CHAPTER 3

Drug Development

1. PROCESS FROM DEVELOPMENT TO APPROVAL

New drugs are defined as drugs with active ingredients, dosage, administration route, or indications, which are clearly different from those of drugs, which have already been approved for manufacture and marketing or those listed in the JP. Applications for approval to manufacture and market new drugs must be submitted to the Ministry of Health, Labour and Welfare with results of nonclinical and clinical studies required to show the quality, efficacy, and safety of a new drug attached to the approval application form (Article 14-3 of the Law).

1.1 Development of New Drugs

It is important to prepare data for the review process during the course of drug development. Results to show quality, efficacy, and safety of new drugs must be obtained in nonclinical and clinical studies. The nonclinical studies include physicochemical studies and animal studies on pharmacology, pharmacokinetics, and toxicity. The clinical studies usually consist of Phase I, II and III studies (or human pharmacology, therapeutic exploratory, therapeutic confirmatory, and therapeutic use categories). On starting each phase of clinical studies, it is necessary to adequately confirm the safety of the drug product from the results of nonclinical studies or of previous clinical studies.

The Drugs and Medical Devices Law specifies that the data submitted to obtain approvals must be obtained and compiled according to the standards specified in its Article 14, Paragraph 3. Related ordinances include the Ordinance on Standards for Conduct of Clinical Trials (GCP) (MHW Ordinance No. 28 dated March 27, 1997, partially revised by MHW Ordinance No. 127 dated October 20, 2000, MHLW Ordinance No. 106 dated June 12, 2003, MHLW Ordinance No. 172 dated December 21, 2004, MHLW Ordinance No. 72 dated March 31, 2006, MHLW Ordinance No. 24 dated February 29, 2008, MHLW Ordinance No. 163 dated November 28, 2008, MHLW Ordinance No. 68 dated March 31, 2009, and MHLW Ordinance No. 161 dated December 28, 2012; the Ordinance on Standards for Conduct of Nonclinical Studies on the Safety of Drugs (GLP) (MHW Ordinance No. 21, March 26, 1997, partially revised by MHW Ordinance No. 127 dated October 20, 2000 and MHLW Ordinance No. 114 dated June 13, 2008) and Standards for the Reliability of Application Data (Article 43 in the Enforcement Regulations) which were enforced from April 1, 1997. Therefore, the acceptance of the data is conditioned on adherence to the standards. It is important that studies to obtain data for approval reviews should be performed by standard methods whenever possible in order to assure proper evaluations of drugs. Reviews on compliance with these standards are performed by the Pharmaceuticals and Medical Devices Agency (PMDA, KIKO) at the request of the MHLW.

A flowchart from development to approval of new drugs is shown in **Fig. 8** (Flowchart of New Drug Development and Approval).

1.2 Procedures for Clinical Trials

For clinical studies (trials) to be conducted for collection of data to be submitted in marketing approval application of a new drug, etc., the Law and the GCP specified sponsor's responsibility for submitting a notification of the clinical trial plan in advance and matters that a sponsor must comply with in requesting a medical institution to conduct a clinical trial.

Scope of GCP includes not only clinical trials in patients but also Phase I studies in healthy volunteers, bioequivalence studies in human, studies for additional indication of an approved drug and post-marketing clinical trials after marketing. Furthermore, its partial amendment 2003 specifies investigator-initiated clinical trials as well.

According to the new GCP, when a clinical study is requested, a contract for clinical trials can be concluded only when 30 days have passed from the initial notification of the study protocol is received by the PMDA (KIKO) (at least 2 weeks for subsequent notifications, as a rule). The sponsor must report to the authorities any severe adverse reactions or infections that occur during the study, and the authorities may undertake on-site inspections concerning GCP compliance in the sponsor's facilities and the medical institution performing the study when problems arise during the study. For drugs required in emergencies to prevent diseases that have a major effect on the life or health of the patient or to prevent other damage to the health, clinical study protocols may be submitted within 30 days after the start of the study (MHLW Ordinance No. 89 dated May 15, 2003).

At the time of the clinical trial protocol notification, a system by which the PMDA reviews the contents of the initial notification at the request of the MHLW is now specified by law, and a "clinical trial consultation system" in which the PMDA gives guidance and advice concerning study protocols has also been established (refer to Section 1.4: Interview Advice Meetings).

It is necessary to submit clinical trial (protocol) notifications in the following instances:

(1) Drugs with new active ingredients

(2) Drugs with new administration routes (excluding bioequivalence studies)

(3) New combination drugs, drugs with new indications or new dosage and administration (excluding bioequivalence studies)

(4) Drugs containing the same active ingredients with the drugs with new active ingredients, for which the reexamination period has not been completed yet (excluding bioequivalence studies)

(5) Drugs considered to be biological products [excluding (1) to (4)] (excluding bioequivalence studies)

(6) Drugs manufactured using gene recombinant technology [excluding (1) to (5)] (excluding bioequivalence studies)

The types of clinical trial protocol notifications and documents to be submitted are shown below.

(1) Clinical trial protocol notifications (when notifications are first made for drugs with new active ingredients or

new routes of administration and new combination drugs, they must be submitted at least 31 days before the planned start date of the trial stated in the contract with the medical institution performing the clinical study. Otherwise, they must be submitted at least 2 weeks before the planned date of the trial.)

a. Document that gives the reason why the request for the clinical study was judged to be scientifically appropriate (from the 2nd notification, it should include a description of the results of new clinical studies since the previous notification and a summary of information)

b. Clinical study protocol

c. Explanatory materials and consent form used for obtaining informed consent

d. Sample of the case report form (CRF) (The sample is not required if information to be contained in the CRF is explicitly stated in protocol.)

e. Latest investigator's brochure

(2) Notification of changes in clinical study protocols (submitted as a rule for each clinical trial protocol notification before changes in notification items)

Data related to the changes as required:

(3) Clinical study discontinuation notification (This notification must be submitted for each clinical trial protocol notification without delay when a clinical study is discontinued.)

Data related to the reason for discontinuation as required (including information on study subjects collected until discontinuation):

(4) Clinical study completion notification (This notification must be submitted for each clinical trial protocol notification without delay when a notification of completion of the clinical study is received from all medical institutions and recovery of the investigational product is completed.)

(5) Development discontinuation notification (to be submitted, when development for the drug is discontinued as a whole in Japan.)

From April 1, 2011, attachments to the clinical trial notification (including protocol revision notification, clinical trial completion notification, clinical trial discontinuation notification and development discontinuation notification) are required to be submitted in electronic format as well as in paper format (Notification No. 1227-(1) of PFSB dated December 27, 2010).

In view of a recent increase of international multi-center clinical trials, the sponsor of a clinical trial is required to include information concerning international clinical trials in the clinical trial notification submitted on or after April 1, 2008 (Notification No. 0321001 of the Evaluation and Licensing Division, PFSB dated March 21, 2008). Additionally, in view of a trend of development of drugs with associated companion diagnostics relating to the individualized medicine, a sponsor is required to include whether a companion diagnostics is being developed for the drug with its development status, if any, in the remarks in a clinical trial notification of a drug to be submitted since February 1, 2014 (Notification No. 0701-(10) of the Evaluation and Licensing Division, PFSB dated July 1, 2013).

1.3 Safety information on Adverse Reactions and Infections during the Study

Safety information obtained during the study must be reported promptly, as is specified in the ICH guidelines (ICH E2A) on Clinical Safety Data Management (Notification No. 227 of the Evaluation and Licensing Division, PAB dated March 20, 1995).

In the revision of the Enforcement Regulations of the Law in April 1997 for which the ICH guidelines served as a reference, the obligation to report adverse reactions, etc. related to the investigational product, including those occurring in foreign countries, to the Minister was specified by law. These provisions are outlined below.

A: 7-Day reports (When either of the following events is suspected to be caused by an adverse reaction of the investigational product concerned or by an infection suspected of being caused by the investigational product concerned, and the event is not expected from the description in the investigator's brochure of the investigational product concerned: the report must be made within 7 days.)

a) Death

b) Cases that might result in death

B: 15-Day reports (For the following events: the report must be made within 15 days.)

a) Any of the following events suspected to be caused by an adverse reaction of the investigational product concerned or by an infection suspected of being caused by the investigational product concerned, which is not expected from the description in the investigator's brochure of the investigational product concerned.

- Any case that requires hospitalization for treatment or prolongs the duration of hospitalization.
- Disability
- Cases that might result in disability
- Other medically serious condition
- Congenital diseases or abnormalities in the next generation

b) Predicted deaths or events that might result in death.

c) Measures related to safety problems of the investigational product concerned, including discontinuation of manufacture and/or marketing in a foreign country.

d) Research reports showing the possibility of causing cancer or other serious diseases due to adverse reactions, etc. of the investigational product concerned.

The Enforcement Regulation of the Law, which was modified in February 2008 require the sponsor to report to the MHLW cases of serious ADRs, etc. expected according to the IB periodically at 6-month intervals. Later, this reporting period was changed to 1-year intervals by further revising the Enforcement Regulations (Ministerial Ordinance No. 161 entitled "Ordinance for Partially Modifying the Pharmaceutical Affairs Law Enforcement Regulations, etc." dated December 28, 2012) to harmonize the period with relevant ICH guidelines.

Basic standards for periodically reporting safety information during the development phase, common to all drugs, etc., are available in "Development Safety Update Report (DSUR)" (Notification No. 1228-(1) of the Evaluation and Licensing Division, PFSB dated December 28, 2012: ICH E2F)

1.4 Interview advice meetings

The PMDA has established a consultation system for clinical study protocols to improve and reinforce the quality of clinical studies. The consultations and review work have been united under the same teams in the Review Department. With the increasing demand for clinical trial consultations, improvements have been made in the quality of consultations with respect to preparation for consultations, implementation of consultations, preparation of records, etc. as measures to meet the demands for those requesting consultations (Notification No. 0302070 of the PMDA dated March 2, 2012, partially revised on June 30, 2014 and November 21, 2014). Main items of the interview advice meeting (clinical trial consultations and simple consultations) handled by the PMDA are as described below. Details of the consultation items, the latest information on consultation fees, and application procedures for interview advice meeting are available at the following websites of the PMDA. Preparatory consultation is also available to assure smooth interview advice.

-Consultation items and fees:

-Application procedures:

(1) Clinical trial consultation

- Consultations on procedures
- Consultations on bioequivalence studies
- Consultations on safety
- Consultations on quality
- Consultations before start of Phase I studies
- Consultations before start of early Phase II studies
- Consultations before start of late Phase II studies
- Consultations after completion of Phase II studies
- Consultations before license application
- Consultations on post-marketing clinical studies plans of drugs
- Consultation at completion of post-marketing clinical studies of drugs
- Additional consultations on drugs

(2) Consultations on preliminary assessment of new drugs

Assessment of data in preparation for license application (preliminary assessment of data concerning the following areas planned to be submitted for application in order to identify potential issues to be addressed during review):

- Quality
- Nonclinical: Toxicology
- Nonclinical: Pharmacology
- Nonclinical: Pharmacokinetics
- Phase I studies
- Phase II studies
- Phase II/III studies

(3) Consultations on eligibility of drugs for priority review

Evaluation of new drugs to determine the eligibility of drugs, other than orphan drugs, for priority review when an applicant desires a new drug to be designated as a product for priority review. Procedures for handling priority review are available in Notification No. 0901-(1) of the PMDA dated September 1, 2011. The consultation fee is different between the case of only priority assessment consultation and that in conjunction with the consultation before license application.

- Consultations on the applicability of priority review status
- Consultations on the applicability of priority review status

(consultation in conjunction with that before license application)

(4) Consultations on the applicability as pharmacogenomics markers or biomarkers

- Assessment of applicability
- Assessment of major aspects of clinical trial design
- Additional consultation (on the applicability)
- Additional consultation (on major aspects of clinical trial design)

(5) Consultations on generic drugs

- Consultations on bioequivalence of generic drugs
- Consultations on quality of generic drugs

(6) Consultations on generic drugs before start of clinical studies or license application

- Switch OTC drugs
- Major aspects of clinical trial design
- Rationale for clinical development as a new generic drug

(7) Consultations on GCP/GLP/GPSP of a drug

(8) Simple consultations

Brief consultations with reviewers in charge of the approval review of generic prescription drugs, non-prescription drugs, etc. as well as the registration of drug master files

- Generic drugs
- Non-prescription drugs
- Insecticides and rodenticides
- Quasi drugs
- Revision of text in labeling of new drugs
- GCP/GLP/GPSP inspection of a drug
- GMP/QMS inspection
- GCTP inspection

(9) Post-interview consultations

These are additional consultations for matters for which both of PMDA and the consulter agreed to be addressed later in an interview advice meeting.

Matters such as data evaluation should not be addressed in a post-interview consultation, because those should have been addressed already in the previous interview advice meeting. A post-interview consultation may be recorded at an extra charge, if required by the consulter.

(10) Preparatory consultation or meeting

Preparatory consultations or meetings prior to formal consultation to sort out consultation items and assure smooth interview advice. In the preparatory consultation, data are not evaluated and official meeting records are not issued.

(11) Evaluation of drugs for the designation of priority interview advice

Drugs are evaluated to determine if they should be reviewed and discussed at prioritized interview advice meetings.

(12) Consultations on compliance with reliability standards

Based on data planned to be submitted together with the application form, guidance and advice are provided to the applicant concerning GCP and GLP compliance of drugs that have undergone "the evaluation of drug products for the designation of priority interview advice" and of new drugs that have undergone "a preparatory consultation or meeting".

(13) Consultations on regulatory strategies

Consultations to discuss plans for necessary clinical trial or development mainly with universities, research institutes, and venture companies who have found seeds throughout the R&D period from the final stage of lead compound or candidate medical device selection mainly until the early phase of clinical development [Phase IIa]). In addition, guidance and advice for quality and safety may be provided from an early development phase in a regulatory strategy consultation for regenerative medicine products or preventive products to be used for expressing transgenes in the human body (other than regenerative medicine products; e.g., recombinant live vaccine). The verification application system for products for gene therapy has been abolished.

1.5 Approval review

A detailed team review is performed by the review staff in the PMDA in parallel with the confirmation of reliability of submitted data in the compliance review by the PMDA (Refer to Section 4.2: Marketing Approval Reviews of Chapter 2). For the main points concerning reviews, refer to "Points to Consider for Approval Application Data for New Drugs" (Notification No. 0331009 of the Evaluation and Licensing Division, PFSB dated March 31, 2005, partially revised by Office Communication dated April 22, 2005 and by Notification No. 1020002 of the Evaluation and Licensing Division, PFSB on non-prescription drugs dated October 20, 2008, and partially revised by Notification No. 0304015 of the Evaluation and Licensing Division, PFSB dated March 4, 2009). For the purposes of standardizing the criteria/procedures of review, identifying the basic attitude of reviewers toward review, and clarifying main points of review, the document entitled "Points to Be Considered by the Review Staff Involved in the Evaluation Process of New Drug" has been issued and accessible at the following PMDA websites:

http://www.pmda.go.jp/topics/file/ h200417kohyo.pdf/ (Japanese)
http://www.pmda.go.jp/english/service/pdf/points.pdf/ (English). The application is then discussed by the Committees and Department on Drugs of the PAFSC on the basis on the most recent and advanced scientific knowledge and the final decision concerning approval is made by the Minister of Health, Labour and Welfare (refer to Section 4.2: Approval Reviews, Chapter 2).

The current fee for approval of medicines, etc. is available at the following PMDA website:

http://www.pmda.go.jp/operations/shonin/info/fee/file/35_tesuryoiyaku.pdf

The PMDA review period for new drugs is expected to be shortened through the efforts of both the regulatory authorities and the applicants, and the points to consider in the application from the standpoint of shortening the period on the applicant side are specified in the Office Communication entitled "Points to consider in shortening of the PMDA review period for new drugs" dated June 9, 2010. The main points are as follows.

- **Handling of data from long-term clinical studies**

  Data obtained on completion of administration to all patients for at least 6 months should be appended as application data. The final report (including data on completion of administration to all patients for at least one year) and the revised draft of the CTD should be submitted at the earliest possible time as additional data. At the latest, it should be submitted by 6 months before the end of the targeted total PMDA review period.

- **Handling of data from long-term stability studies**

  Additional data should be submitted as a final report (including data required for setting the planned expiration period) at the latest by 6 months before the end of the total targeted PMDA review period. Additional data obtained thereafter should be submitted by the time of data submission to the Committee of Experts.

- **Points to consider when using a drug master file (MF)**
- **Points to consider for adequate contact with the person registering the MF, verification of the MF registration conditions, and submission of information of registered MF corresponding to Module No. 2 of the CTD without delay after filing an approval application for the product.**
- **Application for GMP compliance inspection**

  Application for inspections of the facilities concerned and preparation for receiving inspectors at sites when the applicant judges based on contract, etc. from the department in charge of the inspection that the inspections are likely to take place.

A standard CTD format was shown by PFSB to illustrate points to be considered in the preparation of a CTD with the aim to shorten the review time for the applicant ("CTD Format for Reducing Total Review Time for New Drugs,"

Office Communication dated January 17, 2011).

An anticipated timeline for completing the application review under the standard process is shown in the notice "Timeline for Completing the New Drug Application Review under the Standard Process (Office Communication dated March 30, 2012) (Fig. 9. Timeline of the standard process of new drug approval)."

1.6 Compliance review

Following revision of the Pharmaceutical Affairs Law in June 1996, the PMDA started reviews of compliance with quality standards, GLP, and GCP by verification and comparisons with raw data to determine if the attached data used in approval reviews of new drugs has been compiled correctly based on study results. Compliance reviews are applied after approval applications are filed. They consist of both paper reviews and on-site reviews. Paper review had been conducted as directed in the "Application Procedures for Paper Review of the Conformity of New Drug Application with Relevant Regulations" (Notification No. 0528027 of the PMDA dated May 28, 2010) and on-site inspection as directed in the "Application Procedures for On-site GCP Inspection for Drug Application" (Notification No. 0528028 of the PMDA dated May 28, 2010). These notifications were integrated into the "Application Procedures for Paper Review-Conformity Inspection and On-site GCP Inspection for Drug Application" (Notification No. 1012063 of the PMDA dated October 12, 2012) and paper review and on-site inspection have been regulated to be conducted simultaneously, as a rule.

