Notice to applicant

Central Administration of pharmaceutical Products
General Administration for Human Pharmaceuticals Variations

FAQs For Good Practice of Reliance of Post Approval Changes

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FAQs For Good Practice Of Reliance Of Post Approval Changes

General Questions

Q1-What is Reliance Evaluation Route?

Answer: Reliance Evaluation Route is a process where the EDA leveraging the assessments and evaluations conducted by trusted regulatory agencies **Stringent Regulatory Authority** (SRAs) published in EDA website instead of duplicating the entire evaluation process and the variation administration will assess variations that were already approved by other reference countries in accordance with the Egyptian reliance guidelines and state the approval.

Q2-What are the Stringent Regulatory Authority (SRAs) referenced in the EDA Guidelines and published on the EDA website?

Answer: A regulatory authorities which is:
(a) a member of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), being the European Commission, the US Food and Drug Administration and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency;
(b) or an ICH observer, being the European Free Trade Association, as Represented by Swissmedic, and Health Canada;
(c) Or a regulatory authority associated with an ICH member through a legallybinding, Mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway.

Q3- Does the Reliance Evaluation Route fully delegate regulatory authority?

Answer: Reliance Evaluation Route does not fully transfer EDA's regulatory responsibility. EDA maintains final authority for approving pharmaceutical products within its jurisdiction.

Q4- Does the Egyptian Drug Authority (EDA) rely on companies' commitment of approval rather than regulatory approval?

Answer: No,The Egyptian Drug Authority relies on approvals conducted by stringent regulatory authorities (SRAs).

Eligibility Criteria and Submission Requirements

Q5- What is the eligibility criteria for the Reliance Evaluation Route for imported finished products?

Answer: To be eligible for the Reliance Evaluation Route, an imported finished product must have been approved by at least one Stringent Regulatory Authority (SRA) that published on EDA's website. or have WHO prequalification.

Q6- What specific documents must be included in a submission for the Reliance Evaluation Route?

Answer

- A valid Certificate of Pharmaceutical Product (CPP)
- Updated relevant sections of CTD dossier
- Verification of Sameness (as Sameness Letter) as stated in Egyptian Variation Guidelines
- Unredacted Assessment report and Q&A (unless otherwise justified)
- Proof of approval from at least one reference regulatory authority (SRAs)

Q7- What is the Sameness Letter and its role stated in the documents required for reliance evaluation route?

Answer:

A Sameness Letter is a document issued by License Holder verifies and ensure the product's quality and highlights any differences compared to the reference SRAs approved version.

The same pharmaceutical product is defined as characterized by:
- the same qualitative and quantitative formulation.
- the same manufacturing site(s) for the drug substance and finished product, including specific block(s)/unit(s), manufacturing chain, processes, control of materials and finished product.
- the same specifications for the excipient(s), drug substance and finished product.
- the same essential elements of product information for pharmaceutical products.

Q8- How does the EDA integrate the assessment and evaluation results of other regulatory authorities (IF Available) into its own decision-making process?

Reliance on other SRAs involves leveraging the assessments and evaluations conducted by trusted regulatory agencies instead of duplicating the entire evaluation process and reallocating resources to avoid duplications

Q9- Does EDA have other regulations, beyond its guidelines, that influence its decision-making process?

Answer: Yes, the EDA authority strictly follows the decisions made by the Technical Committee. Any Post-Approval Changes must align with these decisions.

Variation Categorization

Q10-How are variation requests categorized under the Reliance Evaluation Route?

Answer: Variation requests as mentioned in EDA guidelines are categorized into PAC-N, PAC-A, PAC-B, and PAC-II based on their potential impact on safety, efficacy, and quality.

PAC-N (have minimal or no adverse effects on the overall safety, efficacy and quality of the FPP. Submitted and implemented immediately at the time of submission and doesn`t need prior acceptance)

PAC-A (Variations that could have minimal or no adverse effects on the overall safety, efficacy and quality of the FPP and must be submitted annually and doesn`t need prior acceptance)

PAC-B (Variations that may have minor effects on the overall safety, efficacy and quality of the FPP. Implemented when the variation is considered accepted. Need acceptance Letter and final approval to be implemented)

PAC-II (Variations that could have major effects on the overall safety, efficacy and quality of the FPP. Implemented when the variation is considered accepted. Need acceptance Letter and final approval to be implemented)

Q11-How should variations be classified when an application involves two or more types of variations?

