CHAPTER 4

POST-MARKETING SURVEILLANCE OF DRUGS

Post-marketing surveillance (PMS) to assure the quality, efficacy and safety of drugs after they go on the market and to establish proper methods of use of drugs consists of three systems: the ADRs and infections collection and reporting system, the reexamination system, and the reevaluation system (**Fig. 13** Pharmaceutical Post-marketing Surveillance System).

The re-examination system for new drugs was introduced in the October 1979 amendment of the Pharmaceutical Affairs Law, and Good Post-marketing Surveillance Practice (GPMSP) came into effect from April 1993 to assure proper implementation of PMS and also to assure the reliability of such PMS data. Thereafter, major revisions were made in the Pharmaceutical Affairs Law and its Enforcement Regulations in 1996 to 1997 to further strengthen post-marketing safety measures, and the GPMSP, which had formerly been considered as an administrative notification, became law in "MHW Ordinance for Good Post-Marketing Surveillance Practice of Drugs (Drug GPMSP)" and came into effect in April 1997 (MHW Ordinance No. 10 dated March 10, 1997). The Drug GPMSP was partially revised by MHW Ordinance No. 151 dated December 27, 2000, and "Early Post-marketing Phase Vigilance" for new drugs was newly established to reinforce safety measures in an early phase of marketing (enforced from October 1, 2001).

The GPMSP is applied as standards requiring compliance by manufacturers or importers when performing post-marketing surveillance or studies, and also as compliance criteria for preparation of data.

Periodic reporting of safety information on new drugs, etc. was agreed at the ICH in January 1996, and the periodic safety update report (PSUR) system was introduced by Notification No. 32 of the Safety Division, PMSB dated March 27, 1997 to replace the previous annual reporting system with the PSUR (MHW Ordinance No. 29 dated March 27, 1997) and the Guidelines on Methods for Surveillance of Results of Use of Prescription Drugs (Notification No. 34 of the Safety Division, PMSB dated March 27, 1997) were specified for drug use-result surveys to be intensively implemented after marketing. However, because of an increase in post-marketing ADRs not observed in the clinical trial stage of drug development and implementation of safety measures, regulations on safety measured for drugs (Notification No. 25 of the Safety Division, PMSB) and entries in case report forms for ADRs and infections (Office Communication) were specified in March 11, 1998. Furthermore, additional guidelines, "Periodic Infection Reporting System for Biological Products" (Notification No. 0515008 of the PMSB dated May 15, 2003) and "Implementation of Early Post-marketing Phase Vigilance for Prescription Drugs" (Notification No. 0324001, the Safety Division, PFSB dated March 24, 2006) were issued to further strengthen the safety monitoring of medical products (**Fig. 14** Post-marketing Collection and Reporting of Pharmaceutical Safety Information).

In the revised Pharmaceutical Affairs Law enforced on April 1, 2005, the historical manufacturing approval system was changed to the marketing (as well as manufacturing) authorization system to internationally harmonize the concept of approval system, and the part that deals with the collection, evaluation, and assessment of information for appropriate use of post-marketing safety measures of the MHLW Ordinance on GPMSP related to the implementation of safety assurance measures was separated from the part

that deals with tests and surveillance conducted to collect and assess materials for reexamination and reevaluation. The former has been specified in the MHLW Ordinance on GVP (MHLW Ordinance Related to Standards for Post-Marketing Safety Management of Drugs, quasi-drugs, Cosmetics and Medical Devices, MHLW Ordinance No. 135 dated September 22, 2004), and the latter in the MHLW Ordinance on GPSP (MHLW Ordinance Related to Standards for Conducting Post-Marketing Surveys and Studies on Drugs; MHLW Ordinance No. 171 issued by MHLW on December 20, 2004). The MHLW Ordinance on GPMSP was abolished.

The Guidelines on Pharmacovigilance Planning (ICH E2E guidelines) (Notification No. 0916001 of the Evaluation and Licensing Division, PFSB and Notification No. 0916001 of the Safety Division, PFSB both dated September 16, 2005) were issued with an objective of guiding and assisting the applicant in planning pharmacovigilance activities for new drug in the early post-marketing phase. Since the environment for utilizing the medical information database system (MID-NET) in pharmacovigilance is being established, "Basic Concept of the Use of Medical Information Database in Post-marketing Pharmacovigilance " (Notification No. 0609-(8) of the Pharmaceutical Evaluation Division, PSEHB / Notification No. 0609-(4) of the Safety Division, PSEHB dated June 9, 2017) was issued in June 2017. Thus, the basic concept to be applied when a marketing authorization holder for drugs use the medical information database in post-marketing pharmacovigilance was presented. In April 2018, “Handling of administrative procedures for applications, etc. related to the use of MID-NET” (Notification No. 0401001 from Director of Regulatory Science Center, PMDA, dated April 1, 2018) was issued, and the operation of the MID-NET was started on a full scale. Various information on the notifications related to the use of MID-NET is posted on the website of PMDA.

http://www.pmda.go.jp/safety/mid-net/0002.html

The GPSP Ministerial Ordinance was revised on October 26, 2017 to add "post-marketing database survey" as a type of post-marketing survey. "Announcement of Ministerial Ordinance Partially Revising Ministerial Ordinance Related to Standards for Conducting Post-Marketing Surveys and Studies on Drugs (Related to MHLW Ordinance Related to Standards for Conducting Post-Marketing Surveys and Studies on Drugs)" (Notification No. 1026-(1) of the Evaluation and Licensing Division, PSEHB dated October 26, 2017) was issued and enforced on April 1, 2018. In association with this revision, "Procedures for Developing Post-marketing Database Survey Plan" was presented by PMDA in January 2018 as a reference for preparation of a post-marketing database survey plan, and "Points to Consider for Ensuring Reliability in Post-marketing Database Surveys of Drugs" (Notification No. 0221-(1) of the Pharmaceutical Evaluation Division, PSEHB dated February 21, 2018) was issued in February 2018. The Q&As for this notification were issued in June 2019 (Office Communication dated June 19, 2019). Moreover, since this revision clarified the positioning of post-marketing surveys using medical information database as a technique of post-marketing surveys, and implementation of efficient and effective surveys with the choice of the scientific technique for the objectives of the survey has come to be required, "How to Proceed with Examination for Development of Plans for Post-marketing Surveys, etc." was proposed by PMDA on January 23, 2018 and the procedure of basic examination for development of a plan for conducting post-marketing surveys, etc. was proposed.

In 2012, the Risk Management (RMP) Guidance (Notification No. 0411-(1) of the Safety Division, PFSB and No. 0411-(2) of the Evaluation and Licensing Division, PFSB both dated April 11, 2012) was issued to support the manufacturing/marketing authorization holder in developing the RMP

including risk minimization plans for the reduction of treatment-related risks in addition to conventional pharmacovigilance plans following drug approval. These Notifications are applicable to manufacturing/marketing approval application for new drugs and biosimilar products submitted on or after April 1, 2013 and August 26, 2014, respectively. Further, the MHLW Ordinances on GVP and GPSP were revised on March 11, 2013 to ensure the development and subsequent implementation of risk management plan (RMP). In March 2016, “Preparation and publication of drug risk management plan” (Notification No. 0331-(13) of the Evaluation and Licensing Division, PSEHB and Notification No. 0331-(13) of the Safety Division, PSEHB both dated March 31, 2016) and “Points to be considered in submission of publication documents of drug risk management plan” (Notification No. 0331001 of the Office of Safety, PMDA dated March 31, 2016) were issued. To promote use of RMPs in clinical practices, these notifications presented points to be considered in preparation and publication of RMP synopsis as well as submission of publication documents to PMDA."Description on Materials Prepared and Distributed for Additional Risk Minimization Activities in Risk Management Plan (RMP)" (Office Communication dated June 8, 2017) was issued. It was decided to display RMP marks on the materials for health professionals and the materials for patients in order to enable health professionals to be aware that the materials such as the guide to proper use are based on the drug risk minimization activities in RMP. In addition, "Partial Revision of 'Publication of Drug Risk Management Plan'" (Notification No. 1029-(1) of the Pharmaceutical Evaluation Division, PSEHB and Notification No. 1029-(1) of the Safety Division, PSEHB dated October 29, 2018) was issued, and placement of the materials prepared based on RMP for health professionals and for patients on the website of PMDA was decided. In May 2019, “Points to Consider in Preparation of Materials for Minor Changes of Drug Risk Management Plan (Q&As)” was issued (Office Communication dated May 10, 2019).

The Law for Partial Amendment of the Pharmaceutical Affairs Law (Law No. 84, 2013) was issued on November 27, 2013, in which regenerative medicine products were newly defined. In line with the provisions in Article 23-21, Item 2 in the revised Law, the “Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices” (Pharmaceutical and Medical Device Act), the MHLW Ordinance on GVP (MHLW Ordinance for the standards for post-marketing safety management of drugs, quasi-drugs, cosmetics, medical devices and regenerative medicine products) was partially revised to be the standards for licensing manufacturing/marketing business of regenerative medicine product and to include the provisions for subcontract of post-marketing safety management tasks specified in Article 18, Paragraph 3, etc. in the Law (Article 98 in the Enforcement Regulations).

Furthermore, the GPSP Ordinance for regenerative medicine products was newly issued in response to the new approval system established in consideration of characteristics of regenerative medicine products (the MHLW Ordinance for standards for conducting post-marketing surveys and studies on regenerative medicine products; 2014 MHLW Ordinance No. 90, dated July 30, 2014). To conduct use-results survey or post-marketing clinical study of a regenerative medicine product, applicable documents have to be prepared under this ordinance. More specific handling procedures were shown in the notification “Description methods of basic plan for evaluation of post-marketing approval conditions and basic plan of post-marketing surveys for regenerative medicine products” (Notification No. 0826-(1) of the Medical Devices Division, PFSB dated August 26, 2015). Since the environment for using medical information

database for collection of post-marketing safety information, etc. for cellular and tissue-based products, etc. is being established, the GPSP Ordinance was partially revised and enforced also for cellular and tissue-based products in the same way as drugs.