- Paper reviews

Paper reviews are performed based on "the Guidelines for Paper Compliance Review for New Drug Approval Application Data" (Notification No. 0131010 dated January 31, 2006 and partial revision No. 0331009 dated March 31, 2009 of the Evaluation and Licensing Division, PFSB) when the applicant provides the PMDA with data as evidence for approval reviews. The review is basically performed by reviewing approval application data brought into the PMDA ("document-based inspection"); however, the Agency's personnel may visit sites (including those outside Japan) where application data as well as source data are archived, as needed, to inspect such data ("on-site inspection"). The PMDA issued "Checklists for On-site and Document-Based GCP Compliance Review of New Drug Application (for Sponsor's Use)" in November 2012 and Checklists for Compliance Review of New Drug Application (Quality/Non-clinical) in March 2014. The checklists are publicly available for self-compliance review by the applicant.

When case report forms are prepared by using Electronic Data Capture (EDC) system, EDC management sheets are required to be prepared and submitted in advance of application as directed in "Compliance Inspection Procedures for Clinical Trials, Post Marketing Clinical Trials, and Use Results Survey by Using EDC System" (Office Director's Notification No. 0327001 of PMDA dated March 27, 2013).

- On-site reviews

In these reviews, the PMDA review staff examines the data at the sites where it was collected or compiled. The guidelines for on-site GCP compliance reviews are available as the "Inspection Procedures for the On-site Verification of GCP Compliance for Drug Application" (Notification No. 0131006 of the Evaluation and Licensing Division, PFSB dated January 31, 2006; Partially revised by Notification No. 0325001 of the Evaluation and Licensing Division, PFSB dated March 25, 2009) and "Partial Modification of 'the Guidelines for Paper Compliance Review for New Drug Approval Application Data', etc." (Notification No. 0331009 of the Evaluation and Licensing Division, PFSB dated March 31, 2009).

The reviews are generally performed in the applicant's offices and facilities and medical institutions performing the clinical study (four facilities as a rule for new drugs; two facilities for additional indications or orphan drugs). In selection of review facilities, consideration should be given to the number of subjects in clinical trials and dates of GCP reviews performed in the past. The PMDA also provides a checklists, "Checklists for GCP Compliance On-site Review of New Drug Application (for Medical Institution's Use)" and "EDC Checklists" (for Medical Institution's Use), as references for self-inspections before on-site inspections of medical institutions.

Checklists and management sheets for paper reviews and on-site reviews are available at the following PMDA website.

http://www.pmda.go.jp/operations/shonin/outline/shinrai/checklist.html

1.7 GMP compliance inspection

Formal approvals are required for individual formulations of drugs in order to market the drugs in Japan. Formal approval must be obtained prior to market launch from the Minister of the MHLW or prefectural governor by submitting data and documents for required review on product quality, efficacy, and safety.

Marketing approvals require a review to determine whether or not the product in the application is suitable as a drug to be marketed by a person who has obtained a marketing business license (marketing authorization holder) for the type of drug concerned and confirmation that the product has been manufactured in a plant compliant with GMP. Thus, GMP compliance is a requirement for manufacturing and marketing approval of drugs, etc. (Article 14-2, Paragraph 4 of the Pharmaceutical Affairs Law).

When a manufacturing plant does not conform to GMP standards, the MHLW minister or prefectural governor may not grant a license.

1.7.1 GMP Compliance Reviews

When an application is submitted for a new drug manufacturing and marketing approval, the plant must be inspected by the authorities to determine if it actually complies with the GMP standards.

("Establishment/abolishment of the Ministerial Ordinances and Notices on Good Manufacturing Practice and Quality Management System (GMP/QMS) of drugs and medical devices, etc. in association with enforcement of the Law for partial amendment of the Pharmaceutical Affairs Law and the Blood Collection and Donation Service Control Law" Notification No. 0330001 of the Compliance and Narcotics Division, PFSB dated March 30, 2005.)

First, a review is conducted for each product using the following criteria for GMP compliance as to each article in the control regulations and building and facility regulations.

Evaluation rank criteria

A (Compliance): Manufacturing is performed properly.
B (Slightly defective): There is little effect on drug quality but improvement necessary for complete compliance with control regulations.
C (Moderately defective): Effect on drug quality cannot be ruled out and improvement necessary for compliance with control regulations.
D (Seriously defective): Clear violation of control regulations

Next, a review is undertaken for each product using the following criteria on the basis of the results of the review of GMP compliance for each article in the control regulations and building and facility regulations:

- Compliance: Cases of A only.
- General compliance: Cases of A and B or B only.
- Improvement required: Cases of C evaluated for half or less of all items and no D.
- Non-compliance: Cases not corresponding to any of the above.

When GMP compliance by product is determined as "General compliance" or "Improvement required," an order for improvement(s) for the item(s) rated as B is issued in writing.

In such cases, the applicant must submit a concrete plan of improvements. When improvements are completed, a report on the improvement must be submitted. When the improvements have been confirmed, the rating of the corresponding item is changed to "Compliance."

The results of reviews or assessments at each of the above stages are compiled, and a report of the GMP compliance review is prepared for the plant in the application concerned. When the initial GMP compliance review results of a product correspond to "General compliance" or "Improvement required," the subsequent course is entered in the GMP compliance review report.

1.7.2 Global Harmonization of GMP

Japan has concluded mutual agreements for GMP (MOU) approvals with countries with equivalent levels of GMP. These agreements are meant to assure the quality of drugs imported into Japan through mutual acceptance of GMP inspection results and exchange of information on drugs marketed in the two countries. These mutual agreements have been concluded with Germany, Sweden, Switzerland and Australia. Mutual recognition of drug GMP (MRA) with the EU countries has been expanded to include the 15 EU countries (Belgium, Denmark, Germany, Greece, Spain, France, Ireland, Italy, Luxembourg, Netherlands, Austria, Portugal, Finland, Sweden and the United Kingdom) as well as 10 new EU countries (Poland, Hungary, Czech Republic, Slovenia, Slovakia, Estonia, Latvia, Lithuania, Cyprus and Malta) for 25 countries in total since May 29, 2003 (Notification No. 0528001 of the Compliance and Narcotics Division, PFSB dated May 28, 2004, partially revised by Notification No. 0825-(12) of the Compliance and Narcotics Division, PFSB, Notification No. 0528004 of PFSB, and Notification No. 0428001 of PFSB dated April 28, 2004).

Positive utilization of the internationally recognized GMP rules contained in Pharmaceutical Inspection Cooperation Scheme (PIC/S) is recommended by the Office Communication dated February 1, 2012 (partially revised by the Office Communication dated March 28, 2013) to secure closer international standardization and conformity in GMP inspections. MHLW, PMDA, and prefectural governments bid membership to the office of PIC/S in March 2012 and became a member on July 1, 2014.

The enforcement notification of the GMP (Notification No. 0330001 of the Compliance and Narcotics Division, PFSB dated March 30, 2005) was amended in August 2013 in order to align with the GMP guideline in PIC/S (Notification No. 0830-(1) of the Compliance and Narcotics Division, PFSB dated August 30, 2013).

1.7.3 Regulations for Imported Drug Management and Quality Control

Since it is very important to assure the quality of imported drugs in the same way as drugs manufactured in Japan, items related to manufacturing control and quality control, when importers and marketing authorization holders import drugs, were specified in the Import Control and Quality Control of Drugs and Quasi-drugs (MHW Ordinance No.62, June 2, 1999), but since the import business license has been including in the manufacturing/marketing business license, this was abolished on March 31, 2005. Instead, from April 1, 2005, import certificate needs to be submitted for custom clearance prior to the import of products when the manufacturer/marketing authorization holder or manufacturer import drugs for business.

These regulations included matters to be agreed upon with the manufacturer in foreign country by the importer in accordance with the agreement. The importer must confirm that the drug to be imported is manufactured under appropriate manufacturing control and quality control, and must import, store, and conduct testing in accordance with standards, etc.

When a mutual agreement for GMP approvals has been concluded between the exporting country and Japan, part of the quality control work may be omitted if the following two conditions are met: that it is confirmed by the government organization in the exporting country that the plant where the imported drug was manufactured complies with the GMP in the country; and that the records of tests performed by the manufacturer of the drug are provided to the importer in Japan.

2. DATA REQUIRED FOR APPROVAL APPLICATIONS

- The data to be attached to approval applications for drugs is specified in the basic notification entitled "Approval Applications for Drugs" (Notification No. 481 of PMSB dated April 8, 1999 and partial revisions: Notification No. 663 of the PMSB dated June 21, 2001, No. 899 of the Evaluation and Licensing Division, PMSB dated June 21, 2001, No. 0701004 of the Evaluation and Licensing Division, PFSB dated July 1, 2003, No. 0525003 of the Evaluation and Licensing Division, PFSB dated May 25, 2004, and Office Communication dated May 24, 2004). Detailed handling procedures are specified in "Points to Consider in Drug Approval Applications" (Notification No. 666 of the Evaluation and Licensing Division, PMSB dated April 8, 1999). In addition, in association with enforcement of the revised Pharmaceutical Affairs Law in April 2005, revised handling procedures of documents to be attached to manufacturing/marketing approval application for drugs were specified in "Approval Applications for Drugs" (Notification No. 0331015 of PFSB dated March 31, 2005; Notification No. 1020001 of PFSB dated October 20, 2008 for partial amendment on non-prescription drugs; Notification No. 0304004 of PFSB for partial amendment on biosimilar products; Notification No. 0701-(10) of the Evaluation and Licensing Division, PFSB dated July 1, 2013 for partial amendment on companion diagnostics and associated drugs; and Notification No. 0612-(1) of the Evaluation and Licensing Division, PFSB dated June 12, 2014 for partial amendment on guidance-mandatory drugs) with abolishment of Notification No. 481 of PFSB, as well as the handling procedures were detailed in "Points to Consider in Approval Application of Drugs" (Notification No. 0331009 of the Evaluation and Licensing Division, PFSB dated March 31, 2005 ; Office Communication dated April 22, 2005 for its partial amendment; Notification No. 1020002 of the Evaluation and Licensing Division, PFSB dated October 20, 2008 for partial amendment on non-prescription drugs; Office Communication dated October 30, 2008; Notification No. 0304015 of the Evaluation and Licensing Division, PFSB dated March 4, 2009 for partial amendment on biosimilar products ; Notification No.0701-(10) of the Evaluation and Licensing Division, PFSB dated July 1, 2013 for partial amendment for companion diagnostics and associated drugs; and Notification No. 0612-(1) of the Evaluation and Licensing Division, PFSB dated June 12, 2014 for partial amendment on guidance-mandatory drugs).

Later, with the enactment of the Pharmaceutical and Medical Device Law, "Approval Application for Drugs" (Notification No. 1121-(2) of the PFSB) and "Points to Consider in Approval Application of Drugs" (Notification No. 1121-(12) of the Evaluation and Licensing Division, PSFB) were issued. The new notifications were based on the information contained in the old notifications, with some changes such as the addition of information in attached data, etc. as data to be attached to approval applications.

Subsequently, an agreement was reached on the Common Technical Document (CTD) by the ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) and a notification entitled "Handling Data Attached to Drug Approval Applications" (Notification No. 663 of the PMSB dated June 21, 2001), which is a partial revision of the previous notification mentioned above. On the same day, another notification entitled "the Guidelines for Preparation of Data Attached to Applications for Approval to Manufacture or Import New Drugs" (Notification No. 899 of the Evaluation and Licensing Division, PMSB, dated June 21, 2001, partially revised by Notification No. 0701004 of the Evaluation and Licensing Division, PFSB, dated July 1, 2003, Notification No. 0525003 of the Evaluation and Licensing Division, PFSB dated May 25, 2004, Office Communication dated May 24, 2004, and Notification No. 0707-(3) of the Evaluation and Licensing Division, PFSB dated July 7, 2009) was issued to specify guidelines for preparation of data to be attached to approval applications based on the CTD. The data required for approval applications using CTD format is shown below. The data in Modules 2 to 5 are prepared on the basis of the CTD guidelines shown in Attachments 1 and 3 to 5 of these guidelines.

For electronic specifications of the CTD (CTD), "Electronic Specifications of the Common Technical Document" (Notification No. 0604001 of the PFSB dated June 4, 2003, partially revised by Notifications Nos. 0527001 and 0527004 of the Evaluation and Licensing Division, PFSB dated May 27, 2004, and Nos. 0825001, and 0707-(3) dated August 25, 2008, and July 7, 2009, respectively). These specifications were enforced from October 1, 2008. Handling of submissions of electronic data and Q&A are shown in the Handling of Electronic Specifications for Common Technical Documents (Notification No. 0527004 of the Evaluation and Licensing Division, PFSB dated May 27, 2004, partially revised by Notification No. 0707-(3) of the Evaluation and Licensing Division, PFSB dated July 7, 2009), Office Communications dated March 31, 2005, April 27, 2005, October 5, 2006, December 22, 2006, July 7, 2009, February 26, 2010, and January 21, 2013. In Japan, submission of eCTD is not obligatory but it is recommended. It is no longer necessary to submit paper data for approval applications if a CTD is submitted as the original.

It was also decided that, with the start of submission of electronic clinical study data from FY2016, as explained later, data attached to approval applications will, as a general rule, be in eCTD format.

As the PMDA was required to progress further in the "Japan Revitalization Strategy" (Cabinet Decision dated June 14, 2013) and to utilize clinical data for review by itself in the "Health and Medicine Strategy" (Related Ministers' Consensus dated June 14, 2013), the notification entitled "Basic concept of electronic data submission in approval application" (Notification No. 0620-(6) of the Evaluation and Licensing Division, PFSB dated June 20, 2014) was issued with its Q&A (Office Communication dated June 20, 2014). The notification specifies that an applicant should submit the following documents in a form of electronic data in each individual subject among those to be submitted for evaluation in approval application as for prescription drugs in the application categories of (1) through (7), (9) and (9-2). Receipt of electronic data is scheduled to be started since fiscal 2016. Applicable clinical trial data should be submitted in the formats according to the specifications in Clinical Data Interchange Standards Consortium.

A. Outcome data from all Phase II and Phase III studies (including long-term treatment studies) that may commonly be handled as pivotal evidences for efficacy, safety and dosage/administration.

B. Outcome data from the following studies among other Phase I studies and clinical pharmacology studies;
   - Phase I studies for an anticancer drug
   - Phase I studies in both Japanese and non-Japanese (such as multinational clinical studies and bridging studies)
   - QT/QTc studies according to the ICH E14 guideline

1) Module 1: Administrative information such as application forms and prescribing information

(1) Application documentation table of contents (including Module 1)
(2) Approval application (copy)
(3) Certificates (Declarations of those responsible for collection and compilation of data for approval applications, GLP and GCP related data, contracts for codevelopment [copies], and declarations required to be attached in accordance with Notification No. 0527004 of the Evaluation and Licensing Division, PFSB dated May 27, 2004 entitled "Handling of Computer Formatting of the Common Technical Document").
(4) Patent status
(5) Background of origin, discovery, and development
(6) Data related to conditions of use in foreign countries, etc.
(7) List of related products
(8) Package insert (draft)
(9) Documents concerning non-proprietary name
(10) Data for review of designation as poisons, deleterious substances, etc.
(11) Draft of basic protocol for post-marketing surveillance risk management plan (RMP) (draft):
As directed by the Guidelines on Risk Management Plan issued by the PFSB (Notification Nos. 0426-(2) of the Evaluation and Licensing Division and 0426-(1) of the Safety Division of the PFSB both dated April 26, 2012), the applicant is required to attach the RMP (draft), in place of the plan of post-marketing surveillance (draft), to the new drug application submitted on or after April 1, 2013.
(12) List of attached documentation
(13) Other
<1> Data related to approved drugs
<2> Clinical trial consultation records (copies)
<3> Inquiries (copies) and responses to inquiries (copies)
<4> Other data [data submitted to the PMDA (copies), data submitted to the MHLW (copies)]
Laboratory target and set values to be entered in the manufacturing method column of the application form for drugs other than biological products should be tabulated and the list be attached to the application document as directed in "CTD Format for Reducing Total Review Time for New Drugs" (Office Communication of the Evaluation and Licensing Division, PFSB dated January 17, 2011).
Review data on new additives, if any, should be included in the application dossier (copies) as directed in the "Submission of Review Data on New Additives" (Notice of the PMDA dated September 21, 2010).
<5> Points to consider in formatting the eCTD

2) Module 2: Data summaries or CTD "Gaiyo"

(1) Modules 2 to 5 (CTD) table of contents
(2) CTD introduction
(3) Quality overall summary
(4) Nonclinical overview
(5) Clinical overview
(6) Nonclinical summary (text and tables)
<1> Pharmacology
<2> Pharmacokinetics
<3> Toxicity
(7) Clinical summary
<1> Summary of biopharmaceutics and associated analytical methods
<2> Human pharmacology studies
<3> Summary of clinical efficacy
<4> Summary of clinical safety
<5> Literature references
<6> Synopses of individual studies

3) Module 3: Quality

(1) Module 3 table of contents
(2) Data or reports
(3) Literature references

4) Module 4: Nonclinical study reports

(1) Module 4 table of contents
(2) Study reports
(3) Literature references

5) Module 5: Clinical study reports

(1) Module 5 table of contents
(2) Tabular listing of all clinical studies
(3) Clinical study reports
(4) Literature references

(**Fig. 10**. Organization of ICH Common Technical Documents)

2.1 Data to be Attached to Approval Application of Drugs

2.1.1 Prescription drugs

in Attached Tables 1 and 2-(1) of the basic notification of application, "Approval Applications for Drugs"(Notification No. 1121-(2) of the PFSB dated November 21, 2014).

(**Table 3** Data to be Submitted with an Application for Approval to Manufacture/Market: A New Prescription Drug). Data corresponding to (1) to (8), (9), (10-2), and (10-4) in

the application dossier are required to be prepared and submitted by the CTD format.

2.1.2 Non-prescription drugs

The Law for Partial Amendment of the Pharmaceutical Affairs Law and the Pharmacists Law (Law No. 103, 2013) was enacted on June 12, 2014, and a category of guidance-mandatory drugs was newly established in addition to the conventional categories of prescription drugs and non-prescription drugs. The range of data to be submitted with applications for non-prescription drugs is specified as shown in **Table 4** (Data to be Submitted with an Application for a Non-prescription Drug) (Notification No. 1121-(2) of the PFSB dated November 21, 2014). After complete enforcement of the CTD (from July 1, 2003), the present guidelines for preparation of data to be attached to approval applications can be applied to approval applications for non-prescription drugs as in the past. For the time being, data on the manufacturing method and specifications and test methods for non-prescription drugs with new active ingredients are prepared using the CTD only for reference purpose.

