JGA
Japan Generic Medicines Association

Troubles and Issues Experienced by Generic Manufacturers since Implementation of R-PAL in 2005

Japan Generic Medicines Association
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Updating of Approval Documents according to the New Format

- R-PAL was implemented as of April 1, 2005
- The Format of Approval Documents was changed and the already registered Approval Documents were required to be updated and submitted with new formats, especially with detailed production chart (including open part of DMF) before MAH's* business license expired. No review of the contents is given until some regulatory action is taken. But the contents must obviously be correct.

Problems:

1)Needed extra efforts getting appropriate provision of required data for DMF

2)Any irregularity may cause loss of patient safety, registration itself, reliability and financial damages, and criminal prosecution in the worst case.

*MAH: Marketing Authorization Holder

Updating of Drug Master Files

- DMFs are also required to be updated and MAHs are exposed to risks unless importers, suppliers or in-country care-takers would provide required data promptly. (MAHs are required to update the Approval Documents on its corresponding DMF open part.)

Problems:

1) MAHs have risks not knowing whether DMFs are well controlled if they are not given information about the production and necessary QC of APIs, until PMDA reviewers open it for a filed variation or GMP inspection.

2) Change control system and quality agreement need more efforts to be well-maintained between the supplier and the MAH or in-country care-taker on GMP/GQP

3) Any big divergence between the data and the fact will cause a big problem when it is found by the regulators. Anticipated damages are the same as those of the Approval Documents, especially on the part of MAH.

Overseas Manufacturing Site Accreditation (OMA)

- R-PAL requires registration of overseas manufacturing sites for medicinal products and APIs by way of the in-country care-taker or MAH. It also took quite a trouble and time to get correct information for OMA application.

Problems:

1) Change Control System and Quality Agreement (between supplier and MAH) may not be well maintained. Changes affecting the quality must definitely be informed prior to execution.

2) Overseas manufacturing sites may not meet the requirements of PMDA's inspection every 5 years

GMP Conformity Inspection

- Manufacturing Sites are required to be inspected every 5 years. Limited PMDA resources restrict on-site inspection frequency to prioritized places.

Problems:

1) On-site inspection is very costly for small business development. But decided by PMDA based on risks.
2) Application must be made far ahead of planned time(6 months before approval) in consultation with MAH as PMDA's resources are limited.
3) Inspection by Documentation sometimes requires the supplier to submit confidential data and they resist for protection of their data. PMDA sometimes ask them to bring in such documents by themselves for inspection.
4) GMP/GQP compliance, Change Control System and Quality Agreement, 5-year renewal and on-site inspection readiness are important issues.
5) Mutual Recognition Agreement(w/ EU) does not cover API.

Proposals for Solution

- Overseas Manufacturer/Supplier must provide prior to Approval Application, following documents to MAH:

  1)A Copy of Regular MF Certificate; 2)License to use the MF; 3) A copy of open part or applicant part of MF; 4) A copy of Accreditation; 5)GMP/GQP agreement.

Additionally, following actions are important:

For industry:

1)Establishment of Change Control System and GMP/GQP Agreement; 2)Periodical exchange of regulatory information; 3) JGA Seminar and Website Data Provision on regulatory affairs.

For requests to regulatory authorities:

1) Official listing of care-takers; 2)Extended application of MRA; 3)PMDA personnel increase;