Based on the Guidelines, Periodic Safety Update Reports (PSUR) for Marketed Drugs which objective was the standardization of the format and time of safety reporting, the new Guidelines, the Periodic Benefit-Risk Evaluation Report (PBRER: ICH E2C (R2)) with the objective of assessing not only risks but also integrated risk-benefit balance and a guidance for assisting safety report writing was issued (Notification No. 0517-(1) of the Evaluation and Licensing Division, PFSB both dated May 17, 2013). In August 2014, Q&A on PBRER was also issued (Office Communication, August 25, 2014).

The use of the Medical Dictionary for Regulatory Activities (MedDRA) as agreed by ICH is recommended to standardize international regulatory-related medical terminology (M1) use at all regulatory levels before and after marketing for regulatory communication in registration, records, and safety monitoring of drugs. Efforts are being made to achieve international coordination of terminology related to pharmaceutical regulations (adverse reactions, signs and symptoms, diagnosis, indications, laboratory tests, surgical and conservative interventions and patient characteristics). Since the end of March 2000, it has been possible to use MedDRA for clinical trial data, reexamination and reevaluation data and package inserts. It is used in data input, retrieval, evaluation, and presentation at both the pre- and post-marketing regulatory stages for drugs. From October 27, 2003, it became obligatory to use MedDRA in individual case safety reports to be submitted to the PMDA in accordance with the ADRs and Infections Reporting System. MedDRA is maintained by the Maintenance and Support Service Organization (MSSO) and two new versions are generally published each year.

1. GVP

Good Vigilance Practice (GVP) establishes standards for post-marketing safety management related to the collection, evaluation, and assessment of proper use information on the establishment of appropriate safety-related organizations and systems as one of licensing requirements for the manufacturing/marketing authorization holder, development and implementation of relevant SOPs, marketed drugs, etc., and to the implementation of measures for safety assurance. On March 11, 2013, the GVP was revised to incorporate the RMP in the GVP guidelines.

The extent of duties of the manufacturing/market authorization holder in post-marketing safety management to be entrusted to third parties is defined in the Ordinance for Enforcement of the Pharmaceutical and Medical Device Act.

This GVP consists of 17 articles. A summary is provided below.

(1) Purpose (Article 1)

This Ministerial Ordinance establishes the standards established by the MHLW Ordinance related to post-marketing safety management set forth in Article 12-2, Paragraph 2 of the Pharmaceutical and Medical Device Act.

(2) Definitions of terms (Article 2)

[1] Safety management information refers to material relating to the quality, efficacy or safety of drugs etc. and any other information required for the proper use of drugs, etc.

[2] Quality assurance activities refers to any activity related to post-marketing quality control concerned with requisite

measures based on the collection and study of safety management information, or on the results.

[3] The RMP refers to safety assurance activities including clinical information collection, post-marketing surveys, clinical studies, and other activities for minimizing potential risks inherent in the use of new drugs, etc. with an objective of adequate risk control of new drugs, etc. by analyzing safety and efficacy information to be thus obtained and implementing necessary safety assurance measures. These activities are undertaken by the manufacturing/marketing authorization holder following commencement of marketing of new drugs, etc. that poses specific safety and/or efficacy concerns. The RMP is specified as a condition of approval.

[4] Person in charge of drug information and person in charge of medical device information refer to persons whose main duties consist of collecting and providing safety assurance information through visits to health care professionals in order to contribute to the proper use of drugs or medical devices.

Articles 3 to 12 are specified for the first type of manufacturing/marketing authorization holder (manufacturing/marketing authorization holders of prescription drugs, highly controlled medical devices or regenerative medicine product).

(3) Duties of general marketing compliance officer (Article 3)

The general marketing compliance officer must undertake the following duties.

[1] To supervise the safety management supervisor.

[2] To respect the opinions of the safety management supervisor.

[3] To assure close coordination with the safety management supervisor, quality assurance supervisor, and other persons involved in safety management.

[4] To closely collaborate with the supervisor of post-marketing surveys, etc. in implementing the RMP.

(4) Organizations and personnel involved in safety assurance (Article 4)

[1] A department (safety management department) meeting the following requirements must be established to handle all duties related to safety assurance.

- This department is under the supervision of the general manufacturing/marketing supervisor
- This department must employ adequately qualified and competent personnel who are able to undertake safety assurance activities properly and smoothly.
- This department should be independent of all divisions responsible for marketing drugs and other departments that would hinder proper and smooth safety assurance activities.

[2] A safety management supervisor meeting the following requirements must be appointed.

- The safety management supervisor is the supervisor of the safety management department.
- This supervisor must have been engaged for at least 3 years in safety assurance work or related work.
- This supervisor must have the ability to properly and smoothly undertake safety assurance activities.
- This supervisor must not belong to any

division responsible for marketing drugs, and do not have any other factors that may hinder proper and smooth implementation of safety assurance work.

[3] When whole or part of the safety assurance activities are undertaken by persons other than the safety management supervisor, a supervisor of the work concerned (safety management implementation supervisor) must be appointed.

(5) Standard operating procedures for post-marketing surveillance (Article 5)

[1] The following standard operating procedures for post-marketing safety management must be prepared.

- Procedures for collection of safety management information
- Procedures for drafting of safety assurance measures based on examination of safety management information and the results thereof
- Procedures for implementation of safety assurance measures
- Procedures for reporting from safety management supervisors to general marketing compliance officer
- Procedures for reporting from safety management implementation supervisor to safety management supervisors
- Procedures for implementing the RMP (including procedures for early post-marketing phase vigilance) when the RMP is required in practice
- Procedures for in-house inspections
- Procedures for education and training
- Procedures for retention of records
- Procedures for mutual cooperation with quality assurance supervisors and other supervisors engaged in work related to marketing of prescription drugs, highly controlled medical devices, or cellular and tissue-based products
- Procedures for collaborating with the supervisors on post-marketing surveillance and other post-marketing obligations when the RMP is required in practice
- Other procedures necessary for properly and smoothly implementing safety assurance measures of post-marketing surveillance

[2] The duties and management system for persons employed for work related to post-marketing safety management must be specified in writing.

[3] Items required for proper and smooth implementation of safety assurance activities must be specified in writing.

[4] When the procedures in [1] or the documents in [2] and [3] are prepared or revised, they must be dated and retained.

[5] The general marketing compliance officer shall make available the procedures in [1], the documents in [2] and [3] and other documents required for safety assurance work in the office performing the work and also must make available copies of procedures and other related documents in other offices performing safety assurance work.

(6) Duties of the safety management supervisor (Article 6)

[1] The safety management supervisor shall perform the following duties:

- Overall supervision of safety assurance work
- Confirmation that safety assurance work is being performed properly and smoothly and preparation and retention

of records of such confirmation
- Offering of opinions in writing to general marketing compliance supervisor when safety assurance work is required and retention of copies of such opinions
- To closely collaborate with the supervisor of post-marketing surveys, etc. in implementing the RMP.

(7) Collection of safety management information (Article 7)

[1] The following safety management information shall be collected by the safety management supervisor and safety management implementation supervisor and records thereof shall be prepared.
- Information from health professionals
- Information on reports presented at scientific meetings, reports from the literature and other research reports
- Information from the Ministry of Health, Labour and Welfare, other government institutions, prefectural governments and PMDA
- Information from foreign governments and overseas organizations
- Information from other pharmaceutical manufacturing/marketing authorization holders
- Other safety management information

[2] The safety management implementation supervisor shall report the records in [1] in writing to the safety management supervisor.

[3] The safety management supervisor shall preserve the records in [1] and reports in [2].

(8) Drafting of safety assurance measures based on examination of safety management information and the results thereof (Article 8)

[1] The safety management supervisor shall perform the following duties:
- Examine the collected safety management information without delay and record the results thereof.
- Supply all safety information that the quality assurance supervisor, etc. must be familiar with in writing without delay to the quality assurance supervisor, etc.
- When it is confirmed necessary from an examination of safety management information, measures shall be drafted to discard, recall or suspend marketing of the product, revise package inserts, supply information to health professionals by persons in charge of drug information, medical device information, or information about cellular and tissue-based products, make reports to the Minister of Health, Labour and Welfare, and take other safety assurance measures.
- Drafts of safety assurance measures shall be reported in writing to the general marketing compliance officer and copies shall be retained.

[2] When the safety management supervisor has the safety management implementation supervisor examine safety management information, he or she shall issue instructions in writing and retain a copy. Records of the examination performed by the safety management implementation supervisor shall be prepared and reported in writing. The safety management supervisor shall retain these results.

(9) Implementation of safety assurance measures (Article 9)

[1] The general marketing compliance

officer must undertake the following duties:

- Appropriately evaluate drafts of safety assurance measures, decide the safety assurance measures to be taken and prepare and retain records thereof.
- When safety management supervisors undertake safety assurance measures, instructions shall be issued in writing and retained
- When safety management implementation supervisors undertake safety assurance measures, instructions shall be issued in writing and the safety management supervisor shall retain copies. The safety management implementation supervisor shall prepare records and make reports in writing. The copies shall be given to the safety management supervisor.

[2] The safety management supervisor shall perform the following duties:

- Safety assurance measures shall be undertaken based on instructions from the general marketing compliance officer and records thereof shall be prepared and retained.
- When safety assurance measures are undertaken by safety management implementation supervisors, instructions shall be issued in writing and copies shall be retained. Records shall be prepared, reported in writing and retained.
- The results of implementation of safety assurance measures shall be reported in writing to the general marketing compliance officer, and copies shall be retained.
- Copies of reports from the safety management implementation supervisor shall be retained.

[3] Evaluation of drafts of safety assurance measures for which post-marketing safety management standard operating procedures have been specified beforehand, deciding on safety assurance measures to be taken, and preparation and retention of records can be undertaken by the safety management supervisor in place of the general manufacturing/marketing supervisor. In this case, necessary matters regarding the works prescribed in [1] and [2] should be stipulated in the standard operating procedures for post-marketing safety management, etc.