3. GUIDELINES CONCERNING DRUG APPROVAL APPLICATIONS

Guidelines outlining standard test methods and essential criteria for reference in the preparation of data for drug manufacturing and marketing approval applications have been published in order to assure efficient and appropriate research and development. These guidelines have been prepared on the basis of results of studies undertaken by groups of experts in the field concerned.

In recent years, various standards and guidelines have been established and implemented according to ICH harmonization and the reliability and amount of research data has been internationally harmonized. To meet demands for more efficient and less costly development of new drugs, international utilization of data is on the increase.

Japan has taken various measures in keeping with this change in the international environment, and data from nonclinical studies such as physicochemical studies, stability studies and animal studies performed in foreign countries are accepted, in principle, if their study designs comply with the Japanese guidelines.

Two notifications were issued in relation to the acceptance of foreign clinical data: "Handling of Data on Clinical trials on Drugs Performed in Foreign Countries" (Notification No. 739 of the PMSB dated August 11, 1998) and "Ethnic Factors to be Considered in the Acceptance of Foreign Clinical Trial Data" (Notification No. 672 of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau dated August 11, 1998 and partial revision by Office Communication dated January 4, 1999) and its Q and A (Office Communications dated February 25, 2004 and October 5, 2006). According to these notifications, when data from clinical studies performed in foreign countries are used for new drug application in Japan, the data is first checked to assure that it complies with legal requirements in Japan. Whether or not the drug is apt to be affected by ethnic factors (intrinsic or extrinsic factors) is then evaluated. When necessary, a bridging study is performed, and when it is concluded that the clinical study outcome in a foreign population can be extrapolated to the Japanese population, the foreign data can be accepted. Since the possibility of acceptance is actually left up to the authorities concerned, it is recommended that the requirements for bridging studies be confirmed as acceptable for the regulatory agencies through consultations with PMDA.

With the intent to promote global clinical trials to achieve more efficient and rapid development of new drugs and to eliminate drug lag in which the approval timing of new drugs is several years behind that in other countries, basic concepts related to global clinical trials have been compiled (Notification No. 0928010 of the Evaluation and Licensing Division, PFSB dated September 28, 2007). In addition, the notice "Basic Principles on Global Clinical Trials (Reference Cases)" (Office Communication dated September 5, 2012) was issued based on achievements of mutual cooperation and latest knowledge obtained relating to multinational clinical trials among Japanese, Chinese, and South Korean regulatory authorities with an objective of a smooth and appropriate conduct of global clinical trials, especially in East Asia.

In addition, "Basic Approach to Conduct of Phase I Clinical Trial in Japanese Before Start of Global Clinical Trial" (Office Communication of the Evaluation and Licensing Division of the PFSB, MHWL dated October 27, 2014) indicates points to consider when examining whether or not a phase I clinical trial is necessary in the case where Japan takes part in a global clinical trial.

Marketed drugs that have been used for unapproved indications or dosage and administration in clinical practice (off-label use) should be used appropriately by receiving marketing approval based on the Law. But in the cases the indications and dosage and administration related to off-label use are confirmed by medical and pharmaceutical knowledge in the public domain, a judgment is made of whether or not the use can be approved without performing whole or part of the clinical trials again (Notifications No. 4 of the Research and Development Division, Health Policy Bureau and No. 104 of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau dated February 1, 1999). After this notification was issued, applications based on public knowledge have been filed and approved.

(1) Cases where an official approval of indication(s) unapproved in Japan has already been granted overseas (countries with approval systems confirmed to be on the same level as the system in Japan or with corresponding systems; the same hereinafter), sufficient experience of use in medical practice is available, and data appended to the application for the regulatory authorities can be obtained.

(2) Cases where an official approval indication(s) unapproved in Japan has already been granted overseas, sufficient experience of use in medical practice is available, scientific evidence has been published in internationally reputable scientific journals, or review articles, etc. of international organizations can be obtained.

(3) Cases where there are clinical study results that can be

confirmed in terms of ethics, science, and reliability by such means as contract research performed as part of public research projects.

The data attached to applications for approval to manufacture and market drugs must be in Japanese, but as part of the deregulation process, it was specified in Notifications No. 256 of the PMSB and No. 265 of the Evaluation and Licensing Division, PMSB, both dated March 18, 1998, that documents in English in Modules 3, 4, and 5 need not be completely translated into Japanese as long as a Japanese summary is attached. In approval applications using the CTD format, a Japanese summary is not required for entries in the original in English.

3.1 Nonclinical Studies

1) Guidelines on physicochemical properties, specifications, and tests methods

The contents of specifications and test methods in approval applications must include required test items in reference to the specified test guidelines. For drugs with new active ingredients manufactured by chemical synthesis, refer to "Setting of Specifications and Test Methods of New Drugs" (ICH Q6A) (Notification No. 568 of the Evaluation and Licensing Division, PMSB dated May 1, 2001) For new biological products (biotechnological products/drug products derived from living organisms), refer to "Setting of Specifications and Test Methods of Biological Products (biotechnological products/drug products derived from living organisms)" (ICH Q6B) (Notification No. 571 of the Evaluation and Licensing Division, PMSB dated May 1, 2001). These guidelines on specifications and test methods were prepared based on ICH agreements. To achieve sufficient utilization of ICH-Q6A and ICH-Q6B, it is necessary to harmonize the General Test, Processes and Apparatus of Pharmacopoeia among ICH regions, and hence the Guidelines on Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions (Notification No. 0526001 of the Evaluation and Licensing Division, PFSB dated May 26, 2009, No.1; ICH-Q4B) were issued. Based on these guidelines, when it is judged that it is possible to utilize the pharmacopoeial texts in the ICH regions, these texts can be used mutually in accordance with the conditions set in annexes.

The following guidelines have been revised or established concerning physicochemical properties, specifications, and tests methods:

(1) Text (Items) on Analytical Validation (ICH Q2A, currently Q2(R1)) (Notification No. 755 of the Evaluation and Licensing Division, PAB dated July 20, 1995)

(2) Guidelines on Impurities in Bulk Drugs with New Active Ingredients (ICH Q3A, currently Q3A(R2)) (Notification No. 877 of the Evaluation and Licensing Division, PAB dated September 25, 1995, revised in Notification No. 1216001 of the Evaluation and Licensing Division, PMSB dated December 16, 2002, partially revised by Notification No. 1204001 of the Evaluation and Licensing Division, PFSB dated December 4, 2006)

(3) Guidelines on Impurities in Drug Preparations (ICH Q3B, currently Q3B(R2)) (Notification No. 539 of Evaluation and Licensing Division, PAB, dated June 23, 1997, revised in Notification No. 0624001 of the Evaluation and Licensing Division, PMSB dated June 24, 2003, partially revised by Notification No. 0703004 of the Evaluation and Licensing Division, PFSB dated July 3, 2006)

(4) Text (analytical procedures) on Analytical Validation (ICH Q2B, currently Q2(R1)) (Notification No. 338 of the Evaluation and Licensing Division, PAB dated October 28, 1997)

(5) Guidelines on Residual Solvents in Drug Preparations (ICH Q3C, currently Q3C(R3)) (Notification No. 307 of the Evaluation and Licensing Division, PMSB dated March 30, 1998, partially revised by Notification No. 0211-(1) of the Evaluation and Licensing Division, PFSB dated February 21, 2011)

(6) Setting of Specifications and Test Methods of New Drugs (ICH Q6A) (Notification No. 568 of the Evaluation and Licensing Division, PMSB dated May 1, 2001

(7) Setting of Specifications and Test Methods of Biological Products (Biotechnological Products/Drug Products Derived from Living Organisms) (ICH Q6B) (Notification No. 571 of the Evaluation and Licensing Division, PMSB dated May 1, 2001)

(8) Guidelines for Handling Internationally Harmonized Specifications of Japanese Pharmacopoeia (Notification No. 574 of the Evaluation and Licensing Division, PMSB dated May 1, 2001).

(9) Guidelines Related to Formulation Development (ICH Q8) (Notification No. 0901001 of the Evaluation and Licensing Division, PFSB dated September 1, 2006, partially revised by Notification No. 0628-(1) of the Evaluation and Licensing Division, PFSB dated June 28, 2010).

(10) Handling of Application of Drugs Containing a Substance with Different Crystalline (Notification No. 0616-(1) of PFSB dated June 16, 2011).

(11) Guidelines for development and manufacturing of active pharmaceutical ingredients (chemicals and biotechnological products/biological products) (ICH-Q11) (Notification No. 0710-(9) of the Evaluation and Licensing Division, PFSB dated July 10, 2014).

The quality standards published in the Japanese Pharmacopoeia, Japan Pharmaceutical Codex, etc. serve as references for specifications and test methods including content specifications, identification, purity and assay.

For sustained-release drugs, refer to the Guidelines for Design and Evaluation of Sustained-Release (Oral) Preparations (Notification No. 5 of the First Evaluation and Registration Division, PAB dated March 11, 1998) in addition to the above guidelines.

2) Guidelines for stability tests

Stability tests for approval application of drugs are

conducted to evaluate change in quality over time with various environment factors including temperature, humidity or light, through which necessary information may be obtained for establishing a period of retest of an active pharmaceutical ingredient, an available period of a formulation and storing conditions of a drug.

The former guidelines for stability tests of prescription drugs with new active ingredients (Notification No. 565 of the Evaluation and Licensing Division, PMSB dated May 1, 2001) has been abolished and new stability guidelines based on ICH agreements have been established (Revision of Stability Test Guidelines (ICH Q1A(R2)), Notification No. 0603001 of the Evaluation and Licensing Division, PMSB dated June 6, 2003). Stability test guidelines were also established for approval applications in climatic zones III and IV outside the three ICH regions (EU, Japan and the US) (ICH Q1F) (Notification No. 0603007 of the Evaluation and Licensing Division, PMSB dated June 6, 2003) but they were abolished (Notification No. 0703001 of the Evaluation and Licensing Division, PMSB dated July 3, 2006) with the expansion of application of the ICH Q1A guidelines based on ICH agreement (Notification No. 0603001 of the Evaluation and Licensing Division, PMSB dated June 3, 2003). Photostability tests for drugs with new active ingredients and new combinations are performed on the basis of the Guidelines for Photostability Tests of New Bulk Drugs and New Preparations (ICH Q1B) (Notification No. 422 of the Evaluation and Licensing Division, PAB dated May 28, 1997). For drugs with new routes of administration, stability tests must be performed as specified in the Guidelines for Handling Results of Stability Tests of Drugs with New Routes of Administration (ICH Q1C) (Notification No. 425 of the Evaluation and Licensing Division, PAB dated May 28, 1997), and for biological products, stability tests must be performed as specified in the Guidelines for Handling Results of Stability Tests of Biological Products (biotechnological products/drug products derived from living organisms) (ICH Q5C) (Notification No. 6 of the Evaluation and Licensing Division, PMSB dated January 6, 1998).

Concepts concerning simplification of stability tests on a scientific basis have also been specified in Application of Bracketing and Matrixing Methods in Stability Tests on Drug Substances and Drug Products (ICH Q1D) (Notification No. 0731004 of the Evaluation and Licensing Division, PMSB dated July 31, 2002, partially revised by Office Communication dated June 3, 2003).

For generic drugs, etc., standard methods for long-term stability studies, stress stability studies and accelerated stability studies are specified in the Guidelines for Stability Tests Attached to Approval Applications to Manufacture or Import Drugs (Notification No. 165 of the PAB and No. 43 of the Evaluation and Licensing Division, PAB dated February 15, 1991).

3) Guidelines for toxicity tests

The notification entitled "Guidelines for Toxicity Studies for Manufacturing (Importing) Approval Application of Drugs" (Notification No. 24 of the First Evaluation and Registration Division, PAB dated September 11, 1989) was issued to establish the "Guidelines for Toxicity Studies of Drugs" with the purpose of specifying standards how to conduct safety studies for approval application of drugs and contributing proper safety evaluation of drugs. Based on ICH agreements, the following guidelines have been revised or established, and the Guidelines for Toxicity Studies of Drugs (1989) have been replaced by these guidelines:

(1) Revisions of the Guidelines for Single and Repeated Dose Toxicity Studies (ICH S4) (Notification No. 88 of the Evaluation and Licensing Division, PAB dated August 10, 1993)

(2) Guidance for Toxicokinetics (Evaluation of Systemic Exposure in Toxicity Tests) (ICH S3A) (Notification No. 443 of the Evaluation and Licensing Division, PAB dated July 2, 1996)

(3) Guidance on Dose Selection for Carcinogenicity Tests of Drugs (ICH S1C) (Notification No. 544 of the Evaluation and Licensing Division, PAB dated August 6, 1996) and its supplement (ICH S1C(R), currently S1C(R1)) (Notification No. 551 of the Evaluation and Licensing Division, PMSB dated July 9, 1998)

(4) Guidance on Requirements for Carcinogenicity Tests of Drugs (ICH S1A) (Notification No.315 of the Evaluation and Licensing Division, PAB dated April 14, 1997)

(5) Guidelines for Reproductive and Developmental Toxicity Studies (Notification No. 316 of the Evaluation and Licensing Division, PAB dated April 14, 1997 (ICH S5A/S5B) and Notification No. 1834 of the Evaluation and Licensing Division, PMSB dated December 27, 2000 (ICH S5B(M), currently S5(R2))

(6) Guidance on the Need for Carcinogenicity Studies of Pharmaceuticals (ICH S1B) (Notification No. 548 of the Evaluation and Licensing Division, PMSB dated July 9, 1998)

(7) Timing of Preclinical Studies in Relation to Clinical Trials (ICH M3(M), currently M3(R2)) (Notification Nos. 1019 and 1831 of the Evaluation and Licensing Division of PMSB dated November 13, 1998 and December 27, 2000, respectively, partially revised by Notification No. 0219-(4) of the Evaluation and Licensing Division, PMSB dated February 19, 2010, and Q&A: Office Communication dated August 16, 2012)

(8) Guidance on Genotoxicity Tests of Pharmaceuticals (ICH S2) (Notification No. 1604 of the Evaluation and Licensing Division, PMSB dated November 1, 1999)

(9) Guidance on Carcinogenicity Tests of Pharmaceuticals (Notification No. 1607 of the Evaluation and Licensing Division, PMSB dated November 11, 1999, partially revised by Notification No. 1127001 of the Evaluation and Licensing Division, PFSB dated November 27, 2008)

(10) Guidance on Immunotoxicity Studies for Human Pharmaceuticals (ICH S8) (Notification No. 0418001 of the Evaluation and Licensing Division, PFSB dated April 18, 2006)

(11) The non-clinical evaluation of the potential

for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals (ICH S7B) (Notification No. 1023-(4) of the Evaluation and Licensing Division, PFSB dated October 23, 2009)

(12) Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use (ICH S2(R1)) (Notification No. 0920-(2) dated September 20, 2012)

(13) Guidance on non-clinical evaluation of medicinal products in pediatric population using juvenile animals (Notification No. 1002-(5) of the Evaluation and Licensing Division, PFSB dated October 2, 2012)

(14) Guideline on Photosafety Evaluation (ICH-S10) (Notification No. 0521-(1) of the Evaluation and Licensing Division, PFSB dated May 21, 2014)

Data on the following studies that should be conducted in accordance with the above guidelines are required for the review and evaluation of a new drug application by the Ministry (**Table 3** Data to be Submitted with an Application for Approval to Manufacture/Market: A New Prescription Drug):

(1) Single dose toxicity studies
(2) Repeated dose toxicity studies
(3) Genotoxicity studies
(4) Carcinogenicity studies
(5) Reproductive and developmental toxicity studies
(6) Skin irritation studies
(7) Other toxicity studies

Drug dependence studies were specified separately from the toxicity guidelines in the Scope of Application and the Guidelines for Animal Studies and Clinical Observations on Drug Dependence (Notification No. 113 of the Narcotics Division, PAB dated March 14, 1975) and the Guidelines for Animal Studies and Clinical Observations on Drug Dependence (Notification No. 383 of the Narcotics Division, PAB dated June 7, 1978).

For biotechnological products, the guideline "Nonclinical Safety Evaluation of Biotechnological Drugs" (Notification No. 0323-(1) of the Evaluation and Licensing Division, PFSB dated March 23, 2012) should be referred to. For infection prophylactic vaccines, refer to the guideline "Nonclinical safety evaluation of prophylactic vaccines (Notification No. 0527-(1) of the the Evaluation and Licensing Division, PFSB dated May 27, 2010) and for anti-malignant tumor agents, refer to the guideline "Nonclinical safety evaluation of anti-malignant tumor agents (Notification No. 0604-(1) of the the Evaluation and Licensing Division, PFSB dated June 4, 2010).

4) Good Laboratory Practice (GLP)

For toxicity tests conducted to confirm the safety of drugs, the reliability of the data should be assured so that the results obtained are correctly analyzed and assessed. For this purpose, all toxicity tests conducted to support applications for new drug manufacturing and marketing approval and reexamination must be conducted in accordance with the Good Laboratory Practice Standards for Safety Studies on Drugs (GLP). (Notification No. 902 of the Evaluation and Licensing Division, PMSB dated June 21, 2001 requires safety pharmacology studies be performed in accordance with "the Guidelines on Safety Pharmacology Studies" to comply with the GLP Ordinance.)

This ordinance consists of eight chapters and 19 articles as outlined below:

Chapter 1 (Articles 1-4)

Purpose of this ordinance, definition of terms, responsibilities of sponsors

Chapter 2 (Article 5-8)

Responsibilities of management of testing facilities, study directors and Quality Assurance Units

Chapter 3 (Articles 9 and 10)

Structures, facilities and equipment of testing facilities

Chapter 4 (Articles 11 and 12)

Standard operating procedures in testing facilities (prepared by management) and animal caretakers

Chapter 5 (Articles 13 and 14)

Handling of investigational products and comparators

Chapter 6 (Articles 15 and 16)

Study protocols (prepared by study director) and proper conduct of studies.

Chapter 7 (Articles 17 and 18)

Final reports (prepared by study director) and retention of study data

Chapter 8 (Article 19)

Requirements for conducting studies at more than one testing facilities

Verification of the GLP ordinance compliance of study facilities performing nonclinical studies in compliance with the GLP ordinance (GLP-compliant studies) at the time of approval reviews is performed as a rule based on the results of paper and on-site reviews by the PMDA at the request of the MHLW and the MHLW decides on whether or not to accept the data concerned as approval review data.

