GUIDANCE NOTES

ACTIVE PHARMACEUTICAL INGREDIENT (API) INFORMATION (PART II S) FOR QUEST3+ PRODUCT REGISTRATION APPLICATION

CENTRE FOR PRODUCT REGISTRATION
NATIONAL PHARMACEUTICAL REGULATORY AGENCY (NPRA)

Please read *Drug Registration Guidance Document (DRGD): Appendix 6 : Guideline on Regulatory Control of Active Pharmaceutical Ingredients (APIs)*and these notes carefully before completing QUEST3+ product registration application form **Part II Section S.** An incomplete application form or dossier (with major deficiencies) is likely to be rejected during submission.

A. New Product Registration Application

1) All Part II Section S information should be submitted through QUEST3+ (except for Closed part of Drug Master File(DMF) for DMF option). Please refer to **'Help Button**' in QUEST3+ for assistance during online submission.

2) All Part II Section S information in mandatory field should be filled up according to the original dossier.

3) Original document should be uploaded to QUEST3+ for all API information (S1 to S10).

4) Separate Part II Section S information (in the same product registration application form) should be submitted when:
    i. A finished product contains more than one API
    ii. An API is manufactured from more than one manufacturing site
    iii. An API is manufactured using more than one synthesis route

5) Please select the **correct API manufacturer** (with the exact name & address) from QUEST3+ database and ascertain your selection. Changes to the name or address of an API manufacturer are NOT possible once a saved form is created.

6) There are three options for Part II Section S information submission. Requirements for each submission option are available in *Drug Registration Guidance Document (DRGD): Appendix 6: Guideline on Regulatory Control of Active Pharmaceutical Ingredients (APIs).* A summary of these requirements is provided in Appendix 1.

7) A change of submission option is NOT allowed once screening approval is obtained.

8) Change or addition of API manufacturer is not allowed once screening approval is obtained.

9) Please also refer to Appendix 2 for *API Administrative Procedure.*

10) Once screening approval is obtained, applicants are required to submit API information (in electronic copy) to API Section, Centre of Product Registration (PPP) and Laboratory Services Section, Centre of Quality Control (PKK) within 5 working days from the approved payment date. Please refer to template letter in NPRA's website template for
    i. Template Letter for API Submission to PPP
    ii. Template Letter for API Submission to PKK

B. Product Registration Application Using Same Source of an Approved API

1) This section outlines the requirements when preparing submissions, whereby the new finished product is manufactured using an approved API of a registered product. Both new and registered product shall use the same API, which is manufactured by the same API Manufacturer, by the same API synthetic route. This new submission shall be made by the same Product Registration Holder (PRH) through the same Part II Section S submission option.

2) **Approved API** refers to an API (in a registered product) which is regulated and approved following the implementation of Directive on Regulatory Control of API in Malaysia dated 17 Mar 2011, thus previously reviewed and approved by API Section, Centre for Product Registration, NPRA.

3) The PRH should keep the content of their dossier updated with respect to the actual synthesis/manufacturing process. The quality control methods should be kept in line with the current regulatory and scientific requirements. Where there are changes affecting an approved API in a registered product which requires variation application, the variation application shall be made and approved for every affected registered productprior to submission of a new product registration containing an Approved API.

4) PRH are required to declare that the quality of the API, in respect of the methods of preparation and control, has been regularly updated by variation procedure to take account of technical and scientific progress. PRH should also declare that, no changes have been made to the API other than those approved by the NPRA.

5) In cases where some minor textual changes have been introduced, and not affecting the major content of the dossier, PRH shall be able to provide a summary of changes made to previously approved dossier compared to current dossier. NPRA will review the changes introduced and may consider to accept or reject the dossier as an Approved API.

6) Please refer to NPRA's website for template of '*Declaration Letter for An Approved API in New Product Registration Application*'.

C. Regulatory Control of API for Product Registered Before the Implementation of Directive on Regulatory Control of API in Malaysia

1) This section is applicable for registered products containing Scheduled Poison in ALL dosage forms with the expiration of the registration period starting 1 January 2020. All PRH shall submit required Part II S information between 12 to 15 months before the end of the expiration of the registration period.

2) Submissions less than 12 months prior to expiry of product registration will not be accepted, thus may affect product renewal status.