(10) Risk management plan (RMP) (Article 9-(2))

[1] The general marketing compliance officer or the safety management supervisor must undertake the following duties in implementing the RMP:

- Preparation of protocol for individual RMPs (“RMP protocol”) that contain the following information:
- Specific safety and efficacy issues to be addressed
- Outline of plans and procedures for information collection, survey, and study of safety and efficacy issues to be resolved
- Outline of risk minimization activities
- Time schedules of the RMP implementation status and evaluation
- Other necessary items
- Revision of the RMP protocol as situations may require
- When the RMP protocol is prepared or revised, the protocol shall be dated and retained.

[2] The general marketing compliance officer must make available the RMP

protocol in his/her office and also must make available copies of the RMP protocol specifying assigned activities and procedures in other offices performing the compliance activities.

[3] The safety management supervisor must confirm that the RMP is being adequately and smoothly implemented, and shall retain records of such confirmation.

[4] Whenever performing RMP-related activities, the safety management implementation supervisor must records the activities performed and report the activities in writing to the safety management supervisor, and the safety management supervisor must retain the reports.

(11) Early post-marketing phase vigilance (Article 10)

[1] The general marketing compliance officer and the safety management supervisor must undertake the following duties in implementing early post-marketing phase vigilance (a survey performed for risk management of new drugs, etc. over a 6-month period following launch to promote optimal use in practice and closely monitor serious ADRs of new drugs, etc.).

- Preparation of a protocol based on the RMP for individual post-marketing phase vigilances (early post-marketing phase vigilance protocol) containing the following information:
- Objective of early post-marketing phase vigilance
- Method of early post-marketing phase vigilance
- Period of early post-marketing phase vigilance
- Other necessary items
- Revision of the early post-marketing phase vigilance protocol, as situations may require
- When the early post-marketing phase vigilance protocol is prepared or revised, the protocol shall be dated and retained.

[2] The general marketing compliance officer shall make available early post-marketing phase vigilance protocol in the office performing the work and also must make available copies in other offices performing surveillance work.

[3] The safety management supervisor shall confirm that early post-marketing phase vigilance is being performed appropriately and smoothly and records of such confirmation shall be prepared and retained.

[4] When early post-marketing phase vigilance is performed by the safety management implementation supervisor, the safety management implementation supervisor shall prepare records and report in writing to the safety management supervisor, and the safety management supervisor shall retain such reports.

(12) In-House inspections (Article 11)

[1] In-house inspections of duties related to post-marketing safety management shall be performed on a regular schedule by a person appointed beforehand.

[2] When the person appointed beforehand in [1] is the safety management supervisor, the safety management supervisor shall prepare and retain records of in-house inspections.

[3] When the person appointed beforehand in [1] is a person other than the safety management supervisor, that person

shall prepare records of in-house inspections and report in writing to the safety management supervisor. The safety management supervisor shall retain these reports.

[4] The safety management supervisor shall report the results of the in-house inspection in writing to the general marketing compliance officer and shall retain a copy of the report.

[5] The general marketing compliance officer shall examine the necessity of improvements in post-marketing safety management based on the results of in-house inspections and when improvements are necessary, the general marketing compliance officer shall undertake the specified measures and prepare records thereof. The safety management supervisor shall retain these records.

(13) Education and training (Article 12)

[1] The general marketing compliance officer shall prepare and retain education and training protocols for employees engaged in duties related to post-marketing safety management

[2] Education and training shall be performed as planned by a person appointed beforehand.

[3] When the person appointed beforehand in [2] is the safety management supervisor, the safety management supervisor shall prepare and retain records of education and training.

[4] When the person appointed beforehand in [2] is a person other than the safety management supervisor, that person shall prepare records of education and training and report in writing to the safety management supervisor. The safety management supervisor shall retain these reports.

[5] The safety management supervisor shall report the results of the education and training in writing to the general marketing compliance officer and shall retain a copy of the report.

(14) Standards for post-marketing safety management of type 2 marketing authorization holders (marketing authorization holders of drugs other than prescription drugs and controlled medical devices, including marketing authorization holders of in vitro diagnostics) (Articles 13 and 14)

The standards for type 1 marketing authorization holders shall apply *mutatis mutandis* with the exception of the following:

[1] Establishment of a safety management division is not specified.

[2] No qualifications for safety management supervisors are specified.

[3] No qualifications for a safety management implementation supervisor are specified.

(15) Standards for post-marketing safety management of type 3 marketing authorization holders (Marketing authorization holders of quasi-drugs, cosmetics and ordinary medical devices) (Articles 15)

The standards for type 1 marketing authorization holders shall apply mutatis mutandis with the exception of the following:

[1] [1] to [3] in Article (14) above.

[2] Standard operating procedures for post-marketing safety management are not specified.

[3] Collection of safety information in (7) for quasi-drugs and cosmetics is limited to research reports and other safety

management information.

[4] In-house inspections and education and training are not specified.

(16) Retention of records related to safety assurance (Article 16)

[1] The period of retention of 5 years from the date when the records are no longer utilized. However, the period shall be 10 years for biological products and cellular and tissue-based products, 30 years for specified biological products and specified cellular and tissue-based products, and 15 years for designated controlled medical devices and highly controlled medical devices. Records related to in-house inspections and education and training shall be kept for 5 years from the date of preparation

[2] Records specified by Ministerial Ordinance can be retained by persons designated by the marketing authorization holder based on the standard operating procedures for post-marketing safety management, etc.

2. GPSP

The GPSP (Good Post-marketing Study Practice) specifies items that are to be strictly complied with in order to achieve appropriate post-marketing surveillance and studies conducted by manufacturing/marketing authorization holders, and to assure the reliability of data submitted when applying for reexamination or re-evaluation. On March 11, 2013, the GPSP was revised to harmonize its provisions with those of GVP in view of the incorporation of the RMP in the GVP. Furthermore, some ordinances were revised on April 1, 2018 because the environment for using medical information database for collection of information of post-marketing safety, etc. of drugs is being established.

The GPSP consists of 12 articles, which are summarized below.

(1) Purpose (Article 1)

This Ministerial Ordinance sets forth the items that must be strictly complied with by manufacturing/marketing authorization holders of drugs in conducting post-marketing surveillance and studies.

This GPSP applies to inspections, etc. of documents and data related to reexamination and reevaluation of prescription drugs. For post-marketing clinical studies forming part of post-marketing surveillance, GCP is also applicable, in addition to GPSP.

(2) Definitions of terms (Article 2)

[1] Post-marketing surveys, etc. refers to drug use-results surveys, post-marketing database surveys, or post-marketing clinical studies that the manufacturing/marketing authorization holder of drugs conducts in order to collect, screen, confirm or verify information relating to the quality, efficacy and safety of drugs.

[2] Drug use-results survey refers to a survey to screen or confirm information related to the incidence of each disease due to adverse drug reactions, together with the quality, efficacy and safety of drugs. Such surveys include general use-results surveys, special use results surveys, and surveys for comparing use-results.

[3] Post-marketing database survey refers to a survey conducted to screen or confirm information related to the incidence of each disease due to adverse drug reactions, together with quality, efficacy and safety using medical information databases offered by the

business handling information database.

[4] Post-marketing clinical study refers to a study performed to verify assumptions arrived at as a result of studies undertaken with regard to results of clinical studies, drug-use surveys, or post-marketing database survey, or a study conducted in accordance with approved dosage and administration, and indications to collect information on quality, efficacy and safety unobtainable in routine medical practice..

(3) Standard operating procedures for post-marketing surveillance (Article 3)

The following standard operating procedures for post-marketing surveillance shall be prepared by the manufacturing/marketing authorization holder for the proper and smooth conduct of post-marketing surveillance. When standard operating procedure for post-marketing surveillance is prepared or revised, the written procedure should be dated and retained.

[1] Procedures related to drug use-results surveys

[2] Procedures related to post-marketing database surveys

[3] Procedures related to post-marketing clinical studies

[4] Standards related to in-house inspections

[5] Procedures related to education and training of personnel involved in post-marketing surveys, etc.

[6] Procedures related to the outsourcing of duties in post-marketing surveys, etc.

[7] Procedures related to the preservation of records involving duties in post-marketing surveys, etc.

[8] Any other procedures necessary for appropriate and smooth implementation of post-marketing surveys, etc.

(4) Supervisor of post-marketing surveys, etc. (Article 4)

[1] A supervisor of the manufacturing/marketing authorization holder must be appointed to coordinate the duties involved in post-marketing surveys, etc. (supervisor of post-marketing surveys, etc.).

[2] The supervisor of post-marketing surveys, etc. must not be a member of a department involved in marketing.

[3] Duties to be performed by the supervisor of post-marketing surveys, etc.:

- To prepare and preserve a basic protocol for post-marketing surveys, etc. describing the overview of drug-use results, post-marketing database surveys, and post-marketing clinical studies for each drug individually.
- To set forth in writing protocols for the implementation of drug use-results surveys, protocol for post-marketing database survey, protocol for post-marketing clinical studies, and any other matters necessary for conducting post-marketing surveys, etc. in accordance with the standard operating procedures for post-marketing surveys, etc. and the basic protocol on post-marketing surveys, etc. (instead, the RMP, if available)
- To revise the basic protocol for post-marketing surveys, etc. as required.
- In cases in which a basic protocol for post-marketing surveys, etc. is prepared or revised, to date and preserve it.
- When it is considered necessary for the conduct of post-marketing surveys, etc., to provide written opinions to the manufacturing/marketing authorization holder, and to preserve these documents

or copies thereof.

[4] A basic protocol for post-marketing surveys, etc. is not required to be prepared or retained when the RMP is available and retained.

[5] The manufacturing/marketing authorization holder must respect the opinions provided by the supervisor of post-marketing surveys, etc.