GLP compliance reviews conducted by the PMDA are performed on the basis of "the System of Guidelines for On-site Reviews Based on the Pharmaceutical GLP and Medical Device GLP" (Notification No. 23 of the PMDA date April 1, 2004; partially revised Notifications No. 530 of the PMDA dated June 29, 2004, No. 529 dated March 30, 2007, No. 0620058 dated June 20, 2008, No. 0815008 dated August 15, 2008, and No. 1121005 dated November 21, 2014) GLP compliance conditions are evaluated in two categories: compliant or non-compliant, based on the results of the GLP compliance review.

Compliant: The inspected testing facility has no items that deviate from GLP for drugs, etc. or, if it does, appropriate improvement measures have been taken with respect to such aspects or the effects of such aspects on the operation and management of testing facility in general are considered tolerable.Non-compliant:.The effects of items that deviate from GLP for drugs, etc. at

the inspected testing facility are not tolerable and inspected testing facility cannot be considered compliant with GLP.

When evaluated as compliant in the GLP compliance reviews, the results of the tests performed in the facility will be accepted, in principle, for use as review data for a period of 3 years from the date of the GLP Compliance Confirmation Letter.These GLP requirements also apply to data generated in other countries when they are used to support applications in Japan. In principal, a judgment on the GLP compliance of a trial conducted at a testing facility in a foreign country is made based on data submitted by a government agency, etc. of the foreign country evidencing that the trial is conducted in accordance with GLP (Notification No. 1121-(9) of the Evaluation and Licensing Division, PFSB and Notification No. 1121-(13) of the Evaluation and Licensing Division, PFSB dated November 21, 2014).

5) Guidelines for general pharmacological studies

The general policies for selection and planning of test systems to prepare data on safety pharmacology studies are specified in the Safety Pharmacology Study Guidelines (ICH-S7A) (Notification No. 902 of the Evaluation and Licensing Division, PMSB dated June 21, 2001) and it is required that safety pharmacology studies are performed in accordance with the GLP Ordinance as a rule. The objectives of the Safety Pharmacology Study Guidelines are as follows and a research protocol that complies with these objectives should be prepared. (1) Undesirable pharmacodynamic properties of investigational products considered to be related to safety in humans must be specified; (2) adverse pharmacodynamic or pathophysiological actions of investigational products confirmed in toxicity studies or clinical studies must be evaluated; and (3) the mechanisms of pharmacodynamic adverse actions confirmed to date or posing a risk must be investigated.

Secondary pharmacology studies to understand the type and severity of pharmacological actions and to clarify the pharmacological profile of the investigational product together with primary pharmacology studies are performed with reference to the Guidelines for General Pharmacology Studies (Notification No. 4 of the New Drugs Division, PMSB dated January 29, 1991) (Notification No. 902 of the Evaluation and Licensing Division, PMSB dated June 21, 2001). For other pharmacology studies, reference should be made to Notification No. 813 of the Evaluation and Licensing Division, PMSB dated June 4, 2001 entitled "Methods of Investigating Drug Interactions" when preparing data related to pharmacodynamic drug interactions.

6) Guidelines for pharmacokinetic studies

Pharmacokinetic data is useful in determining doses and other conditions for toxicity and pharmacological tests in animals. Moreover, the assessment and understanding of these data may provide very useful information for the assessment of efficacy and safety in humans. The Guidelines on Nonclinical Pharmacokinetic Studies (Notification No. 496 of the Evaluation and Licensing Division, PMSB dated June 26, 1998) were issued requiring applicants to study the absorption, distribution, metabolism, and excretion of test drugs in animal and in vitro study systems to clarify their pharmacokinetic profile. In these guidelines, the distribution studies are single dose studies as a rule, and the Guideline for Repeated Dose Tissue Distribution Studies (Notification No. 442 of the Evaluation and Licensing Division, PAB dated July 2, 1996; ICH S3B) should be used for reference for repeated dose studies.

A guidance for the reliability assurance of drug concentration analysis in pharmacokinetic study is available as "the Guidelines on Bioanalytical Methods Validation for Human Studies in New Drug Development" (Notification No. 0711-(1) of the Evaluation and Licensing Division, PFSB dated July 11, 2013) and Q&A on this guidance (Office Communication dated July 11, 2013).

The notification entitled "Methods of Investigating Drug Interactions" (Notification No. 813 of the Evaluation and Licensing Division, PMSB dated June 4, 2001) was enacted to be referred in investigation of pharmacokinetic interaction. Additionally, the "Guidelines for Pharmacokinetic Drug Interaction for Drug Development and Proper Information Provision (Final Draft)" was published on July 8, 2014.

7) Guidelines for bioequivalence studies

The following guidelines have also been issued concerning bioequivalence:

(1) Guidelines for Bioequivalence Testing of Generic Drugs (Notification No. 487 of the Evaluation and Licensing Division, PMSB dated December 22, 1997, partially revised by Notification No. 786 of the Evaluation and Licensing Division, PMSB dated May 31, 2001, Notification No. of 1124004 the Evaluation and Licensing Division, PFSB dated November 24, 2006, and Notification No. 0229-(10) of the Evaluation and Licensing Division, PFSB dated February 29, 2012)

(2) Guidelines for Bioequivalence Testing of Oral Solid Dosage Forms with Different Content (Notification No. 64 of the Evaluation and Licensing Division, PMSB dated February 14, 2000, partially revised by Notification No. 786 of the Evaluation and Licensing Division, PMSB dated May 31, 2001, Notification No. 1124004 of the Evaluation and Licensing Division, PFSB dated November 24, 2006, and Notification No. 0229-(10) of the Evaluation and Licensing Division, PFSB dated February 29, 2012)

(3) Guidelines for Bioequivalence Testing of Oral Solid Dosage Forms with Formulation Modifications (Notification No. 67 of the Evaluation and Licensing Division, PMSB dated February 14, 2000, partially revised by Notification No. 786 of the Evaluation and Licensing Division, PMSB dated May 31, 2001, Notification No. 1124004 of the Evaluation and Licensing Division, PFSB dated November 24, 2006, and Notification No. 0229-(10) of the Evaluation and Licensing Division, PFSB dated February 29, 2012).

(4) Guidelines for Bioequivalence Testing of Products with Different Dosage Forms (Notification No. 783 of the Evaluation and Licensing Division, PMSB dated May 31, 2001, and partially revised by Notification No. 0229-(10) of the Evaluation and Licensing Division, PFSB dated February 29, 2012)

(5) Guidelines for Bioequivalence Studies of Generic Products for Topical Dermatological Use (Notification No. 0707001 of the Evaluation and Licensing Division, PFSB dated July 7, 2003, partially revised by Notification No. 1124004 of the Evaluation and Licensing Division, PFSB dated November 24, 2006).

(6) Guidelines for Bioequivalence Testing of New Additional Topical Dermatological Dosage Forms (Notification No. 1124001 of the Evaluation and Licensing Division, PFSB dated November 24, 2006).

(7) Guidelines for Bioequivalence Testing of Topical Dermatological Dosage Forms with Formulation Modifications (Notification No. 1101-(1) of the Evaluation and Licensing Division, PFSB dated November 1, 2010).

A guidance for partial changes in the manufacturing method of solid oral immediate-release, enteric-coated, and controlled-release preparations is available as "the Guidelines for Bioequivalence Studies of Solid Oral Preparations for Handling Changes in Manufacturing Method" and Q&A on this guidance (Office Communication dated April 19, 2013).

3.2 Clinical Studies

1) Basic requirements

The primary objectives of clinical studies are to evaluate therapeutic and prophylactic efficacy of investigational new drugs for target diseases or symptoms as well as their risks and possible ADRs in humans, and ultimately to assess their clinical usefulness based on a comparison of their efficacy and safety. In performing clinical studies, investigators must give scientific and ethical consideration to the subjects' human rights to minimize their risk relative to the expected benefits.

Guidance concerning drug development strategies and evaluation processes has been issued in the three ICH regions. In 1998, General Considerations for Clinical Studies (Notification No. 380 of the Evaluation and Licensing Division, PMSB dated April 21, 1998, ICH E8) was prepared as one aspect of MHLW's efforts to promote international harmonization of approval review data for new drugs. This notification consists of the objective of the guidelines, general principles (protection of clinical trial subjects and scientific approach in design and analysis) and development methods (points to consider for development plans and for individual clinical studies).

In order to protect the study subjects these Guidelines specify that, as a condition to start a clinical study, the safety of the drug must be shown from nonclinical studies or previous human studies. Throughout drug development, qualified clinicians and other experts should review and evaluate all newly obtained data from toxicity studies on animals and human studies to assess their implications for the safety of the subjects.

Clinical studies should be designed, conducted, and analyzed in keeping with sound scientific principles in order to achieve their objectives, and they should be reported appropriately. The essence of rational drug development is to pose important questions and answer them with the results of carefully controlled clinical studies. The primary objectives of any study should be clear and explicitly stated.

Clinical studies can be classified by their objectives. The basic logic behind serially conducted studies of a drug is that the results of prior studies should influence the protocols of later studies (**Table 5**. Classification of Clinical Studies According to Objectives).

Following an ICH agreement to issue common GCP for scientific and ethical conduct of clinical studies in three regions, the MHLW Ordinance on Standards for Implementation of Clinical Studies on Drugs (GCP) (MHW Ordinance No. 28 dated March 27, 1997, partial revision by MHLW Ordinance No. 106 dated June 12, 2003, MHLW Ordinance No. 172 dated December 21, 2004, MHLW Ordinance No. 72 dated March 31, 2006, MHLW Ordinance No. 24 dated February 29, 2008, and MHLW Ordinance No. 161 dated December 28, 2012) was issued with the aims of specifying the requirements for the planning, conduct, monitoring, auditing, records, analysis, and reports of clinical studies performed to collect data to be submitted with applications for approval to manufacture and market drugs; to protect the human rights, safety, and welfare of study subjects; and to assure the scientific quality of the study and the reliability of its results.

The importance of precision control of laboratory data in clinical trial to ensure the reliability of laboratory data and the trial is shown in "the Basic Concept of Precision Control of Laboratory Data in Clinical Trial" (Office Communication of the Evaluation and Licensing Division, PFSB dated July 1, 2013).

2) Considerations for the development plan

2.1) Nonclinical studies

Important considerations for determining the nature of nonclinical studies and their timing with respect to clinical studies include:

(1) Duration and total exposure (dose) in individual patients
(2) Characteristics of the drug
(3) Disease or condition targeted for treatment
(4) Use in special populations
(5) Route of administration

The actual timing of each nonclinical safety study is specified in the Guidelines on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (Notification No. 1019 of PMSB dated November 13, 1998, partially revised on February 19, 2010: ICH M3R(R2), and Office Communication (Q&A on the guidelines) dated August 16, 2012).

(i) Safety studies

For the first studies in humans, the dose used should be determined by careful examination of the prerequisite nonclinical pharmacological and toxicological evaluations. Early nonclinical studies should provide sufficient information to support

selection of the initial human dose and safe duration of exposure, to provide information about the physiological and toxicological effects of a new drug.

(ii) Pharmacological studies

The basis and direction of the clinical exploration and development rests on the nonclinical pharmacology profile, which includes the following information:

(1) Pharmacological basis of principal effects (mechanism of action).
(2) Dose-response or concentration-response relationships and duration of action.
(3) Study of the potential clinical routes of administration.
(4) Systemic general pharmacology, including pharmacological effects on major organ systems and physiological processes.
(5) Absorption, distribution, metabolism, and excretion

2.2) Quality of investigational products

Products used in clinical studies should be well characterized, with information on bioavailability wherever feasible. The product should be appropriate for the stage of drug development. Ideally, the preparation should be adequate to allow testing in a series of studies that examine a range of doses. The standards that should be met when manufacturing investigational products were specified in the "Manufacturing Control and Quality Control Standards for Investigational Products and Standards for Buildings and Facilities of Manufacturing Plants for Investigational Products" (former Investigational Product GMP) (Notification No. 480 of the PAB dated March 31, 1997). Thereafter, this was revised in Notification No. 0709002 of the PFSB dated July 9, 2008 entitled "Manufacturing Control and Quality Control Standards for Investigational Products" (New Investigational Product GMP) and Q&A on this notification (Office Communication dated July 2, 2009) to permit quality assurance of investigational products in accordance with each phase of clinical studies in consideration of the characteristics of clinical studies, including the exploratory early clinical trials.

2.3) Phases of clinical development

Clinical studies have been conventionally classified by phase of development (I to IV). The ICH conference proposed a new classification system according to the objective of studies as described in the General Considerations for Clinical Studies (Notification No. 380 of the Evaluation and Licensing Division, PMSB dated April 21, 1998, ICH E8), and according to this system clinical studies are classified to the following four types:

(1) Human pharmacology studies
(2) Therapeutic exploratory studies
(3) Therapeutic confirmatory studies
(4) Therapeutic use studies

Objectives and types of studies in these four categories are listed in **Table 5** (Classification of Clinical Studies According to Objectives) and the close but variable correlations between the development phase and study type are shown in **Fig. 11** (Correlation between Development Phase and Type of Study).

The distribution of the circles, open circles and shaded circles, in the figure shows that the types of study do not automatically define the phases of development.

Clinical development is ideally a step-wise process in which information from small early studies is used to support and plan later larger, more definitive studies. To develop new drugs efficiently, it is essential to identify characteristics of the investigational product in the early stages of development and to plan appropriate development based on this profile. The four clinical development phases are described below.

(i) Phase I (typical study: clinical pharmacology)

Phase I entails the initial administration of an investigational new drug to humans. The most typical study is that on clinical pharmacology. Although clinical pharmacology studies are typically identified with Phase I, they may also be indicated at other points in the development sequence. Studies conducted in Phase I typically involve one or a combination of the following aspects:

(1) Estimation of initial safety and tolerability
(2) Characterization of pharmacokinetics
(3) Assessment of pharmacodynamics
(4) Early assessment of efficacy

As a reference, the basic concepts concerning the study items and conduct of all clinical pharmacokinetic studies for the purpose of drug development are given in Clinical Pharmacokinetic Studies on Drugs (Notification No. 796 of the Evaluation and Licensing Division, PMSB dated June 1, 2001) and Guidance on Ensuring Safety of Human Subjects in the Initial Clinical Trial of New Investigational Medicinal Product (Notification No. 0402-(1) of the Evaluation and Licensing Division, PFSB dated April 2, 2012).

(ii) Phase II (typical study: therapeutic exploratory)

Phase II is usually considered to be the phase in which studies with the primary objective of exploring therapeutic efficacy in patients are initiated. The most typical Phase II study is the therapeutic exploratory study performed on a group of patients who are entered into the study according to clearly defined criteria and whose condition is monitored. An important goal for this phase is to determine the dose(s) and regimen for Phase III studies. Dose response designs should be used to assess and confirm the dose-response relation for the indication concerned. Additional objectives of Phase II clinical studies include evaluation of study endpoints, therapeutic regimens (including concomitant medication) or target populations for further study in Phase II or III.

(iii) Phase III (typical study: therapeutic confirmatory)

The primary objective of Phase III studies is to confirm the therapeutic effects. Studies in Phase III are designed to confirm the preliminary evidence accumulated in Phase I and II that a drug is safe and

effective for use in the proposed indication and recipient population. These studies are intended to provide data to serve as an adequate basis for manufacturing approval.

"Arrangements for supplying and receiving of control drugs" were established as voluntary arrangements among member companies of the JPMA in July 1981 for the smooth supply and receipt of control drugs by the companies developing new drugs and the manufacturing/marketing authorization holders of control drugs when pharmaceutical companies developing new drugs evaluate efficacy and safety of new drugs with approved drugs already on the market as controls. After four subsequent revisions, the most recent version appeared on November 1, 2005.

(iv) Phase IV (various types of study: therapeutic use)

The Phase IV studies are conducted after approval to confirm therapeutic efficacy and safety when used for the proposed indication and targeted population in general clinical practice. Studies include clinical experience surveillance to assess the incidence of adverse drug reactions, special survey to assess efficacy and safety in special populations, and post-marketing clinical trials to obtain additional information.

2.4) Studies concerning new indications, new dosage regimens, etc.

Development of additional indications, dose levels, dosage regimens, administration routes, etc. requires new protocols for both clinical and nonclinical studies. Human pharmacology may also be necessary for application.

2.5) Special considerations

Consideration should be given to special circumstances and populations when they are targeted as part of the development plan.

(i) Studies of drug metabolites

The main metabolites must be identified and detailed pharmacokinetic studies performed. The timing for studies to evaluate metabolism is decided in accordance with the characteristics of the drug concerned.

(ii) Drug interactions

If a potential for drug interaction is suggested by the metabolism profile, by the results of nonclinical studies or by information on similar drugs, studies on drug interaction are highly recommended. To explore interaction with the drugs that are frequently coadministered, it is usually important that drug interaction studies be performed in nonclinical and, if appropriate, in clinical studies.

(iii) Special populations

Some groups in the general population may require special study because they deserve unique risk/benefit considerations, or because they may need modification of use of a drug or schedule of a drug compared to general adult use. Pharmacokinetic studies in patients with renal and hepatic dysfunction are important to assess the impact of the potentially altered drug metabolism or excretion. Other special populations are as follows:

(1) Elderly.
(2) Ethnic populations.
(3) Pregnant women.
(4) Nursing women.
(5) Children.

(iv) Microdose studies

Clinical studies to obtain information on pharmacokinetics of the investigational product in humans and desired information at the preclinical stage in development candidate screening studies based on pharmacokinetic information. A dose not exceeding 1/100 of the dose expressing pharmacological effects or a dose of 100 μg/human, whichever is smaller, is administered once to healthy subjects. The range of application is mainly low molecular weight compounds. Even though test doses are extremely low, microdose studies must also be conducted in accordance with the cGCP. Basic concepts for the microdose studies, including points to consider, are given in the Guidance for Conducting Microdose Clinical Studies (Notification No. 0603001 of the Evaluation and Licensing Division, PFSB dated June 3, 2008).

3) Considerations for Individual Clinical Studies

The following important principles should be followed in planning the objectives, design, conduct, analysis and reporting of a clinical study. Each item from the objectives to reporting should be defined in a written protocol before the study starts.

3.1) Objectives

The objective(s) of the study should be clearly stated. They may include exploratory or confirmatory characterization of the safety and/or efficacy and/or assessment of pharmacological, physiological or biochemical effects.

