, OPIR News* 44, 30-31 (2015).

The latter is that studies conducted as basic research do not meet the standards in the PMD Act because basic research is not necessarily conducted for the purpose of approval under the PMD Act. Therefore, for practical application of innovative products originating in Japan, it is necessary to further develop science (establishment of new test methods, evaluation methods, etc.) and collect data efficiently under full knowledge of the regulatory requirements of the PMD Act.

1-2 Elements necessary for practical application

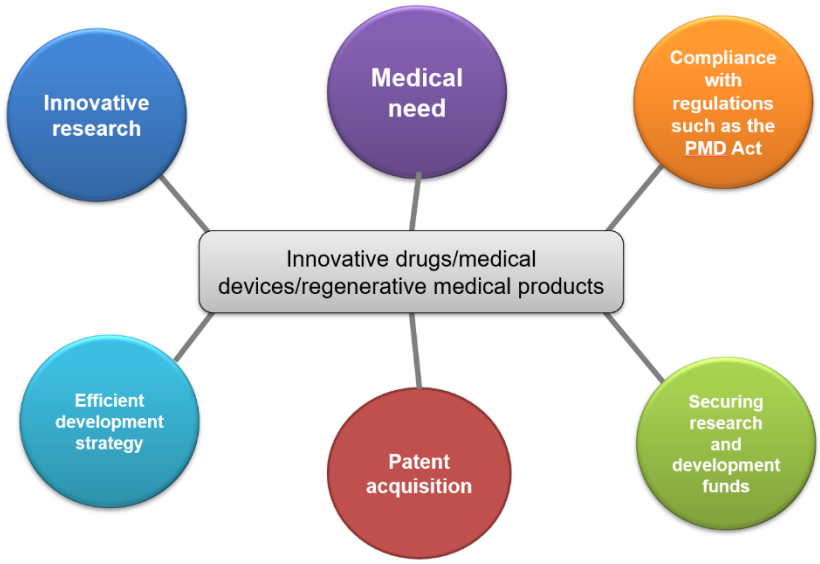


Figure 2 Elements generally required for practical application of innovative drugs, medical devices, and regenerative medical products

There are six main elements considered necessary for practical application of innovative drugs, medical devices, and regenerative medical products (Figure 2). The first element is innovative research that creates development items. In this regard, the fact that Japan's basic research capabilities are high is also mentioned in the previous section. The second element is meeting highmedical needs with the development items. Even if research results are innovative, it is difficult to build a development strategy itself unless the new potential for current healthcare is clear. The third element is compliance with regulations such as the PMD Act. In order to obtain approval under the PMD Act, it is important to understand what materials and data are necessary to be submitted in the first place. The fourth element is building an efficient development strategy. With the aim of obtaining approval based on the PMD Act, it is necessary, by drawing an overall picture, to plan necessary tests and the timing of implementation to effectively clarify development issues and make appropriate judgments. This will make it possible for researchers and developers themselves to be aware of the positioning of the research and study they are going to conduct in order to make the approval application based on the PMD Act. Then, the purpose of conducting the research and study will be clearer, which will be useful for drawing up an appropriate study plan. Also, in planning the study, it is important to consider the medical positioning of the development item while taking into account the presence of competing products, future medical care, etc. from a long-term perspective. The fifth element is acquisition of patents for development items. This is an important element in the final licensing-out of development items to companies, etc., rather than required under the PMD Act. No matter how innovative research results are, if patents are not secured, it will not work as a business, and therefore it will be difficult for companies to adopt a strategy of continuing development and marketing with the use of the research results. For this reason, it is essential for practical application to apply for substance patents, etc. for development items and secure intellectual property rights, and therefore it is necessary to receive advice from experts at an early stage to take action‡. The sixth element is securing research and development funds. It seems that researchers have greatest difficulty with securing research expenses. Needless to say, it is an essential element for practical application. Recently, various research grants to promote practical use have appeared; however, it is important to build an appropriate development strategy to secure research expenses. The specific package and rationale for what

‡: The Pharmaceuticals and Medical Devices Agency (PMDA) does not give advice on how to obtain patents or research expenses.

purpose, what kinds of studies and how long they will be conducted will provide a convincing explanation for research funding applications. If the final goal is approval under the PMD Act, a clear description of the research to be done and the milestones to be achieved in the next several years will enable efficient development.

1-3 Importance of regulatory science in promoting practical application

Recently, the importance of regulatory science in promoting the practical application of innovative drugs, medical devices, and regenerative medical products has been pointed out. Regulatory science is defined in the fourth Basic Plan for Science and Technology as "a science for adjusting the results of science and technology to the most desirable form in harmony with humans and society by making accurate predictions, evaluations, and judgments based on evidence for the purpose of utilizing the results of science and technology to humans and society." For example, when an innovative technology is developed, new test methods and evaluation methods need to be established to appropriately evaluate the applicability of the technology to medical care. In general, such test methods and evaluation methods will be established in basic research, but the important thing here is that these new test methods and evaluation methods must be acceptable to society as well. In other words, if the new test method or evaluation method is acceptable only to some experts, it is not sufficient from the viewpoint of regulatory science. It is required to establish a method that is feasible and widely accepted in general based on the consideration from the multifaceted viewpoint. In order to promote regulatory science, the Pharmaceuticals and Medical Devices Agency (PMDA) has promoted personnel exchanges with academia including universities and research institutions by establishing a Science Board and concluding comprehensive partnership agreements, and also promoted regulatory science research, etc. in PMDA. Through these efforts, we will evaluate various data with a more scientific and socially acceptable approach, strive to improve the quality of regulatory review, etc., and contribute to the development of regulatory science in Japan. With further development of regulatory science in Japan, it will become possible to more scientifically examine the issues and limitations of new research results and technologies, implement the development of innovative products originating in Japan more smoothly, and put them into practical use ahead of other countries.

2. Development for practical use

2-1 Development process of drugs

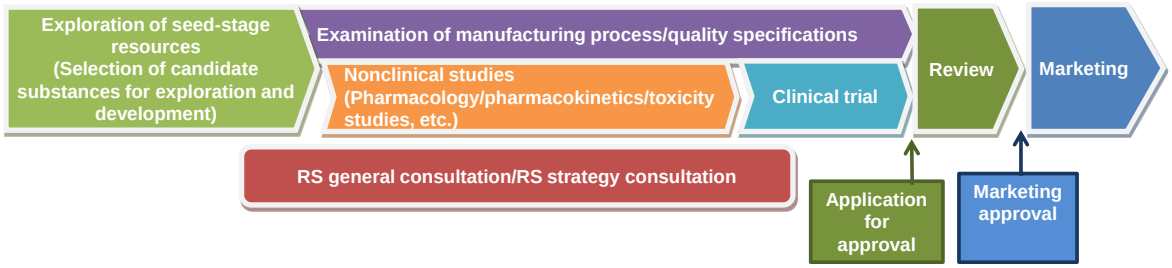


Figure 3 General drug development process

The general process of development of drugs. is shown in Figure 3. Candidate substances are selected in the exploration of seed-stage resources, and the development item is decided. Consideration of manufacturing method, quality and specifications of the development item is started, and in parallel, the safety and efficacy in humans are predicted based on the data in non-clinical studies such as pharmacology studies, toxicity studies, and pharmacokinetic studies. After the safety is confirmed in nonclinical studies, the clinical study (clinical trial) will be started to confirm the efficacy and safety in humans. When all of these results are obtained, an approval application based on the PMD Act will be made, and if the approval is judged to be appropriate, marketing will be finally approved by the Minister of Health, Labour and Welfare and marketing of the drugs. developed will become possible. In general, the success rate of development of new drugs is very low, and it takes about 10

years or more per product item, requiring a large amount of development expenses. For successful development of new drugs, it is necessary that many experts collaborate with each other and evaluate from various perspectives to build efficient development strategies. In addition, it is necessary to continuously collect information on changes in treatment methods, development trends of other drugs and appropriately confirm and modify the development plan throughout the development.

The outline of each stage of development is as follows. Refer to "5. Examples of RS general consultation/RS strategy consultation" for some cases.

1) Exploration of seed-stage resources

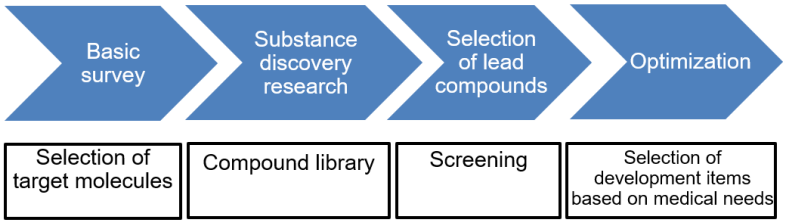


Figure 4 General process for exploration of seed-stage resources for drug discovery

At this stage, identification of target molecules is attempted based on the results of basic research on the target disease. In drug discovery research, a method for screening development candidates for target molecules is generally established, and lead compounds are selected from a compound library. Then, while chemically modifying the lead compound, the optimal development item will be determined in consideration of medical needs based on the results of pharmacological activity, metabolism, and safety, etc. (Figure 4). In recent years, methods for drug discovery research have been diversified, including creation of antibodies to inhibit the action of target molecules and creation of antisense to control the action of disease-related genes. Accurate understanding of medical needs in Japan is important for selecting the most appropriate development item, and it is useful to collect opinions from as many healthcare professionals such as physicians as possible at this stage.

2) Examination of manufacturing/quality specifications and non-clinical studies

In this stage, the manufacturing method will be established for the selected development items, and certain specifications will be established to assure the quality of the development items. In addition, the pharmacological action, toxicity, and pharmacokinetics are investigated in non-clinical studies in animals such as mice and cultured cells using the development item whose quality is guaranteed (Figure 5).

For drugs. manufactured using human or animal cells/tissues or other biological ingredients, risks caused by biological ingredients used in the manufacturing process (infection risks due to contamination of viruses/bacteria, etc.) need to be evaluated from the viewpoint of safety.

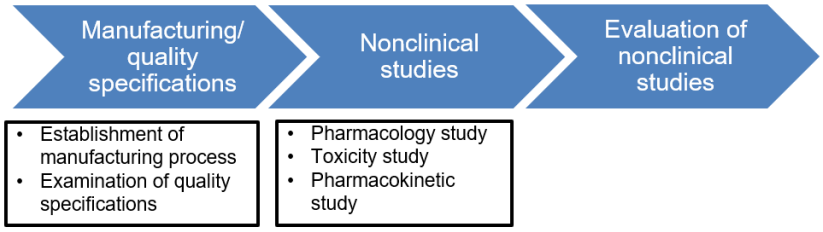


Figure 5 General Processes for Examination of Manufacturing/Quality Specifications and Non-clinical Studies in Drug Discovery

Based on the results of these non-clinical studies, the effective dose and toxic dose of the development item will be clarified. Usually, chemicals are more potent when the dose is increased and more toxic when the dose exceeds a certain dose. If there is a significant difference between the effective dose and the toxic dose, it can be said that the drug has a wide safety margin and a low risk, but attention is required for some drugs with a narrow safety margin. Clarifying the degree of safety margin is useful for appropriately planning clinical studies (clinical trials) in humans. A summary of the examination of manufacturing/quality specifications, pharmacology studies, toxicity studies, and pharmacokinetic studies is shown below. For details, please refer to the list of guidelines for drugs in the "Annex List of guidelines."

[1] Examination of manufacturing/quality specifications

When a development item is selected, it is necessary to establish a method that can efficiently manufacture the item while maintaining the quality at a certain level, therefore, the synthesis method and purification method, etc. will be examined. It is also important to confirm whether the quality is stable even when the item is stored for a certain period of time in consideration of the period of clinical studies (clinical trials). On the basis of these examinations, it is possible to conduct necessary studies while securing a certain level of quality by specifying the quality of the developed item to be used in clinical studies (clinical trials) as a specification. In general, the final quality and specifications are examined in parallel after the start of nonclinical and clinical studies (clinical trials) and determined before the approval application, therefore the final quality and specifications are not required in this stage. It is important to assure a certain level of quality even at the stage before the start of non-clinical or clinical studies so that appropriate actions can be taken when there is a significant change in the manufacturing method or quality after the start of studies. In other words, the certain level of quality can be used to scientifically demonstrate the equivalence to the item before the change in order to judge the necessity of additional studies, when a change is made to the manufacturing method, etc.,. If equivalence cannot be demonstrated, the results of non-clinical studies and clinical studies (clinical trials) conducted using the item before the change may not be available, and the studies may need to be started over. Since additional study and restudy lead to a significant delay in the time of application for approval in addition to the cost increase, the development schedule for ensuring quality and specifications should be thoroughly examined before starting the study.

[2] Pharmacology study

The objective of a pharmacology study is to investigate the efficacy and mechanism of the development item, and it is useful to estimate the dosage and administration in humans and predict adverse reactions that occur. Furthermore, before the start of clinical studies (clinical trials), it is necessary to conduct safety pharmacology studies on the central nervous, respiratory, and cardiovascular systems with guaranteed reliability based on the Good Laboratory Practice (GLP) in order to predict adverse reactions.

[3] Toxicity study

In the development of drugs, it is important to conduct studies to confirm the safety in consideration of administration in humans in addition to the viewpoint of efficacy. Based on the results of toxicity studies, types and degrees of adverse events that may occur when the development item is administered in humans will be examined. Conduct of toxicity studies will allow us to estimate the maximum tolerated dose and whether unexpected effects occur in humans. Toxicity studies are generally conducted in rodents such as mice and rats and non-rodents such as dogs and monkeys, and include single-dose toxicity studies, repeated-dose toxicity studies, genotoxicity studies, reproductive and developmental toxicity studies, and carcinogenicity studies depending on the objectives of the studies. Considering future application for approval, it is useful to conduct studies after assuring the reliability based on Good Laboratory Practice (GLP) in principle.

[4] Pharmacokinetic study

The administered drug is absorbed in the body, distributed, metabolized, and excreted. The purpose of pharmacokinetic studies is to clarify the mechanisms of absorption, distribution, metabolism, and excretion of development candidate substances in animals. Since pharmacokinetic profiles are often different between animals and humans, it is important to scientifically evaluate the relation between the time course in blood drug concentrations and the results of pharmacology and toxicity studies in animals in order to discuss the efficacy and safety in humans based on the time course in blood drug concentrations in humans obtained in clinical studies (clinical trials).

3) Clinical study (clinical trial)

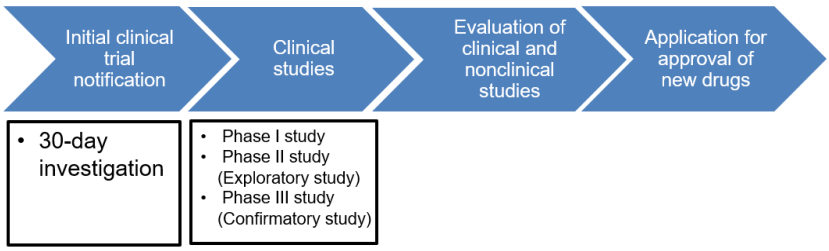


Figure 6 General process from clinical development to an approval application in drug discovery

At this stage, the candidate substance for development, which is considered to have no major issue in the efficacy and safety in non-clinical studies, is actually administered to humans to confirm the efficacy and safety. This is called a clinical study (clinical trial) (Figure 6). Usually, there are three studies to be conducted before approval: a phase I study, a phase II study (exploratory study), and a phase III study (confirmatory study). To start a clinical study (clinical trial), it is necessary to submit a clinical trial notification to the Minister of Health, Labour and Welfare. In particular, when a first-in-human clinical study (clinical trial) is conducted, the clinical study (clinical trial) cannot be started unless 30 days have passed since the date of notification of the clinical trial plan (initial clinical trial notification). At the time of submission of the initial clinical trial notification, the PMDA conducts an investigation necessary to prevent the occurrence of health hazards in relation to the clinical study (clinical trial) plan. If there is any significant issue in terms of safety, etc., the PMDA will request the sponsor of the clinical trial to consider the resolution of the issue within 30 days. If the issue is not solved, implementation of a clinical study (clinical trial) will not be permitted, and a clinical study (clinical trial) cannot be started. Clinical study (clinical trial) should be conducted according to Good Clinical Practice (GCP).

[1] Phase I study

Usually, the main objective of phase I studies is to investigate the safety of the item under development by administering it to healthy adults. Any drug causes adverse effects when administered in an overdose. Therefore, this study will investigate the tolerability of the development item in humans and confirm the degree of dose that can guarantee the safety (maximum acceptable dose). In addition, it is common to measure blood drug concentration over time when the development item is administered to humans and investigate the relation between the dose and the time course in blood drug concentration and clearance rate. These data provide important basic information for examining the dosage and administration of the development item in subsequent clinical studies (clinical trials) in patients.

[2] Phase II study

Usually, the main objective of phase II studies is to investigate the efficacy and safety of the item under development in the target disease by administering it to patients. At this stage, although the number of patients is relatively small, the development item will be administered to actual patients to confirm the presence or absence of the expected therapeutic effect. In general, it is planned to confirm the recommended clinical dose of the item under development by examining the relation with the efficacy and safety using different doses.

[3] Phase III study

Usually, the main purpose of phase III studies is to verify the efficacy and safety of the item under development in a larger number of patients using the recommended clinical dose confirmed in phase II studies. The phase III study is the most important study to demonstrate the efficacy and safety of the item under development. The study plan needs to be fully examined before the start of the study.

4) Application for approval

If results up to phase III studies become available, approval application data on the efficacy and safety of the development item will be prepared after comprehensively evaluating the results of non-clinical studies and clinical

studies (clinical trials) that have been conducted to date. An application for approval must be submitted by a company with a license for the marketing authorization holder. Therefore, even if the academia develops the item by itself in investigator-initiated clinical trials, etc., the academia cannot be the applicant unless the license for the marketing authorization holder is obtained.

Approval applications for new drugs are to be made using the Common Technical Document (CTD), and as a general rule, the submission data listed in Table 1 are required (for details, see the Annex List of guidelines 1) (7) "Guidelines for Preparation of Documents to be Attached to an Approval Application for Marketing or Import of a New Drug (PMSB/ELD Notification No. 899, dated June 21, 2001) Attachment 1"). However, these are just general items, and the necessary data differ depending on the novelty and characteristics of the development item.

After the approval application, the propriety of approval is judged through the review and inspection by the PMDA and deliberation at the Pharmaceutical Affairs Council, which is an advisory body to the Minister of Health, Labour and Welfare. If the approval is judged to be appropriate, the drug will be finally approved[§] for marketing by the Minister of Health, Labour and Welfare and it will be possible to manufacture and market the drug developed.

Table 1 Dossiers generally required for approval applications for drugs

Items	Sub Items
A Origin or history of discovery and usage conditions in foreign countries	1 Origin or history of discovery
	2 Usage conditions in foreign countries
	3 Properties and comparison with other drugs
B Manufacturing process and specifications	1 Structure determination and physicochemical properties
	2 Manufacturing method
	3 Specifications
C Stability	1 Long-term stability study
	2 Stress study
	3 Accelerated study
D Pharmacological action	1 Studies to support efficacy
	2 Secondary pharmacology and safety pharmacology
	3 Other pharmacology
E Absorption, distribution, metabolism, and excretion	1 Absorption
	2 Distribution
	3 Metabolism
	4 Excretion
	5 Bioequivalence
	6 Other pharmacokinetics
F Acute toxicity, subacute toxicity, chronic toxicity, teratogenicity, and other toxicities	1 Single-dose toxicity
	2 Repeated-dose toxicity
	3 Genotoxicity
	4 Carcinogenicity
	5 Reproduction toxicology
	6 Local tolerance
	7 Other toxicity
G Clinical study results	Clinical study results
H Items listed in the package inserts specified in Article 52, Paragraph 1 of the PMD Act	Items listed in the package inserts

5) Marketing

Even if a development item is approved, this will not be the last. Measures should be taken based on Good Vigilance Practice (GVP), etc. to ensure the safety of drugs. Data obtained before approval are often limited both qualitatively and quantitatively. For an innovative drug, certain data collection is often necessary even after approval in general. In some cases, a post-marketing clinical study may need to be conducted. This is to confirm that the approved drug can be used effectively and safely also in actual medical environment because the drug is used in patients with more various backgrounds after marketing compared with subjects enrolled in clinical

[§]: Drugs designated by the Minister of Health, Labour and Welfare are approved by prefectural governors.

studies. The collected data will be used for post-marketing safety measures and appropriate provision of information, etc.

2-2 Development process of medical devices

The development process of a medical device starts with the development of a new technology. Unlike in phase I to phase III studies of drugs, there is not much concept of phase in a clinical study (clinical trial). As shown in Figure 7, it starts with market research, a medical device which meets medical needs is designed, and then a confirmatory clinical study (clinical trial) is conducted with the final product of the development item.

The outline of each stage of development is as follows. Refer to "5. Examples of RS general consultation/RS strategy consultation" for some cases.

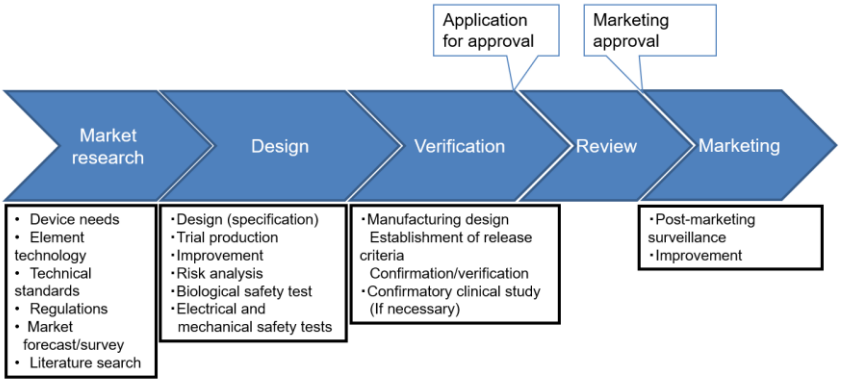


Figure 7 General medical device development process

1) Market research

In medical device development, it is important to accurately grasp the needs of the medical practice based on the market research on the device to be developed and survey of specialists. It is necessary to prepare the final form of medical devices that meet medical needs. At this stage, it is useful to investigate whether existing elemental technologies can be used, what kinds of regulations should be noted, and the size of the market expected. The results of these investigations should be organized.

Without identifying medical needs, medical devices cannot be designed properly, and endpoints such as the effectiveness of medical devices cannot be determined. Therefore, it is difficult to design and develop medical devices efficiently.

2) Design

At this stage, design is started to meet the target medical needs. It is important to clarify at least the following points: target diseases, treatment effects and purpose of use (for example, diagnosis and treatment). This is referred to as design input.

Once the product specifications such as the target disease and purpose of the medical device are determined, a design based on risk assessment is started to realize them. In this stage, prototypes are created and various tests are conducted to check the functions of each element technology, etc., to confirm whether the device under development meets the initial design input mostly in terms of efficacy. These tests are conducted mainly as non-clinical studies, and include not only biological safety studies using animal models but also studies to confirm electrical or mechanical safety. During this process, the key is to estimate the use status of the medical device (use environment and user) and reduce risks as much as possible on the assumption that the device is used by humans. You should confirm whether you have built the initially targeted function, and, if necessary, make improvements while changing the design to make it closer to the design of the final product. In addition, there will be various things in designing such as functions that could not be realized and functions that were considered for realization but were not adopted. It is useful to appropriately record these matters in preparing approval application data based on the PMD Act later.

In any case, it is important to remember that the medical device is used by people and is also used for people. In order to appropriately design medical devices that meet medical needs, it is important that medical practice

and developers make good communications, and it is necessary to continue collecting information on changes in treatment methods, development trends of other medical devices, etc. and confirm and modify the development plan even in the middle of the development.

3) Verification

Once the final design has been determined, you should check if the target function is as expected. This step is accomplished by repeating confirmation (validation) and verification of the designed functionality. Depending on the type of medical device, it may be possible to verify it by conducting non-clinical studies. If verification in humans is required due to risks, etc. of the developed device, the device as close as possible to the final device used in clinical practice will be manufactured and a clinical study (clinical trial) will be conducted. In this stage, it is required to design based on the Standards for Manufacturing Control and Quality Control for Medical Devices and In Vitro Diagnostics (Quality Management System: QMS). It is important to examine these matters while taking into consideration the data required at the time of application for approval (for QMS, see the section of "5. RS general consultation/RS strategy consultation Example 5-2 Medical devices 1) Matters related to quality of medical devices").