[6] The manufacturing/marketing authorization holder must not make any statements that would interfere with the supervisor of post-marketing surveys, etc. in the performance of his or her duties.

(5) Post-marketing surveys, etc. (Article 5)

[1] Duties to be performed by the supervisor of post-marketing surveys, etc.:

- To prepare plans, proposals and surveys for implementation of post-marketing surveys, etc.
- To confirm that post-marketing surveys, etc. are conducted properly and smoothly in accordance with the standard operating procedures for duties for post-marketing surveys, etc. and the basic protocol on post-marketing surveys, etc. (instead the RMP, if available)
- To provide notification in writing of the results of post-marketing surveys, etc. to the manufacturing/marketing authorization holder (instead the manufacturing/marketing authorization holder and the safety management supervisor, if the RMP is available)

[2] The manufacturing/marketing authorization holder must arrange that, for each drug use-results survey, post-marketing database survey, or post-marketing clinical trial, records are prepared and preserved in order that the supervisor of post-marketing surveys, etc. understands the conditions under which the surveys or tests were conducted.

[3] The manufacturing/marketing authorization holder must instruct the supervisors on post-marketing surveillance and other post-marketing obligations to report in writing the conduct and outcomes of each drug-use results survey, post-marketing database survey, and post-marketing clinical studies to the safety management supervisor when the RMP is available for practice.

(6) Drug use-results surveys (Article 6)

[1] The manufacturing/marketing authorization holder must instruct the supervisor or other designated person to conduct drug use-results surveys according to the post-marketing surveillance SOP, etc.

[2] Contracts in writing must be concluded with the medical institutions competent in conducting the drug use-results survey and preserved.

[3] Contract may be handled by electronically.

[4] In protocols for drug use-results surveys, the purpose of the survey, subjects to be investigated, range of subjects to be investigated, survey method, survey period, items surveyed, analytical items and method and other necessary matters must be established.

The procedures [1] to [3] shall be adopted when a post-marketing database survey is conducted. In this case, "use-results survey" should be read as "post-marketing data base survey," and "medical institution" as " the business handling information database."

(7) Post-marketing clinical studies (Article 7)

[1] The manufacturing/marketing authorization holder must perform post-marketing studies by the post-marketing surveillance supervisor or other person designated by the manufacturing/marketing authorization holder based on the post-marketing surveillance, etc.

[2] The studies must be conducted in compliance with GCP

(8) In-House inspections (Article 8)

[1] The manufacturing/marketing authorization holder must conduct in-house inspections on a regular schedule. Items that have been audited based on GCP do not require in-house inspections.
In cases in which a person other than the supervisor of post-marketing surveys, etc. conducts an in-house inspection, the supervisor of post-marketing surveys, etc. is to be notified in writing of the results of the inspection. Records of the results of the in-house inspection are prepared and preserved.

[2] Post-marketing surveillance supervisors must report in writing the results of the self-inspections to the manufacturing/marketing authorization holder.

[3] When it is found that improvements must be made in the work based on the results of the self-inspection, the necessary measures must be taken, and records of these measures must be prepared and retained.

(9) Education and training (Article 9)

[1] Planned education and training related to post-marketing surveillance must be performed by the post-marketing surveillance supervisors or other persons designated by the manufacturing/marketing authorization holder for persons employed in post-marketing surveillance work.

[2] In cases in which education and training are performed by a person other than the supervisor of post-marketing surveys, etc., the supervisor of post-marketing surveys, etc., is notified in writing of the conditions of its implementation.

[3] Records of education and training are prepared and preserved.

(10) Delegation of duties of post-marketing surveys, etc, (Article 10)

The manufacturing/marketing authorization holder may assign some of the duties of post-marketing surveys, etc. to persons who are capable of properly and effectively carrying out these activities.

(11) Preservation of records in connection with post-marketing surveys, etc. (Article 11)

Records of reexamination and reevaluation data must be retained for 5 years from the date that reexamination or reevaluation is completed. Other records must be preserved for 5 years from the date they are no longer in actual use or date of the final entry.

(12) Standards for Compliance of Reexamination and Reevaluation Data in Connection with Post-marketing Surveillance (Article 12)

In addition to provisions of the GCP MHLW Ordinance, the provisions of Article 3 through Article 8, Article 10, and Article 11 of this GPSP MHLW apply mutatis mutandis to the collection and preparation of data for reexamination and reevaluation applications in

connection with post-marketing surveys, etc.

3. PAPER COMPLIANCE REVIEW AND ON-SITE GPSP SURVEYS OF DATA FOR REEXAMINATION AND REEVALUATION

Documents and data submitted for reexamination and reevaluation of a drug are subject to paper compliance review and on-site GPSP surveys in order to examine whether the materials for evaluation have been collected in accordance with the standards specified by the MHLW minister. Detailed procedures for the compliance review and on-site surveys are available as “the Guidelines on Compliance Paper Reviews on Approval Application Data for New Drugs” (Notification No. 1121-(5) of the Evaluation and Licensing Division, PFSB dated November 21, 2014), and “the Guidelines for Implementation of GPSP On-site Surveys” (Notification No. 0330003 of the Evaluation and Licensing Division, PFSB dated March 30, 2005). The "Guidelines for Implementation of GPSP On-site Surveys” is partially revised in September 2018 (Notification No. 0913-(9) of the Pharmaceutical Evaluation Division, PSEHB dated September 13, 2018). Procedures for applying paper review and on-site surveys are specified in the “Application Procedures for Paper Review-Conformity Inspection and On-site GCP Inspection of Data for the Reexamination and Reevaluation of Drugs” (Notification No. 1121007 of the PMDA dated November 21, 2014). The notification is partially revised in September 2018 (Notification No. 0913026 of the PMDA dated September 13, 2018). On July 21, 2016, a service of consultation on compliance review for drug reexamination was introduced. This service has allowed an applicant to consult about compliance of the following documents with the reliability standards: applicable documents are planned to be attached in the application for drug reexamination and are related to the previously completed post-marketing clinical studies and use-results surveys.

4. ADVERSE DRUG REACTIONS AND INFECTIONS REPORTING SYSTEM

Programs for collecting and reporting safety information on drugs such as adverse drug reactions include an adverse drug reaction reporting system undertaken by pharmaceutical companies, the drug and medical device safety information reporting system undertaken by medical personnel, and the WHO International Drug Monitoring Program whereby drug safety information is exchanged among various countries (

Fig. 15 Collection and Reporting of Pharmaceutical Safety Information).

4.1 Adverse Drug Reaction and Infectious Disease Reporting System by Pharmaceutical Companies

This system, based on the Pharmaceutical and Medical Device Act (Article 68-10), requires the reporting of safety findings by pharmaceutical companies to the PMDA for information processing. In light of the medical problems such as the development of AIDS associated with the use of HIV-contaminated, unheated blood products, provisions were established in the revised Pharmaceutical Affairs Law, which came into effect in April 1997, to mandate reporting of "adverse drug reactions" and the "occurrence of infections suspected to be caused by the use of the drug concerned."

Revisions in the Enforcement Regulations of the Pharmaceutical Affairs Law, which became effective at the same time, based on items agreed to at the International Conference on Harmonization (ICH), also have defined the scope of "serious cases" subject to reporting. In addition, regulatory information such as measures adopted in overseas to discontinue marketing of a drug due to safety

concerns must now be reported.

The collection and examination of Japanese and overseas drug safety information, as well as the adoption of specific measures based on this information, must be carried out in accordance with the standard operating procedures for post-marketing safety management (GVP).

The provisions in Article 228-20 of the Enforcement Regulations for reporting adverse drug reactions specify reporting within 15 days and within 30 days. The type of cases requiring reporting within 15 days was specified in Notification No. 0317006 of the PFSB dated March 17, 2005 for enforcement of MHLW Ordinance for Partial Amendment of the Enforcement Regulations of Pharmaceutical Affairs Law (Reporting of Adverse Drug Reactions. etc). This change was intended to assure focused supervision of serious cases caused by adverse reactions of drugs with little post-marketing clinical experience and to coordinate reporting criteria for adverse drug reactions with international standards. A summary of these provisions is presented below.

(1) Reporting within 15 days

The following must be reported within 15 days from the time they are first known:

a) The cases described below include suspected adverse reactions to the drug concerned reported both in Japan and overseas. These also include cases where the occurrence of an adverse reaction, its incidence, and/or the conditions of onset was unexpected based on the precautions in the package insert of the drug concerned (previously unknown serious cases).
   (1) Death
   (2) Disability
   (3) Any events possibly leading to death or disability
   (4) Any case that requires hospitalization for treatment or prolongs the duration of hospitalization.
   (5) Any other serious cases involving items (1) through (4) above
   (6) Any congenital disease or anomaly in the offspring of a treated patient.

b) Any case involving items (1) through (6) above resulting from any unknown or known infections due to use of the drug concerned, including cases both in Japan and overseas.

c) Any implementation of measures by regulatory authorities in foreign countries such as suspension of marketing of the drug.

d) Known deaths

e) Changes in onset trends of known serious adverse drug reactions that would result in or increase public health hazards.

f) Serious cases considered to be caused by adverse reactions of drugs with new active ingredients within 2 years from the date of approval (known or unknown).

g) Serious cases discovered in early post-marketing phase vigilance among adverse reactions of drugs other than drugs with new active ingredients for which early post-marketing phase vigilance is an approval condition (known or unknown).

(2) Reporting within 30 days

The following must be reported within 30 days from the time they are first known:

a) Any cases involving items (2) through (6) in subsection (a) of the previous section attributed to a known adverse reaction of the drug concerned occurring in Japan (known serious cases).

b) Research reports about the drug concerned, which demonstrate that it

does not have an approved indication in Japan and overseas.