3) PRH shall prepare all required Part II S information. This information shall be uploaded to QUEST3+ system.

4) Uploaded Part II S information is accepted as part of the quality document required in support of renewal of product registration. However, this information may be subjected to assessment by NPRA.
5) At the point of writing, NPRA has identified anti-infective APIs as the selected category for assessment purposes. This category was selected based on current public health needs and risk-based approach which may be extended to other categories from time to time.

6) Closed part information (for DMF option) is ONLY required for anti-infective APIs. PRH shall request DMF holder to submit complete DMF to NPRA prior to submission.

7) Please refer to Appendix 3 for *Administrative Procedure for Regulatory Control of Active Pharmaceutical Ingredient (API) In Registered Product Containing Scheduled Poison*.

8) Once all required Part II S information are ready for updating, PRH shall fill and submit *Application Form for Updating Part II S information for Product Registered Before the Implementation of Directive on Regulatory Control of API* (Form RegA1). Form RegA1 is an online form available at NPRA's website.

9) All submissions will be screened for eligibility based on product registration expiration date and category of API.

10) NPRA will enable "Section S Revision" function in QUEST 3+ for the indicated product. PRH will be given strictly 30 calendar days to upload all required Part II S information. Failure to update complete Part II S information by the end of the given timeframe will affect product renewal status.

11) For product with anti-infective APIs,
    a. Submission by DMF option- complete DMF (both open & closed part) shall be submitted in electronic copy (preferably in compact disc) together with a Letter of Access. This document shall reach NPRA before submission of Form RegA1. Open part information shall also be uploaded to QUEST3+.
    b. Submission by ACTD or CEP option- all documents shall be uploaded to QUEST 3+.

12) For product other than anti-infective APIs, all Part II S information shall be uploaded to Quest 3+, closed part information in DMF is NOT required.

13) During assessment, additional information may be requested via email, if necessary.

14) For non-anti-infective APIs, NPRA reserves the right to conduct assessment on the submitted Part II S documents and request for additional information (if necessary). If the outcome of the assessment is unsatisfactory or if there is any doubt in the submitted document, appropriate regulatory action may be taken against the relevant product and/or the status of the product registration will be reviewed for product recall, suspension or revoking of registration status.

15) The PRH should maintain the content of their dossier with respect to the actual manufacturing process same as the time of approval. Where there are changes affecting the

API in a registered product which requires variation application, the variation application shall be made and approved prior to “Section S Revision” submission.

16) Variation application is discouraged within one year post-renewal.

D. Good Manufacturing Practice Compliance Evidence for Manufacturers Involved

1) This section outlines the level evidence required to support that the manufacturing of API (including intermediate manufacturing and milling sites) are complying to an appropriate Good Manufacturing Practices (GMP) quality system.

2) The term **Main API Manufacturer** refers to manufacturer involved in final API manufacturing process and responsible for batch release. The GMP compliance evidence accepted for main API manufacturer are:

    a) GMP Certificate or GMP Inspection Report issued by:

        i. Pharmaceutical Inspection Co-Operation Scheme (PIC/S) Participating Authorities or;
        ii. World Health Organization(WHO)or;
        iii. Drug Regulatory Authority

3) Manufacturers involved in manufacturing of **API intermediate** should be able to provide GMP compliance evidence as below:

    a) GMP Certificate or GMP Inspection Report issued by:
        i. PIC/S Participating Authorities or;
        ii. World Health Organization(WHO)or;
        iii. Drug Regulatory Authority or;

    b) Self-declaration from competent person of API Intermediate Manufacturer (refer template letter GMP_CP_V1) or;

    c) Declaration from Qualified Person (QP) (for EU countries)

4) When an **atypical API** (e.g. excipient, food additive or cosmetic ingredient) is used as an active ingredient in pharmaceutical products, the GMP compliance evidence accepted are:

    a) GMP Certificate or GMP Inspection Report issued by:
        i. PIC/S Participating Authorities or;
        ii. World Health Organization (WHO)or;
        iii. Drug Regulatory Authority or;

    b) Self-declaration from competent person from Finished Pharmaceutical Product (FPP) Manufacturer whereby the supplier of atypical API is an approved supplier according to the FPP manufacturer’s quality system.

5) NPRA reserves the right to determine the acceptability of any GMP compliance evidence.