4) Application for approval

If results of confirmatory studies become available, approval application data on the efficacy and safety of the development item will be prepared after comprehensively evaluating the results of non-clinical studies and clinical studies (clinical trials) (if necessary) that have been conducted to date. An application for approval must be submitted by a company with a license for the marketing authorization holder. Therefore, even if the academia develops the item by itself in investigator-initiated clinical trials, etc., the academia cannot be the applicant unless the license for the marketing authorization holder is obtained.

In general, the items listed in Table 2 need to be submitted for approval applications for medical devices. However, these are just general items, and the necessary data differ depending on the development item.

After the approval application, the propriety of approval is judged through the review by the PMDA and deliberation at the Pharmaceutical Affairs and Food Sanitation Council, which is an advisory body to the Minister of Health, Labour and Welfare. If the approval is judged to be appropriate, the marketing approval will be finally granted by the Minister of Health, Labour and Welfare and it will be possible to manufacture and market the medical device developed.

Table 2 Dossiers generally required for approval applications for medical devices

Items	Sub Items
A Development and usage conditions in foreign countries	1 Development
	2 Comparison with similar medical devices
	3 Usage conditions in foreign countries
B Design and development	1 Performance and safety
	2 Other design verification
C Conformity to the standards specified under Article 41, Paragraph 3 of the PMD Act	1 Declaration of conformity to essential principles
	2 Conformity to essential principles
D Risk management	1 Risk management implementation system
	2 Hazards for which safety measures were taken
E Manufacturing method	1 Manufacturing process and manufacturing site
	2 Sterilization
F Results of clinical studies or data approved by the Minister of Health, Labour and Welfare as an alternative	1 Clinical study results
	2 Clinical evaluation
G Plan of post-marketing surveillance, etc. specified in Article 2, Paragraph 1 of the Ministerial Order on Standards for Post-Marketing Surveillance and Test of Medical Devices	1 Plan of post-marketing surveillance, etc.
H Items listed in the package inserts specified in Article 63-2, Paragraph 1 of the PMD Act	1 Package inserts

5) Marketing

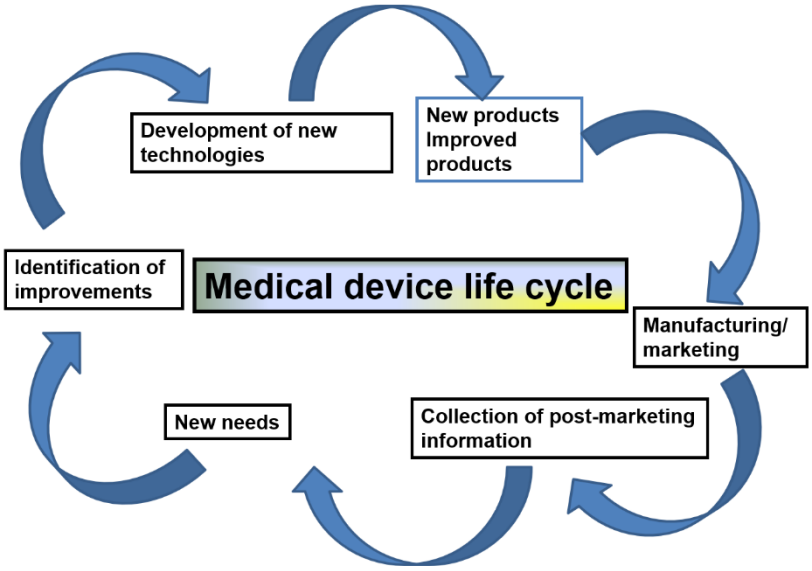


Figure 8 Medical device life cycle

Even if a development item is approved, this will not be the last. Measures should be taken based on Good Vigilance Practice (GVP), etc. to ensure the safety of medical devices. Data obtained before approval are often limited both qualitatively and quantitatively. For an innovative medical device, certain data collection is often necessary even after approval in general. This is to confirm that the approved medical device can be used effectively and safely also in actual medical environment because the medical device is used in patients with various backgrounds after marketing. The collected data will be used for post-marketing safety measures and appropriate provision of information, etc.

In addition, since medical devices are tools to be used by users, they are characterized to be used in patients through humans. In general, they are improved when necessary based on opinions of physicians who actually use the approved medical devices and advances in science and technology. Medical devices have a shorter life cycle than drugs. In medical devices, repeated modifications throughout the life cycle shown in Figure 8 lead to development of new technologies and practical application of innovative medical devices.

2-3 Development process for regenerative medical products

Regenerative medical products have traditionally been handled as drugs or medical devices on the basis of the characteristics of individual products. For product groups that have characteristics different from drugs or medical devices, they are newly categorized under the PMD Act enforced on November 25, 2014. Specifically, they are manufactured by culturing or other processes on human or animal cells used for reconstruction and repair of the structure or function of the human body or treatment and prevention of diseases, or by transferring genes expressed in human cells, and used for treatment of diseases.

Regarding regenerative medical products, conditional and time-limited approval can be obtained under the PMD Act when the safety is confirmed and the efficacy is estimated. On the other hand, as informed consent for users and retention of records on marketing are required, it is important for handling of these products to fully understand the PMD Act.

Regenerative medical products have various characteristics, including recombinant viruses used in gene therapy, cell sheets used in wound covering, or recombinant cells used in cancer immunotherapy. Since this is a new field, it is difficult to show general development processes. However, basically, while referring to the development processes for drugs and medical devices, PMDA considers it important to have developers utilize RS general consultation/RS strategy consultation, etc. and proceed with the process together. The submission data required for approval applications for regenerative medical products are shown in Table 3.

Table 3　Dossiers generally required for approval applications for regenerative medical products

Items	Sub Items
1 Origin or history of discovery and usage conditions in foreign countries	A Origin or history of discovery
	B Usage conditions in foreign countries
	C Comparison with other similar treatment methods
2 Manufacturing process and study methods	A Product structure, component cells, and introduced gene
	B Raw materials and materials used or their raw materials
	C Manufacturing process
	D Specifications and study methods
3 Stability	Rationale for transportation, storage conditions, and expiration date
4 Indications or performance	Tests to support efficacy or performance
5 Disposition of the product	A Biodistribution
	B Other disposition
6 Non-clinical safety	A General toxicity
	B Other safety
7 Clinical study	Clinical study results
8 Risk analysis	A Risk control plan
	B Post-marketing use-results survey plan
	C Proposed clinical study plan
9 Items listed in the package inserts specified in Article 65-3, Paragraph 1 of the PMD Act	A Draft package inserts
	B Indications or performance, dosage and administration or directions for use, precautions (draft), etc. and their rationale

3. Dealing with the Pharmaceutical and Medical Device Act (PMD Act) necessary for practical application

3-1 What is the Pharmaceutical and Medical Device Act?

The PMD Act is a very relevant law for practical application of innovative drugs, medical devices, and regenerative medical products. The PMD Act may be difficult to handle for academia and venture companies, etc. who are unaccustomed to development. However, various measures to put these products into practical use need to be taken in accordance with the rules specified in the PMD Act. To that end, it is important to understand what the PMD Act is and what regulations must be observed at each stage for practical application.

The PMD Act consists of 17 chapters and 91 articles as shown in Table 4, and in Article 1, it is stated that the purpose of the PMD Act is "to improve public health and hygiene by providing regulations necessary for ensuring the quality, efficacy, and safety of drugs, quasi-drugs, cosmetics, medical devices, and regenerative medical products and preventing the occurrence and spread of health and hygiene hazards due to the use of them, taking measures related to the regulation of designated drugs, and taking other measures necessary for promoting the research and development of drugs, medical devices, and regenerative medical products that are particularly needed in medical practice." In other words, the PMD Act is a basic law for handling drugs, medical devices, regenerative medical products, etc., and has three aspects: "quality, efficacy, and safety assurance," "prevention of drug abuse," and "promotion of research and development."

Table 4　Composition of the Pharmaceuticals and Medical Devices Act

Chapter 1	General Provisions (Articles 1 and 2)	Section 2	Handling of Drugs (Articles 49 to 58)
Chapter 2	Local Pharmaceutical Affairs Council (Article 3)	Section 3	Handling of Quasi-drugs (Articles 59 and 60)
Chapter 3	Pharmacy (Articles 4 to 11)	Section 4	Handling of Cosmetics (Articles 61 and 62)
Chapter 4	Marketing and Manufacturing of Drugs, Quasi-drugs and Cosmetics (Articles 12 to 23)	Section 5	Handling of Medical Devices (Articles 63 to 65)
Chapter 5	Marketing and Manufacturing of Medical Devices and In Vitro Diagnostics	Section 6	Handling of Regenerative Medical Products (Article 65-2 to Article 65-6)
Section 1	Marketing and Manufacturing of Medical Devices and In Vitro Diagnostics (Article 23-2 to Article 23-2-22)	Chapter 10	Advertisement of Drugs, etc. (Articles 66 to 68)
Section 2	Section 2. Registered Certification Bodies (Article 23-2-23 to Article 23-19)	Chapter 11	Safety Measures for Drugs, etc. (Article 68-2 to Article 68-15)
Chapter 6	Marketing and Manufacturing of Regenerative Medical Products (Article 23-20 to Article 23-42)	Chapter 12	Exceptions of Biological Products (Articles 68-16 to 68-25)
Chapter 7	Selling of Pharmaceuticals, Medical Devices and Regenerative Medical Products	Chapter 13	Supervision (Article 69 to Article 76-3-3)
Section 1	Selling of Pharmaceuticals (Articles 24 to 38)	Chapter 14	Administrative Evaluation and Monitoring Committee for Drugs, etc. (Article 76-3-4 to Article 76-3-12)
Section 2	Selling, Leasing and Repairing of Medical Devices (Article 39 to Article 40-4)	Chapter 15	Handling of Designated Substances (Article 76-4 to Article 77)
Section 3	Selling of Regenerative Medical Products (Articles 40-5 to 40-7)	Chapter 16	Designation of Orphan Drugs, Orphan Medical Devices, and Orphan Regenerative Medical Products (Article 77-2 to Article 77-7)
Chapter 8	Standards and Official Verification of Pharmaceuticals, etc. (Articles 41 to 43)	Chapter 17	Miscellaneous Provisions (Article 78 to Article 83-5)
Chapter 9	Handling of Pharmaceuticals	Chapter 18	Applicable Penal Provisions (Article 83-6 to Article 91)
Section 1	Handling of Poisonous and Powerful drugs (Articles 44 to 48)	Supplementary Provisions	

Since its enforcement in 1960, the current PMD Act has undergone several amendments to the current form. In 2005 and 2014, the act was fully revised, and the licensing system was significantly changed by the marketing approval system, regulations for marketing and manufacturing, reinforcement of safety measures, and implementation of regulations on medical devices and regenerative medical products. Detailed regulations for smooth enforcement and operation of the PMD Act include cabinet orders, ministerial ordinances, and ministerial announcements. For example, it is specified in the PMD Act that "designated by the cabinet order," "designated by the ordinance of the Ministry of Health, Labour and Welfare," or "designated by the Minister of Health, Labour and Welfare." These regulations are specified by cabinet orders, ministerial ordinances, and ministerial announcements. The outline is shown in Table 5.

Table 5　Detailed regulations related to the Pharmaceutical and Medical Device Act

Type	Example
Cabinet Order: There are those which implement the provisions of law and those based on delegation of law.	"Order for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices," etc.
Ministerial Ordinance: An order issued by the Minister under the enforcement of, or special delegation of, a law or cabinet order.	"Regulation for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices" "Ministerial Ordinance on Good Laboratory Practice for Nonclinical Safety Studies of Drugs (GCP Ordinance for Drugs)" "Ministerial Ordinance on Good Clinical Practice for Drugs (GCP Ordinance for Drugs)"
Ministerial Announcement: Act to widely inform the general public of matters requiring public announcement	"Specially designated maintenance-and-management-required medical devices designated by the Minister of Health, Labour and Welfare (Ministry of Health, Labour and Welfare Ministerial Announcement No. 297)" "Biological products and specified biological products designated by the Minister of Health, Labour and Welfare (Ministry of Health, Labour and Welfare Ministerial Announcement No. 209)," etc.

In addition, "Notification" or "Administrative Notice" is often issued to publicize the policy of interpretation,

operation, and enforcement of the PMD Act, cabinet orders, and ministerial ordinances (hereinafter referred to as laws and regulations). Please see the "Annex List of guidelines" for major notifications (guidelines) related to the development of innovative products. For the system and content search of the PMD Act, cabinet orders, ministerial ordinances, ministerial announcements, and notifications, please use the Ministry of Health, Labour and Welfare Laws and Regulations Database Service (https://www.mhlw.go.jp/hourei/).

When actual operations such as planning of studies necessary for practical application of innovative products and preparation of data necessary for approval applications are conducted, it is not enough to understand laws and regulations. It is also necessary to understand the contents of related notifications. We consider that understanding the legal system related to the PMD Act will clarify the positioning of cabinet orders, ministerial ordinances, and ministerial announcements as well as the relation between laws and notifications, thereby making it easier to understand the contents.

However, it is not easy for academia and venture companies, etc. who are unaccustomed to development to understand all the regulations related to the PMD Act, to accurately extract the standards necessary for the products under development, and to consider action plans. Development may be abandoned due to difficulty in responding to the PMD Act.

The purpose of RS general consultations/RS strategy consultations conducted by the PMDA is to help the understanding of these laws, ministerial announcements, notifications, etc. and to provide guidance and advice on how to handle them. For smooth development of innovative products, you can consult about necessary actions (For details, see "4. What is Regulatory Science (RS) general consultations/Regulatory Science (RS) strategy consultations.")

3-2 Roles of the Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA)

Administration of pharmaceutical affairs based on the PMD Act is managed by the Pharmaceutical Safety and Environmental Health Bureau of MHLW. But three duties, "review-related duties," "safety measures duties," and "relief services for adverse health effects" have been entrusted to PMDA. PMDA is an independent administrative institution that was established in April 2004 by combining two organizations, the Organization for Pharmaceutical Safety and Research and the Pharmaceuticals and Medical Devices Evaluation Center of the National Institute of Health Sciences, and a part of the Japan Association for the Advancement of Medical Equipment. The establishment of PMDA has made it possible to conduct consultations at the stage of clinical studies (clinical trials) of drugs and medical devices, as well as consistently conduct regulatory review and GLP/GCP/GPSP compliance assessment of application data.

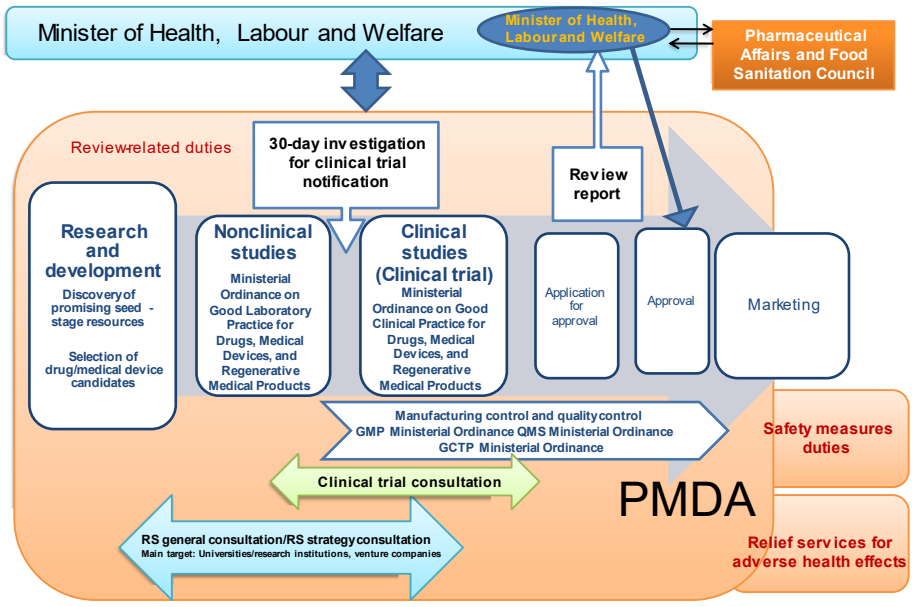


Figure 9 Relationship between PMDA's duties and MHLW

Specifically, in the development of drugs, medical devices, and regenerative medical products, PMDA provides scientific advice on studies necessary for proper development, safety evaluation on planning and implementation of first-in-human studies (clinical trials), scientific evaluation of regulatory review materials, reviews of compliance with Good Manufacturing Practice (GMP)/Quality Management System (QMS)/Good Gene, Cellular and Tissue-based Product Manufacturing Practice (GCTP), Good Clinical Practice (GCP) standards, etc., scientific evaluation of safety based on reports of adverse reactions, etc. The results of evaluation performed at PMDA are submitted to MHLW. On the basis of evaluation conducted by PMDA, the MHLW takes administrative measures based on the PMD Act. The cooperation between MHLW and PMDA has made it possible to efficiently carry out multifaceted operations, such as reviews and safety measures, from clinical studies (clinical trials) to regulatory reviews and to post-marketing settings based on scientific evaluation (Figure 9). PMDA conducts the following operations in relation to the development of drugs, medical devices, and regenerative medical products.

[1] Guidance and advice on clinical studies (clinical trials), etc.
[2] Survey on initial clinical trial notification (first-in-human study)
[3] Regulatory review for drugs, medical devices, and regenerative medical products
[4] Review of compliance with standards such as Good Clinical Practice (GCP), Good Laboratory Practice (GLP)
[5] Review of compliance with standards such as Good Manufacturing Practice (GMP)/Quality Management System (QMS)
[6] Implementation of re-examination/re-evaluation

4. What is Regulatory Science (RS) general consultation/Regulatory Science (RS) strategy consultation

4-1 Significance and purposes of RS general consultation/RS strategy consultation in the development process

1) Significance of RS general consultation/RS strategy consultation in development

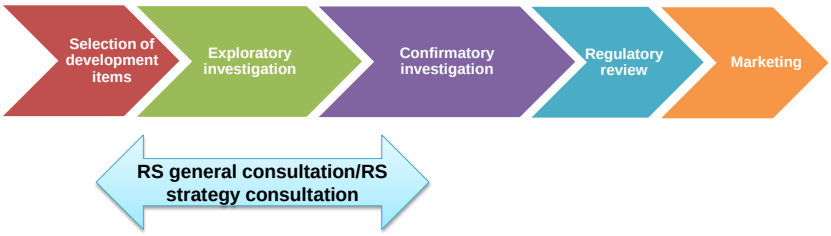


Figure 10 Development process and RS general consultation/RS strategy consultation

The general development process for drugs, medical devices, and regenerative medical products is as described in "2. Development for practical use." Figure 10 shows the process that is further generalized. After a development item is selected, an exploratory investigation will be performed first, and then an approval application will be made after a confirmatory investigation, and if it is approved, it will be marketed. Among these, exploratory investigation is very important because it determines the direction of subsequent development. Exploratory investigation needs to be considered based on state-of-the-art scientific knowledge because it is the stage of clarifying the value of the development item as a drug, medical device, or regenerative medical product. Particularly when developing items based on innovative research results, as shown in Table 6, study methods and evaluation methods are often not established. It is necessary to conduct multifaceted investigation from a viewpoint of regulatory science, and collect compelling data not only in a scientific but also in a realistic and reliable manner, and it is required to find concrete solutions by utilizing expert knowledge of universities and research institutions, etc. And of course, when it comes to providing clinical value, you need to have a good understanding of the medical needs and the involvement of clinicians is essential. The developer must consider the appropriate study methods and evaluation methods based on the results of the investigations, and not forget to confirm whether they are acceptable from the viewpoint of review based on the PMD Act. Therefore, not only companies but also

researchers from universities, research institutions, etc. involved in the development of innovative drugs, medical devices, and regenerative medical products need to be fully familiar with the regulatory requirements of the PMD Act to proceed with the investigations.

Table 6 Examples of matters to be considered in the development of innovative products

Quality	• Establishment of efficient manufacturing process • Establishment of efficient purification process • Establishment of methods for reducing biological raw materials and impurities
Nonclinical	• Establishment of a new model animal for efficacy evaluation • Establishment of methods for toxicity evaluation, etc.
Clinical	• Establishment of efficacy endpoints • Establishment of methods for evaluation of pharmacokinetics in humans, etc.

PMDA's RS general consultation/RS strategy consultation was established for the above purpose. In other words, it is intended to clarify the path to practical application of promising seed-stage resources discovered in basic research, mainly targeting academia and venture companies, in order to create innovative products in Japan. This is considered to play a part in important functions to promote "creation of innovative products in Japan." For details of RS general consultation/RS strategy consultation system, see the following section.

2) Outline and purpose of RS general consultation/RS strategy consultation

In RS general consultation/RS strategy consultation, guidance and advice are provided regarding the types of studies necessary for approval applications, formulation of study plans to be conducted, development plans, etc. from the final stage of selecting drug, medical device, and regenerative medical product candidates to the stage of clinical development. As mentioned in the previous section, active discussion between PMDA and researchers at developing companies, universities, research institutions, etc. will lead to finding appropriate and efficient development strategies for effective and safe innovative products. Specifically, mainly targeting academia, venture companies, etc., PMDA gives advice on the best way and solutions by working together with the applicant for the points to be considered and the right direction for making evaluations based on the PMD Act while listening to the applicant's opinions on methods and types of studies to be conducted, interpretation of results obtained, etc. in the course of development of innovative products.

Table 7 Examples of consultation items for RS general consultation/RS strategy consultation

(1) For drugs
- Matters related to non-clinical studies required before the start of first-in-human study
- Matters related to protocols of early exploratory clinical studies (phase I and II studies), etc.

(2) For medical devices
- Matters related to non-clinical studies required before the start of clinical study (clinical trial) in humans
- Matters related to conformity to basic requirements
- Matters related to items of specifications for performance and safety
- Matters related to data necessary at the time of the approval application regarding the safety and performance of the subject device, such as validation items for design verification and their outline
- Matters related to the data package required before the approval application, etc.

(3) For regenerative medical products
- Matters related to compliance with the standards for biological ingredients
- Matters related to quality of products used in the first-in-human study (e.g., specifications, safety and stability of process-related impurities)
- Matters related to non-clinical safety studies required before the start of first-in-human study
- Matters related to exploratory clinical study protocols, etc.

Examples of consultation items in RS general consultation/RS strategy consultation are as shown in Table 7. If you discover new seed-stage resources in basic research, we will provide guidance and advice on the quality assurance and safety studies necessary until the start of clinical studies (clinical trials), and how to plan clinical study (clinical trials) protocols. As for medical devices, specially controlled medical devices and controlled medical devices that are reviewed by PMDA are subject to RS general consultation/RS strategy consultation, and items that fall under the category of products notified by self-certification (general medical devices) and designated specially controlled medical devices handled by a registered

certification body are not subject to consultation. Since the information listed in Table 7 is just an example, please contact the Division of Innovation Support and Pharmaceuticals Affairs Consultations (R&D), Office of Review Management, PMDA by phone (+81-3-3506-9562), e-mail (rs-contact@pmda.go.jp), or fax (+81-3-3506-9593), or consult in the RS general consultation about whether or not the case is subject to RS strategy consultation.

In RS general consultations/RS strategy consultations, mainly technical experts at the Division of Innovation Support and Pharmaceuticals Affairs Consultations (R&D) handle the consultations in cooperation with related review offices, etc. After properly understanding the effectiveness and significance of each product, PMDA concretely considers and gives advice on issues and solutions for the approval application of the product from an objective standpoint through various meetings. We try to deliver effective and safe drugs, medical devices, and regenerative medical products to the medical front as soon as possible from the viewpoint of patients.