To the Enforcement Regulations of the Pharmaceutical and Medical Device Act, a provision was added on malfunction reports involving a part of device or equipment in drug products approved to be manufactured/marketed with other components including devices or equipment in an integrated form (combination products). It specifies that such reports shall be handled in accordance with provisions for reporting criteria and deadline of malfunction reports of medical devices. In addition, as the Pharmaceutical and Medical Device Act specifies reporting requirements for adverse drug reactions of regenerative medicine products, the Enforcement Regulations included provisions for reporting criteria and deadline of malfunction reports of regenerative medicine products. (Notification No. 1002-(20) of PFSB dated October 2, 2014 “Reporting of adverse drug reactions”)

This notification imposes manufacturers and marketing authorization holders on the following reporting obligations: if a reportable malfunction occurs on the device part without reportable adverse drug reactions, they must submit malfunction report only; and if a reportable malfunction occurs with adverse drug reaction, they must submit both malfunction report and adverse drug reaction report.

In June 2017, "Amendment to "Q&As on Reports of Adverse Reactions to Combination Products" (Office Communication dated June 9, 2017) was issued.

(3) Periodic reports of unknown non-serious adverse reactions of drugs

The degree of seriousness of cases of adverse drug reactions was conventionally classified into three grades: serious, moderate and mild, but the classification has been changed to the two-stage serious and non-serious system used internationally. Cases suspected of being caused by adverse drug reactions that are unknown and non-serious must be reported periodically.

To further expedite assessments of adverse drug reactions by pharmaceutical companies, and to promote reporting of these adverse reactions in a more timely and proper manner, specific criteria for assessment of cases subject to reporting have been established by the Standards for Classification of Serious Adverse Drug Reactions (Notification No. 80 of the Safety Division, PAB dated June 29, 1992).

This seriousness classification of adverse drug reactions includes the following nine categories: liver, kidneys, blood, hypersensitivity, respiratory tract, gastrointestinal tract, cardiovascular system, neuropsychiatry, and metabolic and electrolyte abnormalities.

The scope of “seriousness” was defined in April 1997 based on agreements at the ICH conference and details of the agreement on the ICH E2D guideline were announced as “the Standards for expediting reporting of post-approval safety data” (Notification No. 0328007 of the Safety Division, PFSB dated March 28, 2005).

From October 27, 2003, three submission methods have been specified for E2B/M2: (1) via the Internet, (2) mainly FD (disk) reports together with paper reports, and (3) mainly paper reports with FD reports attached. In July 2013, the Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs) (ICH E2B [R3]) was summarized and then its Japanese version was issued (Notification No. 0708-(5) of the Evaluation and Licensing Division and Notification No. 0708-(1) of the Safety Division, PFSB both dated July 8, 2013). Then, “ADR Reporting in Post-marketing Surveillance and Clinical Trials in accordance with the

Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs) (E2B (R3))" (Notification No. 0917-(1) of the Evaluation and Licensing Division and Notification No. 0917-(2) of the Safety Division, PFSB both dated September 17, 2013) was issued for guiding principles on how to handle safety reporting and recommends reporting via internet to further promote electronic data processing and electronic database compilation. In March 2017, this notification was revised completely (Notification No. 0331-(6) of the Evaluation and Licensing Division, PSEHB / Notification No. 0331-(1) of the Safety Division, PSEHB dated March 31, 2017). Handling of reports of post-marketing adverse reactions before unblinding in post-marketing blinded clinical trials, etc., was stipulated. Handling of electronic transmission of the reports of adverse reactions to quasi drugs and cosmetic products was also stipulated. In addition, this notification was partially revised because of the partial changes in the handling of electronic reports of post-marketing overseas cases of infection and overseas cases of adverse reactions (Notification No. 0710-(1) of the Pharmaceutical Evaluation Division, PSEHB and Notification No. 0710-(1) of the Safety Division, PSEHB). Furthermore, "Q&As on ADR Reporting in Post-marketing Surveillance and Clinical Trials in accordance with the Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs) (E2B (R3))" (Office Communication dated November 28, 2017) was published, and Q&A was revised in association with the partial revision of the previous notification mentioned above (Office Communication dated July 10, 2019).

Furthermore, the procedures including precautions for reception and reporting of the reports of post-marketing adverse reactions and adverse reactions in clinical studies were partially revised, and "Points to Consider in ADR Reporting in Post-marketing Surveillance and Clinical Trials in accordance with the Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs) (E2B (R3))" (Notification No. 0331001 of the Office of Review Management of PMDA / Notification No. 0331001 of the Office of Safety I of PMDA / Notification No. 0331002 of the Office of Safety II of PMDA dated March 31, 2017) was issued. As related notifications, "Corrections on Implementation Guide for electronic Transmission of Individual Case Safety Reports" (Notification No. 0315-(6) of the Pharmaceutical Evaluation Division, PSEHB / Notification No. 0315-(1) of the Safety Division, PSEHB dated March 15, 2017) and "Q&A on Electronic Transmission of Individual Case Safety Reports" (Office Communication dated November 8, 2018), and the “User guide regarding the use of EDQM terms for the dosage form and route of administration in safety reports of individual patients in E2B (R3) messages” (Office Communication dated November 8, 2018) were issued, and Q&A was revised in September 2019 (Office Communication dated September 26, 2019).

From January 2006, access to all cases of suspected adverse drug reactions reported by companies has been possible on the homepage of the PMDA.
http://www.pmda.go.jp/safety/info-services/drugs/adr-info/suspected-adr/0005.html

4.2 Drug and Medical Device Safety Information Reporting System by Medical Personnel

This is a MHLW reporting system that directly collects safety information from health professionals. Because of the need for collection of further information required for post-marketing product safety strategies, the limitation on reporting facilities was eliminated in July 1997. This system has been expanded and revised to include all medical

institutions and pharmacies, and the reporting format has been simplified in order to further increase the number of reports from physicians, dentists, and pharmacists. Furthermore, the need of report as the duty of medical personnel was specified in the Pharmaceutical Affairs Law in July 2003 (Article 77-(4)-2-2).

* The Pharmaceutical Affairs Law revised on June 14, 2006 also requests the registered manufacturing/marketing authorization holder to report safety information.

The information subject to reporting includes adverse reactions associated with the use of prescription medicines, over-the-counter drugs, medical devices, etc. with the exception of mild, well-known adverse events, even though a causal relationship with the drug concerned is unclear.

When drugs and related products require especially intensive investigation and collection of information, the MHLW selects medical institutions and, if necessary, performs "early post-marketing phase safety information collection program (fixed-point survey)" in collaboration with them.

4.3 Reporting of Adverse Drug Reactions from Patients

With the aim of collecting reports on the suspected cases of adverse drug reactions directly from patients or their families, thereby utilizing the information in taking safety measures for drugs, the implementation guidelines for “Reporting of adverse drug reactions from patients” were established, and the reception was started at PMDA (Notification No. 0326-(1) of the Safety Division, PSEHB dated March 26, 2019). The contents of the reports from the patients were as shown below.

(1) Reporter: Patients who experienced symptoms suggestive of adverse drug reactions after the use of the drug or their families

(2) Drugs to be reported: Prescription drugs, guidance-mandatory drugs, and non-prescription drugs manufactured and marketed in Japan

(3) Reporting method: PMDA website or postage mail

(4) Items reported:

- Information on the reporter
- Information on patients
- Information on the drug which is suspected to have caused the symptoms suggestive of adverse drug reactions
- Information on other drugs used
- Information on symptoms
- Information on medical institutions that can provide detailed information

When information is reported, the PMDA will confirm the contents reported, and enter the information on the database, except for personal information including the name, etc. PMDA will organize the information reported, and report them to the Ministry of Health, Labour and Welfare periodically. The Ministry of Health, Labour and Welfare will report the status of reporting to the Committee on Safety of Drugs of the Council on Drugs and Food Sanitation, and will take any necessary safety measures.

Information on the reported cases will be publicized on the website of PMDA after being processed in a way that individual patients cannot be identified.

4.4 WHO International Drug Monitoring Program

Because of the necessity of safety measures to be implemented for drugs on an international level in view of the deformation scandal caused by thalidomide in 1961, the World Health Organization (WHO) first implemented an international drug-monitoring program in 1968. Adverse drug reaction data is collected from all participating

member states, and a summary of the results of evaluation of this information is sent back to each country. Japan became a member of this program in 1972. Information about adverse drug reactions that occur in Japan has been reported to WHO, and likewise, WHO has provided any necessary information to Japan. There is also information exchange with countries including the United States, Great Britain, and Germany.

5. PERIODIC INFECTION REPORTS FOR BIOLOGICAL PRODUCTS (ARTICLE 68-14 AND 68-24 IN THE LAW)

With the revision of the Pharmaceutical Affairs Law in July 2002, drugs manufactured from materials derived from humans or other living organisms (excluding plants) that require caution in terms of public health and hygiene are designated as biological products by the MHLW, as a lesion from incidents of AIDS infection and Creutzfeldt-Jacob disease due to contaminated blood coagulation factors. From July 30, 2003, the system of periodic infection reports was introduced by which manufacturers of such biological products must evaluate their products based on findings obtained from the latest reports on infections caused by raw materials of the products and report the results every 6 months to the Minister.

In April 2017, "Notification on the System of Periodic Infection Reports for Regenerative Medicine Products and Biological Products" (Notification No. 00428-(1) of the PSEHB dated April 28, 2017) was issued to change the format of reports, and to require submission of the reports by electronic media. Moreover, "Q&A on the System of Periodic Infection Reports for Regenerative Medicine Products and Biological Products" (Office Communication dated July 29, 2017) was issued in July 2017.

6. REEXAMINATION SYSTEM (ARTICLE 14-4 AND 23-29 OF THE PHARMACEUTICAL AFFAIRS LAW)

The reexamination system is aimed at reconfirmation of the clinical usefulness of drugs by performing GPSP or GVP as one aspect of PMS, through collecting information on the efficacy and safety of the drug during a specified period of time after approval. This system was commenced in April 1980. Based on the revision of October 1993, the reexamination period for orphan drugs was extended to a maximum of 10 years.