3.2) Design

The appropriate study design should be chosen to provide the desired information in consideration of the following points by referring to relevant clinical guidelines:

(1) Selection of subjects.
(2) Selection of control group.
(3) Number of subjects.
(4) Safety and efficacy variables.
(5) Methods to minimize bias (randomization, blinding, and compliance).

3.3) Conduct

The study should be conducted according to the principles described in the General Considerations for Clinical Studies or in accordance with other pertinent elements outlined in the GCP or other guidelines related to clinical studies. Adherence to

the study protocol is essential.

3.4) Analysis

The study protocol should cite a specified analysis plan that is appropriate for the objectives and design of the study. Methods of analysis of the primary endpoints and surrogate endpoints should be included in the protocol. The results of the clinical study should be analyzed in accordance with the plan prospectively stated in the protocol.

3.5) Reporting

Clinical study reports should be appropriately prepared in accordance with the Structure and Content of Clinical Study Reports (Notification No.335 of the Evaluation and Licensing Division, PAB dated May 1, 1996: ICH E3).

4) Statistical analysis of clinical study results

The MHW (currently MHLW) published the Guidelines for Statistical Analysis of Clinical Study Results (Notification No. 20 of the New Drugs Division, PAB dated March 4, 1992) which list examples of misuse of statistical methods and indicate the methods which are considered most appropriate then to prevent errors and scientifically assess drug efficacy.

The ICH guidelines, Statistical Considerations in the Design of Clinical Trials (ICH E9) (Notification No. 1047 of the Evaluation and Licensing Division, PMSB dated November 30, 1998), have been published to replace Notification No. 20 issued in 1992. The new guidelines are intended to propose approaches when the sponsor designs, conducts, analyzes and assesses a clinical study of an investigational product as part of the overall clinical development. These guidelines should attract interest from individuals in many fields of science, and they state as a prerequisite that the actual responsibility for all statistical work related to a clinical study should be borne by statisticians with appropriate qualifications and experience. The participation of statisticians is intended to verify together with other clinical study experts that statistical principles have been appropriately applied in the study to support drug development. Therefore, to implement the principles explicitly stated in these guidelines, the statisticians must combine adequate theoretical and practical education and experience. The principles stated in these guidelines are meant primarily to be applied in the latter half of development, mainly in therapeutic confirmatory studies.

In confirmatory studies, the primary variables are not limited to those related to efficacy but may include those concerning safety, pharmacodynamics and pharmacokinetics. In addition, some of the confirmatory knowledge is derived from data compiled for several studies, and under such conditions, some of the principles in the guidelines are applied. The studies in the initial phases of drug development mainly involve therapeutic exploratory studies, but statistical principles are also applied to these studies. Therefore, these guidelines should be applied to all phases of clinical development whenever feasible.

5) Guidelines for clinical evaluation

Data on the results of clinical studies must be analyzed precisely and objectively as they are the means of identifying the drug's expected efficacy and ADRs, when the drug is used, thereby playing an important role in the evaluation process by the regulatory authority.

Guidelines on the methodology for clinical studies and the evaluation criteria have been published as "the Guidelines for Clinical Evaluation." The results from ICH are also introduced into Japanese regulations as ICH guidelines.

Currently, the following guidelines for clinical evaluations by therapeutic category, common for clinical evaluation, and otherwise related to clinical evaluations have been published:

[1] Guidelines for clinical evaluation of drugs classified by therapeutic category

(1) Guidelines on Clinical Evaluation of Oral Contraceptives (Notification No. 10 of the First Evaluation and Registration Division, PAB dated April 21, 1987).

(2) Guidelines for Clinical Evaluation of Drugs to Improve Cerebral Circulation and/or Metabolism in Cerebrovascular Disorders (Notification No. 22 of the First Evaluation and Registration Division, PAB dated October 31, 1987).

(3) Guidelines on Clinical Evaluation of Antihyperlipidemic Drugs (Notification No. 1 of the First Evaluation and Registration Division, PAB dated January 5, 1988)

(4) Guidelines on Clinical Evaluation of Antianxiety Drugs (Notification No. 7 of the First Evaluation and Registration Division, PAB dated March 16, 1988).

(5) Guidelines for Clinical Evaluation of Antibacterial Drugs (Notification No. 743 of the New Drugs Division, PMSB dated August 25, 1998).
The draft amendment was presented on August 3, 2010.

(6) Guidelines on Clinical Evaluation of Drugs to Treat Osteoporosis (Notification No. 742 of the Evaluation and Licensing Division, PMSB dated April 15, 1999)

(7) Principles for Clinical Evaluation of New Antihypertensive Drugs* (ICH E12A, currently E12) (Notification No. 0128001 of the Evaluation and Licensing Division, PMSB dated January 28, 2002)

(8) Guidelines on Clinical Evaluation of Antiarrhythmic Drugs (Notification No. 0325035 of the Evaluation and Licensing Division, PFSB dated March 25, 2004)

(9) Guidelines on Clinical Evaluation of Antianginal Drugs (Notification No. 0512001 of the Evaluation and Licensing Division, PFSB dated May 12, 2004)

(10) Guidelines for Clinical Evaluation of

Antimalignant Tumor Drugs (Notification No. 1101001 of the Evaluation and Licensing Division, PFSB dated November 1, 2005, partially revised by Office Communication dated November 2, 2005).

(11) Guidelines for Clinical Evaluation of Antirheumatoid Drugs (Notification No. 0217001 of the Evaluation and Licensing Division, PFSB dated February 17, 2006).

(12) Guidelines for Clinical Evaluation of Drugs for Overactive Bladder or Incontinence (Notification No. 0628001 of the Evaluation and Licensing Division, PFSB dated June 28, 2006).

(13) Guidelines for Clinical Evaluation of Prophylactic Vaccines against Infections (Notification No. 0527-(5) of the Evaluation and Licensing Division, PFSB dated May 27, 2010).

(14) Guidelines for Clinical Evaluation of Oral Hypoglycemic Drug (Notification No. 0709-(1) of the Evaluation and Licensing Division, PFSB dated July 9, 2010).
The draft amendment was presented on May 19, 2014.

(15) Guidelines for Clinical Evaluation of Antidepressant Drugs (Notification No. 1116-(1) of the Evaluation and Licensing Division, PFSB dated November 16, 2010).

(16) Guidelines on Clinical Evaluation of Drugs to Treat Heart Failure (Notification No. 0329-(18) of the Evaluation and Licensing Division, PFSB dated March 29, 2011).

(17) Guidelines for Clinical Evaluation of Therapeutic Drugs for Renal Anemia (Notification No. 0930-(1) of the Evaluation and Licensing Division, PFSB dated September 30, 2011).

(18) Guidelines on Clinical Evaluation of Hypnotics (Notification No. 1213-(1) of the Evaluation and Licensing Division, PFSB dated December 13, 2011).

[2] Guidelines for clinical evaluation in general

(19) Studies in Support of Special Populations: Geriatrics (ICH E7)* (Notification No. 104 of the New Drugs Division, PAB dated December 2, 1993 and Q&A dated September 17, 2010).

(20) Dose-Response Information to Support Drug Registration* (ICH E4) (Notification No. 494 of the Evaluation and Licensing Division, PAB dated July 25, 1994).

(21) Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions* (ICH E1) (Notification No. 592 of the Evaluation and Licensing Division, PAB dated May 24, 1995)

(22) Structure and Content of Clinical Study Reports* (ICH E3) (Notification No. 335 of the Evaluation and Licensing Division, PAB dated May 1, 1996)

(23) General Considerations for Clinical Trials* (ICH E8) (Notification No. 380 of the Evaluation and Licensing Division, PMSB dated April 21, 1998).

(24) Ethnic Factors to be Considered in the Acceptance of Foreign Clinical Trial Data* (ICH E5, currently E5(R1)) (Notification No. 672 of the Evaluation and Licensing Division, PMSB dated August 11, 1998, Q&A by Office Communication dated February 25, 2004, and Q&A-(2) by Office Communication dated October 5, 2006)

(25) Statistical Principles for Clinical Trials* (ICH E9) (Notification No. 1047 of the Evaluation and Licensing Division, PMSB dated November 30, 1998)

(26) Clinical Investigation of Medicinal Products in the Pediatric Population* (ICH E11) (Notification No. 1334 of the Evaluating and Licensing Division, PMSB dated December 15, 2000)

(27) Choice of Control Group and Related Issues in Conducting Clinical Studies* (ICH E10) (Notification No. 136 of the Evaluating and Licensing Division, PMSB dated February 27, 2001, partially revised by Office Communication dated April 10, 2001)

(28) Guidance for Conducting Microdose Clinical Studies (Notification No. 0603001 of the Evaluating and Licensing Division, PFSB dated June 3, 2008)

(29) Clinical Investigation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs* (ICH E14) **(Notification No. 1023-(1) of the Evaluating and Licensing Division, PFSB dated October 23, 2009, Q&A by Office Communication dated October 23, 2009, and Q&A-(2) by Office Communication dated July 3, 2012)**

(30) Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (ICH M3(R2)) (Notification No. 0219-(4) of the Evaluation and Licensing Division, PFSB dated February 19, 2010 and Q&A by Office Communication dated August 16, 2012)

[3] Other guidelines

(31) Research on Evaluation of Immunotherapeutic Agents for Malignant Tumors (Iyakuhin Kenkyu 11(4), 1980).

(32) Research on Evaluation of Blood Preparations, Especially Plasma Fraction Preparations (Iyakuhin Kenkyu 15(2), 1984).

(33) Research on Overall Evaluation of Interferon Preparations (Iyakuhin Kenkyu 15(6), 1984).

(34) Guidelines on Clinical Evaluation of Anti-inflammatory Analgesic Drugs (Iyakuhin Kenkyu 16(3), 1985).

(35) Guidelines on the Design and Evaluation of Sustained-release (Oral) Preparations (Notification No. 5 of the First Evaluation and Registration Division, PAB dated March 11, 1988).

(36) Guidance for Developing Prototype Vaccines in Preparation for Influenza Pandemic (Notification No. 1031-(1) of the Evaluation and Licensing Division, PFSB dated October 31, 2011)
(37) Guidance for Clinical Evaluation of Diagnostic Radiopharmaceuticals (Notification No. 0611-(1) of the Evaluation and Licensing Division, PFSB dated June 11, 2012)
(38) Points to Consider in Application of Companion Diagnostics and Related Drug Products (Notification No. 0701-(10) of the Evaluation and Licensing Division, PFSB dated July 1, 2013)
Technical Guidance for Companion Diagnostics and Related Drug Products (Office Communication dated December 26, 2013)

*:ICH guidelines

6) GCP

The first GCP, Standards for Conduct of Clinical Trials on Drugs, intended to assure that clinical studies are performed on the basis of ethical considerations and from the proper scientific standpoint were issued as Notification No. 874 of the PAB dated October 2, 1989, and this GCP was applied in the form of administrative guidance from October 1, 1990. Thereafter, the MHW undertook various studies to improve the quality of clinical studies in Japan in accordance with changes in the international regulatory situation, and a new GCP was issued as an MHW ordinance (No. 28, March 27, 1997) based on a report of the Central Pharmaceutical Affairs Council (March 13, 1997). This new GCP, which is legally binding, went into effect from April 1, 1997.

The Ministerial Ordinance on the GCP was amended thereafter (partially revised by MHW Ordinance No. 127 dated October 20, 2000, MHLW Ordinance No. 106 dated June 12, 2003, MHLW Ordinance No. 172 dated December 21, 2004, MHLW Ordinance No. 72 dated March 31, 2006, MHLW Ordinance No. 24 dated February 29, 2008, MHLW Ordinance No. 163 dated November 28, 2008, MHLW Ordinance No. 68 dated March 31, 2009 and MHLW Ordinance No. 161 dated December 28, 2012), and the current GCP Ordinance is comprised of 6 chapters and 59 articles. The contents are briefly divided into the 3 parts consisting of "Standards for sponsoring clinical trials" and "Standards concerning management of clinical trials" for persons intending to request or conduct a clinical trial, and "Standards for conduct of clinical trials" for medical institutions.

The major points of revision in Ordinance No. 161 dated December 28, 2012 are as follows:

(1) Paragraphs 22 and 23 in Article 2, etc.

To enhance the efficiency of clinical trial to be conducted by "a person who intends to conduct a trial" or "a person who conducts a trial," "a person who intends to conduct a trial" or "a person who conducts a trial" may be not only an investigator of the trial but also, in the case of multicenter trial with a common protocol, a coordinating investigator who is going to submit or has submitted a trial application to the Ministry as the representative of the investigators.

(2) Paragraph 1-(2) in Article 7, etc.

Operating procedures related to a request (preparation for trial conduct) and/or control of a clinical trial may be contracted out in part or in whole to a third party(ies) in order to enhance the efficiency of clinical trial.

(3) Paragraph 1 in Article 13

It is not necessary to state the title of investigators, name and title of subinvestigators, and target number of study subjects in a trial contract in order to enhance the efficiency of negotiating and exchanging a contract between parties.

(4) Paragraph 2 in Article 13

"A person who intends to conduct a trial" may exchange a trial contract with a medical institution(s), etc. by electronic means instead of in paper format if the institution(s), etc. accepts electronic means.

(5) Paragraph 6 in Article 16 and Paragraph 6 in Article 26-(2), etc.

SOPs for the control or accountability of investigational products may be provided to the medical institution instead of to the director of medical institution.

(6) Paragraph 2 in Article 20

The sponsor shall notify investigators and the director of medical institution of any diseases or other ADRs suspected to be related to investigational product within 3 months after the end of each 1-year period.

(7) Article 20 referred to in Article 56

The scope of information (limited to ADRs, etc. occurring in Phase IV studies) that the sponsor of post-marketing study is required to report to investigators and the director of medical institution in accordance with Article 77-(4)-2 of the PAL (Law No. 145 issued in 1960) is limited to that stipulated in Paragraph 1-(1) and (2) in Article 253.

Chapter 1: General provisions (Articles 1 to 3)

The general regulations consist of Article 1 (Outline), Article 2 (Definitions of terms) and Article 3 (Standards for review data). The GCP specifies the following standards (Article 1). The GCP is intended to protect the human rights, maintain the safety, and improve the welfare of subjects, and to assure the scientific quality and the reliability of results of clinical studies. (Article 1)

1) Standards to be followed by prospective sponsors in the collection and preparation of data related to results of clinical trials on drugs to be attached to approval applications.
2) Standards to be followed by prospective sponsors of clinical trials, institutions or persons performing clinical trials and sponsors of clinical trials to conduct or manage clinical trials which are both ethically and scientifically sound.
3) Standards to be followed by sponsors in the collection and preparations of data from

post-marketing clinical trials for reexamination or reevaluation of drugs.

Among data to be submitted by persons submitting applications to receive approval in Article 3, data concerning the results of clinical studies specified in Chapter 2, Section 1 (Articles 4 to 15), Chapter 3, Section 1 (Articles 16 to 26) and Chapter 4 (Articles 27 to 55, excluding Article 29, Paragraph 1, Item 2, Article 31, Paragraph 4, Article 32, Paragraph 4 and 7, Article 33, Paragraph 3, and Article 48, Paragraph 3); and data concerning the results of clinical studies performed by persons specified in Chapter 2, Section 2 (Articles 15-2 to 15-9), Chapter 3, Section 2 (Articles 26-2 to 26-12) and Chapter 4 (Articles 27 to 55, excluding Article 29, Paragraph 1, Item 1, Article 32, Paragraphs 6 and 8, and Article 48, Paragraph 2) must be submitted.

Chapter 2: Standards for Sponsoring Clinical Trials Articles 4 to 15-9)

Provisions to be followed when clinical trials are sponsored or managed in medical institutions by persons who wish to sponsor clinical trials and provisions to be followed when clinical trials are prepared or managed by persons who wish to conduct clinical trials by themselves ("investigator-initiated trials").

- Prospective sponsors (persons who wish to sponsor clinical trials) must prepare standard operating procedures so that all work related to sponsoring (or preparation) and management of the clinical trial such as preparation of the clinical trial protocol, selection of a medical institution(s) and investigator(s) to perform the trial, control of the investigational product, collection of information on adverse reactions and retention of records can always be performed properly.
- Studies on the quality, toxicity and pharmacological action, as well as other studies on the investigational product required for sponsoring (or preparation of) the clinical trial must be completed.
- The clinical trial protocol and an investigator's brochure based on information concerning the quality, efficacy and safety of the investigational product must be prepared.
- A contract must be concluded between the sponsor and clinical research organization when whole or part of the clinical trial management is contracted out.
- When persons or participating medical institutions who perform clinical trials on their own outsource whole or part of the work related to preparation to conduct or management of clinical trials, a contract must be concluded with the party undertaking the work.
- A contract must be concluded with the medical institution(s) performing the clinical trial. Persons who wish to perform clinical trials on their own must obtain the approval of the director of the participating medial institution beforehand.
- Insurance coverage and other measures required for compensation in cases of trial-related injury must be undertaken beforehand.
- Persons who wish to sponsor clinical trials may with the prior approval of the other party submit beforehand documents to the director of the participating medical institutions, and conclude contracts for outsourcing work or contracts for clinical trials by electronic methods.

Chapter 3: Standards concerning management of clinical trials (Article 16 to 26-12)

Provisions to be followed by the sponsor or persons performing clinical trials on their own for the scientific and ethical conduct of clinical trials

- The specified items must be included on the labels of the investigational products.
- Manufacturing records, quality test records and other records related to the investigational product must be prepared.
- Investigational products manufactured in factories fulfilling the Investigational Product GMP requirements must be supplied to or used by the medical institutions that perform the clinical trial. Delivery of investigational products can be conducted via marketing authorization holders or other third parties if it is possible to perform reliable quality control, transport, and acceptance of the investigational product under the responsibility of the sponsor.
- Adverse reactions that cannot be predicted from the investigator's brochure for items specified in the provisions of Article 80-2, Paragraph 6 of the Law must be reported without delay to the investigator and director of the medical institutions performing the study. When the event can be predicted, a list of patients with the event must be notified within 3 months after completion of the period every 12 months from the date of the first clinical trial protocol notification.
- Standard operating procedures (SOP) concerning monitoring must be prepared and monitoring must be performed on the basis of these SOP.
- Monitors must confirm that the trial is being performed properly and that reliability of the data is adequately maintained by visits to the medical institutions performing the trial and direct access to the source data, and they must submit a monitoring report to the sponsor, the person who performs the trial, or the director of the medical institution involved.
- An audit plan and audit SOP must be prepared and the audit must be performed in accordance with these documents. The auditor must prepare an audit report and an audit certificate proving that the audit has been performed, and these documents must be submitted to the sponsor, the person who performs the trial, or the director of the medical institutions involved.
- When the trial is completed or discontinued, the results obtained must be compiled in a clinical study report.
  When the person conducting the clinical trial learns that the study results collected from the trial

concerned were not attached to the application form as application data, this fact and the reason for it must be notified in writing to the directors of the medical institutions performing the trial.

