Points to Consider regarding the Pharmaceutical Regulatory Procedures in Japan

For suppliers who are planning to export APIs to Japan

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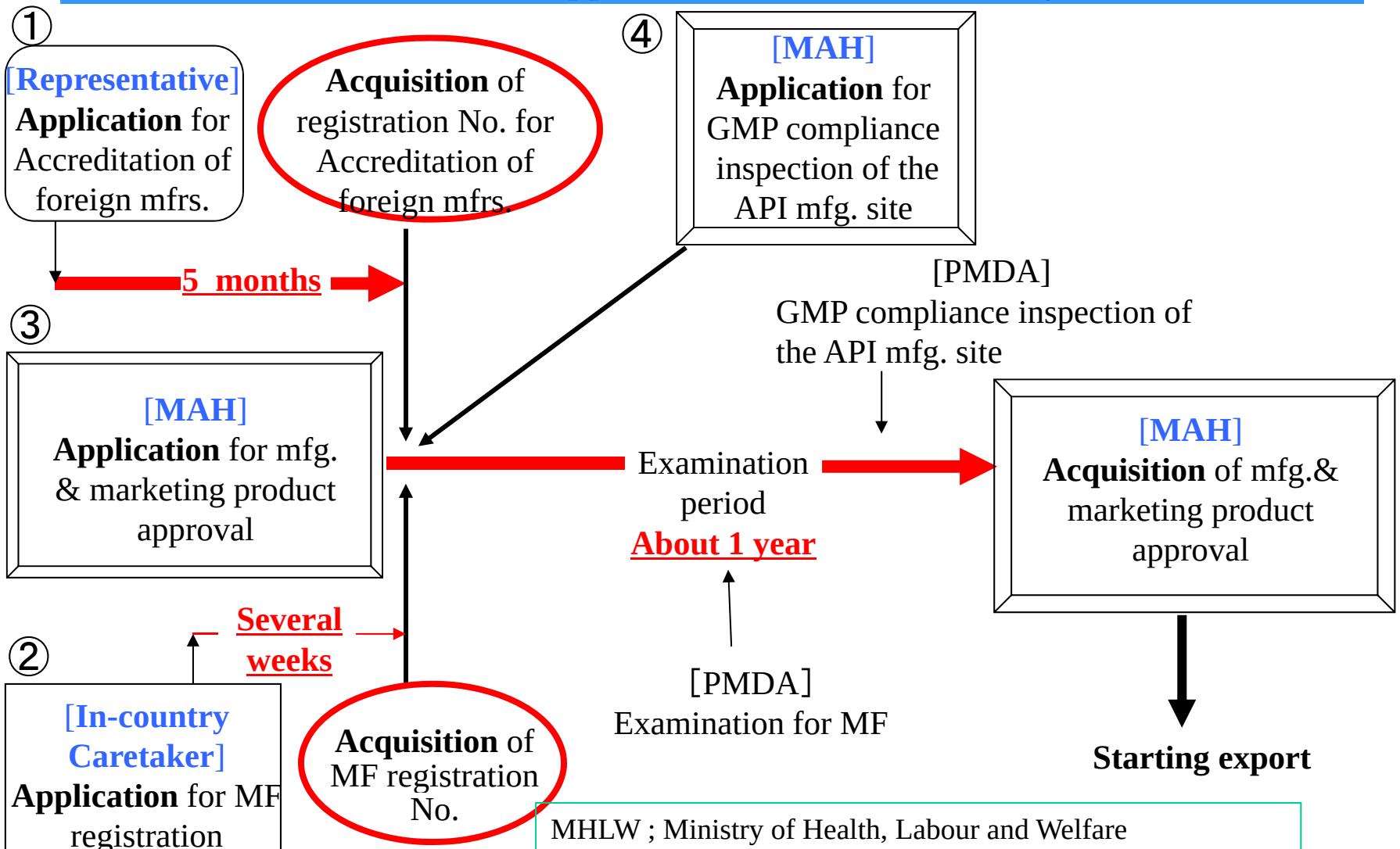
Time schedule for procedures necessary to export APIs to Japan for the first time

- Procedures API suppliers need to follow, and by when -



MHLW ; Ministry of Health, Labour and Welfare
PMDA ; Pharmaceuticals and Medical Devices agency, Japan
MAH ; Manufacturing and Marketing Authorization Holder

Points to consider when exporting APIs to Japan for the first time

- **Acquisition of accreditation of foreign mfrs. on the API mfg. site.**
  - In case where application is made from the foreign country directly, the documents should be prepared in Japanese and the fees should be paid.
  - Or the procedures may be performed by MAH or a representative who lives in Japan.
- **Preparation of the CTD (Modules 2 and 3) on the mfg. of the API**
  - A MAH who applies for marketing approval should be provided with documents (CTD) as reference documents for review of PMDA.
  - When such information is registered in the MF, the procedures should be performed by an In-country Caretaker who can make a registration in Japanese and also perform the subsequent maintenance thereof.
- **Compliance with the Japan- GMP**
  - Inspection is conducted by PMDA according to the J-GMP standards. The same manner as the renewal.
- **Making an agreement on Good Quality Practice (GQP)**
  - An agreement should be made with a MAH concerning the quality of the API to be manufactured.

Points to consider at the accreditation of foreign mfrs.