There are limitations on the quantity and quality of data submitted for review at the time of approval of a new drug. Examples of such limitations include relatively small numbers of subjects in clinical studies performed prior to approval, relatively short use data of the drug, and lack of experience using the drug under diverse conditions such as concomitant medication, complications, and age. There are limitations on confirmation of all of these aspects before approval.

It is, therefore, obligatory for manufacturing/marketing companies to perform postmarketing surveillance of their drugs after approval in order to determine if any problems have arisen with efficacy when the drug is used in actual practice, or to see if the level of efficacy has not been changed by factors such as dosage, duration of administration, complications or concomitant medication. In terms of safety, any marked increase in the incidence of ADRs and changes in the incidence of ADRs due to factors such as dosage, duration of administration, complications, or concomitant medication should be detected and assessed.

When the revised Pharmaceutical Affairs Law was enforced from April 1997, the surveillance and studies required for reexamination applications must be performed in compliance with the GPMSP, GCP or GLP depending on their objective. It is also

obligatory to prepare application data in accordance with these standards. Based on the revision of the Law in April 2005, the GPMSP has been abolished and replaced with the GPSP and GVP.

6.1 Designation for Reexamination of Drugs

The drugs subject to reexamination include products designated by the MHLW at the time of marketing approval as drugs with, for example, active ingredients, quantities of ingredients, dosage and administration, and/or indications that are distinctly different from drugs that have already been approved (Article 14-4 of the Law).

The timing when these drugs should be reexamined is designated by the MHLW at the time of their approval as new drugs. The times that reexaminations should generally be conducted for specific products are given below.

(1) Reexamination 10 years after the date of approval:
- Orphan drugs

(2) Reexamination 8 years after the date of approval:
- Drugs containing new active ingredients

(3) Reexamination 6 years after the date of approval:
- Drugs with new routes of administration

(4) Reexamination from 4 to within 6 years after the date of approval:
- New prescription combination drugs
- Drugs with new indications
- Drugs with new dosages

When pharmacoepidemiological surveys or clinical studies for setting pediatric doses performed, the study period can be prolonged before completion of the reexamination period as required (maximum reexamination period: 10 years).

When an additional indication is obtained during the reexamination period, the reexamination period for the additional indication will be as described below.

- When the existing indication is a usual indication
  When the additional indication is a usual indication: 4 years or the residual period of the reexamination period for the existing indication
  When the additional indication is an indication of an orphan drug: 10 years
- When the existing indication is an indication of an orphan drug
  When the additional indication is a usual indication: 5 years and 10 months
  When the additional indication is an indication of an orphan drug: 10 years

6.2 Periodic Safety Reports (Article 63 of the Enforcement Regulations of the Law)

On the basis of agreements at the ICH concerning the periodic safety update report (PSUR) system, however, a "periodic safety report system" was enacted into law at the time of revision to the Pharmaceutical Affairs Law in April 1997. In May 2013, the PSUR system was replaced with the periodic benefit-risk evaluation report (PBRER) system following the release of ICH E2C (R2) guidelines.

As the base date for the reporting period of these reports, the concept of the international birth date in the PBRER system was introduced. Based on this concept, the date designated by the MHLW at the time of approval is established as the base date. The frequency of reports is every 6 months during the first 2 years from this base date. Thereafter, reports are to be submitted once each year during the remaining period of reexamination. The drugs for which these reports are applicable include prescription medicines designated for reexamination (medical devices are subject to annual reporting as

previously). In the event that a drug is marketed in a foreign country, reports must specify any adverse drug reactions that appeared in that country and information about any regulatory measures adopted. In addition, when PBRER prepared by foreign companies should be appended to the Japanese Periodic Safety Report together with the information obtained in drug use-results survey in the section "Future Safety Measures Planned on the Basis of Surveillance Results" in the Periodic Safety Report, and submitted, or the contents of the PBRER should be compiled and incorporated into the Japanese Periodic Safety Report and submitted. Either method is acceptable. A summary of the report items to be submitted includes the following:

- Period of the survey
- Number of cases surveyed
- Quantity of product shipped
- Status of implementation of drug use-results survey
- Summary of the surveillance results and analysis of the data
- Incidence of adverse drug reactions classified by type
- A list of cases in which adverse drug reactions occurred
- Measures adopted to ensure proper product use such as revisions of the precautions
- Package inserts
- Future safety measures planned on the basis of surveillance results

6.3 Data Required for Reexamination Applications and Reexamination Procedures

Post-marketing surveillance to acquire data required for reexamination applications, including drug use-results surveys, post-marketing database surveys, and post-marketing clinical trials, must be implemented in accordance with the GPSP. The data must also be collected and prepared in accordance with these standards (post-marketing clinical trials must be conducted also in compliance with the GCP).

Applications for reexamination must be completed within 3 months from the time of the designated base date. The data submitted and organization of this data should generally be as described below, with a focus on data from post-marketing surveys, etc. In addition, for any other research data acquired after drug approval related to indications and/or safety of the drug concerned, a Periodic Safety Report submitted near the date of the reexamination application should be attached.

(1) Summary of data for reexamination applications

The data should include a summary of the drug specified in the application; specific details up to the time of reexamination application including the changes in quantity and value of product shipped and the estimated number of patients who used the drug, the status of approval and sales overseas; summary of post-marketing surveillance; information about safety and efficacy; conclusion; and references.

(2) Data Attached to Reexamination Applications

This data should include summary of drug use-results surveys; post-marketing database surveys, and post-marketing clinical trial reports; data from patients who have developed adverse drug reactions or infections; data from research reports; reports of specific measures adopted in Japan and overseas; and reports of serious adverse drug reactions.

(3) Compliance survey data

This includes data from GPSP compliance reviews as well as data from GCP and/or GLP compliance reviews as required.

(4) Reference data

This includes, for example, case report forms

used in drug use-results surveys, package inserts at the time of reexamination application, summaries of replies, review reports, a summary of the data at the time of product approval application (for Evaluation Committees), copies of approval forms, and a copy of periodic safety report submitted closest to the reexamination application.

Reexamination is based on submission of the above application data. **Fig. 16** Reexamination System is a flow diagram of this reexamination process. After the application is received, the PMDA evaluates compliance with standards such as GPSP and conducts surveys on quality, efficacy, and safety. The application is next reviewed by the Department on Drugs of the PAFSC. Then, the MHLW issues an official report of the results of the examination. The results of these examinations are classified into one of the three approval categories shown below, and any required specific measures are adopted. Article 14 Paragraph 2-3 of the Pharmaceutical Affairs Law specifies three reasons for refusal of approval. These include cases where (1) the indications of the drug stated in the application have not been demonstrated; (2) the drug exhibits prominent harmful effects that outweigh any target indications, thus rendering the product not useful; and (3) the drug is judged to be markedly inappropriate with respect to public health and hygiene because of its characteristics or quality.

* Designated Classifications

[I] Approval refused (manufacturing and marketing suspended, approval revoked)
[II] Changes in approval (modifications in approved items as directed)
[III] Approved (as per application for reexamination)

In November 2017, "Documents to be Attached to Application for Reexamination of New Prescription Drugs" (Notification No. 1128-(2) of the Pharmaceutical Evaluation Division, PSEHB dated November 28, 2017) was issued, and handling of reexamination documents was reconsidered to incorporate the concept of RMP in reexamiation, to evaluate the benefit-risk balance of drugs more appropriately and to seek its maintenance and improvement, and to cope with revision of GPSP Ordinance. This notification will be applied to the application for reexamination to be filed on October 1, 2019 or after that. In association with issuance of this notification, "Partial Revision of 'Format of Appendix to Periodic Safety Update Report and Other Procedure of Description'" (Notification No. 1128-(5) of the Pharmaceutical Evaluation Division, PSEHB and Notification No. 1128-(4) of the Safety Division, PSEHB dated November 28, 2017, and "Partial Revision of 'Procedures of Paper Compliance Review and On-site GPSP Surveys of Data for Reexamination and Reevaluation of Drugs '" (Notification No. 1128005 of the Evaluation and Licensing Division, PFSB dated November 28, 2017) were also issued. In June 2018, "Questions and Answers (Q&As) for 'Documents to be Attached to Application for Reexamination of New Prescription Drugs'" (Office Communication dated June 1, 2018) was issued.

7. REEVALUATION SYSTEM (ARTICLES 14-6 AND 23-31 OF THE LAW)

The reevaluation of drugs is a system whereby the efficacy and safety of a drug, which has already been approved, is reconsidered on the basis of the current status of medical and pharmaceutical sciences. This system was initiated in December 1971 on the basis of administrative guidance in Notification No. 610 of the PMSB dated July 7, 1971. From January 1985, reevaluations were based on the Pharmaceutical Affairs Law, and the new reevaluation system came into effect from May

1988.

New Reevaluation System:

This new reevaluation system aimed at reevaluations of the efficacy and safety of all prescription drugs was started in May 1988. These reevaluations are at first performed by means of a review by the PAFSC. When the Council's decision requires further literature surveys by the manufacturers, they are required to perform such surveys according to the provisions of the Pharmaceutical Affairs Law (**Fig. 17** Reevaluation System).

The new reevaluations were designated from February 1990.

The MHLW has implemented various measures related to generic drugs. In the final report of the Council on the Pharmaceutical Sector in the 21st Century issued on May 28, 1993, it was suggested that manufacturing control and quality control must be thoroughly implemented for all products including original drugs. For this purpose the dissolution test was proposed as a routine verification method. In February 1997, "quality reevaluation" was started, and dissolution test conditions and specifications were set for original drugs that had no specified dissolution test. This step was intended to assure the quality of generic drugs by confirming their equivalence to the original products.

Thereafter, a notification entitled the "Guidelines for Bioequivalence Studies on Generic Drugs" was issued in December 22, 1997 and partially revised on May 31, 2001 (Notification No. 786 of the Evaluation and Licensing Division, PMSB) and on November 24, 2006 (Notification No. 1124004 of the Evaluation and Licensing Division, PFSB) and February 29, 2012 (Notification No. 0229-(10) of the Evaluation and Licensing Division, PFSB) to guarantee the therapeutic equivalence of generic drugs to the original drugs.