4-2 Consultation procedures

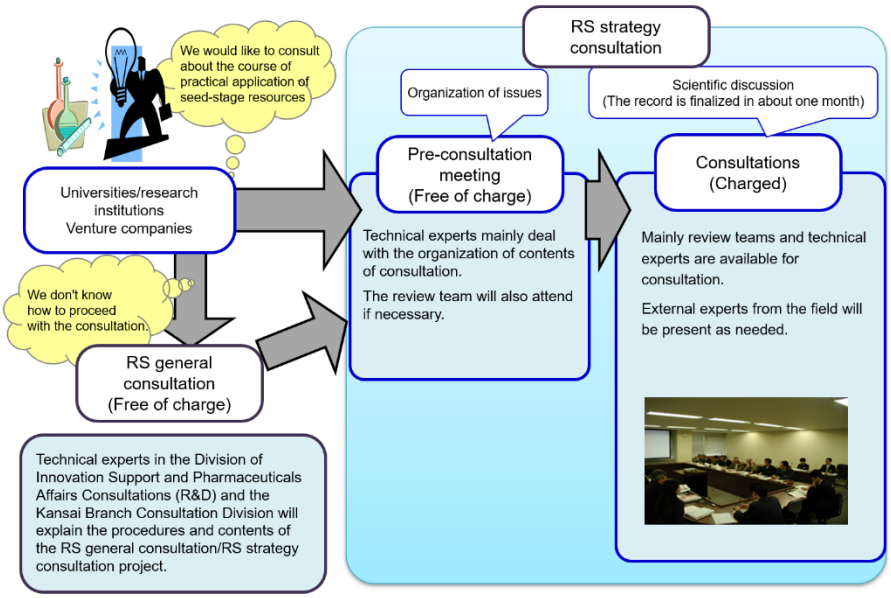


Fig. 11 Process of RS general consultation/RS strategy consultation and its relationship

As shown in Figure 11, there are three types of RS consultation including "RS general consultation," "RS strategy consultation (pre-consultation meeting)," and "RS strategy consultation (Consultations)." The outline of each process and the method of application are as follows. RS general consultations can be conducted at the Tokyo office, the Kansai Branch of PMDA (Osaka City) or the Center for Cooperation on strategy consultation of PMDA (Kobe City). RS strategy consultation (pre-consultation meeting) can be conducted at the Tokyo office or the Kansai Branch of PMDA (application method is common regardless of the place where the consultation is conducted).

Although the consultation category differs depending on the product to be consulted, the relation between the consultation subject and consultation category is as shown in Table 8.

If you have any questions about the procedures for RS general consultation/RS strategy consultation, please contact the Division of Innovation Support and Pharmaceuticals Affairs Consultations (R&D), Office of Review Management, PMDA by telephone (+81-3-3506-9562), e-mail (rs-contact@pmda.go.jp), or FAX (+81-3-3506-9593), referring to this pamphlet and the implementation guidelines for each consultation.

Table 8　Relation between consultation subject and consultation category

Consultation category	Consultation subject			
	Drugs	Medical devices	Regenerative medical products	
Strategy consultation for drugs	○	-	-	From the early stage of development, we provide guidance and advice for consultations on matters that involve data evaluation for necessary studies, etc. in order to obtain approval for drugs, medical devices, in vitro diagnostics, and regenerative medical products in the future.
Strategy consultation for medical devices	-	○	-	
Strategy consultation for regenerative medical products	-	-	○	
Consultation on the quality and safety of regenerative medical products[*1]	-	-	○	We provide guidance and advice for regenerative medical products or products intended to express an introduced gene in the human body for the purpose of prevention from the early development stage to the time of clinical trial notification.
Additional consultation on the quality and safety of regenerative medical products				
Strategy consultation on the development plan[*2]	○	○	○	We provide guidance and advice on the general way of thinking and proceeding of the study plan such as the roadmap of the development plan.

[*1] This is the consultation category corresponding to the former confirmation application. In addition to products classified as regenerative medical products, recombinant live vaccines are handled in this category.

[*2] Matters related to specific development plans for individual products (e.g., sufficiency of non-clinical studies and appropriateness of endpoints in clinical studies) are handled in the strategy consultation for drugs/medical devices/regenerative medical products.

1)　RS general consultation

[1] Overview

In the RS general consultation, the technical experts of the Division of Innovation Support and Pharmaceuticals Affairs Consultations (R&D) or the Kansai Branch Consultation Division will confirm the propriety of the desired contents of the consultation and explain the contents and procedures of the RS strategy consultation. For example, RS general consultation items include when and how to consult PMDA for a product under development and what kinds of notifications, etc. should be basically referred to when preparing data.

The fee for RS general consultation is not necessary, but consultation records or minutes are not prepared. The duration of each meeting is approximately 20 minutes. Please feel free to use RS general consultations, which are conducted not only at the PMDA but also locally by dispatched consultants.

[2] How to apply

For application for RS general consultation, download the "Application Form for Question of Regulatory Science General Consultation" from the PMDA website (https://www.pmda.go.jp/review-services/f2f-pre/strategies/0006.html), fill in the necessary items, and submit the application form by e-mail or FAX to the following address. Please check the e-mail address and fax number carefully to prevent incorrect transmission.

(Application destination)
Division of Innovation Support and Pharmaceuticals Affairs Consultations (R&D), Office of Review Management, Pharmaceuticals and Medical Devices Agency (PMDA)
e-mail: yakujisenryaku@pmda.go.jp
FAX: +81-3-3506-9593
(Reception period) As needed (Monday to Friday [excluding national holidays and other holidays])

[3] Handling after application

After receiving the application form, the schedule, etc. will be notified by telephone or e-mail from the technical

expert of the Division of Innovation Support and Pharmaceuticals Affairs Consultations (R&D) or the Kansai Branch Consultation Division. Depending on the contents, the consultation may be conducted by telephone, not by meeting.

PMDA cannot answer any question about the applicability of medical devices or business licenses. Please consult with the competent government agency, etc.

2) Pre-consultation meeting (RS strategy consultation)

[1] Overview

It is necessary to have the pre-consultation meeting in advance of the Consultations. The main purpose of the pre-consultation meeting is to arrange issues for consultation items and confirm the contents of documents required for the consultation in order to effectively conduct the Consultations. In the pre-consultation meeting, in addition to the technical experts at the Division of Innovation Support and Pharmaceuticals Affairs Consultations (R&D) or the Kansai Branch Consultation Division, the review staff of the review office will attend the meeting as necessary so that applicants can directly confirm their concerns and questions with them. The fee for the pre-consultation meeting is not necessary, but consultation records or minutes are not prepared. The duration of each meeting is approximately 30 minutes.

[2] How to apply

For application for the pre-consultation meeting, download the "Application Form for Question of Regulatory Science Strategy Consultation Pre-consultation meeting" from the PMDA website (https://www.pmda.go.jp/review-services/f2f-pre/strategies/0008.html), fill in the necessary items, and submit the application form by e-mail or FAX to the following address. Please check the e-mail address and fax number carefully to prevent incorrect transmission.

(Application destination)
Division of Innovation Support and Pharmaceuticals Affairs Consultations (R&D), Office of Review Management, Pharmaceuticals and Medical Devices Agency (PMDA)
e-mail: yakujisenryaku@pmda.go.jp
FAX: +81-3-3506-9593
(Reception period) As needed (Monday to Friday [excluding national holidays and other holidays])

[3] Handling after application

After receiving the application form, the schedule, etc. will be notified by telephone or e-mail from the technical expert of the Division of Innovation Support and Pharmaceuticals Affairs Consultations (R&D) or the Kansai Branch Consultation Division. Depending on the contents, the consultation may be conducted by telephone, not by meeting.

See "6. What to do at times like this (Q & A) Q2-1" for materials necessary for the pre-consultation meeting and points to consider.

At the pre-consultation meeting, you may be proposed to have another pre-consultation meeting after adjusting points of discussion and materials. Please make an application with a sufficient schedule.

3) Consultations (RS strategy consultation)

[1] Overview

The Consultations is a process in which the review team of the review office carefully checks the materials submitted by the applicant regarding the consultation items from the applicant and issues the PMDA's official opinion on each consultation item. Additional data and materials should be submitted as required. For the

Consultations, you need to pay a certain fee (see "(4) Consultation fee" below for details) by the due date before the Consultations.

Figure 12 shows the flow from the conduct of the pre-consultation meeting to the Consultations.

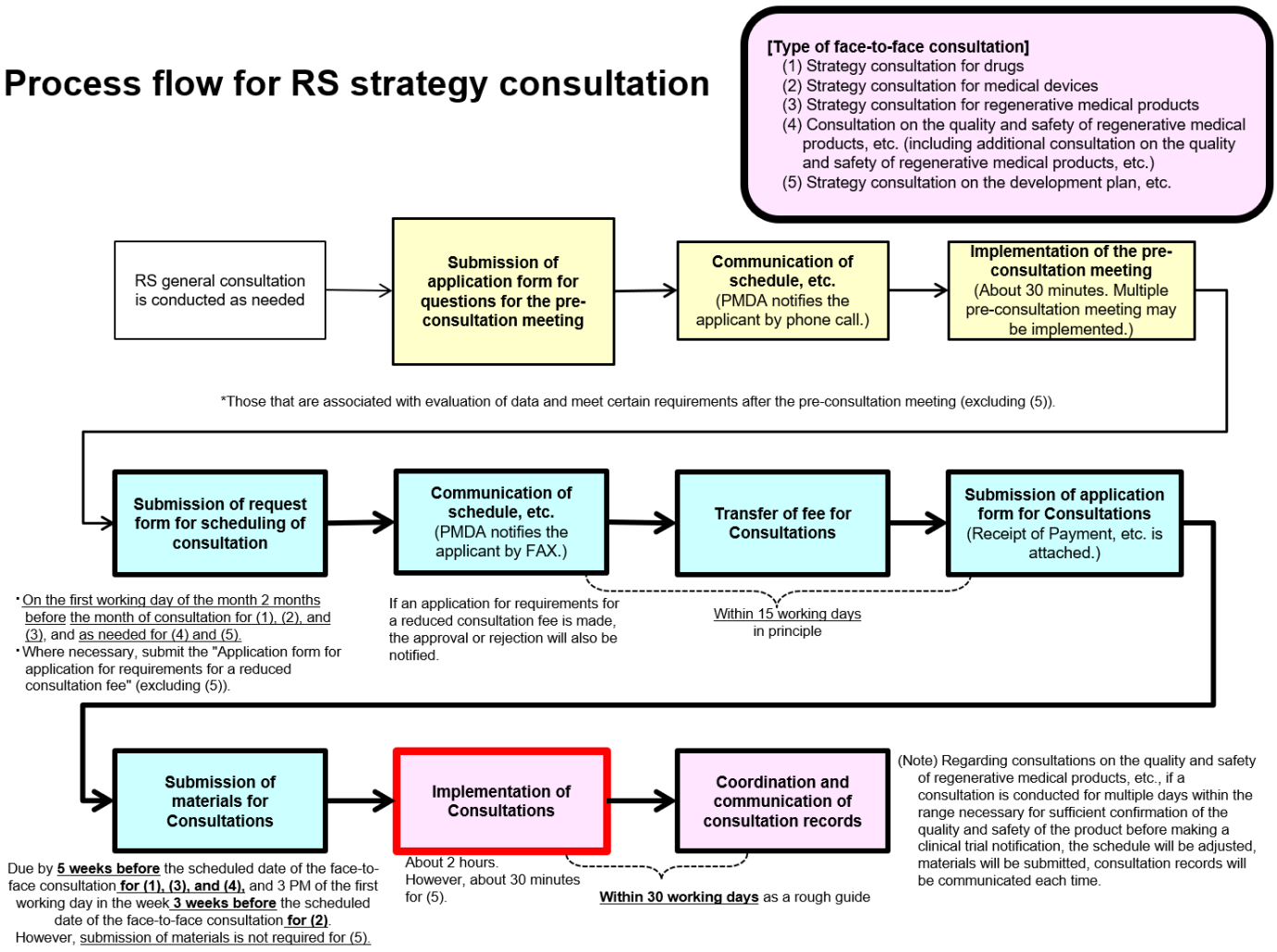


Figure 12　Process from pre-consultation meeting to Consultations

[2] Start of application procedures

Application procedure for the Consultations begins with submission of a request form for scheduling (application for strategy consultations for drugs, strategy consultations for medical devices, and strategy consultations for regenerative medical products are accepted only at the beginning of the month two months before the desired timing of consultation). From the PMDA website (https://www.pmda.go.jp/review-services/f2f-pre/strategies/0005.html), download the "Request Form for Scheduling of Strategy Consultation for Drugs" (Form No. 28) for drugs, "Request Form for Scheduling of Strategy Consultation for Medical Devices" (Form No. 29) for medical devices, "Request Form for Scheduling of Strategy Consultation for Regenerative Medical Products" (Form No. 30) for regenerative medical products, and "Request Form for Scheduling of Consultations on Quality and Safety of Regenerative Medical Products" (Form No. 31) for consultation on quality and safety of regenerative medical products, etc., (including additional consultation on quality and safety of regenerative medical products), and "Request Form for Scheduling of Strategy Consultation on the Development Plan" (Form No. 32) for strategy consultation on the development plan.Then fill in the necessary information and submit the

form to the following by e-mail in principle. If it is difficult to submit it by e-mail, submit it by fax. Because the timing of submission differs depending on the type of consultation, please check the following. Also please check the address and fax number carefully.

There is a check column in the request form for scheduling to confirm that you have received the pre-consultation meeting about the contents of consultation and got agreement to proceed to the Consultations. If the pre-consultation meeting has not been completed, please apply for the pre-consultation meeting first.

(Application destination)

Review Management Division, Office of Review Management, Pharmaceuticals and Medical Devices Agency (PMDA)
Shin-Kasumigaseki Building, 3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013
e-mail: yakujisenryaku@pmda.go.jp
FAX: +81-3-3506-9443

(Reception period)

- Strategy consultation for drugs, strategy consultation for medical devices, and strategy consultation for regenerative medical products: Usually, on the first working day of the month two months before the month of consultation (please check the PMDA website as it may be changed during the year-end and New Year holidays, etc.). In the case of submission by mail, etc., it must be received on the above day.

- Consultation on the quality and safety of regenerative medical products (including additional consultation on the quality and safety of regenerative medical products) and strategy consultation on development plans. (please confirm whether or not this consultation category is applicable at the pre-consultation meeting)

  As needed (Monday to Friday [excluding national holidays and other holidays])

Please fill in the desired date of the Consultations (morning or afternoon) as much as possible in the desired date of consultation column of the request form for scheduling.

[3] Actions after submission of the request form for scheduling

After submitting a request form for scheduling, PMDA will send the "Guide to Consultations" to the applicant by e-mail or FAX usually on the fifth working day. Please transfer the fees specified by PMDA from a city bank, etc. within 15 working days counting from the day following the date of receipt of the guide, in principle. Upon completion of the transfer, from the PMDA website (https://www.pmda.go.jp/review-services/f2f-pre/strategies/0005.html), download the "Application Form for Strategy Consultations for Drugs" (Form No. 28) for drugs, "Application Form for Scheduling of Strategy Consultations for Medical Devices" (Form No. 29) for medical devices, "Request Form for Scheduling of Strategy Consultations for Regenerative Medical Products" (Form No. 30) for regenerative medical products, and "Application Form for Consultations on Quality and Safety of Regenerative Medical Products" (Form No. 31) for consultation on quality and safety of regenerative medical products, etc., (including additional consultation on quality and safety of regenerative medical products), and "Application Form for Strategy Consultations on Development Plans, etc." (Form No. 32) for strategy consultation on development plans, etc. Then fill in the necessary information and submit the form with a copy of the transfer receipt, etc. and an electronic file of the outline of the contents of consultation attached by e-mail (shinyaku-uketsuke@pmda.go.jp) to the Review Management Division, Office of Review Management, PMDA (please consult if it is difficult to submit the form by e-mail). Please note that even if you have submitted a request form for scheduling, you will not be regarded as having completed the application procedures without sending this application form.

Please submit the materials for Consultations (electronic files) to the Review Management Division, Office of Review Management by mail or bringing an electronic medium (CD or DVD) or online submission using the Electronic Application Data System (gateway system), in principle, by 3:00 pm (JST) of the first working day, five weeks before the scheduled date of Consultations (three weeks before for medical devices) (For details, see "6. What to do at times like this (Q & A) Q2-2." The deadline for submission of the application form and the delivery date of materials are described in the "Guide to Consultations").

For strategy consultations on development plans, etc., it will not be necessary to submit materials for the Consultations in advance. However, please submit materials in the cases when the expert of the Division of Innovation Support and Pharmaceuticals Affairs Consultations (R&D) requests submission.

[4] Consultation fee

A) Fee

For the Consultations, the fee shown in Table 9 is required. The fee may be reduced depending on the total amount of research expenses received.

Table 9 Fee for RS strategy consultation

Consultation category	Consultation fee per application
Strategy consultation for drugs	1,541,600 yen (154,100 yen)*1
Strategy consultation for medical devices*2	874,000 yen (87,400 yen)*1
Strategy consultation for regenerative medical products	874,000 yen (87,400 yen)*1
Consultation on the quality and safety of regenerative medical products*3	1,541,600 yen (154,100 yen)*1
Additional consultation on the quality and safety of regenerative medical products*3	496,800 yen
Strategy consultation on the development plan	73,600 yen

*1: Universities/research institutions and venture companies that meet the requirements specified separately
*2: In vitro diagnostics are handled in strategy consultation for medical devices.
*3: More than one Consultations is possible with one application. For a company that does not correspond to the venture company meeting the requirements specified separately, if consultation is held over multiple days, the fee for one consultation will be charged for up to three consultations. The fee for additional consultation on the quality and safety of regenerative medical products will be charged for the fourth and subsequent consultations.

"Universities/research institutions and venture companies that meet the requirements specified separately" refer to cases where all the requirements for reduced fee in Table 10 below are met.

Table 10 Requirements for reduced fee (universities/research institutions and venture companies that meet the requirements specified separately)

(Universities/research institutions)
- Having not received research expenses of the following amount or more for the relevant seed-stage resources from the government
  Strategy consultation for drugs or consultation on the quality and safety of regenerative medical products: 90 million yen
  Strategy consultation for medical devices or strategy consultation for regenerative medical products: 50 million yen
- Having not received research expenses from a pharmaceutical company/company developing medical device under a joint research agreement, etc. for practical application of the seed-stage resources

(Venture companies)
- Being a small or medium-sized enterprise (number of employees 300 or less or capital 300 million yen or less)
- Other corporations do not have shares or investments of half or more of the total number of shares or total investment
- Multiple corporations do not have shares or investments of two-thirds or more of the total number of shares or total investment
- In the preceding business year, the profit for the current year is not recorded, or the profit for the current year is recorded but there is no business profit

(Precautions)
For application of requirements for reduced fee for venture companies, please pay attention to the following points. If you are considering application of requirements for reduced fee and have any questions, please contact the Review Management Division, Office of Review Management, PMDA (phone: +81-3-3506-9556).
(1) For "corporation" included in the above items related to venture companies, handling of investment unions such as venture capital firms is determined individually in accordance with the relevant laws and regulations, standards, etc.
(2) If development expenses are recorded as deferred assets for accounting purposes, the amount equivalent to the current profit in the case of processing them as expenses is used as a reference.
(3) If there are special circumstances, etc. in the settlement of accounts for the preceding business year and it is considered necessary to make a judgment based on the settlement status in the preceding two fiscal years, you may be requested to submit the related materials and judgment is made after confirmation of these materials.

B) Request for application of requirements for reduced fee

If you think you have met the requirements for reduced fee shown in Table 10 above, submit the "Request form for application of requirements for reduced consultation fee" with the materials shown in Table 11 by e-mail, postal mail, or bringing so that it can be reached by the submission date of the "Request form for Scheduling of Strategy

Consultation." When sending it by postal mail, write in red "Request form for application of requirements for reduced consultation fee related to RS strategy consultation is enclosed" on the front of the envelope.

Based on the documents you submitted, PMDA will check whether or not it corresponds to the requirements for reduced fee, and inform the applicant of the fee, time limit for transfer, etc. through the "Guide to Consultations."

Table 11 Documents** to be submitted when application is made for application of requirements for reduced fee

✧ For universities/research institutions

- Request form for application of requirements for reduced consultation fee related to RS strategy consultation (universities/research institutions)
  - The format is posted on the RS strategy consultation website.
  - Submit the format by e-mail.
  - Enter the same person as the applicant in the Request form for Scheduling as much as possible in the column of "Name of applicant."
  - Enter the name of the person in charge of finance or clerical work as much as possible in the column of "Name of person in charge."

<If you have received a government subsidy (from the Ministry of Health, Labour and Welfare, the Ministry of Education, Culture, Sports, Science and Technology, the Ministry of Economy, Trade and Industry, etc.)>

- Notification of decision on grant of government subsidy for the seed-stage resources and themes in the current consultation (for the last three years)
- Business plans at the time of application for government subsidy for the seed-stage resources and themes in the current consultation (for the last three years)

(You do not need to submit these documents for subsidies not related to the seed-stage resources and themes for consultation.)
(You may send a copy by fax or e-mail.)

<If you have not received a government subsidy>

- Account book, budget balance book, etc. for which the revenue and expenditure of research expenses of the seed-stage resources to date can be confirmed (for the last three years)

(You may send a copy by fax or e-mail. Personal information that you want to be masked can be blacked out.)

- List of subsidies from the government received by the representative researchers, joint researchers, and co-researchers of the seed-stage resources during the three fiscal years

✧ For venture companies

- Request form for application of requirements for reduced consultation fee related to RS strategy consultation (venture companies)
  - The format is posted on the RS strategy consultation website.
  - Submit the format by e-mail.
  - Enter the same person as the applicant in the Request form for Scheduling as much as possible in the column of "Name of applicant."
  - Enter the person in charge of finance or clerical work as much as possible in the column of "Name of person in charge."
- Balance sheet and profit and loss statement (business reports or business overview statements are also acceptable)
  - For profit for the year and business profit, the amount of the entire corporation is subject to judgment.
- Corporation tax return, Appendix 2 (copy) (or list of shareholders (investors))
- If the capital is 300 million yen or more, one of the following materials (copy)
  - Application form for rough estimate of insurance premium for labor insurance
  - Summary table of basic notification for calculation of monthly remuneration for health insurance and welfare pensions for an insured person
  - Calculation sheet for the amount of tax collected for salary income, retirement income, and other income

[5] How to proceed with Consultations

A) From delivery of materials to the date of Consultations

For the Consultations (excluding strategy consultation on the development plan), the materials submitted will be checked. If there are any unclear points or insufficient information, etc., inquiries regarding the contents of the consultation will be sent approximately one to two weeks after submission of the materials in principle, and you may be requested to submit responses to the inquiries. After that, we will send our opinions on the consultation items in advance, and you will be requested to submit your response to the opinions.

For strategy consultation on the development plan, the burden on the applicant will be reduced as much as possible by using the materials submitted at the time of the pre-consultation meeting, but additional materials may be requested to be submitted.

B) Day of Consultations

Consultations (excluding strategy consultation on the development plan) will be conducted by the review

** For the foreign applicants, please ask about required documents through 7.contact information.

office responsible for the products, in addition to technical experts of the Division of Innovation Support and Pharmaceuticals Affairs Consultations (R&D). The duration of each Consultations is approximately two hours. Usually, we ask the applicant to give a presentation about the consultation items for about 10 minutes at the beginning. Please check with the person in charge about the timing of submission of presentation materials.

Strategy consultation on the development plan will be conducted by the review office responsible for the products in principle, in addition to technical experts of the Division of Innovation Support and Pharmaceuticals Affairs Consultations (R&D), to give advice on general ways of thinking and proceeding of study plan such as roadmap of development plans. The duration of each Consultations is approximately 30 minutes. We may ask the applicant to give a presentation about the consultation items for about five minutes at the beginning.

C) After the date of Consultations

If the applicant wishes to obtain a voice recording (CD) at the time of the Consultations, it will be given to you by mail or hand within a few days after the completion of the Consultations. After the Consultations, the consultation record will be prepared and sent to the applicant in about 30 working days.

For strategy consultation on the development plan, no action will be taken on voice recording as it is related to general matters.

5. Examples of RS general consultation/RS strategy consultation

In this chapter, we will introduce some examples subject to RS general consultation/RS strategy consultation. These are just general cases, so for individual cases, please consult individually at RS general consultation/RS strategy consultation.

5-1 Drugs

1) Matters related to the quality of drugs

Example: What are points to consider in setting specifications in the early stage of drug development?