- Records related to the clinical trial must be retained for the specified period.

Chapter 4: Standards for conduct of clinical trials (Articles 27 to 55)

Provisions to be followed by the medical institutions performing clinical trials scientifically and ethically

1) Provisions concerning the Institutional Review Boards (IRB) (Articles 27 to 34)

- An Institutional Review Board (IRB), which should meet the requirements specified in Article 28, must be established by the director of the medical institution performing the trial to review and discuss the proper conduct of clinical trials and other matters related to the trials. (However, it is not always necessary to establish an IRB in each medical institution performing the study.)
- The IRB must review the ethical and scientific appropriateness of the clinical trial subject to review on the basis of the documents specified in Article 32, and state its opinion.
- The person establishing the IRB must keep records of meetings and prepare a summary and retain these documents for set periods such as 3 years after completion of the clinical study. The standard operating procedures, list of members, and summary of meeting records prepared for the IRB must be made public.
- The director of the medical institution performing the study must heed the opinions of the IRB concerning whether it is appropriate or not to perform the clinical study in the medical institution concerned.
- The medical institution is not allowed to conduct a clinical trial when the opinion of the IRB is that it is not appropriate to conduct the trial.
- When it is impracticable to organize an IRB for a planned trial at each institution, alternative IRB may be selected from other IRBs inside or outside the institution in the judgment of the director of medical institution.
- IRB may disclose information related to IRB review to enhance the level of transparency and secure quality of its review activities.

2) Provisions related to medical institutions performing clinical trials (Articles 35 to 41)

- Medical institutions performing clinical trials must have the facilities and personnel to undertake adequate clinical observations and laboratory testing, and they must be able to take the measures required when emergencies arise among the trial subjects.
- The director of the medical institution performing the trial must prepare SOP for work related to the trial, and take the necessary measures so that the clinical trial is conducted properly and smoothly in compliance with the trial protocol and the SOP.
- The director of the medical institution performing the trial must cooperate with monitoring or audits by the sponsor or the person conducting the clinical trial and review by the IRB.
- The director of a medical institution must appoint a person or persons to carry out trial-related clerical work.

3) Provisions related to investigators (Articles 42 to 49)

- The investigator must have sufficient clinical experience to be able to conduct the trial properly.
- The investigator must select the trial subjects in accordance with the objectives of the trial from the ethical and scientific standpoints. The necessary measures so that appropriate treatment can be given to subjects when adverse events occur must be taken beforehand.
- The investigator must prepare the proper case report forms as specified in the protocol, etc. and sign or seal them.
- When deaths suspected of being caused by adverse reactions of the investigational product or other serious adverse events occur, the investigator must immediately report this to the director of the medical institution performing the trial and inform the sponsor or the person supplied with the investigational product when the trial is investigator-initiated.

4) Provisions concerning informed consent of subjects (Articles 50 to 55)

- When a prospective subject is asked to participate in a clinical trial, the investigator must appropriately explain the contents of the clinical trial and other matters beforehand to the subject using "written information" containing required items, and obtain the written consent of the subject.
- The investigator making the explanation and the prospective subject must date and sign or seal the consent form to make the consent effective.

Chapter 5: Standards concerning reexamination data (Article 56)

GCP standards also apply to the collection and preparation of data concerning the results of post-marketing clinical trials to be submitted for reexaminations or reevaluations, but taking account of the nature of post-marketing clinical trials, certain provisions for clinical trials for new drug application are applied to those for reexamination and the required changes in reading shall be made accordingly in this article.

Chapter 6: Standards concerning sponsoring of clinical trials (Article 57 to 59)

These GCP standards also contain provisions concerning the acts of prospective sponsors of clinical trials or persons conducting the clinical trials (Article 57), institutions requested to perform clinical trials (Article 58) and clinical trial sponsors

(Article 59). However, since the scope of application differs from that of the standards related to approval review data, certain provisions for clinical trials for new drug application are applied for those for reexamination and the required changes in reading shall be made accordingly in this article.

Clinical trials performed to obtain data for approval applications must be conducted, results collected and data prepared in accordance with the GCP. In addition to clinical trials sponsored by companies, it is also possible for investigator-initiated clinical trials to be performed for the preparation of approval application data in compliance with the GCP.

Application data from clinical trials submitted to the MHLW must first undergo a GCP compliance review to assure that it meets GCP standards. This review consists of a paper inspection and on-site inspection at the medical institution(s) performing the trial, etc. The review is intended to confirm the reliability of the data as application data. These GCP compliance reviews are performed by the PMDA at the request of the MHLW for data collected and prepared in Japan. The approval review is then undertaken by the MHLW in accordance with the results of PMDA review. The on-site inspections are performed at both the sponsor's facilities and the medical institution(s) performing the trial.

Inspections of the sponsor's facilities examine the organization, structure and management of the GCP-related division, GCP compliance of clinical trials and confirmation of the items included in the trial results. Inspections in the medical institutions review the outline of the facilities and organization, the structure and operation of the IRB, GCP compliance of the clinical trial, and items in the case report forms.

Practices of GCP initially stipulated in Notification No. 1001001 of PFSB dated October 1, 2008 (entitled "Implementation of the Standard Operating Procedures for the Conduct of Clinical Trials of Medicinal Products") were modified as Notification No. 1024-(1) of PFSB dated October 24, 2011 and will be enforced from April 1, 2012 for more efficient conduct of clinical trials.

7) Investigational Product GMP

In Article 17, Supply of the Investigational Product, in the GCP ordinance, it specifies that the sponsor shall supply to the medical institution performing the study investigational product manufactured in factories applying appropriate manufacturing control and quality control methods and with the buildings and facilities required to assure the quality of the investigational product. To that end, requirements for manufacturing investigational products have been issued in the form of Notification No. 480 of the PAB dated March 31, 1997 entitled "Standards for Manufacturing Control and Quality Control of Investigational Products and Standards for Buildings and Facilities of Plants Manufacturing Investigational Products" in order to assure the reliability of clinical studies by guaranteeing the quality of investigational products and to protect subjects from poor quality investigational products. In light of the specificities of the investigational product, such as the use in an early exploratory development phase, Standards for Manufacturing Control and Quality Control of Investigational Products and Standards for Buildings and Facilities of Plants Manufacturing Investigational Products ("new" Investigational Product GMP) were issued in the form of Notification No. 0709002 of the PFSB on July 9, 2008 as a replacement of the old Investigational Product GMP in order to assure the quality of investigational products depending on development phase. In addition to the protection of human subjects and reliability assurance of clinical trials, the new regulations aim to ensure not only the efficacy and safety of drug product but also adequateness of clinical studies themselves in the post-marketing phase by securing pharmaceutical consistency between the investigational product and marketed product following the final selection of research compound to be developed and by assuring the equivalence between the two products following the establishment of manufacturing method and test methods of investigational product. Q&A on the standards for manufacturing control and quality control of investigational products (Investigational Product GMP) were published in Office Communication dated July 2, 2009.

The Investigational Product GMP is applied to all investigational products used in clinical studies conducted in accordance with the GCP ordinance. The GMP is a set of requirements to be followed by the study sponsor and investigators and also applied to investigational products manufactured at foreign facilities. The system/procedure-related provisions of the Investigational Product GMP require the sponsor to establish investigational product manufacturing division and investigational product quality control division at each manufacturing facility. The release of investigational product from factory must be judged by personnel of the quality control division designated for individual investigational product items. The provisions require the preparation and retention of documents pertaining to ingredients/quantities, specifications, test methods, manufacturing procedures, etc. for each investigational product item and those pertaining to manufacturing hygiene control procedures, manufacturing control procedures, and manufacturing control procedures for each manufacturing facility. It is also required to prepare and retain documents standardizing manufacturing and quality control. The GMP also contains provisions concerning the use of contract testing facilities, validation/verification, change control, deviation control, quality test results, handling of inferior quality products, recall, self-inspections, education/training, document/record control, contracted manufacture, buildings/facilities manufacturing investigational products, etc.

The building/facility-related provisions of the Investigational Product GMP specify requirements for individual facilities manufacturing investigational products other than bulk products, investigational bulk products, investigational sterile preparations, investigational sterile bulk product, investigational biological products and investigational blood products.

The requirements for manufacturing control and quality control methods for drug substances are

specified in the Guidelines on GMP for Drug Substances (ICH Q7A, currently Q7) (Notification No. 1200 dated November 2, 2001), which includes 20 requirements for drug substances including quality management, buildings and facilities, and validation, as approved at ICH5 held in San Diego in November 2000.

Further, the adoption of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S) Guidelines in Japan has been proposed by the Ministry in light of the need for international harmonization and other reasons (Office Communication dated February 1, 2012).

Since requests from overseas regulatory authorities to submit investigational product GMP certificates are made when a clinical study is performed overseas using an investigational product produced in Japan for a global clinical trial, the issue of such certificates is specified in the "Supply of investigational product GMP certificates" (Office Communication dated March 30, 2009) and the procedures for requesting the issue of investigational product GMP certificates are given in the "Procedures for Issuing Investigational Product GMP Certificates" (Notification No. 0330023 dated March 30, 2009).

4. Other

4.1 Biotechnological Products

The Guidelines for Manufacturing Drugs by using Recombinant DNA Technology were published to ensure manufacturing safety of products during the manufacture of pharmaceuticals with recombinant DNA technology (Notification No. 1051 of the PAB dated December 11, 1986, partially revised by Notification Nos. 434 and 769 of the PAB dated May 21, 1987 and August 18, 1995, respectively). The guidelines specify methods of safety evaluation of recombinants (live cells), classify the level of each working process into four levels, i.e. GILSP (Good Industrial Large Scale Practice), Category 1, Category 2, and Category 3, at the manufacturing stage based on the degree of safety, identify the type of facilities and equipment necessary for the manufacture, and also specify the requirements for the establishment of an institutional biosafety committee, the appointment of a biological safety officer (BSO), and supervision by a product security pharmacist. Thereafter, based on the Law for Securing Multiplicity of Living Organisms under the Use Control of Genetically-Engineered Living Organisms (so-called "Cartagena Law") (Law No. 97 dated June 18, 2003), the MHLW Ordinance on Measures to Prevent Spread of Industrial Use among Secondary Uses of Genetically-Engineered Living Organisms (Ordinance No. 1 of the Ministry of Finance, MHLW, Ministry of Agriculture, Forestry and Fisheries, Ministry of Economy, Trade and Industry and Ministry of Environment dated January 29, 2004; partially revised in Ordinance No. 2 dated June 6, 2006) was enforced on February 19, 2004 (the preceding guidelines were replaced by the Ordinance).

Separately, a notification entitled "Preparation of Data Required for Approval Applications for Drugs Manufactured by Using Recombinant DNA Technology" was issued as Notification No. 243 of the Evaluation and Regulation Division, PAB dated March 30, 1984 for the evaluation of the quality, efficacy, and safety of drugs produced by recombinant DNA technology, and then "Preparation of Data Required for Approvals Applications for Drugs Manufactured by Cell Culture Technology" was issued as Notification No. 10 of the First Evaluation and Regulation Division, PAB dated June 6, 1988.

In addition, the following notifications were issued based on discussion at ICH:

(1) Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin (ICH-Q5A): Notification No. 329 of the Evaluation and Licensing Division, PMSB dated February 22, 2000
(2) Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of R-DNA Derived Protein Products (ICH-Q5B): Notification No. 3 of the Evaluation and Licensing Division, PMSB dated January 6, 1998
(3) Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products (ICH-Q5C): Notification No. 6 of the Evaluation and Licensing Division, PMSB dated January 6, 1998
(4) Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products (ICH-Q5D): Notification No. 873 of the Evaluation and Licensing Division, PMSB dated July 14, 2000
(5) Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process (ICH-Q5E): Notification No. 0426001 of the Evaluation and Licensing Division, PFSB dated April 26, 2005
(6) Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (ICH-Q6B): Notification No. 571 of the Evaluation and Licensing Division, PMSB dated May 1, 2001
(7) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH-S6(R)): Notification No. 0323-(1) of the Evaluation and Licensing Division, PFSB dated March 23, 2012

There are other notifications issued in relation to medicinal products to be developed and manufactured by using cells and tissues and those products for gene therapy.

- Guidelines of Quality and Safety Assurance of Drugs for Gene Therapy: Notification No. 0701-(4) of the Evaluation and Licensing Division, PFSB dated July 1, 2013
- Reporting of Information and Findings that May Affect the Evaluation of Drugs for Gene Therapy: Notification No. 0701-(7) of the Evaluation and Licensing Division, PFSB dated July 1, 2013

4.2 Drugs Using Materials of Human or Animal Origin as Ingredients (Biological Products)

It is necessary to take measures to assure quality and safety based on current scientific levels for drugs manufactured using materials of human or animal origin as raw materials. Therefore, the Biotechnology Committee of the Pharmaceutical Affairs and Food Sanitation Council established "Basic Concepts for Handling and Use of Drugs and Devices Utilizing Cells or Tissues" (December 1, 2000) and "the Guidelines for Assurance of Quality and Safety of Drugs and Devices Processed from Cells and Tissues of Human Origin" (December 1, 2000) (Notification No. 1314

of the PMSB dated December 26, 2000). In addition, various notifications have been issued, manufacturers have been requested to undertake self-inspection and coordinate application documents, and safety measures have been specified. For ingredients of bovine origin in particular, notifications have been issued as required in accordance with worldwide risk conditions and measures to assure quality and safety have been strengthened (refer to "Safety Measures for Bovine Spongiform Encephalopathy [BSE]" in Section 6.4, Chapter 2). Biological products and specified biological products were newly defined in the revised Pharmaceutical Affairs Law dated July 31, 2002 and measures to assure safety when there is a risk of infection have been designated. The Standards for Biological Materials were specified in May 2003 and specifications for raw materials and packaging materials used in the manufacture of biological products or raw materials and packaging materials manufactured from biological materials and used in the manufacturing process for drugs, quasi-drugs, cosmetics and medical devices based on the Law were designated (Notice No. 210 issued by the MHLW in 2003).

In 2013, regenerative medicine products were characterized in the law separately from drugs or medical devices, and biological materials used in regenerative medicine products have been discussed to be standardized. In conjunction with global trends for the BSE risk in bovine-derived raw materials or the like in addition to the above, the Standards for Biological Materials were partially amended (Notice No. 375, issued by MHLW in 2014).

4.3 Biosimilar Products

With the advances made in biotechnological products, the development of similar biotechnological products (biosimilar products or follow-on biologics) equivalent to and the same quality as existing biotechnological products is being promoted overseas. Based on such technological advances, a Health Sciences Council Research Project entitled "Research on Quality, Efficacy, and Safety Evaluation Methods for Biosimilars" was established with funding from MHLW, and the Guidelines on the Assurance of Quality, Efficacy, and Safety of Biosimilar Products were formulated (Notification No. 0304007 of the Evaluation and Licensing Division, PFSB dated March 4, 2009). Biosimilars are defined as drugs developed by different marketing authorization holders as drugs with the same quality, efficacy, and safety as biotechnological products already approved as drugs with new active ingredients in Japan. "Biosimilar" does not mean that the drug has exactly the same quality with the original biotechnological product, but that they are highly similar in quality and characteristics and even if there are differences in quality and characteristics, the differences can be scientifically judged not leading to any unintended effects on the efficacy and safety profiles of the final product. To prove the comparability, appropriate studies are necessary based on the concepts in the ICH Q5E guidelines "Comparability of Biotechnological/ Biological Products Subject to Changes in their Manufacturing Process." It is also necessary to evaluate the comparability of biosimilars using clinical studies.

Q&A on the Guidelines on the Assurance of Quality, Efficacy, and Safety of Biosimilar Products were published in an Office Communication dated July 21, 2009. Views of the regulatory authorities on timing, definitions of equivalent products, evaluations of comparability, development of formulations and test methods, and safety evaluations for biosimilar applications are included.

The application for a biosimilar product is required to contain detailed procedures and programs of postmarketing surveillance and risk management as directed in Appendix 9 of the Guidelines on the Assurance of Quality, Efficacy, and Safety of Biosimilar Products (Notification No. 0304007 of the Evaluation and Licensing Division, PFSB dated March 4, 2009). However, the Guidelines on the Risk Management Plan (RMP) issued later (Notification No. 0426-(2) of the Evaluation and Licensing Division, PFSB dated April 26, 2012) requires to attach an RMP, in place of post-marketing surveillance plan, to be included in the biosimilar product application submitted on or after April 1, 2013.

4.4 Public Disclosure of Information on New Drug Development

A notification concerning publication of information on new drug approvals was issued (Notification No. 1651 of the Evaluation and Licensing Division, PMSB dated November 11, 1999), and New Drug Approval Information Packages containing summary reviews prepared by the MHLW and nonclinical and clinical data submitted by the applicant have been published. Thereafter, the methods of submitting data for application were changed as specified in "Disclosure of Information Concerning Approval Reviews of New Drugs" (Notification No. 0529003 of the Evaluation and Licensing Division, PMDA dated May 29, 2002). Basic procedures for submission and disclosure have also been specified (Notification No. 0422001 of the Evaluating and Licensing Division, PFSB dated April 22, 2005, Notification No. 0422004 of the PMDA dated April 22, 2005, Notification No. 1126005 of the Licensing and Evaluation Division of PFSB dated November 26, 2007, and Notification No. 0325-(1) of the Evaluation and Licensing Division, PFSB dated March 25, 2013).

Information on approval reviews for new drugs is provided on the following websites: Japanese: http://www.info.pmda.go.jp/info/syounin_index.html,

English (part of product items): http://www.pmda.go.jp/english/service/review.html

"A Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases" was issued on January 6, 2005 as a joint communiqué by four organizations: International Federation of Pharmaceutical Manufacturers Associations (IFPMA), Pharmaceutical Research and Manufacturers of America (PhRMA), European Federation of Pharmaceutical Industry Associations (EFPIA) and Japan Pharmaceutical Manufacturers Association (JPMA). The communiqué declared that registration for all clinical trials except exploratory studies must be disclosed and information on the results of all studies (except exploratory studies) on drugs approved or marketed in at least one foreign country must be disclosed.