For products with dissolution tests established after completion of quality reevaluation, "official dissolution tests" were included in the third section of the Japanese Pharmaceutical Codex, which was published on March 23, 1999.

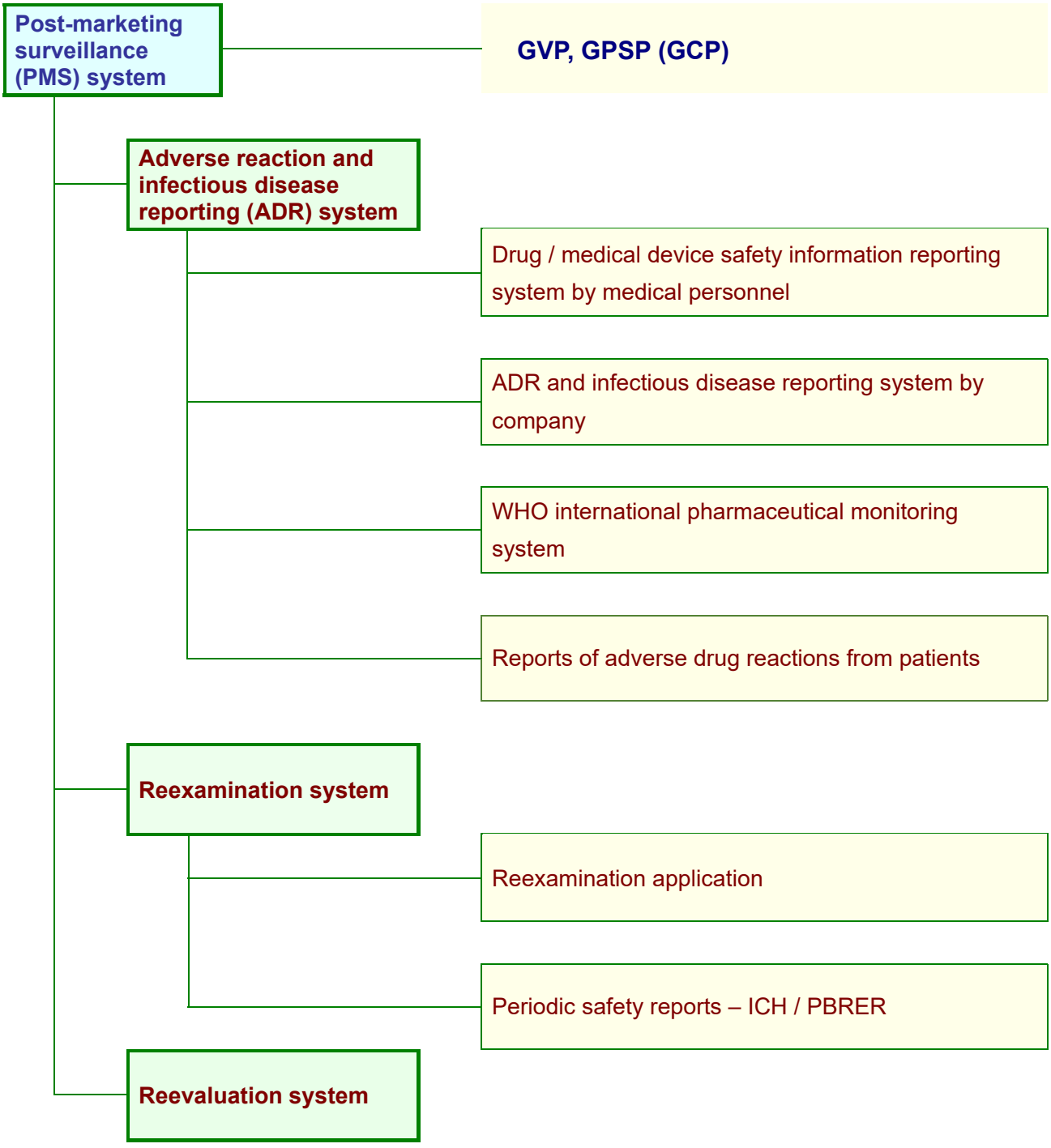

Fig. 13 Pharmaceutical Post-marketing Surveillance System

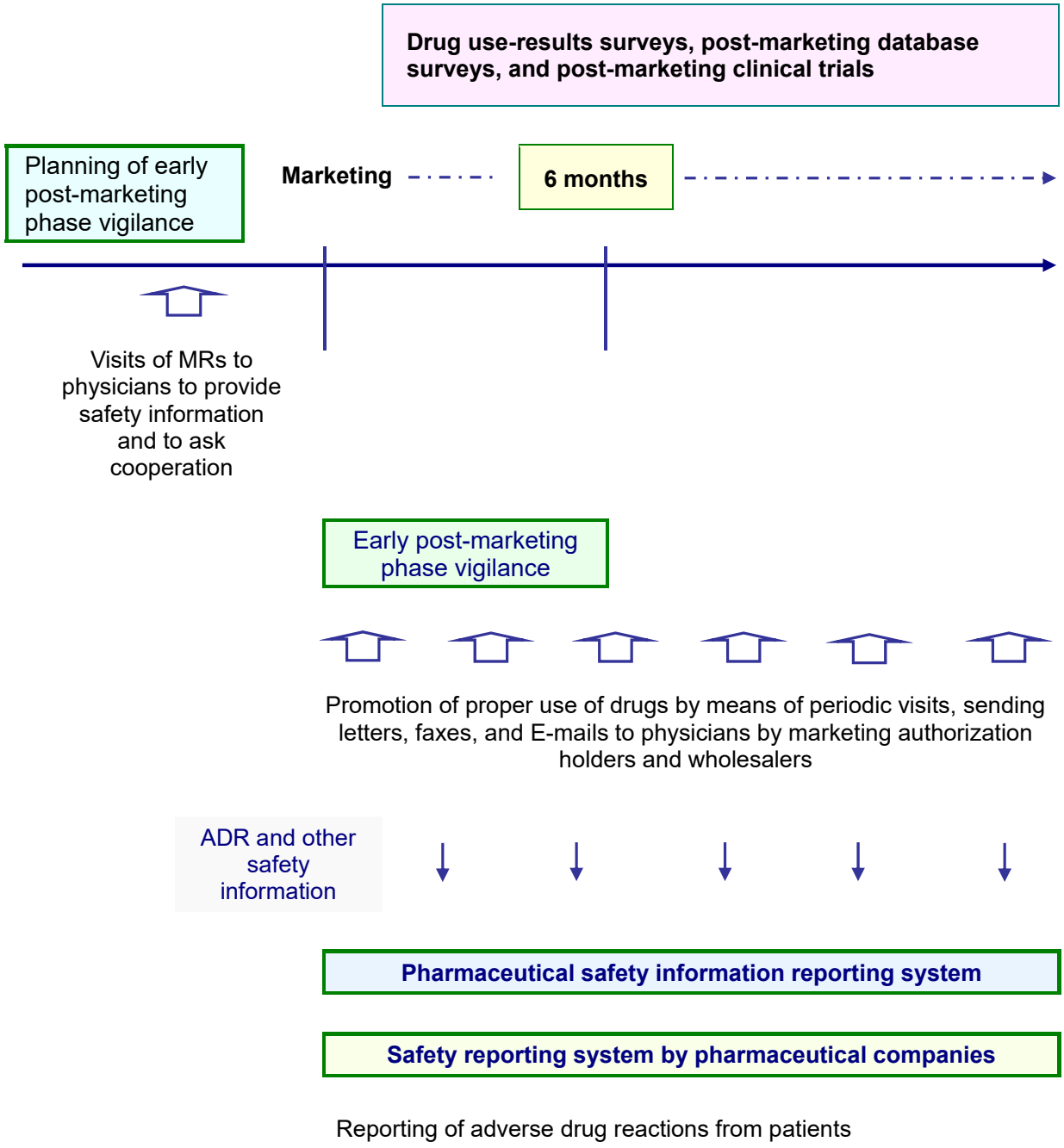

Fig. 14 Post-marketing Collection and Reporting of Pharmaceutical Safety Information