The first step toward practical application of innovative drugs is to ensure a certain level of quality of development items (seed-stage resources). Implementation of non-clinical studies and clinical studies (clinical trials) with products of certain quality will improve the reliability of the results.

In the early development stage, it is necessary to clarify the quality characteristics of the development item as much as possible. Its objectives are establishing the manufacturing process from obtaining raw materials to manufacturing of the final product and confirming the consistency, formulating the in-process control test, and setting the specifications and stability of the final product.

Example: The manufacturing process of drugs is expected to be changed in the future. What are the points to consider when conducting non-clinical studies, etc. with the current manufacturing method?

Changes in the manufacturing process during the development process should be carefully considered. If there is a major change in the manufacturing process after the start of non-clinical studies, it is necessary to scientifically demonstrate the equivalence to the item before the change. If equivalence cannot be demonstrated, the results of non-clinical studies conducted using the item before the change may not be available, and it may be necessary to conduct the study again.

Therefore, if the manufacturing process is planned to be changed, it is useful to carefully consider the timing of implementation of non-clinical studies, etc. first and to construct the development strategy so that there will be no major change in the manufacturing process.

In addition, for appropriate evaluation of the equivalence, it is necessary to specify the specifications (solubility, stability, purity, potency, etc.) for the items to be used in the non-clinical studies, etc., and confirm that they conform to the specified specifications in advance; to use the items manufactured in the facilities conforming to

GMP as much as possible; and to accurately record the manufacturing-related information (date of manufacturing, lot number, manufacturing facility, etc.). Based on this information, it will be possible to clarify what kind of investigation should be conducted in order to examine the impact of the change in the manufacturing process on the quality of the final product, and to provide a more scientific explanation on the equivalence.

2) Matters related to non-clinical studies of drugs

Example: Which non-clinical safety study is considered necessary before the start of the first-in-human study (FIH) of drugs?

See ICH M3 (R2) Guideline (Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals;https://www.pmda.go.jp/files/000156128.pdf) for non-clinical study considered necessary before the start of the first-in-human study (FIH) of drugs.

The outline is as follows.

Table 12 Classification of Pharmacology Studies

Pharmacology study		Purpose/item, etc.	Points to consider	Cited guidelines, etc.
Primary pharmacodynamics	*In vitro* or *in vivo*	Studies necessary to scientifically and theoretically explain the mechanism of action of clinical efficacy	(1) Whether the test systems and test designs used are appropriate (2) Whether an appropriate target group is set (3) Whether non-specific value is not included in the obtained measurement (4) Whether dose correlation (concentration dependence) is evaluated (5) Whether the route of administration is the same as the clinical route of administration	
Secondary Pharmacodynamics		Concerns specific to candidate compound other than core battery study		
Safety Pharmacology		(1) Core battery study 1) Study on the central nervous system 2) Study on the cardiovascular system 3) Study on the respiratory system (2) Follow-up and supplemental safety pharmacology	(1) Whether the study items are sufficient (2) Whether the study dose range is sufficient (3) Whether the safety has been sufficiently discussed	S7A; SAFETY PHARMACOLOGY STUDIES FOR HUMAN PHARMACEUTICALS https://www.pmda.go.jp/files/000156011.pdf S7B; The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceutical https://www.pmda.go.jp/files/000156513.pdf

There are three pharmacology studies including primary pharmacodynamics, secondary pharmacodynamics, and safety pharmacology. The objectives and points to consider for each study are as shown in Table 12. From a safety perspective, safety pharmacology study results for the central nervous, cardiovascular, and respiratory systems (called core battery studies) generally need to be evaluated before FIH. It should also be considered that these assessments are incorporated into general toxicity studies to the extent possible to reduce the number of animals used. Depending on the characteristics of the development items, it may be necessary to conduct additional follow-up studies or secondary pharmacodynamic studies for reasons such as concerns in core battery studies.

Pharmacokinetic studies in non-clinical stages usually require evaluation of the results of *in vitro* studies on drug metabolism and plasma protein binding data in animals and humans, as well as systemic exposure data in the animal species used in repeated-dose toxicity studies before FIH.

Table 13　Toxicity studies that generally need to be investigated before the first-in-human clinical study (clinical trial)

Type of toxicity study	Maximum duration of clinical study	Minimum duration of repeated-dose toxicity study	Major guidelines/guidance, etc.
Repeat-dose toxicity study	Up to 2 weeks	2 weeks	M3 (R2); Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals https://www.pmda.go.jp/files/000156128.pdf Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals Questions & Answers（R2） https://www.pmda.go.jp/files/000156455.pdf S3A; Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies https://www.pmda.go.jp/files/000156031.pdf S4; Duration of Chronic Toxicity Testing in Animals（Rodent and Non Rodent Toxicity Testing） https://www.pmda.go.jp/files/000156229.pdf S4A; Revision of Guidelines for Toxicity Studies of Drugs Manual ([2] Repeated dose toxicity study; Guidelines for the duration of chronic toxicity studies in animals) https://www.pmda.go.jp/files/000156632.pdf S6 (R1); Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals https://www.pmda.go.jp/files/000156596.pdf
	More than 2 weeks and up to 6 months	Same as the clinical study period	
Genotoxicity	S2 (R1); Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use https://www.pmda.go.jp/files/000156595.pdf		
Local Tolerance	M3 (R2); Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals https://www.pmda.go.jp/files/000156128.pdf		
Reproductive and Developmental Toxicity	S5（R2）Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility https://www.pmda.go.jp/files/000156671.pdf		
Immunotoxicity	S8; Immunotoxicology Studies for Human Pharmaceuticals https://www.pmda.go.jp/files/000156956.pdf		

As toxicity studies, it is usually necessary to conduct toxicity studies as shown in Table 13 before FIH. These studies should be conducted based on Good Laboratory Practice (GLP) standards in principle. For drugs, necessary toxicity studies are different in case of early exploratory clinical studies (clinical trials) such as microdose clinical studies. For more information, see ICH M3 (R2) Guideline (Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals; https://www.pmda.go.jp/files/000156128.pdf).

The nonclinical studies required may differ not only depending on the characteristics of the development item but also depending on the plan for the clinical study (clinical trial) (target patients, route of administration, treatment duration, dose, etc.). Therefore, it is necessary for efficient development to examine the plans for the clinical study (clinical trial) from the nonclinical study stage.

For biotechnological products, you should also refer to the ICH S6 (R1) guideline "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals" (https://www.pmda.go.jp/files/000156596.pdf).

3)　Matters related to clinical studies (clinical trials) of drugs

Example: What are points to consider when setting endpoints in clinical studies (clinical trials) that are conducted for exploratory purposes?

The objective of an exploratory clinical study (clinical trial) such as a phase II study is generally to collect scientific data on the efficacy and safety of the development item in patients, and efficacy indicators are set as primary endpoints. In setting the primary endpoint, several indicators will be selected as matters to be examined

after examining the symptoms of the target disease, what is the clinically significant improvement effect, and what is the effect assumed from the mechanism of action of the development item, etc. Since exploratory clinical studies (clinical trials) are conducted in a relatively small number of subjects, it is common to select the most sensitive and clinically significant indicator among the selected indicators as the primary endpoint. In some cases, biomarkers, etc. are set as primary endpoints. The results of an exploratory clinical study (clinical trial) are important for determining the primary endpoint and dose, etc. in a confirmatory study to be conducted later. The primary endpoint in an exploratory clinical study (clinical trial) must have a clear relation with the primary endpoint set up in a confirmatory study and be clinically meaningful.

Example: Is it essential to include a placebo group?

It is appropriate to include a placebo group in order to obtain clear evidence for the clinical effect of the development item. However, not all cases require a placebo group. Basically, it is recommended to include a placebo group, but it is necessary to make a decision after sufficiently examining the seriousness of the target disease, presence or absence of existing treatment methods, number of target patients, placebo effects for the target disease, etc. If a placebo group is not included, it is necessary to explain in the dossiers that the clinical effect can be scientifically confirmed without a placebo group, together with the rationale.

Table 14 Considerations (study objectives) and usefulness of control group

	Type of control							
Study objectives	Placebo	Active drug (non-inferiority)	Active drug (superiority)	Dose response	Placebo + Active drug	Placebo + dose response	Active drug + dose response	Placebo + active drug + dose response
Measurement of "absolute" effect size	Y	N	N	N	Y	Y	N	Y
Proof of existence of effect	Y	P	Y	Y	Y	Y	Y	Y
Proof of dose-response relationship	N	N	N	Y	N	Y	Y	Y
Comparison of treatments	N	P	Y	N	Y	N	P	Y

Y = Yes, N = No, P = Possible

Even if a placebo group is not included, it may be appropriate to conduct a randomized comparative study using existing drugs (active drugs) or some doses in order to design a more scientific clinical study (clinical trial). The matters that can be examined differ depending on the control group to be included, and the outline is as shown in Table 14. For details, see the ICH E10 guideline (Choice of Control Group and Related Issues in Clinical Trials; https://www.pmda.go.jp/files/000156803.pdf).

5-2 Medical devices and in vitro diagnostics

1) Matters related to the quality of medical devices

Example: Manufacturing control and quality control (QMS) of medical devices

The important thing for securing the quality of medical devices is to comply with the quality management system based on the Ministerial Ordinance on Quality Management System (QMS) for Medical Devices and In vitro Diagnostics (Quality Management System (QMS) Ministerial Ordinance (ISO13485)). Design control includes the processes of design verification and design confirmation as shown in Figure 13, along with risk analysis. The data obtained in these processes will be important data for the approval application, etc. Therefore, it is important to consider bearing that in mind.

In design and development, in order to reflect the intended use and directions for use, etc. in the design,

specifications related to performance and safety will be set based on conformity to basic requirements, use status in Japan and overseas, information on similar devices, and risk analysis, etc. Risk analysis will be performed also when a prototype is manufactured, and design changes will be made as necessary. In addition, the validity as a medical device is examined by performance tests and clinical studies (clinical trials, etc.), to confirm whether the intended use/customer needs are met, and to give feedback to design again where necessary. Once the design is determined, mass production design is performed after validation in animals and humans to finalize a product with assured performance and safety as a medical device while validation is performed in the manufacturing process (Figure 13). Medical devices must be manufactured in accordance with the QMS Ministerial Ordinance for a series of flows from design to manufacturing and shipment. Records, etc. for each process from the trial production stage to mass production equipment should also be appropriately retained as supporting data for reliability assurance. To manufacture a single medical device, parts, etc. are generally procured from companies other than development companies. For materials and intermediate parts, etc., it is necessary to prepare order placement criteria and acceptance criteria and to establish acceptance inspection methods and acceptance inspection criteria to ensure the quality.

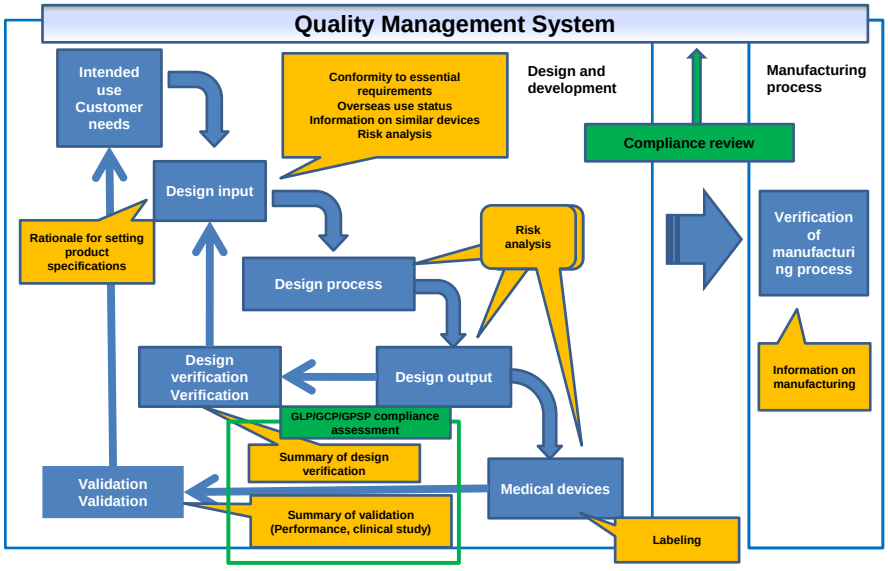


Figure 13 Quality Management System for Medical Devices

2) Matters related to non-clinical studies of medical devices

Example: Non-clinical study to evaluate the performance and safety of the medical device

In non-clinical safety studies of medical devices, physical, chemical properties, electrical safety, and biological safety, etc. are generally evaluated as shown in Table 15 (Reference: PFSB/ELD/OMDE Notification No. 0120-9 [January 20, 2015]). It is necessary to consider what kind of evaluation tests need to be performed based on the intended purpose, positioning, significance, and directions for use of the device under development.

If the test method is specified in the JIS or ISO/IEC specifications, the specified test method should be used. For medical devices with high novelty, the JIS or ISO/IEC specifications for reference may not exist. In such cases, developers should develop scientifically valid evaluation methods.

In principle, biological safety tests should be performed in compliance with Good Laboratory Practice (GLP). If the device is intended to come into contact with the human body or body surface, appropriate biological safety tests should be performed, depending on the part or duration of contact. For devices requiring sterilization, the requirements differ depending on single or repeated use, and the appropriateness of the sterilization method should be explained and validated. In addition, for devices involving Internet connection, measures should be taken for cybersecurity.

In order to evaluate whether the device under development achieves its intended use in terms of efficacy, you should consider what kind of non-clinical performance tests should be conducted, taking into account the purpose, positioning, significance, and directions for use. A non-clinical performance test is the validation of a device indicator to achieve the intended use and clinical outcome, and physicochemical models or animal models are

generally used for evaluation. The contents validated by the performance test are specified as performance specifications.

Table 15 Overview of Nonclinical Studies to Ensure the Safety of Medical Devices

	Overview
Physical and chemical properties	Overall, settings for physicochemical properties and summary of test results For devices using dental materials and polymer materials, (1) infrared absorption, (2) atomic absorption, (3) durability, (4) hardness, (5) extractables, etc. are required in consideration of characteristics. For dentistry, PFSB/ELD/OMDE Notification No. 0131-6 (January 31, 2014)
Electrical safety and electromagnetic compatibility	Tests for electrical safety are conducted based on JIST0601-1. These include (1) Power input test, (2) Resistance test of protective earth, (3) Temperature test, (4) Earth leakage current test, (5) Enclosure leakage current test, (6) Patient leakage current test, (7) Patient measured current and (8) Withstand voltage test, etc. Test for electromagnetic compatibility is conducted based on JIST0601-2. Reference: For dentistry, PFSB/ELD/OMDE Notification No. 0131-6 (January 31, 2014)
Biological safety	Examine how the device is affected by chemical substances, etc. used and whether the chemical substances may come into contact with the living body. ・ The test needs to be performed for the medical devices that may come into contact with the living body. ・ The safety tests required differ depending on surface contacting devices, devices connecting inside and outside the body, and implantable devices. ・ Tests considering the period of contact with the living body (temporary contact, short- and medium-term contact, long-term contact) are necessary. These include (1) Cytotoxicity test, (2) Sensitization test, (3) Genotoxicity test, (4) Implantation test, (5) Irritation test,(6) Systemic toxicity test, (7) pyrogen test, and (8) hemocompatibility test. Reference: PFSB/ELD Notification No. 0106-1 (January 6, 2020) For dentistry, PFSB/ELD/OMDE Notification No. 0301-1 (March 1, 2012)
Radiation safety	Test is conducted based on JIST0601-3. Compliance with other regulations such as the Ordinance for Enforcement of the Medical Care Act should also be considered.
Mechanical safety	These include (1) Strength test, (2) Repeated bending test, (3) Tensile test, and (4) Wear test. Test of fail-safe mechanisms, such as emergency stop functions, may be required.
Stability and durability	These include (1) Long-term storage test, (2) accelerated test, (3) stress test, etc. For devices requiring re-sterilization, the influence, etc. of sterilization should be examined. Reference: For shelf life, PFSB/ELD/OMDE Notification No. 0815001 (August 15, 2007) PFSB/ELD/OMDE Notification No. 0905001 (September 5, 2008)

3) Matters related to clinical studies (clinical trials) of medical devices

Example: Points to consider for planning clinical studies (clinical trials) of medical devices

If extrapolation of the efficacy and safety of the developed product to humans is difficult only with the results of nonclinical studies, these items will be verified in clinical studies (clinical trials). Clinical studies include exploratory clinical research or clinical trials and confirmatory clinical trials to verify the hypothesis obtained from the research or clinical trials. When clinical study results are attached to an application for marketing approval, they must be obtained from a confirmatory clinical trial in principle.

What is important for planning a clinical study (clinical trial) is to clarify the purpose of development and clinical positioning. By clarifying the target patients, how to use the device under development, whether it is an alternative to existing therapies or diagnostic methods, or whether it is a new medical device with no similar devices, matters to be confirmed in clinical studies (clinical trials) will become clear (see Table 16).

For example, such information is important in setting the target patients, primary endpoint, or control group, and it is possible to draw up a protocol smoothly by clarifying it in advance. If it is difficult to build a hypothesis to be verified in a confirmatory clinical trial, an exploratory clinical research or clinical trial is generally conducted.

In order to conduct a clinical study (clinical trial) with a high level of evidence, it is recommended to conduct a randomized controlled study with a control group in a blinded manner. However, it is not uncommon that a controlled clinical trial cannot be conducted in a clinical study (clinical trial) of a medical device. In such a case, a clinical study (clinical trial) in a single group will be planned, but sufficient consideration will be required in advance to make an appropriate plan as much as possible.

Importantly, studies with a high level of evidence are performed to demonstrate that the benefits of the developed product outweigh the risks and that the residual risks are acceptable.

Table 16 Considerations for planning clinical studies (clinical trials) of medical devices

・ Number of patients with the target disease and background ・ Natural history of target disease ・ Presence or absence of existing treatment methods or diagnostic methods for the target disease and the clinical study results if present ・ Objectivity of the endpoints investigated and the primary endpoint to be set out ・ Factors affecting efficacy or safety

4) Matters related to QMS for in vitro diagnostics

Example: QMS for in vitro diagnostics

As with medical devices, the marketing authorization holders of in vitro diagnostics are required to comply with QMS from design and development of products to manufacturing and post-marketing. The registered manufacturing sites (design, filling, and storage) for the product are also required to comply with QMS. QMS inspections related to a product is implemented for the marketing authorization holder and all registered manufacturing sites at the time of application for marketing approval (certification) of the product. In addition to the above application for approval (certification), QMS inspections are conducted at the time of partial changes in approved (certification) items and every five years after approval (certification) (periodic compliance assessment).

A system has been introduced that streamlines QMS inspections of manufacturing sites of in vitro diagnostics and medical devices by omitting review by means of presentation of "standard conformity certificate" issued for items manufactured in the same "product group category" and at the same registered manufacturing site. If a QMS inspections application is required at the time of approval (certification) application, it is necessary to confirm in advance whether the "product group category" and the "standard conformity certificate" of the manufacturing site correspond to the developed product.

5) Matters related to clinical performance studies of in vitro diagnostics

Example: Clinical performance study of in vitro diagnostics

A study of an in vitro diagnostic to collect clinical study results is called a "clinical performance study." Since in vitro diagnostics are not subject to the GCP standards, the study must be performed in compliance with Article 67 "Standards for Requesting Clinical Trials" of the old regulations (MHW Ordinance No. 27, 1996).

When applying for approval of a new in vitro diagnostic, it is necessary to submit the results of the clinical performance study.

Also, the protocol, case report form, IRB records, informed consent to patients, manufacturing records of developed products used for the clinical performance study, etc. will be confirmed for the scientific reliability of data by checking raw data related to the clinical performance study at the time of application for approval. Therefore, it is important to consider in advance so that adequate measures can be taken at the time of planning the clinical performance study.

As with medical devices, when claiming a new in vitro diagnostic or new significance in the clinical diagnosis, it is necessary to present the study results of the clinical performance study as the grounds for the claim so that the clinical usefulness can be explained.

5-3 Regenerative medical products

1) Matters related to the quality of regenerative medical products

Example: What are points to consider in setting specifications in the early stage of development of regenerative medical products?

For regenerative medical products, it is important to first consider the compliance with the Standards for Biological Ingredients in order to eliminate the risk due to infectious factors such as viruses that raw materials of biological origin have. That consideration is required by the time of application for regulatory approval, and at the start of the clinical trial, minimum response is required to ensure the safety of subjects. For example, when collecting cells/tissues to be used as raw materials, etc., it is necessary to conduct donor screening to confirm the eligibility of providing cells/tissues when the donor is a human. When the donor is an animal, it is necessary to confirm the origin, control status, implementation status of virus inactivation treatment, etc. in consideration of the microbiological characteristics of each animal species such as endogenous retroviruses. In addition, it is necessary to confirm the compliance with the Standards for Biological Ingredients for not only reagents used for cell processing but also media, added ingredients, etc. used in the manufacturing process, and inquiries to distributors, etc. may be necessary. For points to consider concerning the quality of regenerative medical products, please refer to the PMDA website (https://www.pmda.go.jp/review-services/drug-reviews/about-reviews/ctp/0007.html).

Example: Virus free tests have been performed for regenerative medical products. What are points to consider demonstrating the safety of developed products?

For regenerative medical products, it is necessary to ensure the safety of manufacturing staff and healthcare professionals, prevent cross-contamination in the manufacturing process, and consider transmission of various infections and various diseases from donors to recipients. As a safety measure, it is important to appropriately set the selection criteria for donors. On that basis, it is useful to implement a virus free test for known viruses in order to deny the contamination of the final product with viruses. On the other hand, it is also important to ensure safety measures assuming contamination of unknown viruses. For this purpose, it is necessary to consider strict control of raw materials, etc. and setting of the virus inactivation process, etc.

2) Matters related to non-clinical studies of regenerative medical products

Example: Which non-clinical safety study is considered necessary before the start of the first-in-human study (FIH) of regenerative medical products?

Please consider non-clinical safety studies necessary before the start of FIH study (clinical trial) with reference to "Ensuring the Quality and Safety of Gene Therapy Products (PSEHB/MDED Notification No. 0709-2 dated July 9, 2019)" for gene therapy products, "Guideline on Quality and Safety Assurance," "Examples of important points of investigation (30-day investigation) in initial clinical trial notification for cell/tissue products" and "Technical guidance on the quality, nonclinical studies and clinical studies of regenerative medical products (human cell-based products) (Administrative Notice dated June 27, 2016)" for cell-based products. Since necessary non-clinical safety studies differ depending on the characteristics of each regenerative medical product, we recommend that you utilize RS strategy consultation and consult the PMDA from the study planning stage.

Details of the preparation method of materials necessary for RS strategy consultation are also described in "Points to Consider (Checkpoints) for Efficient Implementation of Pharmaceutical Affairs Consultation on R & D Strategy Concerning the Quality and Safety from the Initial Stage of Development of Cell/Tissue-based Products or Gene therapy Products." Please refer to the PMDA website (https://www.pmda.go.jp/review-services/drug-reviews/about-reviews/ctp/0007.html) for the above notifications, etc.

6. What to do at times like this (Q&A)

This chapter contains general responses to common inquiries about procedures for RS general consultation/RS strategy consultation. If you have any questions, please feel free to contact the Division of Innovation Support and Pharmaceuticals Affairs Consultations (R&D), Office of Review Management, PMDA by telephone (+81-3-3506-9562), e-mail (rs-contact@pmda.go.jp), or FAX (+81-3-3506-9593).

<1. Subject for consultation>

Q1-1. With regard to "consultation on the quality and safety of regenerative medical products," is it possible to have a consultation on contents other than the investigation (30-day investigation items) of the initial clinical trial notification (for example, "Further improvement of quality" or "GCTP of manufacturing facilities," etc.)?
Q1-2. What products are subject to consultation on the quality and safety of regenerative medical products?
Q1-3. Is it possible to request consultation on the quality and safety of regenerative medical products and consultation on clinical study (clinical trial) protocol, etc. at the same time?
Q1-4. Are companies other than universities/research institutions and venture companies subject to RS general consultation/RS strategy consultation?
Q1-5. The catchphrase of RS strategy consultation states "for creation of innovative drugs, medical devices, and regenerative medical products originating in Japan." Are those originating from foreign countries excluded from this consultation?
Q1-6. What is a strategy consultation on the development plan?
Q1-7. What is a clinical study (clinical trial) subject to RS strategy consultation?