Answer: An application involving two or more types of variations will be considered as the highest risk type, e.g. a variation grouping both PAC-B and PAC-II will be classified as PAC-II variation.

Q12-Can Applicant submit a Post-Approval Change (PAC) that not covered by EDA Guidelines?

Answer: Yes, applicants can submit Post-Approval Changes (PACs) that is not stated in EDA Guidelines. However, EDA will evaluate the change through a risk-based assessment.to ensure compliance with safety, efficacy, and quality standards. If a PAC is found to be non-compliant to the EDA regulations and guidelines.

Specific Questions for Implementation of the Reliance Evaluation Route

Q13- What are the best practices for submitting a successful Reliance Evaluation Route?

Answer: Submitted documents should include:

- Approval issued by the SRA
- Updated sections of the CTD
- Application submitted to the SRA
- A linking between the application and the approval from the Reference Authority (unless otherwise justified)
- A linking between the application and supportive documents (unless otherwise justified)
- Unredacted Assessment report and Q&A (unless otherwise justified)

Q14- Can an applicant submit a single variation stated in approval of multiple variations?

Answer: EDA relies on the approval of the entire group of variations as a grouping variation, therefore, the applicant must submit all variations for approval. For example, but not limited the approval stated consequential changes to each other e.g. change of coloring agents that requires a new physical character change in this case the applicant must submit all variations at the same time to rely on these variations in parallel.

Q15- Is it permissible to rely on a case where updates were made to versions of the Common Technical Document (CTD) that do not constitute a continuous, sequential update?

Answer: The non-sequential order of versions makes the reliance evaluation unreliable as the company should submit the updated version contains all sequential updates (unless otherwise justified).

Q16- What are the limitations to relying on assessments from other regulatory authority especially for changes not evaluated by other SRAs for example climatic zone differences?

Answer: Variations related to climatic zone differences, which may not be subject to evaluation by other SRAs, must undergo a comprehensive assessment by EDA as according to EDA regulations the Stability studies must adhere to the requirements for climate zone IV.

Q17-What are the potential challenges and risks associated with the best practices for smooth implementation of the Reliance Evaluation Route?

Answer:

1. **Differences in Regulatory Requirements**: Regulatory frameworks vary between authorities, which can lead to inconsistencies in the data requirements for product submissions.
2. **Interpretation of Guidelines**: Regulatory guidelines may be interpreted differently by different authorities. What is considered acceptable or sufficient in one jurisdiction might not meet the standards or expectations in another.
3. **Data Quality Issues**: The quality and completeness of data submitted to different regulatory authorities can vary. In some cases, certain data might be considered sufficient for approval by one authority but may require further clarification when evaluated by another. Differences in the level of evidence required can impact the smooth integration of assessments.
4. **Different Submission Dates Between Authorities**: If submissions to different regulatory authorities are made on different dates, there could be delays in the timing of approvals, which may affect the overall timeline for bringing a product to market. The pace at which information is updated or new requirements are implemented can also lead to timing issues.
5. **Different Packages of PAC (Post-Approval Changes) Submitted to Different Authorities**: If different packages of post-approval changes (PAC) are submitted to various authorities, inconsistencies may arise in the approval or acceptance of these changes. This could lead to confusion about which regulatory requirements apply to the product in different markets.
6. **Lack of Clear Guidelines for PAC Reliance Practices**: The lack of clear, standardized guidelines for PAC reliance practices between authorities can lead to confusion and

inconsistency in how post-approval changes are handled. This may result in delays or errors in the regulatory process, potentially compromising product availability and compliance.

7. **Mindset of Assessors**: Assessors in different authorities may have varying mindsets or approaches to evaluating data and submissions. Some may be more open to relying on assessments from other regulatory bodies, while others may be more cautious, requiring additional justification or data.

For best practices for submitting variation requests and ensuring a smooth implementation of the Reliance Evaluation Route the applicant should Submit clear and concise documentation. Ensure compliance with EDA and reference regulatory authority requirements. Justify any deviations from reference regulatory authority decisions. Maintain open communication with the EDA. Respond promptly to queries and information requests. Adhere to EDA timelines and procedures