Based on this declaration, the Ministry of Education, Culture, Sports, Science and Technology in Japan initiated the UMIN Clinical Trial Registration System (UMIN-CTR; http://www.umin.ac.jp/ctr/index-j.htm) and the MHLW publishes information concerning nonclinical trials via

"Clinical trial information" (http://www.japic.or.jp/index.html), a database for registration and disclosure of clinical trial information through cooperation with the Japan Pharmaceutical Information Center and JPMA.

Using these systems, pharmaceutical companies disclose information on nonclinical trials with adequate consideration given to privacy of individual subjects, intellectual property rights, and contractual rights in order to improve the transparency of clinical trials.

In a system unique to Japan, information on institutional review boards is made public voluntarily (Notification No 1001013 of the Evaluation and Licensing Division, PFSB dated October 1, 2008 and Office Communication dated April 2, 2009).

4.5 ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use)

ICH is operated via the steering committee. The committee is the governing body of the ICH that determines policies and procedures and is consisted of six parties of regulators and research-based pharmaceutical industry representatives of the EU, Japan, and the United States: the Ministry of Health, Labour and Welfare (MHLW), Japan Pharmaceutical Manufacturers Association (JPMA), Food and Drug Administration (FDA), Pharmaceutical Research and Manufacturers of America (PhRMA), European Medicines Agency (EC/EMEA or EMEA as from December 2009), and European Federation of Pharmaceutical Industries' Associations (EFPIA). World Health Organization (WHO), Canadian and the European Free Trade Association (EFTA) attend ICH meetings as observers. At present, ICH has expert working groups (EWG) consisting of specialists, representing the six groups and government officials on each topic.

The harmonization in five steps is known as the ICH process.

Step 1: Selection and analysis of topics to be addressed, analysis of issues, establishment of EWGs, and preparation of draft ICH guidelines

Step 2: Consensus on technical issues for the drafted ICH guidelines and approval for public consultation in each ICH region

Step 3: Regulatory consultation in the three regions, call for public comments, and revision of the draft guidelines based on comments received

Step 4: Sign-off and adoption of the guidelines

Step 5: Regulatory implementation of the guidelines according to regional requirements

Currently, over 70 topics (guidelines), including revised versions, have been agreed and approved (Step 4 or 5) based on ICH activities. As shown in **Fig. 12** (ICH Topics and Guidelines—Progress of Harmonization).

In June 2012, ICH parties agreed on new principles of governance as summarized below:

(1) To better define the roles of the parties in the process of guideline development, Step 2 was divided into 2a and 2b to request regulators and industry parties cooperate in developing ICH guidelines as consensus technical documents at Step 2a and request regulators to release draft guidelines in each region for public consultation at Step 2b. Thereafter, the regulators have the ultimate responsibility in implementing the guidelines.

(2) Each EWG is led by chairperson other than rapporteur during the guideline development process, and the chairperson is a representative of the regulators.

(3) In circumstances when regulators and industry in 3 regions may not agree on a proposed topic for harmonization, the three ICH regulatory parties, when agree, may proceed with the topic, as an exceptional measure, irrespective of whether or not the topic is supported by the industry parties.

Visit the following websites for details of ICH guidelines.

Japanese:

http://www.pmda.go.jp/ich/ich_index.html

English:

http://www.ich.org/cache/compo/276-254-1.html

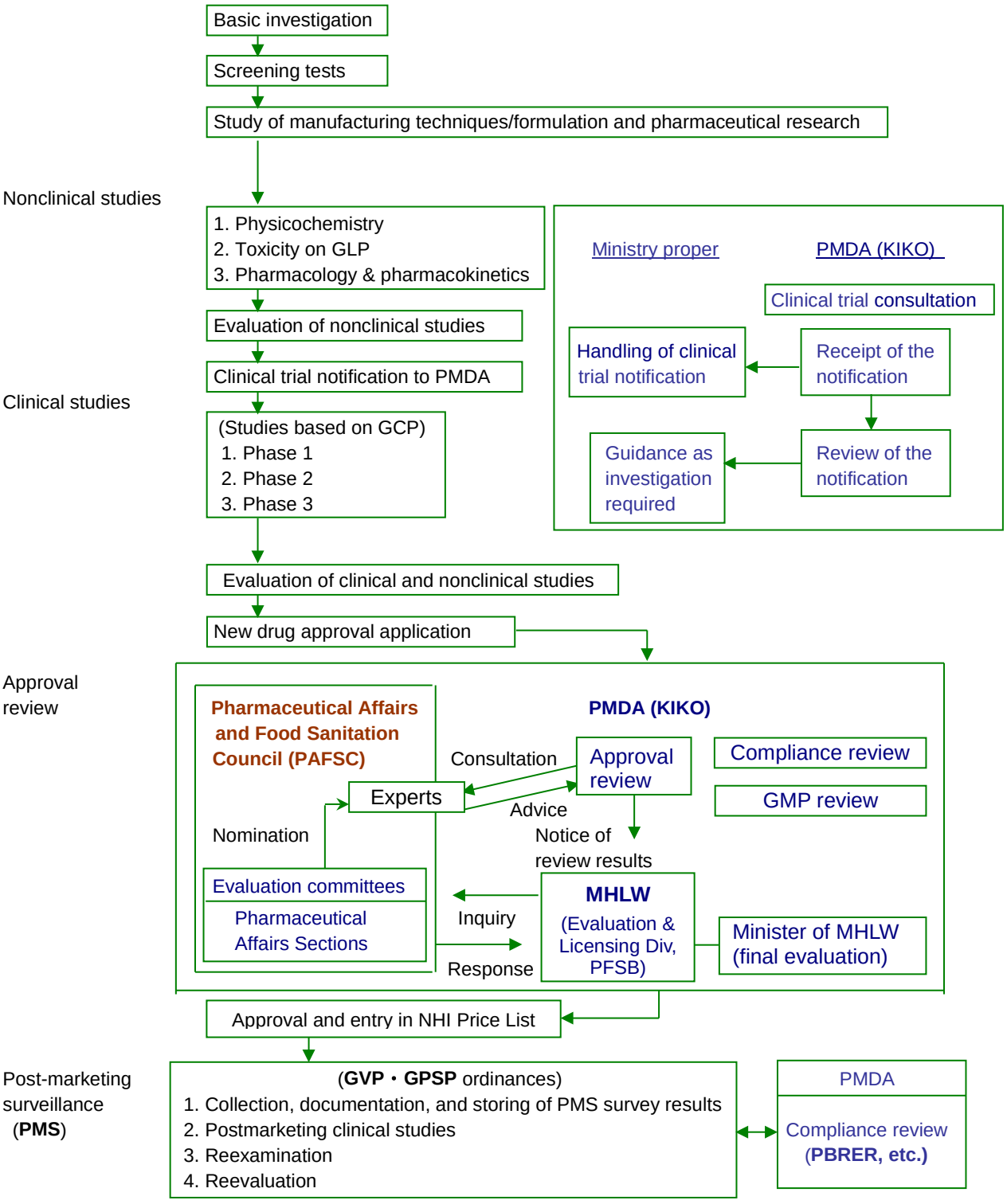
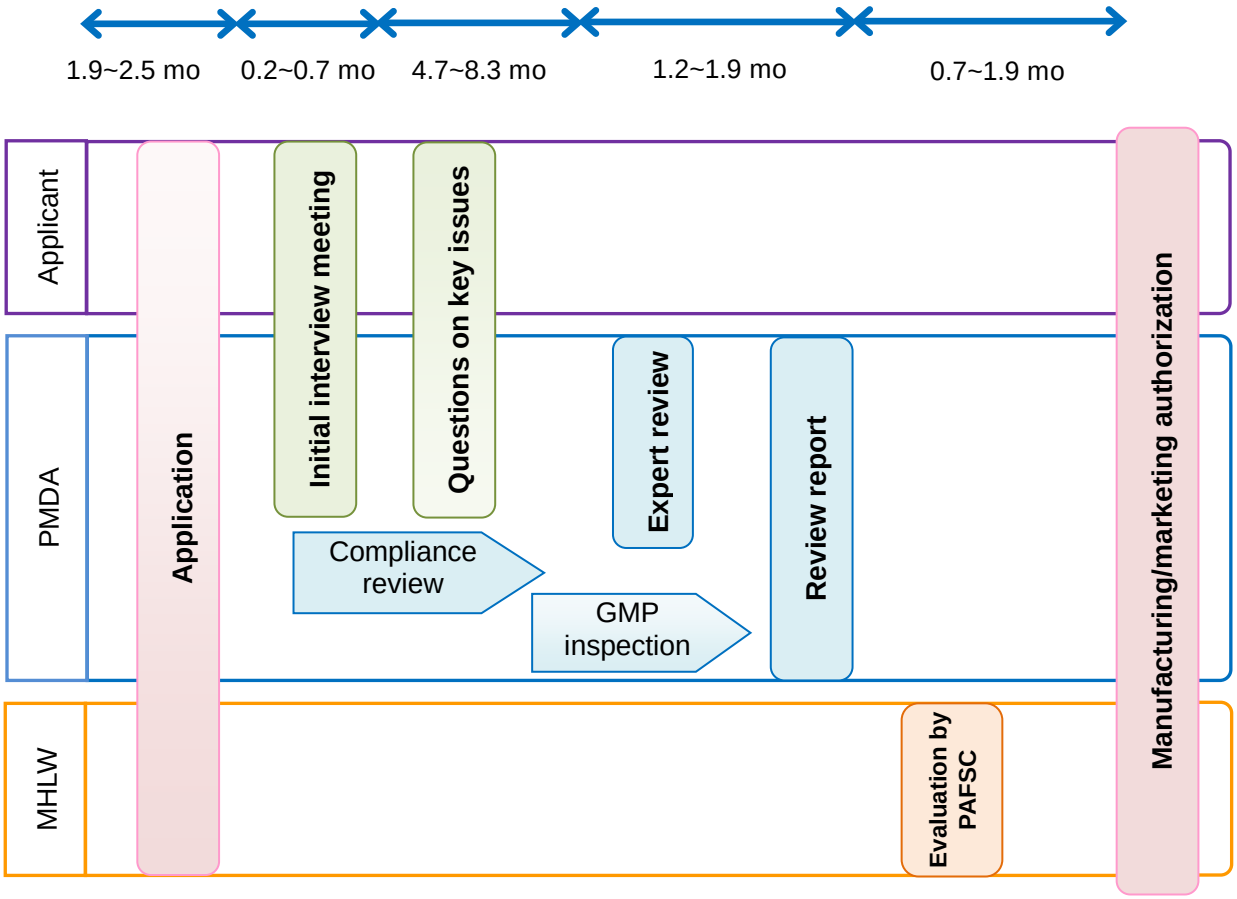


Fig. 8 Flowchart of New Drug Development and Approval

review time of 12 months from application to approval for new drugs for which applications are made from FY2014, assuming that no specific time-consuming situation may occur during the review.



Note 1) Past records of approval reviews for new drugs in FY2013 were used to determine a rough indication of review time. The number of individual processes from application to approval used in the calculation were as follows: Initial interview meeting: 35, Questions on key issues: 31, Expert review: 85, Evaluation by PAFSC: 83, Manufacturing/marketing authorization: 96.

Note 2) Questions on key issues: First questions issued following the initial interview

Fig. 9 Timeline of the standard process of new drug approval

Table 3 Data to be Submitted with an Application for Approval to Manufacture/Market: A New Prescription Drug

(Attached Table 2-1 in PFSB Notification No. 1121-(2) dated November 21, 2014)

Left Column		Right Column						
	A 1 2 3	B 1 2 3	C 1 2 3	D 1 2 3	E 1 2 3 4 5 6	F 1 2 3 4 5 6 7	G	H
(1) Drugs containing new active ingredients	○ ○ ○	○ ○ ○	○ ○ ○	○ ○ Δ	○ ○ ○ ○ × Δ	○ ○ ○ Δ ○ Δ Δ	○	○
(2) New prescription combination drugs	○ ○ ○	× ○ ○	○ ○ ○	○ Δ Δ	○ ○ ○ ○ × Δ	○ ○ × × × Δ ×	○	○
(3) Drugs with new routes of administration	○ ○ ○	× ○ ○	○ ○ ○	○ Δ Δ	○ ○ ○ ○ × Δ	○ ○ × Δ ○ Δ Δ	○	○
(4) Drugs with new indications	○ ○ ○	× × ×	× × ×	○ × ×	Δ Δ Δ Δ × Δ	× × × × × × ×	○	○
(5) Prescription drugs with new dosage forms	○ ○ ○	× ○ ○	○ ○ ○	× × ×	○ ○ ○ ○ × Δ	× × × × × × ×	○	○
(6) Drugs with new dosages	○ ○ ○	× × ×	× × ×	○ × ×	○ ○ ○ ○ × Δ	× × × × × × ×	○	○
(7) Biosimilar Products	○ ○ ○	○ ○ ○	○ Δ Δ	○ × ×	Δ Δ Δ Δ × Δ	Δ ○ × × × Δ Δ	○	○
(8) Prescription drugs with additional dosage forms (during reexamination period) (8-2) Prescription drugs with additional dosage forms (not during reexamination period)	○ ○ ○	× ○ ○	Δ Δ ○	× × ×	× × × ×○ ×	× × × × × × ×	×	○
(9) Prescription combination drugs with similar formulations (during reexamination period) (9-2) Prescription combination drugs with similar formulations (not during reexamination period)	○ ○ ○	× ○ ○	○ ○ ○	Δ Δ ×	× × × × × ×	○ Δ × × × Δ ×	○	○
(10) Other prescription drugs (during reexamination period) (10-2) Other prescription drugs (Same with (10), changes in manufacturing method of biological products, etc.) (10-3) Other prescription drugs (not during reexamination period) (10-4) Other prescription drugs (Same with (10-3), changes in manufacturing method of biological products, etc.)	× × ×	× Δ ○	× × ○	× × ×	× × × ×○ ×	× × × × × × ×	×	○ 1)

Note 1) The marks and numbers in the columns on the right indicate the marks and numbers of the data specified in Attached Table 1, and the marks have the following meanings, in principle: ○: Data required ×: Data not required △ : Data required depending on individual cases

Note 2) Note 1) in column on the right signifies as follows.

1) Only for applications that do not involve any change to information contained in the attached data, including change to the manufacturing method or change to the testing method, the attachment of data under H is not required, in principle.

(Table 3) **Drug classification system**

(1) “Prescription drugs with new active ingredients” refer to drugs that have ingredients never before been used as active ingredients in drugs that have already been approved for manufacture/marketing or are specified in the Japanese Pharmacopoeia (“approved drugs, etc.” hereinafter).
(2) “New combination prescription drugs” refer to drugs with different active ingredients or combining ratios from those of combination drugs specified in the Japanese Pharmacopoeia or combination drugs that have already been approved for manufacture/marketing as prescription drugs. However, combination prescription drugs with similar formulations specified in (8) and drugs such as digestive enzyme combination drugs and mild acting poultices that are judged not to be new from an overall evaluation are excluded.
(3) “Prescription drugs with new administration routes” refer to drugs that have the same active ingredients as approved drugs, etc. but have different routes of administration (oral, subcutaneous, intramuscular, intravenous, percutaneous, per-rectal, transvaginal, eye drops, nasal drops, inhalation, etc.).
(4) “Prescription drugs with new indications” refer to drugs that have the same active ingredients and routes of administration as approved drugs, etc. but have different indications.
(5) “Prescription drugs with new dosage forms” refer to drugs that have the same active ingredients, routes of administration and indications as approved drugs, etc. but have new dosage forms with different administration, etc. because of pharmaceutical changes such as sustained release. However, drugs with additional dosage forms specified in (7) are excluded.
(6) “Prescription drugs with new doses” refer to drugs that have the same active ingredients and routes of administration as approved drugs, etc. but have different doses.
(7) “Biosimilar products” refer to biotechnological products equivalent to existing (approved) biotechnological products in quality
(8) “Prescription drugs with additional dosage forms” refer to drugs that have the same active ingredients, routes of administration, indications and dosage and administration as approved drugs, etc., but have different dosage forms or contents.
(9) “Combination prescription drugs with similar formulations” refer to prescription drugs with active ingredients and combining ratios that are judged to be similar to those of combination drugs specified in the Japanese Pharmacopoeia or combination drugs that have already been approved for manufacture/marketing as prescription drugs.
(10) “Other prescription drugs” refer to biological products such as vaccines and blood products entered in the Biological Product Standards; recombinant DNA drugs, cell culture drugs and other drugs applying biotechnology or drugs derived from living organisms.

A	Origin or background of discovery, conditions of use in foreign countries	1. Origin or background of discovery 2. Conditions of use in foreign countries 3. Special characteristics, comparisons with other drugs, etc.
B	Manufacturing methods, standards and test methods	1. Chemical structure and physicochemical properties, etc. 2. Manufacturing methods 3. Standards and test methods
C	Stability	1. Long-term storage tests 2. Tests under severe conditions (stress tests) 3. Accelerated tests
D	Pharmacological action	1. Tests to support efficacy 2. Secondary pharmacology, 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, subacute, and chronic toxicity, teratogenicity, and other types of toxicity	1. Single dose toxicity 2. Repeated dose toxicity 3. Genotoxicity 4. Carcinogenicity 5. Reproductive toxicity 6. Local irritation 7. Other toxicity
G	Clinical studies	Clinical trial results
H	Information in the attached data, etc. provided for in Article 52, Paragraph 1 of the Law	Information in the attached data, etc.