<2. Procedures>

Q2-1. What are points to consider when applying for a pre-consultation meeting?
Q2-2. How should the materials for the Consultations be submitted?
Q2-3. Is it possible to have the consultation record sent to the person in charge of application, not the applicant representative, when the applicant representative and the person in charge of application belong to different organizations?
Q2-4. Is it possible to receive the Consultation record early?
Q2-5. What should be done for withdrawal of the Consultations and change of the schedule?

<3. Others>

Q3-1. Will the information presented in the RS general consultation/RS strategy consultation be kept confidential?
Q3-2. Utilizing RS strategy consultation, will the studies for the approval application be reduced or exempted?
Q3-3. Utilizing RS strategy consultation, Utilizing RS strategy consultation, is it correct to assume that the approval based on the PMD Act will be assured?

<1. Subject for consultation>

Q1-1. With regard to "consultation on the quality and safety of regenerative medical products," is it possible to have a consultation on contents other than the investigation (30-day investigation items) of the initial clinical trial notification (for example, "Further improvement of quality" or "GCTP of manufacturing facilities," etc.)?

A. Since the consultation category corresponds to the drugs that are subject to the confirmation application for cell/tissue-based drugs, etc. abolished in June 2011 and July 2013 (former confirmation application), only the matters related to the 30-day investigation are subject to the consultation. Therefore, consultation categories such as "Strategy consultation for regenerative medical products" will correspond to consultation items that are not considered to be subject to 30-day investigation, for example, study plans for primary pharmacodynamics. If you are not sure about the consultation category, please ask that at the time of the pre-consultation meeting.

Q1-2. What products are subject to consultation on the quality and safety of regenerative medical products?

A. Products subject to consultation include the following:

(1) Regenerative medical products

(2) Products intended to express an introduced gene in the human body for the purpose of prevention (Example: Recombinant live vaccine)(excluding those falling under the category of regenerative medical products).

In RS strategy consultation, we are available to consult on quality and safety from the early stage of development to before submission of clinical trial notification, including how data will be collected in addition to evaluation of collected data.

Q1-3. Is it possible to request consultation on the quality and safety of regenerative medical products and consultation on clinical study (clinical trial) protocol, etc. at the same time?

A. It is possible to conduct two consultations at the same time. For the former consultation, you need to pay

the fee for consultations on the quality and safety of regenerative medical products, etc. For the latter consultation, you need to pay the fee for RS strategy consultation on drugs or regenerative medical products.

Q1-4. Are companies other than universities/research institutions and venture companies subject to RS general consultation/RS strategy consultation?

A. The main targets are academia such as universities and research institutions and venture companies. If the contents of consultation are appropriate for RS general consultation/RS strategy consultation, it is possible to have consultation from companies other than venture companies.
For consultations on the quality and safety of regenerative medical products, etc., there are no restrictions on applicants.

Q1-5. The catchphrase of RS strategy consultation states "for creation of innovative drugs, medical devices, and regenerative medical products originating in Japan." Are those originating from foreign countries excluded from this consultation?

A. Seed-stage resources, etc. originating from foreign countries may be accepted at the consultation if they are intended to lead to application for approval in Japan for the purpose of creating innovative products. Please check whether or not they are subject to the consultation at RS general consultation, etc.

Q1-6. What is a strategy consultation on the development plan?

A. In the strategy consultation on the development plan, advice is provided on development policies, etc. that are generally required in the area of the product to be developed, instead of contents related to specifically required test items and endpoints based on the development status of the product. It is assumed to be utilized by academia and venture companies, etc. with little experience in the development in the area of the target product when a written opinion of PMDA is required.

Q1-7. What is a clinical study (clinical trial) subject to strategy consultation?

A. The main subjects include POC (Proof of Concept) studies (early phase II studies) in the early phase of clinical development. In addition, if a university or research institution conducts a study on its own for the item with a high medical need that meets all of the following requirements, a confirmatory study after the early phase of clinical development is also subject to consultation.

- Items to be reviewed or selected in the "Study Group on Unapproved and Off-label Drugs of High Medical Need" or "Study Group on the Early Introduction of Medical Devices, etc. with High Medical Need"
- All or part of the expenses of the confirmatory study (matching fund, etc.) are covered by public research funds.

Please check the website (https://www.pmda.go.jp/review-services/f2f-pre/strategies/0005.html) for necessary documents, etc.

<2. Procedures>

Q2-1. What are points to consider when applying for a pre-consultation meeting?

A. Please summarize and briefly describe the background leading to the application for questions and the contents of the questions in the Question field of "Application Form for Questions for the Pre-Consultation meeting for Regulatory Science Strategy" (see below). Also, please prepare a separate consultation material. The contents will be grasped at the pre-consultation meeting, the contents of consultation will be organized, materials necessary at the Consultations will be confirmed, and general advice on the approval application, etc. will be provided.
(1) Background leading to application for questions

Outline of the item including the following items:
- Background of discovery
- Intended use, anticipated indications (performance)
- Expected clinical positioning (comparison with existing products, etc.)
- Relation with national projects (Ministry of Health, Labour and Welfare, Grants-in-Aid for Scientific Research/Clinical Research Promotion, Ministry of Education, Culture, Sports, Science and Technology, Translational Research Project, Super Special Consortia for development of the state-of-the-art medicine, etc.) (Described in Remarks)

(2) Contents of questions
- Issues you have in particular under the PMD Act (Be as specific as possible)

Example:
- ○○ Study, etc. will be conducted as an item of non-clinical studies, but ×× Study is considered not necessary for the reason of ○○, so the Applicant would like to confirm it.
- We are concerned about ○○ in the protocol design, so we would like advice. etc.

(3) Information that should be attached or sent in advance

Even if the materials cannot be prepared, it is recommended to provide the items to be prepared and their outline because the consultation can be efficiently conducted if they are available.

<<Drugs/regenerative medical products>>
- Outline of the drug/regenerative medical product subject to consultation
- Summary of nonclinical and clinical studies (existing and future plans)
- Status of patent applications, etc. for seed-stage resources
- Scientific literature references in Japan and overseas (Existing/Not)
- Cooperation with companies or medical institutions for practical application (Yes/No)
- Outline of the project plan (periods, expected value, amount, etc.) etc.

<< Medical device>>
- Acquisition of license for marketing authorization holder
- Outline of prototype
- Outline of product specifications (specific purpose of use, application, efficacy (performance), medical usefulness, etc.)
- Target patients and indications
- Test items including performance and safety specifications (data not required). For test items, describe the outline of test methods. Please describe clearly the items implemented so far and those scheduled to be implemented.
- Milestones for commercialization
- Status of patent applications, etc. for medical devices
- Scientific literatures in Japan and overseas (Existing/Not)
- Cooperation with companies or medical institutions for practical application (Yes/No)
- Outline of the project plan (periods, expected value, amount, etc.) etc.

Q2-2. How should the materials for the Consultations be submitted?

A. Please submit an electronic file of documents for the Consultations, excluding strategy consultation on the development plan to the Review Management Division, Office of Review Management by 3 p.m. on the 1st working day of the week 5 weeks before the scheduled date of the Consultations in principle (3 weeks before for medical devices) by one of the following methods.
- Submission of electronic media (CD or DVD) by postal mail or bringing
- Online submission using the application electronic data system (gateway system)

The submitted electronic media will be discarded by PMDA in principle after completion of the consultation.

Q2-3. Is it possible to have the consultation record sent to the person in charge of application, not the applicant representative, when the applicant representative and the person in charge of application belong to different organizations?

A. If you wish to send the consultation record to an organization different from the one to which the applicant representative belongs, please submit the "Request form for sending consultation record to the organization to which the person in charge belongs" with the application form. The format of the request form for sending consultation records to the organization to which the person in charge belongs is optional. However, the document should contain the following contents.

(1) The fact that the applicant wishes to send a consultation record to the organization to which the person in charge of

application for consultation belongs.
(2) The following information about the person in charge of application for consultation
- Address of the organization (including postal code)
- Name of the organization/department
- Name
- Telephone number and FAX number of the person in charge
- Relationship with the applicant representative

(3) The following information about the applicant representative
- Address of the organization
- Name of the organization/department
- Name

Q2-4. Is it possible to receive the Consultation record early?

A. Before the Consultations record is finalized, it will usually take about 30 working days after the Consultations since detailed examination of the contents is necessary. Unfinalized records of the Consultations cannot be given to you early. During that time, you will have an opportunity to check the draft. If you wish the documents will be sent to a destination different from the applicant for consultation, please see Q2-3.

Q2-5. What should be done for withdrawal of the Consultations and change of the schedule?

A. When applying for the Consultations, please consider in advance so that the Consultations will not be withdrawn or the schedule will not be changed. If withdrawal of the Consultations or change of the schedule is made due to unavoidable circumstances, the following procedure will be followed.

(1) If withdrawal is made for the applicant's circumstance after application for the Consultations is made, download the "Request for Withdrawal of Application for Consultations" from the PMDA website (https://www.pmda.go.jp/review-services/f2f-pre/strategies/0005.html), fill in the necessary information, and submit it by e-mail to the Review Management Division, Office of Review Management, PMDA.

(2) If the date of consultation is changed for the applicant's circumstance, submit the "Request for withdrawal of application for Consultations" and apply again. In addition, if necessary information is entered in the "Claim for refund of review fee for drugs, etc." and the form is submitted to the division, a half of the fee will be refunded.

(3) If the date of consultation is changed for the PMDA's circumstance or if the PMDA considers that it is inevitable to change the date, it is not necessary to submit the "Request for withdrawal of application for Consultations."

(4) Even if withdrawal is made, the fee may be refunded in full when PMDA considers it unavoidable and necessary information is entered in the "Claim for refund of review fee for drugs, etc." which is submitted to the division.

(5) For a venture company that does not meet the requirements specified separately (p. 20), if consultations on quality and safety of regenerative medical products will be made for more than one day, and if the applicant withdraws the application for the applicant's convenience after the submission date of materials for the Consultations by the date of consultation, the consultation is regarded as having been made for the day.

<3. Others>

Q3-1. Will the information presented in the RS general consultation/RS strategy consultation be kept confidential?

A. PMDA staff members are obligated to maintain confidentiality, and we will strictly keep confidential information on consultation items obtained in conducting RS general consultation/RS strategy consultation.

Q3-2. Utilizing RS strategy consultation, will the studies for the approval application be reduced or exempted?

A. At the time of the approval application, it is necessary to attach dossiers according to the application classification in principle. The Consultations for RS strategy consultation will not reduce or exempt studies necessary for the approval application, but will provide guidance and advice on the study items and contents so that development can be carried forward efficiently.

Q3-3. Utilizing RS strategy consultation, is it correct to assume that the approval based on the PMD Act will be assured?

A. Implementation of the Consultations does not guarantee approval based on the PMD Act. Approval may not be granted in some cases, such as when the expected results are not obtained in the course of development or when a new safety issue occurs.

7. Contact information

For the procedures for RS general consultation/RS strategy consultation, such as various application forms, request forms for scheduling, application forms for application for requirements for reduced fee, materials for the Consultations, etc., please contact the following.

Department name	Pharmaceuticals and Medical Devices Agency (PMDA) Review Management Division, Office of Review Management
Address	Shin-Kasumigaseki Building 10F, 3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013
Telephone (dial-in)	+81-3-3506-9556
Email address	 yakujisenryaku@pmda.go.jp * QR code may not function properly depending on application, etc.
Facsimile	+81-3-3506-9443

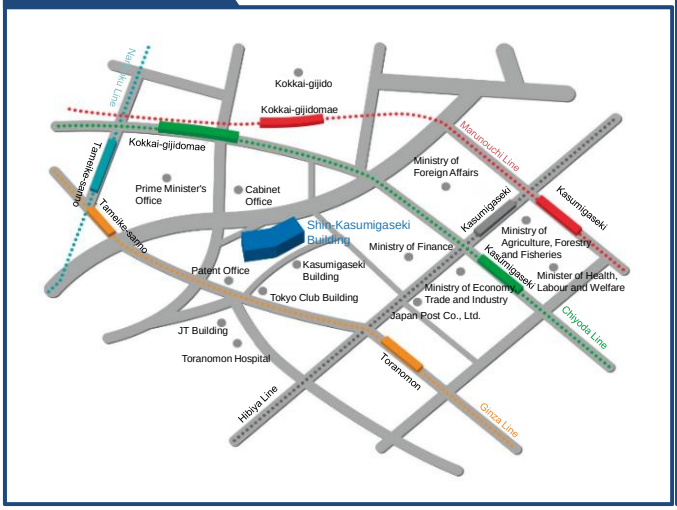
For the contents of RS general consultation/RS strategy consultation, please contact the following.

Department name	Pharmaceuticals and Medical Devices Agency (PMDA) Division of Innovation Support and Pharmaceuticals Affairs Consultations (R&D), Office of Review Management
Address	Shin-Kasumigaseki Building 10F, 3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013
Telephone (dial-in)	+81-3-3506-9562
Email address	 yakujisenryaku@pmda.go.jp rs-contact@pmda.go.jp * QR code may not function properly depending on application, etc.
Facsimile	+81-3-3506-9593

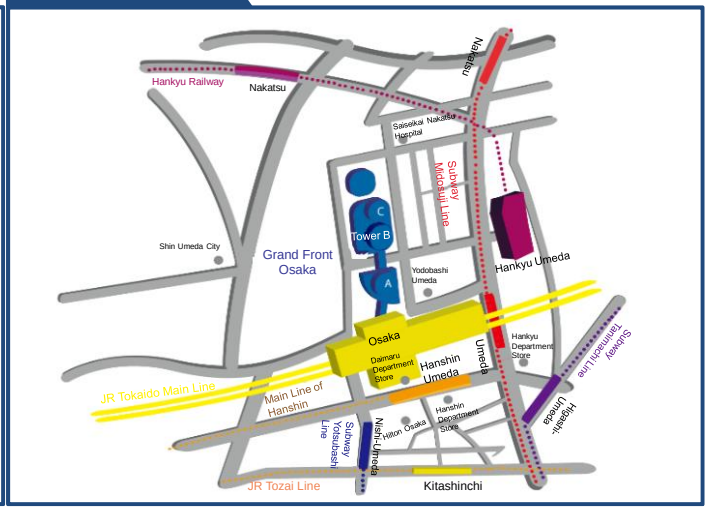
Various inquiries are received from 9:30 am to 5:00 pm (JST) on weekdays.

8. Access

Tokyo



Kansai



- Subway Ginza Line, Toranomon Station Exit 11 and 5
- Subway Hibiya Line, Chiyoda Line, Marunouchi Line, Kasumigaseki Station Exit A13
- Subway Chiyoda Line and Marunouchi Line, Kokkai-gijidomae Station Exit 3
- Subway Nanboku Line and Ginza Line Tameike-sanno Station Exit 8
- Subway Hibiya Line Toranomon Hills Station Exit A2

- JR Osaka Station Central North Exit (2nd floor)

1. Go through the communication passage, go through the South Building, and pass through the deck connecting to the South Building and the North Building.
2. After entering the North Building, enter the Tower B Office on the right-hand side.
3. Go to the 9th floor (Sky Lobby) by elevator, and take the elevators for the offices on 11 to 18th floors. Go to the 12th floor.
4. After getting out of the elevator, proceed to the right-hand side, and the innermost room

Address

<Tokyo>
Office of Review Management, PMDA
Division of Innovation Support and Pharmaceuticals Affairs Consultations (R&D)
〒100-0013
Shin-Kasumigaseki Building, 3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo (Reception 6F/14F)
TEL +81-3-3506-9562
FAX +81-3-3506-9593
E-mail yakujisenryaku@pmda.go.jp
rs-contact@pmda.go.jp

<Kansai Branch>
PMDA Kansai Branch Consultation Division
〒530-0011
3-1 Ofuka-cho, Kita-ku, Osaka-shi, Osaka
Grand Front Osaka North Building Tower B 12F
TEL +81-6-6374-6820
FAX +81-6-6374-6825
E-mail yakujisenryaku@pmda.go.jp

Annex; List of guidelines

Here, the major guidelines published as of March 2023 concerning drugs, regenerative medical products and medical devices are listed. Please refer to related guidelines depending on the characteristics of the product under development and use them for preparation of materials, etc. for RS strategy consultation. Guidelines are newly added or updated. Please be sure to check the latest guidelines from the following database, etc.

<Notification/guideline database>

- Ministry of Health, Labour and Welfare Laws and Regulations Database Service: https://www.mhlw.go.jp/hourei/
- Pharmaceuticals and Medical Devices Agency (PMDA)
  - ICH Guideline information: https://www.pmda.go.jp/int-activities/int-harmony/ich/0070.html
  - Information related to regenerative medical products: https://www.pmda.go.jp/review-services/drug-reviews/about-reviews/ctp/0007.html
    Points to consider (checkpoints) for efficient conduct of Pharmaceutical Affairs Consultation on R&D Strategy for quality and safety from the initial stage of regenerative medical products: https://www.pmda.go.jp/review-services/drug-reviews/about-reviews/ctp/0007.html
  - Information related to medical devices: https://www.pmda.go.jp/review-services/drug-reviews/about-reviews/devices/0039.html
  - Information related to Software as a Mefical Device（SaMD）: https://www.pmda.go.jp/review-services/drug-reviews/about-reviews/devices/0048.html
  - Information related to in vitro diagnostics: https://www.pmda.go.jp/review-services/drug-reviews/about-reviews/ivd/0002.html
  - Regulatory science guidance/guideline page: https://www.pmda.go.jp/rs-std-jp/standards-development/guidance-guideline/0001.html
  - Notifications and Administrative Notices（in English）: https://www.pmda.go.jp/english/review-services/regulatory-info/0003.html

1) Drugs

[1] Guidelines for quality of drugs

Notification/Guideline Title	Notification No.	Date of issuance	Issued by
Text on Validation of Analytical Procedures (implementation item) (ICH-Q2A)	PAB/ED Notification No. 755	July 20, 1995	Pharmaceutical Affairs Bureau, Ministry of Health and Welfare Director of Evaluation Division
Text on Validation of Analytical Procedures (implementation method) (ICH-Q2B)	PMSB/ELD No. 338	October 28, 1997	Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare Director of Evaluation and Licensing Division
Impurities in New Drug Substances (ICH-Q3A(R1))	PMSB/ELD Notification No. 1216001	December 16, 2002	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Partial Revision of "Impurities in New Drug Substances (ICH-Q3A(R2))	PFSB/ELD Notification No. 1204001	December 4, 2006	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Impurities in New Drug Products (ICHQ3B(R1))	PMSB/ELD Notification No. 0624001	June 24, 2003	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Revision of "Impurities in New Drug Products" (ICH-Q3B(R2))	PFSB/ELD Notification No. 0703004	July 3, 2006	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Impurities: Residual Solvents Guideline (ICH-Q3C)	PMSB/ELD No. 307	March 30, 1998	Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare Director of Evaluation and Licensing Division
Revision of Impurities: Residual Solvents Guideline (ICH-Q3C(R3))	PMSB/ELD Notification No. 1225006	December 25, 2002	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Limits for Residual Solvents	Administrative Notice	December 3, 2002	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Revision of Impurities: Residual Solvents Guideline (ICH-Q3C(R5))	PFSB/ELD Notification No. 0221-1	February 21, 2011	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Revision of Impurities: Residual Solvents Guideline (ICH-Q3C(R6))	PSEHB/PED Notification No. 0719-3	July 19, 2018	Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare

Revision of Impurities: Residual Solvents Guideline (ICH-Q3C(R8))	PSEHB/PED Notification No. 0813-3	August 13, 2021	Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Questions and Answers (Q & A) on Control of Residual Solvents in Drugs Listed in the Japanese Pharmacopoeia (Part 1)	Administrative Notice	November 12, 2015	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Questions and Answers (Q & A) on Control of Residual Solvents in Drugs Listed in the Japanese Pharmacopoeia (Part 2)	Administrative Notice	June 3, 2016	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Guideline on Evaluation and Recommendation for Use of Pharmacopoeial Texts in ICH Regions (ICH-Q4B Guideline)	PFSB/ELD Notification No. 0526001	May 26, 2009	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Questions and Answers (Q & A) on Application for Approval of Drugs, etc. based on the ICH-Q4B guideline	Administrative Notice	May 26, 2009	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Topic-specific annex based on the ICH-Q4B guideline (residue on ignition test method)	PFSB/ELD Notification No. 0526002	May 26, 2009	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Topic-specific annex based on the ICH-Q4B guideline (Test for Extractable Volume of Parenteral Preparations)	PFSB/ELD Notification No. 0208-1	February 8, 2010	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Topic-specific annex based on the ICH-Q4B guideline (Insoluble Particulate Matter Test for Injections)	PFSB/ELD Notification No. 0208-2	February 8, 2010	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Topic-specific annex based on the ICH-Q4B guideline (Microbial Limit Test and Microbial Attributes of Non-sterile Pharmaceutical Products)	PFSB/ELD Notification No. 0917-2	September 17, 2010	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Topic-specific annex based on the ICH-Q4B guideline (Disintegration test)	PFSB/ELD Notification No. 0917-3	September 17, 2010	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Topic-specific annex based on the ICH-Q4B guideline (Dissolution test)	PFSB/ELD Notification No. 0726-1	July 26, 2011	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Topic-specific annex based on the ICH-Q4B guideline (Sterility test)	PFSB/ELD Notification No. 0917-1	September 17, 2010	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Topic-specific annex based on the ICH-Q4B guideline (Tablet friability test)	PFSB/ELD Notification No. 0127-2	January 27, 2011	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Topic-specific annex based on the ICH-Q4B guideline (SDS-polyacrylamide gel electrophoresis)	PFSB/ELD Notification No. 0127-1	January 27, 2011	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Topic-specific annex based on the ICH-Q4B guideline (Capillary electrophoresis)	PFSB/ELD Notification No. 0127-3	January 27, 2011	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Topic-specific annex based on the ICH-Q4B guideline (Particle size determination (Analytical Sieving Method))	PFSB/ELD Notification No. 0127-4	January 27, 2011	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Topic-specific annex based on the ICH-Q4B guideline (Determination of Bulk and Tapped Densities)	PFSB/ELD Notification No. 1108-3	November 8, 2012	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Topic-specific annex based on the ICH-Q4B guideline (Bacterial endotoxins test)	PFSB/ELD Notification No. 0321-1	March 21, 2013	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Topic-specific annex based on the ICH-Q4B guideline (Uniformity of dosage units)	PFSB/ELD Notification No. 0417-1	April 17, 2014	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (ICH-Q6A)	PMSB/ELD Notification No. 568	May 1, 2001	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
"Guidance for Quality Evaluation of Antibody Drugs"	PFSB/ELD Notification No. 1214-1	December 14, 2012	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Questions and Answers (Q & A) on "Guidance for Quality Evaluation of Antibody Drugs"	Administrative Notice	December 14, 2012	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (ICH-Q7)	PMSB Notification No. 1200	November 2, 2001	Director of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
Revision of Guideline for Pharmaceutical Development (ICh-Q8(R2))	PFSB/ELD Notification No. 0628-1	June 28, 2010	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Guideline for Quality Risk Management (ICH-Q9(R1))	PSEHB/PED Notification No. 0831-1 PSEHB/CND Notification No. 0831-1	August 31, 2023	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division Director of Compliance and Narcotics Division
Guideline for Pharmaceutical Quality System (ICH-Q10)	PFSB/ELD Notification No. 0219-1 PFSB/CND Notification No. 0219-1	February 19, 2010	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division Director of Compliance and Narcotics Division
Revisions to Note for Implementation Working Group for the ICH Quality Guideline "Guidance on Implementation of ICH-Q8/Q9/Q10 Approved by ICH" (Q-IWG Q8/Q9/Q10 Points to consider (R2))	Administrative Notice	February 1, 2013	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Compliance and Narcotics Division
Guideline for Development and Manufacturing of Drug Substances (Chemical and Biotechnological/Biological Products) (ICH-Q11)	PFSB/ELD Notification No. 0710-9	July 10, 2014	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division