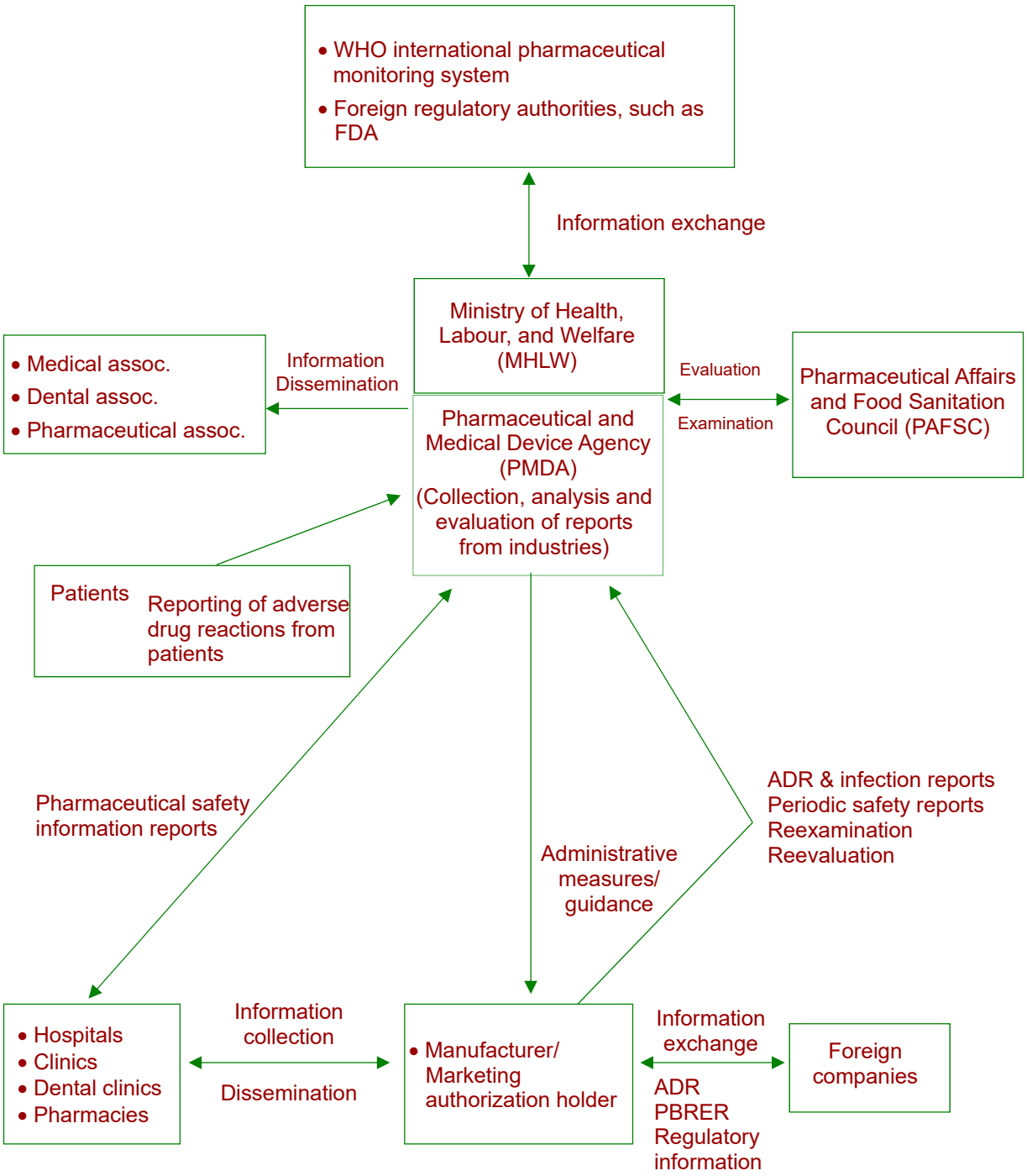

Fig. 15 Collection and Reporting of Pharmaceutical Safety Information

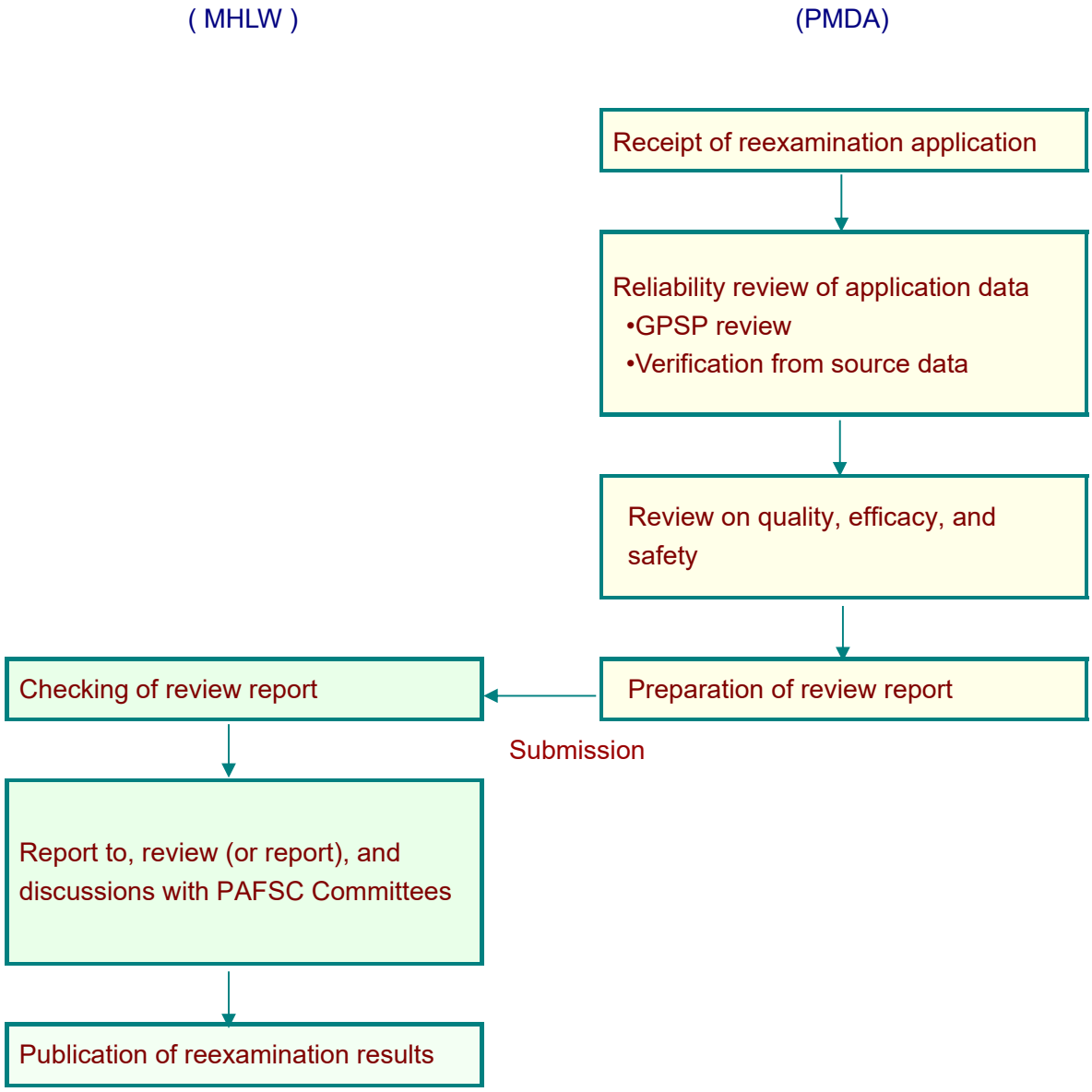

Fig. 16 Reexamination System

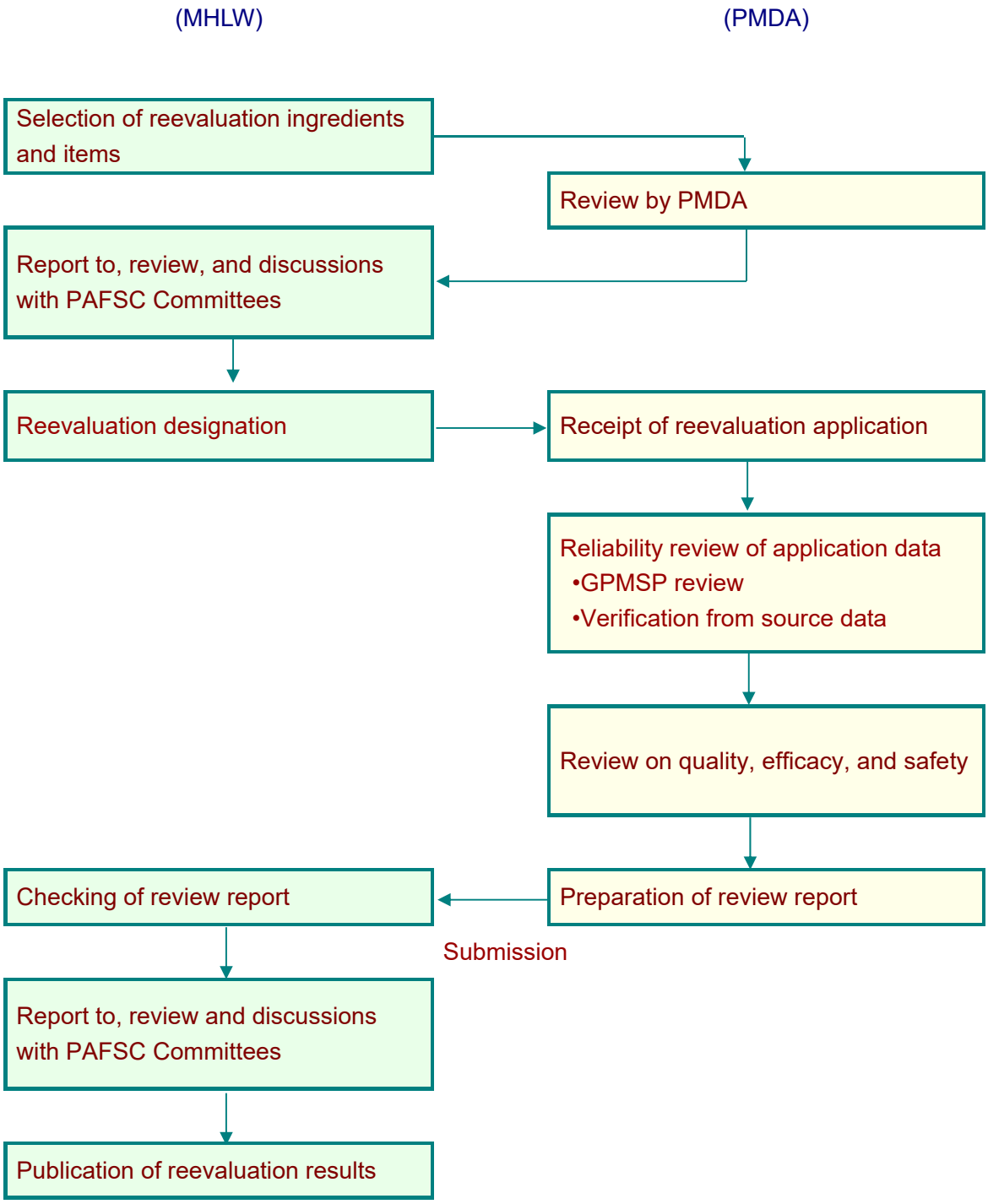

Fig. 17 Reevaluation System