Table 4 Data to be Submitted with an Application for a Non-prescription Drug (Attached Table 2-2 in PFSB Notification No. 1121-(2) dated November 21, 2014

Left Column	Right Column							
	A 1 2 3	B 1 2 3	C 1 2 3	D 1 2 3	E 1 2 3 4 5 6	F 1 2 3 4 5 6 7	G	H
(1) Drugs containing new active ingredients	○ ○ ○	○ ○ ○	○ ○ ○	○ ○ △	○ ○ ○ ○ × △	○ ○ ○ △ ○ △ △	○	○
(2) Drugs with new routes of administration	○ ○ ○	× ○ ○	○ ○ ○	○ △ △	○ ○ ○ ○ × △	○ ○ × △ ○ △ △	○	○
(3-1) Drugs with new indications	○ ○ ○	× × ×	× × ×	○ × ×	△ △ △ △ × △	× × × × × × ×	○	○
(3-2) Prescription drugs with new dosage forms	○ ○ ○	× ○ ○	○ ○ ○	× × ×	○ ○ ○ ○ × △	× × × × × × ×	○	○
(3-3) Drugs with new dosages	○ ○ ○	× × ×	× × ×	× × ×	○ ○ ○ ○ × △	× × × × × × ×	○	○
(4) Non-prescription drugs with new active ingredients for non-prescription drugs	○ ○ ○	× × ○	△ × △ *2	× × ×	△ × × × × ×	△ △ × × × △ △	○	○
(5-1) Non-prescription drugs with new administration routes for non-prescription drugs	○ ○ ○	× × ○	△ × △ *2	× × ×	△ × × × × ×	△ △ × × × △ △	○	○
(5-2) Non-prescription drugs with new indications for non-prescription drugs	○ ○ ○	× × ×	× × ×	× × ×	△ × × × × ×	× × × × × × ×	○	○
(5-3) Non-prescription drug with new formulation for non-prescription drug	○ ○ ○	× × ○	△ × △ *2	× × ×	△ × × × × ×	× × × × × × ×	○	○
(5-4) Non-prescription drugs with new doses for non-prescription drugs	○ ○ ○	× × ×	× × ×	× × ×	△ × × × × ×	× × × × × × ×	○	○
(6) New non-prescription combination drugs	○ ○ ○	× × ○	△ × △ *2	× × ×	△ × × × × ×	△ △ × × × △ ×	○	○
(7-1) Non-prescription combination drugs with similar formulations	× × ○	× × ○	△ × △ *2	× × ×	△ × × × × ×	△ △ × × × × ×	×	○
(7-2) Non-prescription combination drugs with similar dosage forms	× × ○	× × ○	△ × △ *2	× × ×	△ × × × × ×	× × × × × × ×	×	○
(8) Other non-prescription drugs (drugs with approval standards, etc)	× × ○ 1)	× × ○	△ × △ 2)	× × ×	× × × × × ×	× × × × × × ×	×	×

Note 1) The marks and numbers in the columns on the right indicate the marks and numbers of the data specified in Attached Table 1, and the marks have the following meanings, in principle: ○: Data required ×: Data not required △: Data required depending on individual cases

Note 2) Notes 1) and 2) in column on the right signify as follows.

1) A drug product that conforms to approval standards may be applied by submitting a comparison table of the standards and active ingredient(s) and its amount(s). A non-drug product must be documented with the basis of formulation development, efficacy, safety, and other necessary characteristics.

*22) Long-term stability data are necessary if stability for more than 3 years is not ensured by accelerated stability tests. If the product is confirmed to be stable for at least 1 year based on ongoing long-term stability tests, the application itself is acceptable. The final report of the long-term tests must be submitted until approval.

(Table 4) **Drug classification system**

(4) “Non-prescription drugs with new active ingredients for non-prescription drugs” refer to non-prescription drugs other than drugs with new active ingredients and contain ingredients not used as active ingredients in approved non-prescription drugs.
(5) (5-1) “Non-prescription drugs with new administration routes for non-prescription drugs” refer to non-prescription drugs other than drugs with new routes of administration and contain the same active ingredients as approved non-prescription drugs but have different routes of administration. (5-2) “Non-prescription drugs with new indications for non-prescription drugs” refer to non-prescription drugs other than drugs with new indications and have the same active ingredients and routes of administration as approved non-prescription drugs but have different indications. “Non-prescription drugs with new dosage forms for non-prescription drugs” refer to non-prescription drugs other than drugs with new dosage forms and have the same active ingredients, routes of administration and indications as approved non-prescription drugs but have a new dosage form leading to changes in dosage/administration because of pharmaceutical changes such as sustained release, which are classified into either of non-prescription drugs or guidance-mandatory drugs. "Non- prescription drugs with new dosage/administrations for non-prescription drugs” refer to non-prescription drugs other than drugs with new dosage/administrations and have the same active ingredients and routes of administration as approved non-prescription drugs but have different dosage/administrations, which are classified into either of non-prescription drugs or guidance-mandatory drugs.
(6) “New non-prescription combination drugs” refer to non-prescription drugs with the same ingredients as active ingredients of approved non-prescription drugs but with a different active ingredient composition, which are classified into either of non-prescription drugs or guidance-mandatory drugs. Those determined to have a similar active ingredient composition to approved non-prescription drugs are excluded. Basically, the drugs in No. 1. (1)-(1) a) to f) in Notification No. 0331053 of the PFSB dated March 31 2008 are equivalent to new non-prescription combination drugs.
(7) (7-1) “Non-prescription combination drugs with similar formulations” refers to drugs with ingredients the same as active ingredients of approved non-prescription drugs that are non-prescription drugs with similar combinations of active ingredients as approved non-prescription drugs. (7-2) “Non-prescription drugs with similar dosage forms” refer to non-prescription drugs with the same active ingredients, routes of administration and indications as approved non-prescription drugs but with different dosage forms, but they are not equivalent to drugs in (5)-(3) among non-prescription drugs with different dosage forms.
(8) “Other non-prescription drugs” refers to non-prescription drugs that are not equivalent to the drugs in (1) to (7).

A Origin or background of discovery, conditions of use in foreign countries	1. Origin or background of discovery 2. Conditions of use in foreign countries 3. Special characteristics, comparisons with other drugs, etc.
B Manufacturing methods, standards and test methods	1. Chemical structure and physicochemical properties, etc. 2. Manufacturing methods 3. Standards and test methods
C Stability	1. Long-term storage tests 2. Tests under severe conditions (stress tests) 3. Accelerated tests
D Pharmacological action	1. Tests to support efficacy 2. Secondary pharmacology, 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, subacute, and chronic toxicity, teratogenicity, and other types of toxicity	1. Single dose toxicity 2. Repeated dose toxicity 3. Genotoxicity 4. Carcinogenicity 5. Reproductive toxicity 6. Local irritation 7. Other toxicity
G Clinical studies	Clinical trial results
H Information in the attached data, etc. provided for in Article 52, Paragraph 1 of the Law	Information in the attached data, etc.

Table 5 Classification of Clinical Studies According to Objectives

Type of study	Objective of study	Study examples
Human pharmacology studies	• Assess tolerance • Define/describe PK and PD • Explore drug metabolism and drug interactions • Estimate activity	• Dose-tolerance studies • Single and multiple dose PK and/or PD studies • Drug interaction studies • ADME studies
Therapeutic exploratory studies	• Explore use for the targeted indication • Dose-response exploration studies • Provide basis for confirmatory study design, endpoints, methodologies	• Earliest studies of relatively short duration in well-defined narrow patient populations, using surrogate or pharmacological endpoints or clinical measures
Therapeutic confirmatory studies	• Demonstrate/confirm efficacy • Establish safety profile • Provide an adequate basis for assessing the benefit/risk relationship to support licensing	• Adequate, and well controlled studies to establish efficacy • Safety studies • Large simple studies
Therapeutic use studies	• Refine understanding of benefit/risk relationship in general or special populations and/or environments • Identify less common adverse reactions • Refine dosing recommendation	• Comparative effectiveness studies • Studies of mortality/morbidity outcomes • Large simple studies • Pharmacoeconomic studies

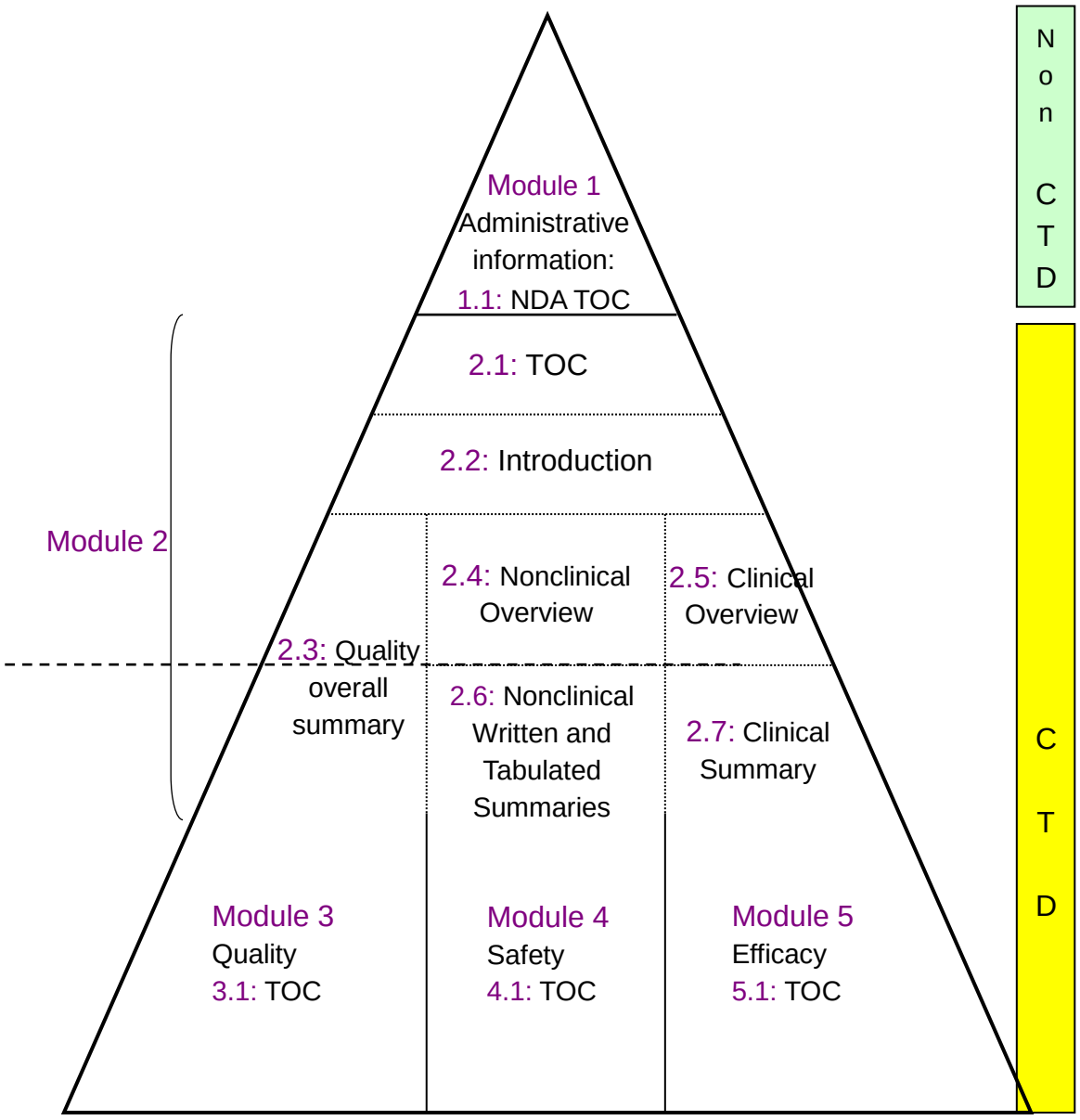


Fig. 10 Organization of ICH Common Technical Documents

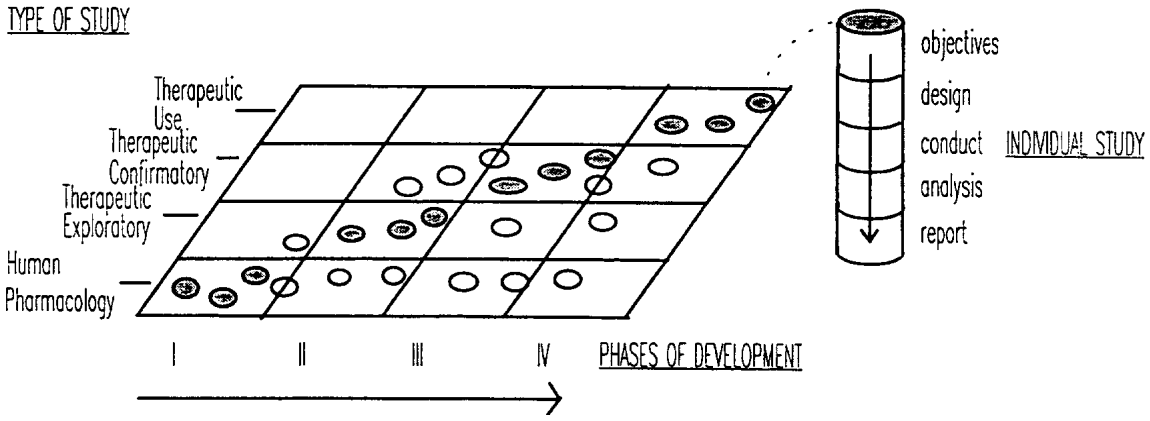


Fig. 11 Correlation between Development Phases and Types of Study

This matrix graph illustrates the relationship between the phases of development and types of study by objective that may be conducted during each clinical development of a new medicinal product. The shaded circles show the types of study most usually conducted in a certain phase of development, the open circles show certain types of study that may be conducted in that phase of development but are less usual. Each circle represents an individual study. To illustrate the development of a single study, one circle is joined by a dotted line to an inset column that depicts the elements and sequence of an individual study.

Table 6 ICH topics and guidelines - Progress of harmonization

as of December 24, 2014 http://www.pmda.go.jp/ich/w/topic.pdf

	Quality		
	Code	Previous code	Topics
Step 5	Q1A(R2)		Stability testing: New drug substances and products
	Q1B		Stability testing: Photostability
	Q1C		
	Q1D		
	Q1E		
	Q2(R1)	Q2A, Q2B	Validation of analytical procedures: Text and methodology
	Q3A(R2)		Impurities in new drug substances
	Q3B(R2)		Impurities in new drug products
	Q3C(R5)	Q3C, Q3C(M)	Impurities: Residual solvents
	Q4B		Pharmacopoeias: Harmonized texts for use in ICH regions
	Q4B(Annex1)(R1)		Test for residue on ignition
	Q4B(Annex2)(R1)		Test for extractable volume of parenteral preparations
	Q4B(Annex3)(R1)		Test for particulate contamination of parenteral preparations
	Q4B(Annex4A, 4B, 4C) (R1)		Microbial limit tests of non-sterile products
	Q4B(Annex6)(R1)		Uniformity of dosage units
	Q4B(Annex5)(R1)		Disintegration test
	Q4B(Annex7)(R2)		Dissolution test
	Q4B(Annex8)(R1)		Sterility test
	Q4B(Annex9)(R1)		Tablet friability test
	Q4B(Annex10)(R1)		Polyacrylamide gel electrophoresis
	Q4B(Annex11)		Capillary electrophoresis
	Q4B(Annex12)		Analytical sieving
	Q4B(Annex13)		Bulk density and tapped density of powders
	Q4B(Annex14)		Bacterial endotoxins test
	Q5A(R1)	Q5A	Quality of biotechnology products: Viral bioburden
	Q5B		Quality of biotechnology products: Genetic stability
	Q5C		Quality of biotechnology products: Stability Testing of products
	Q5D		Quality of biotechnology products: Cell bank control (cell substrates)
	Q5E		Quality of Biotechnology Products: Comparability of products
	Q6A		Specifications/test methods: Chemicals/pharmacopoeial harmonization
	Q6B		Specifications/test methods: Biological products
	Q7	Q7A	GMP for active pharmaceutical ingredients
	Q8(R2)		Pharmaceutical development

	Q9 Q10 Q11		Quality risk management Pharmaceutical quality system Manufacturing and development of active pharmaceutical ingredients
Step 4	Q3D		Guideline for metal impurities
Step 3			
Step 2a/2b			
Step 1	Q12		Technical and regulatory considerations for pharmaceutical product lifecycle management

	Safety		
	Code	Previous code	Topics
	S1A		Need for carcinogenicity studies
	S1B		Testing of carcinogenicity of pharmaceuticals
	S1C(R2)	S1C, S1C(R)	Dose selection for carcinogenicity studies
	S2(R1)		Genotoxicity
	S3A		Toxicokinetics: Assessment of systemic exposure in toxicity studies
	S3B		Pharmacokinetics: Repeated-dose tissue distribution
	S4	S4, S4A	Single- and repeated-dose toxicity studies
	S5(R2)	S5A, S5B	Reproduction studies of medicinal products
	S6(R1)		Safety evaluation of biological products
	S7A		Safety pharmacology studies
	S7B		The non-clinical evaluation of QT interval prolongation potential
	S8		Immunotoxicology studies
	S9		Non-clinical evaluation of anticancer pharmaceuticals
	S10		Guidance on photosafety testing

	Efficacy		
	Code	Previous code	Topics
Step 5	E1		The extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life threatening condition
	E2A		Clinical safety data management: Definitions and standards for expedited reporting in the clinical phase
	E2B(R2)	E2B(M)	Data elements for transmission of individual case safety reports
	E2B(R3)		Implementation guide – data elements and message specification in individual case safety reports (ICSR)
			Periodic Benefit-Risk Evaluation Report(PBRER)
	E2C(R2) E2D		Post-approval safety data management
	E2E E2F		Pharmacovigilance planning (PVP)
	E3		Development of safety update report (DSUR)
	E4		Structure and content of clinical study reports
	E5(R1)		Dose-response information to support drug registration
	E6(R1)	E5	Ethnic factors in the acceptability of foreign clinical data
	E7		Guidance for good clinical practice
	E8	E6	Studies in support of special populations: Geriatrics
	E9		General considerations for clinical trials
	E10		Statistical principles for clinical trials
	E11		Choice of control group and related issues in clinical trials
	E12		Clinical investigation of medicinal products in the pediatric population
	E14		Principles for clinical evaluation of new antihypertensive drugs
	E15	E12A	The clinical evaluation of QT interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs
	E16		Definitions for genomic biomarkers, pharmacogenomics, pharmaco- genetics, genomic data, and sample coding categories
			Genomic biomarkers related to drug response: Context, structure and format of qualification submissions
Step 4			
Step 3			
Step 2a/2b			

Step 1 **Step 5**			
Step 4			
Step 3			
Step 2a/2b			
Step 1	S1 S11		Testing of carcinogenicity of pharmaceuticals (review of guideline) Nonclinical safety testing in support of development of pediatric medicines

	Multidisciplinary		
	Code	Previous code	Topics
Step 5	M1 M2 M3(R2) M4 M8	 M3(M)	Medical dictionary for regulatory activities (MedDRA) Electronic standards for transmission of regulatory information Non-clinical safety studies for the conduct of human clinical trials e-CTD specification (v. 3.2.2)
Step 4			
Step 3	M7		Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to reduce potential carcinogenic risk
Step 2a/2b			
Step 1	M8 M4E(R2)		e-CTD specification (v.4.0) Guideline on enhancing the format and structure of benefit-risk information in CTD