Questions and Answers (Q & A) on "Development and Manufacturing of Drug Substances (Chemical and Biotechnological/Biological Products) (ICH-Q11 Q&As)"	Administrative Notice	September 14, 2018	Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Questions and Answers (Q & A) on "Guideline for Pharmaceutical Development," "Guideline for Quality Risk Management," and "Guideline for Pharmaceutical Development Pharmaceutical Quality System" (ICH Q-IWG Q8/Q9/Q10 Q&As)	Administrative Notice	September 17, 2010	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Compliance and Narcotics Division
Addition of Questions and Answers (Q & A) on "Guideline for Pharmaceutical Development," "Guideline for Quality Risk Management," and "Guideline for Pharmaceutical Development Pharmaceutical Quality System" (ICH Q-IWG Q8/Q9/Q10 Q&As (R4))	Administrative Notice	August 29, 2011	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Compliance and Narcotics Division
Guideline on the technical and regulatory concepts of pharmaceutical life cycle management (ICH Q12)	PSEHB/PED Notification No. 1029-1 PSEHB/CND Notification No. 1029-1	October 29, 2021	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Director of Pharmaceutical Evaluation Division Director of Compliance and Narcotics Division
Guideline on Continuous Manufacturing of Drug Substances and Drug Products (ICH Q13)	PSEHB/PED Notification No. 0531-1	May 31, 2023	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Director of Pharmaceutical Evaluation Division
Guideline on Utilization of Master File for Drug Substances, etc.	PFSB/ELD Notification No. 1117-3 PFSB/ELD/OMDE Notification No. 1117-1	November 17, 2014	Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Counsellor, Minister's Secretariat, Ministry of Health, Labour and Welfare (in charge of review control of medical devices and regenerative medical products)
Questions and Answers (Q & A) on Master File for Drug Substances, etc.	Administrative Notice	July 28, 2005	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Questions and Answers (Q & A) on Master File for Drug Substances, etc. (Part 2)	Administrative Notice	December 20, 2005	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Questions and Answers (Q & A) on Master File for Drug Substances, etc. (Part 3)	Administrative Notice	December 28, 2012	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Questions and Answers (Q & A) on Master File for Drug Substances, etc. (Part 4)	Administrative Notice	October 29, 2013	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Revision of the Guidelines on Stability Testing of New Drug Substances and Products (ICH-Q1A(R2))	PMSB/ELD Notification No. 0603001	June 3, 2003	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Guidelines on Photostability Testing of New Drug Substances and Products (ICH-Q1B)	PAB/ED Notification No. 422	May 28, 1997	Pharmaceutical Affairs Bureau, Ministry of Health and Welfare Director of Examination Division
Guidelines for handling stability study results of drugs with a new route of administration (ICH-Q1C)	PAB/ED Notification No. 425	May 28, 1997	Pharmaceutical Affairs Bureau, Ministry of Health and Welfare Director of Examination Division
Application of Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Products (ICH-Q1D)	PMSB/ELD Notification No. 0731004	July 31, 2002	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Guideline on Evaluation of Stability Data (ICH-Q1E)	PMSB/ELD Notification No. 0603004	June 3, 2003	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Withdrawal of "Stability Data Package for Registration Applications in Climatic Zones III and IV" (ICH-Q1F)	PFSB/ELD Notification No. 0703001	July 3, 2006	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Standards for manufacturing and quality controls of investigational product (investigational product GMP)	PFSB Notification No. 0709002	July 9, 2008	Director of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
Q & A on standards for manufacturing and quality controls of investigational product (investigational product GMP)	Administrative Notice	July 2, 2009	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Compliance and Narcotics Division
Partial Revision of the "Views on Utilization of PIC/S GMP Guidelines"	Administrative Notice	November 28, 2022	Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Basic principles on bioequivalence evaluation of generic drugs of inhalation powder drugs	Administrative Notice	March 11, 2016	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Views on Bioequivalence Studies for Change in Manufacturing Method of Solid Oral Drug Products	Administrative Notice	April 19, 2013	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Revision of "Guidance on the Manufacture of Sterile Pharmaceutical Products by Terminal Sterilization"	Administrative Notice	November 9, 2012	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Compliance and Narcotics Division
Standards for Manufacturing Control and Quality Control of Crude Drugs and Kampo Products (voluntary standards of the Federation of Pharmaceutical Manufacturers' Associations of Japan)	Administrative Notice	February 16, 2012	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Compliance and Narcotics Division
Manufacturing control and quality control standards for medical gases (voluntary standards)	Administrative Notice	February 13, 2012	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Compliance and Narcotics Division
Handling of Prescription Drugs That Have Differing Crystalline Forms, etc.	PFSB/ELD Notification No. 0616-1	June 16, 2011	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Revision of "Guidance on the Manufacture of Sterile Pharmaceutical Products by Aseptic Manipulation"	Administrative Notice	April 20, 2011	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Compliance and Narcotics Division

[2] Standards for Biological Ingredients

Notification/Guideline Title	Notification No.	Date of issuance	Issued by
Standards for Biological Ingredients (established on May 20, 2003, Ministerial Announcement of Ministry of Health, Labour and Welfare No. 210)	Latest partial revision is given in Ministerial Announcement of MHLW No. 37.	February 28, 2018	Minister of Health, Labour and Welfare
Partial revision of the Standards for Biological Ingredients	PFSB Notification No. 0228-3	February 28, 2018	Director of Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Enforcement of partial revision of the Standards for Biological Ingredients	PSEHB/PED Notification No. 0228-3 PSEHB/MDED Notification No. 0228-3	February 28, 2018	Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Operation of the Standards for Biological Ingredients	PFSB/ELD Notification No. 1002-1 PFSB/ELD/OMDE Notification No. 1002-5	October 2, 2014	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division Counsellor, Minister's Secretariat, Ministry of Health, Labour and Welfare (in charge of review control of medical devices and regenerative medical products)
Questions and Answers (Q & A) on the Operation of the Standards for Biological Ingredients	Administrative Notice	June 30, 2015	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division

[3] ICH guidelines related to biological products

Notification/Guideline Title	Notification No.	Date of issuance	Issued by
Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin (ICH-Q5A(R1))	PMSB/ELD No. 329	February 22, 2000	Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare Director of Evaluation and Licensing Division
Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products (ICH-Q5B)	PMSB/ELD No. 3	January 6, 1998	Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare Director of Evaluation and Licensing Division
Stability Testing of Biotechnological/Biological Products (ICH-Q5C)	PMSB/ELD No. 6	January 6, 1998	Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare Director of Evaluation and Licensing Division
Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products (ICH-Q5D)	PMSB/ELD No. 873	July 14, 2000	Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare Director of Evaluation and Licensing Division
Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process (ICH-Q5E)	PFSB/ELD Notification No. 0426001	April 26, 2005	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (ICH-Q6B)	PMSB/ELD Notification No. 571	May 1, 2001	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division

[4] Guidelines for Nonclinical Studies of Drugs

Notification/Guideline Title	Notification No.	Date of issuance	Issued by
Ministerial Ordinance on Good Laboratory Practice for Nonclinical Safety Studies of Drugs	MHW Ordinance No. 21	March 26, 1997	Minister of Health and Welfare
Guidance on the Implementation of the Ministerial Ordinance on the Good Laboratory Practice for Nonclinical Safety Studies of Drugs as Revised by the Ministerial Ordinance for Partial Revision of the Ministerial Ordinance on the Good Laboratory Practice for Nonclinical Safety Studies of Drugs	PFSB Notification No. 0613007	June 13, 2008	Director of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
Revision of “Guidelines for Single and Repeated Dose Toxicity Studies”	PAB/NDD No. 88	August 10, 1993	Pharmaceutical Affairs Bureau, Ministry of Health and Welfare Director of New Drugs Division Director of Examination Division
Partial Revision of “Guideline for Repeated Dose Toxicity Studies”	PMSB/ELD No. 655	April 5, 1999	Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare Director of Evaluation and Licensing Division
Revision of “Guidelines for Reproductive and Developmental Toxicity Studies of Drugs”	PAB/ED Notification No. 316	April 14, 1997	Director of Examination Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare
Revision of “Guidelines for Reproductive and Developmental Toxicity Studies of Drugs”	PMSB/ELD No. 1834	December 27, 2000	Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare Director of Evaluation and Licensing Division
Guideline for Evaluation of Reproductive and Developmental Toxicity of Drugs	PSEHB/PED Notification No. 0129-8	January 29, 2021	Director of Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Director of Pharmaceutical Evaluation Division
Guidelines for Immunotoxicity Studies of Drugs	PFSB/ELD Notification No. 0418001	April 18, 2006	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Guidance on the Need for Carcinogenicity Studies of Pharmaceuticals	PAB/ED Notification No. 315	April 14, 1997	Pharmaceutical Affairs Bureau, Ministry of Health and Welfare Director of Examination Division

Guidance on Testing for Detection of Carcinogenicity of Pharmaceuticals	PMSB/ELD No. 548	July 9, 1998	Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare Director of Evaluation and Licensing Division
Revision of “Guidelines for Carcinogenicity Studies of Drugs”	PSEHB/PED Notification No. 0310-1	March 10, 2023	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Director of Pharmaceutical Evaluation Division
Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use	PFSB/ELD Notification No. 0920-2	September 20, 2012	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Photosafety Evaluation of Pharmaceuticals	PFSB/ELD Notification No. 0521-1	May 21, 2014	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Guidance on Toxicokinetics (Evaluation of Systemic Exposure in Toxicity Studies)	PAB/ED Notification No. 443	July 2, 1996	Pharmaceutical Affairs Bureau, Ministry of Health and Welfare Director of Examination Division
Questions and Answers (Q & A) on Use of Microsampling Methods in "Guidance on Toxicokinetics (Evaluation of Systemic Exposure in Toxicity Studies)"	Administrative Notice	March 15, 2019	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Pharmaceutical Evaluation Division
Guidance on Repeated Dose Tissue Distribution Studies	PAB/ED Notification No. 442	July 2, 1996	Director of Examination Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare
Questions and Answers on Guidelines for Nonclinical Safety Studies of Pediatric Drugs in Juvenile Animals	Administrative Notice	October 2, 2012	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Nonclinical Safety Studies for the Development of Pediatric Drugs	PSEHB/PED Notification No. 0330-1	March 30, 2021	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Director of Pharmaceutical Evaluation Division
Nonclinical Safety Evaluation of Biotechnological Products	PFSB/ELD Notification No. 0323-1	March 23, 2012	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Guideline on Safety Pharmacology Studies for Human Pharmaceuticals	PMSB/ELD Notification No. 902	June 21, 2001	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals	PFSB/ELD Notification No. 1023-4	October 23, 2009	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Questions and Answers (Q & A) on "Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential"	Administrative Notice	July 22, 2022	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Pharmaceutical Evaluation Division
Guideline on Drug Interaction for Drug Development and Appropriate Provision of Information	PSEHB/PED Notification No. 0723-4	July 23, 2018	Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Questions and Answers (Q & A) on "Guideline on Drug Interaction for Drug Development and Appropriate Provision of Information"	Administrative Notice	July 23, 2018	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Pharmaceutical Evaluation Division
Partial correction of "Guideline on Drug Interaction for Drug Development and Appropriate Provision of Information"	Administrative Notice	February 8, 2019	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Pharmaceutical Evaluation Division
Replacement of the errata for " Partial correction of "Guideline on Drug Interaction for Drug Development and Appropriate Provision of Information""	Administrative Notice	February 20, 2019	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Pharmaceutical Evaluation Division
Guidelines for Nonclinical Evaluation of Anticancer Drugs	PFSB/ELD Notification No. 0604-1	June 4, 2010	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Questions and Answers (Q & A) on "Guidelines for Nonclinical Evaluation of Anticancer Drugs"	Administrative Notice	March 27, 2019	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Pharmaceutical Evaluation Division
Guidelines for nonclinical study of vaccines to prevent infections	PSB/PED Notification No. 0327-1	March 27, 2024	Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare Director of Pharmaceutical Evaluation Division
Guidance on the Conduct of Nonclinical Safety Studies for Clinical Trials and Application for Marketing Approval for Pharmaceuticals	PFSB/ELD Notification No. 0219-4	February 19, 2010	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Questions and Answers (Q & A) on "Guidance on the Conduct of Nonclinical Safety Studies for Clinical Trials and Application for Marketing Approval for Pharmaceuticals"	Administrative Notice	August 16, 2012	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Guidance For Establishing Safety in First-in-Human Studies during Drug Development	PFSB/ELD Notification No. 0402-1	April 2, 2012	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Questions and Answers (Q & A) on "Guidance for Establishing Safety in First-In-Human Studies during Drug Development"	Administrative Notice	April 2, 2012	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Revision, etc. of "Guidance For Establishing Safety in First-in-Human Studies during Drug Development"	PSEHB/PED Notification No. 1225-1	December 25, 2019	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Director of Pharmaceutical Evaluation Division
Guidelines for Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (ICH-M7)	PSEHB/ELD Notification No. 1110-3	November 10, 2015	Director of Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Partial Revision of "Guidelines for Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk" (ICH-M7(R1))	PSEHB/PED Notification No. 0627-1	June 27, 2018	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Director of Pharmaceutical Evaluation Division
Partial Revision of "Guidelines for Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk" (ICH-M7(R2))	PSB/PED Notification No.0214-1	February 14, 2024	Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare Director of Pharmaceutical Evaluation Division

Guideline for Development of Liposome Drug Products	PSEHB/ELD Notification No. 0328-19	March 28, 2016	Director of Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Questions and Answers (Q & A) on the Guideline for Development of Liposome Drug Products	Administrative Notice	March 28, 2016	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Guideline for nonclinical safety assessment of oligonucleotide therapeutics	PSEHB/PED Notification No. 0330-1	March 30, 2020	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Director of Pharmaceutical Evaluation Division
Guidelines for Nonclinical Pharmacokinetic Studies	PMSB/ELD No. 496	June 26, 1998	Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare Director of Evaluation and Licensing Division
Guidelines for General Pharmacology Studies Necessary for Application for Manufacturing (Import) Approval of New Drugs, etc.	PAB/NDD No. 4	January 29, 1991	Pharmaceutical Affairs Bureau, Ministry of Health and Welfare Director of New Drugs Division
Guidelines for Toxicity Studies Necessary for Application for Manufacturing (Import) Approval of Drugs	PAB/ED No. 1-24	September 11, 1989	Pharmaceutical Affairs Bureau, Ministry of Health and Welfare Director of Examination Division I Director of Examination Division II Director of Biologics Technology Section

[5] Guidelines for Clinical Studies of Drugs

Notification/Guideline Title	Notification No.	Date of issuance	Issued by
Ministerial Ordinance on Good Clinical Practice for Drugs	MHW Ordinance No. 28	March 27, 1997	Minister of Health and Welfare
Implementation of Ministerial Ordinance on Good Clinical Practice for Drugs	PAB Notification No. 430	March 27, 1997	Director of Pharmaceutical Affairs Bureau, Ministry of Health and Welfare
Revision of "Guidance on "Ministerial Ordinance on Good Clinical Practice for Drugs""	PSEHB/PED Notification No. 0705-3	July 5, 2019	Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Basic principles on quality management in clinical trials	PSEHB/PED Notification No. 0705-5	July 5, 2019	Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Basic Principles of Risk-based Monitoring	PSEHB/PED Notification No. 0705-7	July 5, 2019	Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Documents or records related to clinical trial	Administrative Notice	July 5, 2019	Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
General considerations for clinical trials	PMSB/ELD No. 380	April 21, 1998	Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare Director of Evaluation and Licensing Division
Revision of "General considerations for clinical trials"	PSEHB/PED Notification No. 1223-5	December 23, 2022	Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Statistical Principles for Clinical Trials	PMSB/ELD No. 1047	November 30, 1998	Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare Director of Evaluation and Licensing Division
Revision of Questions and Answers (Q & A) on Notification of Clinical Trial Plan and Implementation of Clinical Trial for Drugs	Administrative Notice	December 14, 2015	Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Clinical Trials Conducted on Ethical Grounds-Japanese Compassionate Use System	PSEHB/ELD Notification No. 0122-7	January 22, 2016	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Questions and Answers (Q & A) on Clinical Trials Conducted on Ethical Grounds-Japanese Compassionate Use System	Administrative Notice	January 22, 2016	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions	PAB/ED Notification No. 592	May 24, 1995	Pharmaceutical Affairs Bureau, Ministry of Health and Welfare Director of Examination Division
Dose-Response Information to Support Drug Registration	PAB/ED Notification No. 494	July 25, 1994	Pharmaceutical Affairs Bureau, Ministry of Health and Welfare Director of Examination Division
Choice of Control Group and Related Issues in Clinical Studies	PMSB/ELD Notification No. 136	February 27, 2001	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Guidelines for Data Monitoring Committee	PFSB/ELD Notification No. 0404-1	April 4, 2013	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Handling of foreign clinical study data on drugs	PMSB Notification No. 739	August 11, 1998	Director of Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare
Q & A on "Ethnic Factors in the Acceptability of Foreign Clinical Data"	Administrative Notice	February 25, 2004	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Q & A on "Ethnic Factors in the Acceptability of Foreign Clinical Data" (Part 2)	Administrative Notice	October 5, 2006	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Basic principles on Global Clinical Trials	PFSB/ELD Notification No. 0928010	September 28, 2007	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Basic Principles on Global Clinical Trials (Reference Cases)	Administrative Notice	September 5, 2012	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division

Partial revision of Basic Principles on Global Clinical Trials (Reference Cases)	Administrative Notice	December 10, 2021	Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Basic principles for conducting phase 1 studies in Japanese prior to initiating multi-regional clinical trials including Japan for drugs in which early clinical development is preceding outside Japan	PSB/PED Notification No.1225-2	December 25, 2023	Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare Director of Pharmaceutical Evaluation Division
Q&A for basic principles for conducting phase 1 studies in Japanese prior to initiating multi-regional clinical trials including Japan for drugs in which early clinical development is preceding outside Japan	Administrative Notice	December 25, 2023	Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare
Guidelines for General Principles for Planning and Design of Global Clinical Trials	PSEHB/PED Notification No. 0612-1	June 12, 2018	Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Studies in Support of Special Populations: Geriatrics	PAB/NDD No. 104	December 2, 1993	Pharmaceutical Affairs Bureau, Ministry of Health and Welfare Director of New Drugs Division
Questions and Answers (Q & A) on "Studies in Support of Special Populations: Geriatrics"	Administrative Notice	September 17, 2010	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Guidance on Clinical Investigation of Medicinal Products in the Pediatric Population	PMSB/ELD No. 1334	December 15, 2000	Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare Director of Evaluation and Licensing Division
Questions and Answers (Q & A) on Guidance on Clinical Investigation of Medicinal Products in the Pediatric Population	Administrative Notice	June 22, 2001	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Addendum to Guidance on Clinical Investigation of Medicinal Products in the Pediatric Population	PSEHB/PED Notification No. 1227-5	December 27, 2017	Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Guidance on Clinical Evaluation Methods for Anticancer Drugs in Pediatric Patients with Malignant Tumors	PFSB/ELD Notification No. 0930-1	September 30, 2015	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs	PFSB/ELD Notification No. 1023-1	October 23, 2009	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Questions and Answers (Q & A) on "Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs"	Administrative Notice	May 23, 2017	Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Questions and Answers (Q & A) on "Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential"	Administrative Notice	July 22, 2022	Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Biomarkers in the Development of Pharmaceuticals or Biotechnology Products: Context, Structure and Format of Qualification Submissions	PFSB/ELD Notification No. 0120-1 PFSB/SD Notification No. 0120-1	January 20, 2011	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division Director of Safety Division
Clinical Trials Using Pharmacogenomics	PFSB/ELD Notification No. 0930007	September 30, 2008	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Guidance For Establishing Safety in First-in-Human Studies during Drug Development	PFSB/ELD Notification No. 0402-1	April 2, 2012	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Revision, etc. of "Guidance For Establishing Safety in First-in-Human Studies during Drug Development"	PSEHB/PED Notification No. 1225-1	December 25, 2019	Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Questions and Answers (Q & A) on "Guidance for Establishing Safety in First-In-Human Studies during Drug Development"	Administrative Notice	April 2, 2012	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Handling of Notifications, etc. of Clinical Trial Plans for Drugs by Person Who Intends to Sponsor a Clinical Trial	PFSB/ELD Notification No. 0531-8	May 31, 2013	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Handling of Notifications, etc. of Clinical Trial Plans for Drugs by Person Who Intends to Be a Sponsor-Investigator	PFSB/ELD Notification No. 0531-4	May 31, 2013	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Basic principles on precision control for laboratory tests, etc. in clinical trials	Administrative Notice	July 1, 2013	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Principles for Clinical Evaluation of New Antihypertensive Drugs	PMSB/ELD Notification No. 0128001	January 28, 2002	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Guideline for Clinical Evaluation of Hypnotics	PFSB/ELD Notification No. 1213-1	December 13, 2011	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Guideline for Clinical Evaluation of Therapeutic Drugs for Renal Anemia	PFSB/ELD Notification No. 0930-1	September 30, 2011	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Questions and Answers (Q & A) on "Guideline for Clinical Evaluation of Therapeutic Drugs for Renal Anemia"	Administrative Notice	September 30, 2011	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Revision of "Guideline for Clinical Evaluation of Heart Failure Drugs"	PFSB/ELD Notification No. 0329-18	March 29, 2011	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Questions and Answers (Q & A) on "Guideline for Clinical Evaluation of Heart Failure Drugs"	Administrative Notice	March 29, 2011	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Guideline for Clinical Evaluation of Antidepressants	PFSB/ELD Notification No. 1116-1	November 16, 2010	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare

			Director of Evaluation and Licensing Division
Guideline for Clinical Evaluation of Oral Hypoglycemic Agents	PFSB/ELD Notification No. 0709-1	July 9, 2010	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Questions and Answers (Q & A) on "Guideline for Clinical Evaluation of Oral Hypoglycemic Agents"	Administrative Notice	July 9, 2010	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Guideline on Development of Prototype Vaccine against Pandemic Influenza	PFSB/ELD Notification No. 1031-1	October 31, 2011	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Guidelines for clinical study of vaccines to prevent infections	PFSB/ELD Notification No. 0527-5	May 27, 2010	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Partial Correction of "Guideline for Evaluation of Effects of Psychotropic Drugs on Driving Performance"	Administrative Notice	January 23, 2023	Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Guidelines for Clinical Evaluation of Antidyslipidemic Drugs	PSEHB/PED Notification No. 0706-1	July 6, 2021	Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Guideline for Clinical Evaluation of Antineoplastic Drugs	PSEHB/PED Notification No. 0331-1	March 31, 2021	Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Guidelines for Clinical Evaluation of Drugs for Neuropathic Pain	PSEHB/PED Notification No. 1228-1	December 28, 2020	Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Guidelines for Clinical Evaluation of Drugs for the Treatment of Acute Spinal Cord Injury	PSEHB/PED Notification No. 0508-1 PSEHB/MDED Notification No. 0508-1	May 8, 2019	Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Guideline for Clinical Evaluation of Antibacterial Topical Ophthalmic Drugs	PSEHB/PED Notification No. 0418-1	April 18, 2019	Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Guideline for Clinical Evaluation of Antibacterial Drugs	PSEHB/PED Notification No. 1023-3	October 23, 2017	Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Revision of Guideline for Clinical Evaluation of Drugs for Osteoporosis	PSEHB/PED Notification No. 0707-1	July 7, 2017	Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Guidance on clinical evaluation of travelers' vaccines, etc.	PSEHB/ELD Notification No. 0407-1	April 7, 2016	Director of Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Guideline for Clinical Evaluation of Therapeutic Drugs for Overactive Bladder	PFSB/ELD Notification No. 0628001	June 28, 2006	Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
Guideline for Clinical Evaluation of Antirheumatic Drugs	PFSB/ELD Notification No. 0217001	February 17, 2006	Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
Guideline for Clinical Evaluation of Antianginal Drugs	PFSB/ELD Notification No. 0512001	May 12, 2004	Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
Guideline for Clinical Evaluation of Diagnostic Radiopharmaceuticals	PFSB/ELD Notification No. 0611-1	June 11, 2012	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Guideline for Clinical Evaluation of Antiarrhythmic Drugs	PFSB/ELD Notification No. 0325035	March 25, 2004	Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
Partial Correction of "Guideline for Clinical Evaluation of Diagnostic Radiopharmaceuticals"	Administrative Notice	August 13, 2012	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Guideline for Structure and Content of Clinical Study Reports	PAB/ED Notification No. 335	May 1, 1996	Director of Examination Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare
Questions and Answers (Q & A) on "Guideline for Structure and Content of Clinical Study Reports"	Administrative Notice	October 18, 2012	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Basic Principles for Conducting Phase I Trials in the Japanese Population Prior to Global Clinical Trials	Administrative Notice	October 27, 2014	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Guidelines for Collection of Genomic Samples and Handling of Genomic Data	PSEHB/PED Notification No. 0118-1	January 18, 2018	Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Points to consider for explanation and consent using electromagnetic methods in clinical trials and post-marketing clinical studies	Administrative Notice	March 30, 2023	Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Questions and Answers (Q & A) on the Notification of the Clinical Trial Plan for Drugs, Machinery and Equipment or Processed Cells	Administrative Notice	March 30, 2023	Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare

Partial Revision of "Handling of Notifications, etc. of Clinical Trial Plans for Drugs by Person Who Intends to Sponsor a Clinical Trial"	Administrative Notice	March 30, 2023	Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Partial Revision of "Handling of Notifications, etc. of Clinical Trial Plans for Drugs by Person Who Intends to be a Sponsor-Investigator"	Administrative Notice	March 30, 2023	Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Partial Revision of "Reporting of Adverse Drug Reactions, etc. by Sponsor-investigators"	Administrative Notice	March 30, 2023	Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Revision of Questions and Answers (Q & A) on Periodic Reports of Cases of Adverse Drug Reactions, etc.	Administrative Notice	March 30, 2023	Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare

[6] Guidelines for Clinical Safety of Drugs

Notification/Guideline Title	Notification No.	Date of issuance	Issued by
Clinical Safety Data Management	PAB/ED Notification No. 227	March 20, 1995	Pharmaceutical Affairs Bureau, Ministry of Health and Welfare Director of Examination Division
Data elements and message specifications for transmission of individual case safety reports	PMSB/SD Notification No. 39 PMSB/ELD Notification No. 334	March 30, 2001	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division Director of Safety Division
Revision of Implementation Guide for Electronic Transmission of Individual Case Safety Reports	PSEHB/PED Notification No. 0315-6 PSEHB/SD Notification No. 0315-1	March 15, 2017	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Director of Pharmaceutical Evaluation Division Director of Safety Division
Questions and Answers (Q & A) on Electronic Transmission of Individual Case Safety Reports	Administrative Notice	September 26, 2019	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Pharmaceutical Evaluation Division Safety Division
Q & A on "Data elements and message specifications for transmission of individual case safety reports" (Part 4)	Administrative Notice	April 13, 2005	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Safety Division
Pharmacovigilance Plan	PFSB/ELD Notification No. 0916001 PFSB/SD Notification No. 0916001	September 16, 2005	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division Director of Safety Division
Safety Update Report of clinical trials	PFSB/ELD Notification No. 1228-1	December 28, 2012	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Reporting of Adverse Drug Reactions, etc. by Sponsor-investigators	PFSB/ELD Notification No. 0701-21	July 1, 2013	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Questions and Answers (Q & A) on Periodic Reports of Cases of Adverse Drug Reactions, etc.	Administrative Notice	July 1, 2013	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Partial Revision of "Reporting of Adverse Drug Reactions" and "Reporting of Adverse Drug Reactions in Clinical Trials to Pharmaceuticals and Medical Devices Agency"	PFSB Notification No. 1002-0	October 2, 2014	Director of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare

[7] Guidelines for Application for Approval of Drugs

Notification/Guideline Title	Notification No.	Date of issuance	Issued by
Handling of Approval Applications for Improvement of Predictability of Approval of New Drugs and Concept of Total Review Time	PFSB/ELD Notification No. 1006-1 PFSB/CND Notification No. 1006-1	October 6, 2014	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division, Director of Compliance and Narcotics Division
Revision of the Guidelines for Handling Import Notifications of Drugs, etc.	PFSB/CND Notification No. 1117-7	November 17, 2014	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Compliance and Narcotics Division
Application for Approval of Drugs	PFSB Notification No. 1121-2	November 21, 2014	Director of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
Partial Revision of the Notification on Documents to be Attached to an Application for Marketing Approval of a New Drug	PFSB/ELD Notification No. 0707-3	July 7, 2009	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Points to consider for the approval application of drugs	PFSB/ELD Notification No. 1121-12	November 21, 2014	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Partial Revision of the "Guidelines for Preparation of Documents to be Attached to an Approval Application for Marketing or Import of a New Drug"	PFSB/ELD Notification No. 0701004	July 1, 2003	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Guidelines for Preparation of Documents to be Attached to an Approval Application for Marketing or Import of a New Drug	PMSB/ELD Notification No. 899	June 21, 2001	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
(Attachment 1) Structure of common technical document (CTD) for an approval application of drugs			
(Attachment 2) Part 1 Guidelines for Preparing Documents Related to Administrative Information such as Application Forms and Information Related to Package Inserts			
(Attachment 3) CTD-Guideline on Preparation of Quality Documents			
(Attachment 4) CTD-Guideline on Preparation of Nonclinical Documents			
(Attachment 5) CTD-Guideline on Preparation of Clinical Documents			

(Attachment 6) Handling of Part 3 Materials Points to consider for lot scale, etc. of submitted data			
Q & A on Guidelines for Preparation of Documents to be Attached to an Approval Application for Marketing or Import of a New Drug	Administrative Notice	October 22, 2001	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Q & A on "Guidelines for Preparation of Documents to be Attached to an Approval Application for Marketing or Import of a New Drug"	Administrative Notice	January 28, 2003	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Q & A on "Guidelines for Preparation of Documents to be Attached to an Approval Application for Marketing or Import of a New Drug"	Administrative Notice	June 27, 2003	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Common Technical Document CTD - Quality Q & A/Items related to description	Administrative Notice	November 5, 2003	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Q & A on "Guidelines for Preparation of Documents to be Attached to an Approval Application for Marketing or Import of a New Drug"	Administrative Notice	November 5, 2003	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Q & A on "Guidelines for Preparation of Documents to be Attached to an Approval Application for Marketing or Import of a New Drug"	Administrative Notice	May 24, 2004	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Q & A on "Guidelines for Preparation of Documents to be Attached to an Approval Application for Marketing or Import of a New Drug"	Administrative Notice	November 24, 2004	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division

2) Regenerative medical products

[1] Standards for Biological Ingredients

Notification/Guideline Title	Notification No.	Date of issuance	Issued by
Standards for Biological Ingredients (established on May 20, 2003, Ministerial Announcement of Ministry of Health, Labour and Welfare No. 210)	Latest partial revision is given in Ministerial Announcement of MHLW No. 37.	February 28, 2018	Minister of Health, Labour and Welfare
Partial revision of the Standards for Biological Ingredients	PFSB Notification No. 0228-3	February 28, 2018	Director of Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Enforcement of partial revision of the Standards for Biological Ingredients	PSEHB/PED Notification No. 0228-3 PSEHB/MDED Notification No. 0228-3	February 28, 2018	Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Operation of the Standards for Biological Ingredients	PFSB/ELD Notification No. 1002-1 PFSB/ELD/OMDE Notification No. 1002-5	October 2, 2014	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division Counsellor, Minister's Secretariat, Ministry of Health, Labour and Welfare (in charge of review control of medical devices and regenerative medical products)
Questions and Answers (Q & A) on the Operation of the Standards for Biological Ingredients	Administrative Notice	June 30, 2015	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division

[2] Notification on Quality and Safety Assurance in Application for Approval of Regenerative Medical Products

Notification/Guideline Title	Notification No.	Date of issuance	Issued by
Technical guidance on quality, non-clinical studies, and clinical studies of regenerative medical products (human cell-processed products)	Administrative Notice	June 27, 2016	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division of Medical Devices
Securing of the quality and safety of drugs, etc. manufactured using ingredients of human or animal origin as raw materials	PMSB Notification No. 1314	December 26, 2000	Director of Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare
Securing of the quality and safety of drugs or medical devices for which human-derived (autologous) cells or tissues are processed	PFSB Notification No. 0208003	February 8, 2008	Director of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
Q & A on guidelines for securing of the quality and safety of drugs, etc. for which human-derived (autologous) cells or tissues are processed	Administrative Notice	March 12, 2008	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Office of Evaluation and Licensing of Medical Devices
Securing of the quality and safety of drugs or medical devices for which human-derived (homologous) cells or tissues are processed	PFSB Notification No. 0912006	September 12, 2008	Director of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
Q & A on guidelines for securing of the quality and safety of drugs, etc. for which human-derived (homologous) cells or tissues are processed	Administrative Notice	October 3, 2008	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Securing of the quality and safety of drugs, etc. for which human (autologous) somatic stem cells are processed	PFSB Notification No. 0907-2	September 7, 2012	Director of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
Securing of the quality and safety of drugs, etc. for which human (homologous) somatic stem cells are processed	PFSB Notification No. 0907-3	September 7, 2012	Director of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
Securing of the quality and safety of drugs, etc. for which human (autologous) iPS (-like) cells are processed	PFSB Notification No. 0907-4	September 7, 2012	Director of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
Securing of the quality and safety of drugs, etc. for which human (homologous) iPS (-like) cells are processed	PFSB Notification No. 0907-5	September 7, 2012	Director of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
Securing of the quality and safety of drugs, etc. for which human ES cells are processed	PFSB Notification No. 0907-6	September 7, 2012	Director of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare

[3] Guidelines for Gene Therapy Products

Notification/Guideline Title	Notification No.	Date of issuance	Issued by
Guidelines for Clinical Studies of Gene Therapy (Ministry of Education, Culture, Sports, Science and Technology/Ministry of Health, Labour and Welfare Ministerial Announcement No. 1)	The latest partial revision is 26 Bunkashin 400 and Kahatsu 1125-2.	November 25, 2014	Minister of Education, Culture, Sports, Science and Technology Minister of Health, Labour and Welfare
Ensuring the Quality and Safety of Gene Therapy Products	PSEHB/MDED Notification No. 0709-2	July 9, 2019	Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms	Ministerial Ordinance No. 1 of the Ministry of Finance, Ministry of Education, Culture, Sports, Science and Technology, Ministry of Health, Labour and Welfare, Ministry of Agriculture, Forestry and Fisheries, and Ministry of Environment	March 5, 2018	Ministers of Ministry of Finance, Ministry of Education, Culture, Sports, Science and Technology, Ministry of Health, Labour and Welfare, Ministry of Agriculture, Forestry and Fisheries, and Ministry of Environment
Ministerial Ordinance Providing Containment Measures to Be Taken in Industrial Use within the Scope of Second-Class Use of Living Modified Organisms	Ministerial Ordinance No. 1 of the Ministry of Finance, Ministry of Health, Labour and Welfare, Ministry of Agriculture, Forestry and Fisheries, and Ministry of Environment	June 24, 2022	Ministers of Ministry of Finance, Ministry of Health, Labour and Welfare, Ministry of Agriculture, Forestry and Fisheries, and Ministry of Environment
Questions and Answers (Q&A) concerning Application for Approval and Other Regulatory Procedures Pertinent to the Act on the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms	Administrative Notice	February 3, 2022	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Abolition of the confirmation application system for gene therapy drugs	PFSB Notification No. 0701-13	July 1, 2013	Director of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
Reports on gene therapy products and living modified organisms	PFSB/ELD Notification No. 0623-1 PFSB/ELD/OMDE Notification No. 0623-1	June 23, 2015	Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, Counsellor, Minister's Secretariat, Ministry of Health, Labour and Welfare (in charge of review control of medical devices and regenerative medical products)
ICH Opinion "Basic Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors"	Administrative Notice	June 23, 2015	Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Office of Counsellor for Medical Devices and Regenerative Medical Products
ICH Opinion "Oncolytic Viruses"	Administrative Notice	June 23, 2015	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Office of Counsellor for Medical Devices and Regenerative Medical Products
ICH Opinion "Basic Principles on Viral and Vector Shedding"	Administrative Notice	June 23, 2015	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Office of Counsellor for Medical Devices and Regenerative Medical Products

[4] Points to consider (checkpoints) for efficient conduct of pharmaceutical affairs consultation on R & D strategy for quality and safety from the initial stage of development of regenerative medical products

Notification/Guideline Title	Notification No.	Date of issuance	Issued by
Points to consider (checkpoints) for efficient conduct of pharmaceutical affairs consultation on R & D strategy for quality and safety from the initial stage of development of cellular and tissue-based products [Quality]		Version dated March 8, 2013	
Points to consider (checkpoints) for efficient conduct of RS strategy consultation for quality and safety from the initial stage of development of cellular and tissue-based products [Non-clinical safety]		Version dated December 25, 2020	
Points to consider (checkpoints) for efficient conduct of RS strategy consultation for quality and safety from the initial stage of development of gene therapy products [Quality]		Version dated October 1, 2021	
Points to consider (checkpoints) for efficient conduct of RS strategy consultation for quality and safety from the initial stage of development of gene therapy products		Version dated December 25, 2020	

[Non-clinical safety]			

[5] Notification on manufacturing control and quality control

Notification/Guideline Title	Notification No.	Date of issuance	Issued by
Concept of manufacturing control/quality control of drugs, etc. for which human-derived (autologous) cells or tissues are processed	PFSB/CND Notification No. 0327025	March 27, 2008	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Compliance and Narcotics Division
Standards for manufacturing and quality controls of investigational product (investigational product GMP)	PFSB Notification No. 0709002	July 9, 2008	Director of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
Q & A on standards for manufacturing and quality controls of investigational product (investigational product GMP)	Administrative Notice	July 2, 2009	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Compliance and Narcotics Division
Partial Revision of the "Views on Utilization of PIC/S GMP Guidelines"	Administrative Notice	November 28, 2022	Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare

[6] Notification on the use of MF registration

Notification/Guideline Title	Notification No.	Date of issuance	Issued by
Guideline on Utilization of Master File for Drug Substances, etc.	PFSB/ELD Notification No. 1117-3, PFSB/ELD/OMDE Notification No. 1117-1	November 17, 2014	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division, Counsellor, Minister's Secretariat, Ministry of Health, Labour and Welfare (in charge of review control of medical devices and regenerative medical products)
Questions and Answers (Q & A) on Master File for Drug Substances, etc.	Administrative Notice	July 28, 2005	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Questions and Answers (Q & A) on Master File for Drug Substances, etc. (Part 2)	Administrative Notice	December 20, 2005	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Questions and Answers (Q & A) on Master File for Drug Substances, etc. (Part 3)	Administrative Notice	December 28, 2012	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Questions and Answers (Q & A) on Master File for Drug Substances, etc. (Part 4)	Administrative Notice	October 29, 2013	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Guidelines for Preparing the Drug Master File Registration Application Form and Data to be Attached to the Application Form for Materials Related to Manufacturing of Drugs, etc. for which Cells or Tissues are processed	Administrative Notice	March 8, 2013	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Q & A on Guidelines for Preparing the Drug Master File Registration Application Form and Data to be Attached to the Application Form for Materials Related to Manufacturing of Drugs, etc. for which Cells or Tissues are processed	Administrative Notice	April 15, 2013	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division

[7] Notification on Guidance Document for the Evaluation of Emerging Technology Medical Devices (only those containing contents related to regenerative medical products)

Notification/Guideline Title	Notification No.	Date of issuance	Issued by
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices (Appendix 1) Guidance document for the evaluation of fracture reduction support devices (Appendix 2) Guidance document for the evaluation of joint surgery support devices (Appendix 3) Guidance document for the evaluation of cell sheets for cell therapy for severe heart failure (Appendix 4) Guidance document for the evaluation of corneal epithelial cell sheets	PFSB/ELD/OMDE Notification No. 0118-1	January 18, 2010	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Director of Office of Evaluation and Licensing of Medical Devices
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices (Appendix 1) Guidance document for the evaluation of corneal endothelial cell sheets (Appendix 2) Guidance document for the evaluation of computer-assisted surgical devices applied to soft tissues	PFSB/ELD/OMDE Notification No. 0528-1	May 28, 2010	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Director of Office of Evaluation and Licensing of Medical Devices
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices (Appendix 1) Guidance document for the evaluation of cell sheets for periodontal tissue treatment (Appendix 2) Guidance document for the evaluation of custom-made artificial hip joint prosthesis for orthopedic surgery (Appendix 3) Guidance document for the evaluation of computer diagnostic support devices	PFSB/ELD/OMDE Notification No. 1207-1	December 7, 2011	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Director of Office of Evaluation and Licensing of Medical Devices
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices (Appendix 1) Guidance document for the evaluation of articular cartilage regeneration (Appendix 2) Guidance document for the evaluation of neurofunctional	PFSB/ELD/OMDE Notification No. 1215-1	December 15, 2010	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division

modification devices - General (Appendix 3) Guidance document for the evaluation of custom-made implants for osteosynthesis materials for orthopedic surgery			Director of Office of Evaluation and Licensing of Medical Devices
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices (Appendix 1) Guidance document for the evaluation of retinal pigment epithelial cells derived from autologous iPS cells (Appendix 2) Guidance document for the evaluation of activity function recovery devices (Appendix 3) Guidance document for the clinical evaluation of medical devices for treatment of severe limb ischemia diseases	PFSB/ELD/OMDE Notification No. 0529-1	May 29, 2013	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Director of Office of Evaluation and Licensing of Medical Devices
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices/Cellular and Tissue-based Products (Attachment 1) Retinal pigment epithelial cells derived from homologous iPS (-like) cells (Attachment 2) Spinal implant to maintain mobility and stability (Attachment 3) Orthopedic implants utilizing 3D lamination technology	PFSB/ELD/OMDE Notification No. 0912-2	September 12, 2014	Counsellor, Minister's Secretariat, Ministry of Health, Labour and Welfare (in charge of review control of medical devices and regenerative medical products)
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices/Cellular and Tissue-based Products (Attachment 1) Nasal cartilage regeneration (Attachment 2) Cardiac catheter ablation device (Attachment 3) Custom-made orthopedic implants, etc.	PFSB/ELD/OMDE Notification No. 0925-1	September 25, 2015	Counsellor, Minister's Secretariat, Ministry of Health, Labour and Welfare (in charge of review control of medical devices and regenerative medical products)
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices/Cellular and Tissue-based Products (Attachment 1) Articular cartilage regeneration using human chondrocytes or somatic stem cell-processed products (Attachment 2) Articular cartilage regeneration using human (homologous) iPS (-like) cell-processed products (Attachment 3) Bioabsorbable vascular stent	PSEHB/MDED Notification No. 0630-1	June 30, 2016	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division of Medical Devices
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices/Cellular and Tissue-based Products (Attachment) Guidance Document for the Evaluation of human (autologous) epidermal (skin) regeneration	PSEHB/MDED Notification No. 0320-1	March 20, 2018	Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices/Cellular and Tissue-based Products (Attachment) Guidance Document for the Evaluation of human (homologous) epidermal (skin) regeneration	PSEHB/MDED Notification No. 0725-1	July 25, 2018	Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices/Cellular and Tissue-based Products (Attachment) Treatment of subacute spinal cord injury (traumatic) using human (homologous) iPS (-like) cell-processed products	PSEHB/MDED Notification No. 0226-1	February 26, 2021	Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices/Cellular and Tissue-based Products (Attachment) Treatment of decompensated cirrhosis using human (homologous) bone marrow-derived mesenchymal stem cell processed product, human (homologous) adipose tissue-derived mesenchymal stem cell processed product, and human (homologous) peripheral blood CD34 positive cell processed product	PSEHB/MDED Notification No. 0217-1	February 17, 2022	Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices/Cellular and Tissue-based Products (Attachment) Guidance Document for the Evaluation of Treatment of Ischemic Cardiomyopathy Using Human (Homologous) iPS Cell-derived Cardiomyocyte Sheet	PSEHB/MDED Notification No. 0331-15	March 31, 2023	Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare

3) Medical devices

[1] Guidelines for Application for Approval of Medical Devices

Notification/Guideline Title	Notification No.	Date of issuance	Issued by
Applications for Marketing Approval for Medical Devices	PFSB Notification No. 1120-5	November 20, 2014	Director of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
Revision of Classification Rules for Specially Controlled Medical Devices, Controlled Medical Devices, and General Medical Devices	PFSB Notification No. 0510-8	May 10, 2013	Director of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
Points to consider for preparation of marketing application forms for medical devices	PFSB/ELD/OMDE Notification No. 1120-1	November 20, 2014	Counsellor, Minister's Secretariat, Ministry of Health, Labour and Welfare (in charge of review control of medical devices and regenerative medical products)
Points to consider for preparation of data attached to marketing application forms for medical devices Partial revision of "Points to consider for preparation of data attached to marketing application forms for medical devices"	PFSB/ELD/OMDE Notification No. 0120-9 PSEHB/MDED Notification No. 0228-7	January 20, 2015, February 28, 2018	Counsellor, Minister's Secretariat, Ministry of Health, Labour and Welfare (in charge of review control of medical devices and regenerative medical products) Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division of Medical Devices
Application of the Essential Requirements Standards for Medical Devices and In Vitro Diagnostics	PFSB/ELD/OMDE Notification No. 0328001	March 28, 2008	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Director of Office of Evaluation and Licensing of Medical Devices
Points to consider when attaching test results to application data for marketing approval for medical devices	PFSB/ELD/OMDE Notification No. 0329-4	March 29, 2013	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division

			Director of Office of Evaluation and Licensing of Medical Devices
Points to consider for marketing notification for medical devices	PFSB/ELD/OMDE Notification No. 1121-41	November 21, 2014	Counsellor, Minister's Secretariat, Ministry of Health, Labour and Welfare (in charge of review control of medical devices and regenerative medical products)
Handling of standards for medical devices and in vitro diagnostics specified by the Minister of Health, Labour and Welfare pursuant to the provisions of Article 41, Paragraph 3 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices	PFSB/ELD/OMDE Notification No. 1105-5	November 5, 2014	Counsellor, Minister's Secretariat, Ministry of Health, Labour and Welfare (in charge of review control of medical devices and regenerative medical products)
Revision, etc. of "Handling of application for approval of combination products"	PSEHB/PED Notification No. 1122-4 PSEHB/MDED Notification No. 1120-10 PSEHB/SD Notification No. 1122-7 PSEHB/CND Notification No. 1122-4	November 22, 2016	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Director of Pharmaceutical Evaluation Division Director of Evaluation and Licensing Division of Medical Devices Director of Safety Division Director of Compliance and Narcotics Division
Handling of Marketing Approval Applications, Marketing Certification Applications, and Marketing Notifications for Combination Medical Devices	PFSB/ELD/OMDE Notification No. 0331002	March 31, 2009	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Director of Office of Evaluation and Licensing of Medical Devices
Handling of marketing certification applications for medical devices with more than one generic name	PFSB/ELD/OMDE Notification No. 0207-1	February 7, 2013	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Director of Office of Evaluation and Licensing of Medical Devices
Handling of Approval Applications for Laser Medical Devices	PSEHB/MDED Notification No. 0629-4	June 29, 2016	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division

[2] Guidelines for Clinical Studies of Medical Devices

Notification/Guideline Title	Notification No.	Date of issuance	Issued by
Ministerial Ordinance on Good Clinical Practice for Medical Devices (GCP Ordinance for Medical Devices)	MHLW Ordinance No. 36	March 23, 2005	Minister of Health, Labour and Welfare
Ministerial Ordinance on Good Post-marketing Study Practice for Medical Devices (GPSP Ordinance for Medical Devices)	MHLW Ordinance No. 38	March 23, 2005	Minister of Health, Labour and Welfare
Necessary scope of clinical study data on medical devices	PFSB/ELD/OMDE Notification No. 0804001	August 4, 2008	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Director of Office of Evaluation and Licensing of Medical Devices
Guidance for Clinical Trials for Rapid and Accurate Approval and Development of Medical Devices		March 2017	Group of "Study on Guidance for Clinical Trials for Rapid and Accurate Approval and Development of Medical Devices"
Clarification of handling of clinical study data on orphan medical devices	PFSB/ELD/OMDE Notification No. 0329-1	March 29, 2013	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Director of Office of Evaluation and Licensing of Medical Devices
Handling on the Required Scope of Submitting "Documents related to Clinical Study Results" on Medical Devices (Operations based on Measures through Pre-and Post-Marketing Phases)	PSEHB/MDED Notification No. 1117-1 PSEHB/SD Notification No. 1117-1	November 17, 2017	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division of Medical Devices Director of Safety Division
Basic concept for utilization of registry in an approval application, etc.	PSEHB/PED Notification No. 0323-1 PSEHB/MDED Notification No. 0323-1	March 23, 2021	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Director of Pharmaceutical Evaluation Division Director of Evaluation and Licensing Division of Medical Devices
Points to consider for reliability assurance when using registry data for an approval application, etc.	PSEHB/PED Notification No. 0323-2 PSEHB/MDED Notification No. 0323-2	March 23, 2021	Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing of Medical Devices
Handling of performance evaluation tests of diagnostic medical devices using existing medical image data without additional invasion/intervention	PSEHB/ELD Notification No. 0929-1	September 29, 2021	Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Questions and Answers (Q & A) on Handling of performance evaluation tests of diagnostic medical devices using existing medical image data without additional invasion/intervention	Administrative Notice	December 8, 2022	Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare

[3] Guidelines for Manufacturing Control, Quality Control, and Safety of Medical Devices

Notification/Guideline Title	Notification No.	Date of issuance	Issued by
Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Medical Devices and In-vitro Diagnostic Reagents (QMS Ministerial Ordinance)	MHLW Ordinance No. 169	December 17, 2004	Minister of Health, Labour and Welfare

Ministerial Ordinance on Standards for System Implementing Operations related to Manufacturing Control and Quality Control for Medical Devices and In-vitro Diagnostic Reagents (QMS System Ministerial Ordinance)	MHLW Ordinance No. 94	August 6, 2014	Minister of Health, Labour and Welfare
Acceptance of MDSAP investigation reports	PSEHB/CND Notification No. 0929-2 PSEHB/ELD Notification No. 0929-2	September 29, 2021	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Director of Compliance and Narcotics Division Director of Evaluation and Licensing Division of Medical Devices
Implementation of inspections, etc. related to MDSAP inspection organizations	PSEHB/MDED Notification No. 1027-1 PSEHB/CND Notification No. 1027-5	October 27, 2021	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division of Medical Devices Director of Compliance and Narcotics Division
Procedures for the use of MDSAP reports in QMS compliance inspections	PMDA Notification No. 1118022	November 18, 2021	Chief Executive, Pharmaceuticals and Medical Devices Agency
Questions and Answers (Q & A) on Acceptance of MDSAP Investigation Reports	Administrative Notice	November 29, 2021	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Compliance and Narcotics Division Evaluation and Licensing Division of Medical Devices
Ministerial Ordinance on Good Vigilance Practice for drugs, quasi-drugs, cosmetics, and medical devices (GVP Ministerial Ordinance)	MHLW Ordinance No. 135	September 22, 2004	Minister of Health, Labour and Welfare
Ministerial Ordinance on Good Laboratory Practice for Nonclinical Safety Studies of Medical Devices (GLP Ordinance for Medical Devices)	MHLW Ordinance No. 37	March 23, 2005	Minister of Health, Labour and Welfare
Handling of long-term stability data of medical devices	PFSB/ELD/OMDE Notification No. 0815001	August 15, 2007	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Director of Office of Evaluation and Licensing of Medical Devices
Establishment of Shelf Life of Medical Devices and Stability Testing	PFSB/ELD/OMDE Notification No. 0905001	September 5, 2008	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Director of Office of Evaluation and Licensing of Medical Devices
Handling of stability testing to establish shelf life for application for marketing approval (certification) of medical devices	PFSB/ELD/OMDE Notification No. 1227-5	December 27, 2012	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Director of Office of Evaluation and Licensing of Medical Devices
Handling of electrical safety data to be attached to marketing application forms for medical devices	PMSB/ELD No. 545	March 30, 2000	Director of Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare
Handling under the Pharmaceutical Affairs Act in association with the revision of the Japanese Industrial Standards related to the electrical safety test of medical devices	PFSB/ELD/OMDE Notification No. 0517-1	May 17, 2013	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Director of Office of Evaluation and Licensing of Medical Devices
Revision of the Japanese Industrial Standards for Electromagnetic Compatibility of Medical Devices	PSEHB/ELD Notification No. 0301-1	March 1, 2018	Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Handling under the Pharmaceutical Affairs Act in association with the revision of the Japanese Industrial Standards related to the electromagnetic compatibility test of medical devices	PFSB/ELD/OMDE Notification No. 0328-1	March 28, 2012	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Director of Office of Evaluation and Licensing of Medical Devices
Revision of Basic Principles of Biological Safety Evaluation Required for Application for Marketing Approval of Medical Devices	PSEHB/MDED Notification No. 0106-1	January 6, 2020	Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Questions and Answers (Q & A) on Basic Principles of Biological Safety Evaluation Required for Application for Marketing Approval of Medical Devices (Part 2)	PSEHB/MDED Notification No. 0106-4	January 6, 2020	Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Standards for Biological Ingredients (established on May 20, 2003, Ministerial Announcement of Ministry of Health, Labour and Welfare No. 210)	Latest partial revision is given in Ministerial Announcement of MHLW No. 37.	February 28, 2018	Minister of Health, Labour and Welfare
Partial revision of the Standards for Biological Ingredients	PFSB Notification No. 0228-3	February 28, 2018	Director of Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Enforcement of partial revision of the Standards for Biological Ingredients	PSEHB/PED Notification No. 0228-3 PSEHB/MDED Notification No. 0228-3	February 28, 2018	Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Operation of the Standards for Biological Ingredients	PFSB/ELD Notification No. 1002-1 PFSB/ELD/OMDE Notification No. 1002-5	October 2, 2014	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division Counsellor, Minister's Secretariat, Ministry of Health, Labour and Welfare (in charge of review control of medical devices and regenerative medical products)
Questions and Answers (Q & A) on the Operation of the Standards for Biological Ingredients	Administrative Notice	June 30, 2015	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division

Partial Revision of Basic Principles of Biological Safety Evaluation of Dental Medical Devices	PSEHB/MDED Notification No. 0531-5	May 31, 2021	Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Handling of Application for Approval of Dental Implants	PFSB/ELD/OMDE Notification No. 0713-1	July 13, 2012	Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Office of Evaluation and Licensing of Medical Devices
Partial Revision of "Handling of Application for Approval of Dental Implants"	PSEHB/MDED Notification No. 1107-1	November 7, 2022	Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Handling of selection of fatigue test samples for application for approval of dental implants	PSEHB/MDED Notification No. 0323-1	March 23, 2017	Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Partial Revision of Basic Principles of Electrical Safety Evaluation and Physical and Chemical Evaluation Required for Application for Marketing Approval of Dental Equipment	PFSB/ELD/OMDE Notification No. 0131-6	January 31, 2014	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Director of Office of Evaluation and Licensing of Medical Devices
Correction of "Establishment of Sterilization Validation Standards"	PSEHB/CND Notification No. 1021-5	October 21, 2022	Director of Compliance and Narcotics Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Securing of Cybersecurity in Medical Devices	PFSB/ELD/OMDE Notification No. 0428-1 PFSB/SD Notification No. 0428-1 PFSB/ELD/OMDE Notification No. 0428-2 PFSB/SD Notification No. 0428-2 PFSB/ELD/OMDE Notification No. 0428-3 PFSB/SD Notification No. 0428-3	April 28, 2015	Counsellor, Minister's Secretariat, Ministry of Health, Labour and Welfare (in charge of review control of medical devices and regenerative medical products)
Guidance on Securing of Cybersecurity in Medical Devices	PSEHB/MDED Notification No. 0724-1 PSEHB/SD Notification No. 0724-1 July 24, 2018	July 24, 2018	Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Director of Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare

[4] Guidelines for Software as a Mefical Device（SaMD）

Notification/Guideline Title	Notification No.	Date of issuance	Issued by
Basic concept of applicability to Software as a Mefical Device（SaMD）	PFSB/CND Notification No. 1114-5	November 14, 2014	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Compliance and Narcotics Division
Partial revision of the guidelines on the applicability of programs to medical devices	PFSB/ELD Notification No. 0331-1 PFSB/CND Notification No. 0331-4	March 31, 2023	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division of Medical Devices Director of Compliance and Narcotics Division
Examples for judging the applicability of Software as a Mefical Device（SaMD）	Administrative Notice	March 31, 2023	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division of Medical Devices Director of Compliance and Narcotics Division
Applicability of dental Software as a Mefical Device（SaMD）	PFSB/ELD Notification No. 1228-4 PFSB/CND Notification No. 1228-6	December 28, 2018	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division of Medical Devices Director of Compliance and Narcotics Division
Q & A on Handling of Software as a Mefical Device（SaMD） Q & A on Handling of Software as a Mefical Device（SaMD） (Part 2)	Administrative Notice Administrative Notice	November 25, 2014, September 30, 2015	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Office of Counsellor for Medical Devices and Regenerative Medical Products Safety Division Compliance and Narcotics Division
Notice concerning the Publication of Guidance Materials concerning Application for Marketing Approval of Medical Device Software	Administrative Notice	March 31, 2016	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Office of Counsellor for Medical Devices and Regenerative Medical Products
Handling of Application for Marketing Certification of Medical Device Software	PFSB/ELD/OMDE Notification No. 1125-6	November 25, 2014	Counsellor, Minister's Secretariat, Ministry of Health, Labour and Welfare (in charge of review control of medical devices and regenerative medical products)
Description examples of marketing approval (certification) application forms and submission data for medical device programs	Administrative Notice	February 10, 2015	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Office of Counsellor for Medical Devices and Regenerative Medical Products

[5] Guidelines for In Vitro Diagnostics

Notification/Guideline Title	Notification No.	Date of issuance	Issued by
Handling of standards for medical devices and in vitro diagnostics specified by the Minister of Health, Labour and Welfare pursuant to the provisions of Article 41, Paragraph 3 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices	PFSB/ELD/OMDE Notification No. 1105-5	November 5, 2014	Counsellor, Minister's Secretariat, Ministry of Health, Labour and Welfare (in charge of review control of medical devices and regenerative medical products)
Checklist for Compliance with Essential Requirements Standards for In Vitro Diagnostics	PFSB/ELD/OMDE Notification No. 0120-1	January 20, 2015	Minister's Secretariat, Ministry of Health, Labour and Welfare (in charge of review control of medical devices and regenerative medical products)
Applications for Marketing Approval of In Vitro Diagnostics	PSEHB Notification No. 0222-5	February 22, 2016	Director of Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Approval standards for in vitro diagnostics	PFSB Notification No. 0120-1	January 20, 2015	Director of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
Points to Consider When Applying for Marketing Approval of In Vitro Diagnostics	PFSB/ELD/OMDE Notification No. 1121-16	November 21, 2014	Counsellor, Minister's Secretariat, Ministry of Health, Labour and Welfare (in charge of review control of medical devices and regenerative medical products)
Partial Revision of "Points to Consider When Applying for Marketing Approval of In Vitro Diagnostics" and "Points to consider When Applying for Marketing Certification of In Vitro Diagnostics"	PFSB/ELD/OMDE Notification No. 0120-5	January 20, 2015	Minister's Secretariat, Ministry of Health, Labour and Welfare (in charge of review control of medical devices and regenerative medical products)
Questions and Answers (Q & A) on Application for Approval of Medical Devices and In Vitro Diagnostics	PFSB/ELD/OMDE Notification No. 1125-22	November 25, 2014	Counsellor, Minister's Secretariat, Ministry of Health, Labour and Welfare (in charge of review control of medical devices and regenerative medical products)
Questions and Answers on Handling of In Vitro Diagnostic Reagents	PFSB/ELD/OMDE Notification No. 0906-1	September 6, 2011	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Director of Office of Evaluation and Licensing of Medical Devices
Handling of Use-Results Evaluation Related to Marketing Approval of Medical Devices and In Vitro Diagnostics	PFSB/ELD/OMDE Notification No. 1121-44	November 21, 2014	Counsellor, Minister's Secretariat, Ministry of Health, Labour and Welfare (in charge of review control of medical devices and regenerative medical products)
Basic Principles on Targets for Use-Results Evaluation at the Time of Marketing Approval of Medical Devices and In Vitro Diagnostics	PFSB/ELD/OMDE Notification No. 1226-3	December 26, 2014	Counsellor, Minister's Secretariat, Ministry of Health, Labour and Welfare (in charge of review control of medical devices and regenerative medical products)
Partial Revision of "Handling of Use-Results Evaluation Related to Marketing Approval of Medical Devices and In Vitro Diagnostics"	Administrative Notice	December 28, 2015	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare (Office of counsellor in charge of review control of medical devices and regenerative medical products)
Handling of Stability Data to be Attached to Marketing Approval Applications and Marketing Certification Applications for In Vitro Diagnostics	PFSB/ELD/OMDE Notification No. 1023-1	October 23, 2009	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Director of Office of Evaluation and Licensing of Medical Devices
Handling of data on setting of the shelf life to be attached to marketing approval applications for in vitro diagnostics	PFSB/ELD/OMDE Notification No. 1023-4	October 23, 2009	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Director of Office of Evaluation and Licensing of Medical Devices
Handling of Stability Tests of In Vitro Diagnostics (Questions and Answers)	PFSB/ELD/OMDE Notification No. 0513-1	May 13, 2010	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Director of Office of Evaluation and Licensing Division of Medical Devices
Handling of generic names of medical devices and in vitro diagnostics that do not fall under any of the generic names	PFSB/ELD/OMDE Notification No. 1125-26	November 25, 2014	Counsellor, Minister's Secretariat, Ministry of Health, Labour and Welfare (in charge of review control of medical devices and regenerative medical products)
Diversion of in vitro diagnostics to OTC test agents	PFSB Notification No. 1225-1	December 5, 2014	Director of Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare
Points to Consider for Securing the Reliability of Application Data for Marketing Approval of In Vitro Diagnostics	Administrative Notice	September 9, 2019	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division of Medical Devices
Ministerial Ordinance on Standards for Manufacturing Control and Quality Control for Medical Devices and In-vitro Diagnostic Reagents (Revised QMS Ministerial Ordinance)	MHLW Ordinance No. 169 Revision of MHLW Ordinance No. 87 Partial Revision of MHLW Ordinance No. 128 Partial Revision of MHLW Ordinance No. 60	December 17, 2004, July 30, 2014, November 21, 2014, March 26, 2021	Minister of Health, Labour and Welfare
Points to Consider for Approval Applications for Companion Diagnostics and Related Drugs	PFSB/ELD Notification No. 0701-10	July 1, 2013	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Director of Evaluation and Licensing Division
Questions and Answers (Q & A) on Companion Diagnostics and Related Drugs	Administrative Notice	July 1, 2013	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division
Technical Guidance on Companion Diagnostics and Related Drugs	Administrative Notice PMDA Notification No. 1224029	December 26, 2013	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division

Points to Consider When Applying for Marketing Approval of In Vitro Diagnostics Falling Under the Category of Companion Diagnostics, etc.	PFSB/ELD/OMDE Notification No. 0219-4	February 19, 2014	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Director of Office of Evaluation and Licensing of Medical Devices
Questions and Answers on Points to Consider When Applying for Marketing Approval of In Vitro Diagnostics Falling Under the Category of Companion Diagnostics, etc.	PFSB/ELD/OMDE Notification No. 0328-7	March 28, 2014	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Director of Office of Evaluation and Licensing of Medical Devices
Questions and Answers (Q & A) on "Technical Guidance on Companion Diagnostics and Related Drugs"	Administrative Notice	July 3, 2018	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Pharmaceutical Evaluation Division Evaluation and Licensing Division of Medical Devices
Questions and Answers (Q & A) on Companion Diagnostics and Related Drugs (Part 2)	Administrative Notice	July 20, 2018	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Pharmaceutical Evaluation Division Evaluation and Licensing Division of Medical Devices
Questions and Answers (Q & A) on Handling of In Vitro Diagnostics, etc., for Companion Diagnosis with Multiple Drugs	Administrative Notice	March 31, 2022	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Pharmaceutical Evaluation Division Evaluation and Licensing Division of Medical Devices Pharmaceutical Safety Division
Handling of In Vitro Diagnostics, etc., for Companion Diagnosis with Multiple Drugs	PSEHB/PED Notification No. 0331-1 PSEHB/MDED Notification No. 0331-1 PSEHB/SD Notification No. 0331-1	March 31, 2022	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Director of Pharmaceutical Evaluation Division Director of Evaluation and Licensing Division of Medical Devices Director of Pharmaceutical Safety Division
Guidance on companion diagnostics with multiple drugs	Administrative Notice	July 4, 2022	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Pharmaceutical Evaluation Division Evaluation and Licensing Division of Medical Devices Pharmaceutical Safety Division
Questions and Answers (Q & A) on "Technical Guidance on Companion Diagnostics and Related Drugs"	Administrative Notice	August 25, 2022	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Pharmaceutical Evaluation Division Evaluation and Licensing Division of Medical Devices
Handling of DNA Sequencers, etc. Used in Genetic Testing System When Marketing Them	PSEHB/MDED Notification No. 0428-1 PSEHB/CND Notification No. 0428-1	April 28, 2016	Counsellor, Minister's Secretariat, Ministry of Health, Labour and Welfare (in charge of review control of medical devices and regenerative medical products) Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Director of Compliance and Narcotics Division
Questions and Answers (Q & A) on Handling of DNA Sequencers, etc. Used in Genetic Testing System When Marketing Them	Administrative Notice	January 26, 2017	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division of Medical Devices Compliance and Narcotics Division
Questions and Answers (Q & A) on Handling of DNA Sequencers, etc. Used in Genetic Testing System When Marketing Them (Part 2)	Administrative Notice	September 12, 2018	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division of Medical Devices Compliance and Narcotics Division

[6] Notification on the Guidance Document for the Evaluation of Emerging Technology Medical Devices

Notification/Guideline Title	Notification No.	Date of issuance	Issued by
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices (Appendix 2) Guidance Document for the Evaluation of Diagnostic Agents for Genotyping using DNA Chips	PFSB/ELD/OMDE Notification No. 0404002	April 4, 2008	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Director of Office of Evaluation and Licensing of Medical Devices
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices (Appendix 1) Guidance document for the evaluation of fracture reduction support devices (Appendix 2) Guidance document for the evaluation of joint surgery support devices (Appendix 3) Guidance document for the evaluation of cell sheets for cell therapy for severe heart failure (Appendix 4) Guidance document for the evaluation of corneal epithelial cell sheets	PFSB/ELD/OMDE Notification No. 0118-1	January 18, 2010	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Director of Office of Evaluation and Licensing of Medical Devices
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices (Appendix 1) Guidance document for the evaluation of corneal endothelial cell sheets (Appendix 2) Guidance document for the evaluation of computer-assisted surgical devices applied to soft tissues	PFSB/ELD/OMDE Notification No. 0528-1	May 28, 2010	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Director of Office of Evaluation and Licensing of Medical Devices
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices (Appendix 1) Guidance document for the evaluation of articular cartilage regeneration (Appendix 2) Guidance document for the evaluation of neurofunctional modification devices - General (Appendix 3) Guidance document for the evaluation of custom-made	PFSB/ELD/OMDE Notification No. 1215-1	December 15, 2010	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Director of Office of Evaluation and Licensing of Medical Devices

implants for osteosynthesis materials for orthopedic surgery			
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices (Appendix 1) Guidance document for the evaluation of cell sheets for periodontal tissue treatment (Appendix 2) Guidance document for the evaluation of custom-made artificial hip joint prosthesis for orthopedic surgery (Appendix 3) Guidance document for the evaluation of computer diagnostic support devices	PFSB/ELD/ OMDE Notification No. 1207-1	December 7, 2011	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Director of Office of Evaluation and Licensing of Medical Devices
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices (Appendix 1) Guidance document for the evaluation of custom-made artificial knee joint prosthesis for orthopedic surgery (Appendix 2) Guidance document for the evaluation of Diagnostic Devices Based on RNA Profiling	PFSB/ELD/ OMDE Notification No. 1120-5	November 20, 2012	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Director of Office of Evaluation and Licensing of Medical Devices
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices (Appendix 1) Guidance document for the evaluation of retinal pigment epithelial cells derived from autologous iPS cells (Appendix 2) Guidance document for the evaluation of activity function recovery devices (Appendix 3) Guidance document for the clinical evaluation of medical devices for treatment of severe limb ischemia diseases	PFSB/ELD/ OMDE Notification No. 0529-1	May 29, 2013	Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division Director of Office of Evaluation and Licensing of Medical Devices
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices/Cellular and Tissue-based Products (Attachment 1) Retinal pigment epithelial cells derived from homologous iPS (-like) cells (Attachment 2) Spinal implant to maintain mobility and stability (Attachment 3) Orthopedic implants utilizing 3D lamination technology	PFSB/ELD/ OMDE Notification No. 0912-2	September 12, 2014	Minister's Secretariat, Ministry of Health, Labour and Welfare Counsellor (in charge of review control of medical devices and regenerative medical products)
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices/Cellular and Tissue-based Products (Attachment 1) Nasal cartilage regeneration (Attachment 2) Cardiac catheter ablation device (Attachment 3) Custom-made orthopedic implants, etc.	PFSB/ELD/ OMDE Notification No. 0925-1	September 25, 2015	Counsellor, Minister's Secretariat, Ministry of Health, Labour and Welfare (in charge of review control of medical devices and regenerative medical products)
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices/Cellular and Tissue-based Products (Attachment 1) Articular cartilage regeneration using human chondrocytes or somatic stem cell-processed products (Attachment 2) Articular cartilage regeneration using human (homologous) iPS (-like) cell-processed products (Attachment 3) Bioabsorbable vascular stent	PSEHB/MD ED Notification No. 0630-1	June 30, 2016	Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare Evaluation and Licensing Division of Medical Devices
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices/Cellular and Tissue-based Products (Attachment) Guidance Document for the Evaluation of human (autologous) epidermal (skin) regeneration	PSEHB/MD ED Notification No. 0320-1	March 20, 2018	Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices/Cellular and Tissue-based Products (Attachment) Guidance Document for the Evaluation of human (homologous) epidermal (skin) regeneration	PSEHB/MD ED Notification No. 0725-1	July 25, 2018	Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices (Attachment 1) Diagnostic device using microfluidic chip (Attachment 2) Medical devices with new functions utilizing biological materials (Attachment 3) Blood flow simulation software (Attachment 4) Medical image diagnosis support system using artificial intelligence technology (Attachment 5) Accelerator-based neutron irradiation equipment system for boron neutron capture therapy	PSEHB/MD ED Notification No. 0523-2	May 23, 2019	Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices (Attachment 1) Home medical devices (Attachment 2) Clinical evaluation of refractory wound therapy devices	PSEHB/EL D Notification No. 0925-2	September 25, 2020	Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices/Cellular and Tissue-based Products (Attachment) Treatment of subacute spinal cord injury (traumatic) using human (homologous) iPS (-like) cell-processed products	PSEHB/MD ED Notification No. 0226-1	February 26, 2021	Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices (Attachment) Medical support equipment with closed loop control system	PSEHB/MD ED Notification No. 0630-4	June 30, 2021	Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices/Cellular and Tissue-based Products (Attachment) Treatment of decompensated cirrhosis using human (homologous) bone marrow-derived mesenchymal stem cell processed product, human (homologous) adipose tissue-derived mesenchymal stem cell processed product, and human (homologous) peripheral blood CD34 positive cell processed product	PSEHB/MD ED Notification No. 0217-1	February 17, 2022	Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare
Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices (Attachment 1) Breast cancer diagnosis support device (Attachment 2) Guidance document for the evaluation of Software as a Mefical Device（SaMD） that involve behavior change (Attachment) Points to Consider for Post-marketing Change Procedures and Change Plan Confirmation Procedure System (IDATEN)	PSEHB/MD ED Notification No. 0609-1	June 9, 2022	Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare

Publication of the Guidance Document for the Evaluation of Emerging Technology Medical Devices (Attachment 1) Guidance document for the evaluation of implantable ventricular assist devices	PSEHB/MDED Notification No. 0331-5	March 31, 2023	Director of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare

独立行政法人 **医薬品医療機器総合機構**

Pharmaceuticals and Medical Devices Agency (PMDA)