- Application can be made directly from overseas; however, the documentation (attachment and application for approval) should be translated into Japanese to create an approval application by using software provided by the MHLW.
  The procedures including the payment method of application fees are complicated; therefore, in many cases, such procedures are entrusted to and performed by a MAH or importer, or a representative who lives in Japan.
- First, the code number should be obtained per mfg. site and the accreditation of foreign mfrs. should be obtained per mfg. category. The review period is five months.
- Categories for accreditation
  (1) drugs (2) radiopharmaceuticals (3) sterile drugs (4) biological drugs (5) packaging, labeling and storage
- Anyone who lives in Japan can act as a representative; however, the representative should be selected in consideration of his/her knowledge based on technical and pharmaceutical affairs, because inquiries from PMDA receive in Japanese even after the application is made.
- At the time of the application for accreditation of foreign mfrs. and every five years at the time of the renewal, the buildings and facilities are inspected according to the Pharmaceutical Affairs Law of Japan.

Requirements for the appointment of representative

- If application and management in Japanese is possible, it is not particularly necessary to appoint representative.
- A representative is not required to have any special qualifications, but is required to be living in Japan.
- Accurately and promptly communicate the contents of the inquiries from PMDA to the applicant.
- Translate the applicant's responses to the inquiries into Japanese and communicate those to PMDA.
- When compliance inspection is conducted, a representative should cooperate in Japanese with the preparation of the necessary documents, etc. for a MAH to which the API is sold.
- Perform the necessary procedures to the change of organization, such as responsible executives, and buildings and facilities.
- Conduct renewal of the accreditation of foreign mfrs. every five years.
- Accurately and promptly communicate the PMDA's notices, inspection information, etc. that are needed by foreign mfr.

Preparation of the CTD on the mfg. of APIs

- Modules 2 and 3 should be provided to a MAH, as reference documents for application for the mfg. & marketing product approval.
- In case API mfr. does not want to disclose Module 3 to the MAH, it can register in MF (free of charge).
- In-country Caretaker should be appointed to register a MF as well as its maintenance .
- Anyone who lives in Japan can act as an In-country Caretaker; however, should be selected in consideration of his/her knowledge because, in case of a review after the registration, he/she must act as the contact for the inquiries, etc. from PMDA in Japanese, and also engage in procedures such as changing the registered contents.
- A CTD can be accepted even if it is written in English.
- An In-country Caretaker can be replaced at any time.

Requirements for the appointment of an in-country caretaker

- Not required to have any special qualifications.
- Living in Japan.
- Translate the contents of registration and documents for review into Japanese based on knowledge both technical and pharmaceutical regulatory affairs.
- Respond to review of the registered contents of the MF and changes, etc.
- At the time of the review, accurately and promptly communicate the contents of inquiries from PMDA to the applicant.
- Translate the responses of the applicant to the inquiries into appropriate Japanese from the pharmaceutical regulatory affairs and promptly communicate it to PMDA.
- When compliance inspection is conducted, should cooperate in Japanese with the preparation of the necessary documents, etc. for a MAH to which the API is sold.
- When compliance inspection is conducted by PMDA, responsible in Japanese with the preparation of the necessary documents for a MAH.

Compliance with the Japan-GMP standards

- Inspection for API is conducted by PMDA according to the J-GMP standards at the time of review for the drug.
- The MAH applies for the inspection; therefore, the foreign API mfr. does not pay an inspection fee (free of charge).
- Only for a documents review may be conducted in place of on-site inspection.
- In case of a document inspection, inquiries are made in Japanese via a representative or an in-country caretaker. Prompt submission of documents are required.
- In case 2 reactions (not 2 processes) are not conducted at the API plant, the upstream mfg. plant may become the object of the J-GMP and GQP as an intermediate mfg. plant. However, in that case, acquisition of the accreditation of foreign mfrs. is not required.

Making an agreement on Good Quality Practice (GQP)

- It has been specified to make an agreement with a MAH concerning the quality control of the API to be exported.
- The contents of the agreement have been specified in the GQP regulations.
- Contents of agreement
  - · The assurance standards, and the procedures for mfg., QC and distribution.
  - · The mfg. method and the analysis and test methods
  - · Periodic inspection (audit) by a MAH
  - · Conditions in transportation and delivery to secure the quality
  - · Method of prior notification regarding change in the mfg. method or the analysis method (if the quality may be affected by those), and the person responsible.
  - · Prompt communication method of information on measures in order to prevent jeopardizing public health and hygiene (including discontinuation of mfg., export, withdrawal, recall, and disposal) and information on quality, and the person responsible for these.
  - · Information on quality, etc.

Procedures necessary after starting export of the API

- The accreditation required to be renewed every five years.
  · The procedures for the application of the renewal should be performed not later than five months prior to the expiry date. This may also be conducted by a representative.

- When mfg. method changes, that may affect the quality of the APIs, prior notice to the MAH is required. After completing the review and approval of the change in the contents of mfg./marketing approval, the change can be made.
  With respect to partial change approval or minor change notification, the change in the registered contents of the MF can be made in the same manner.

- When mfg. methods are changed and/or the accreditation of foreign mfrs. is periodically renewed, the GMP compliance inspection for the API that is being manufactured is conducted. In such a case, documents for review (periodic process review and validation-related, etc.) required by PMDA should be prepared.

Thank you for your attention!

The CD-R 2011 Version available at H-40
Contents : Laws, Ordinances and Administrative Notices relating to API manufactures. Seminars at CPhI Japan and China

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