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GUIDANCE DOCUMENT

PRODUCT QUALITY REVIEW (PQR)

FOR

TRADITIONAL MEDICINES & HEALTH SUPPLEMENTS MANUFACTURERS

1st Edition

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GLOSSARY

Deviation	:	Any unwanted event that represents a departure from approved processes or procedures or instruction or specification or established standard or from what is required.
Non conformances	:	An output that does not meet specifications or requirements
Starting materials	:	Includes raw material (active ingredient) and excipients
Verification	:	An act of checking if the procedures, processes, equipment, materials, activities or systems are consistently working, delivering results in accordance with the requirements.

INTRODUCTION

Product Quality Review (PQR), also known as Annual Product Review (APR), is one of the requirements stated in the Quality Management chapter of the Guidelines on Good Manufacturing Practice for Traditional Medicines and Health Supplements (TMHS), 1st Edition 2008.

It is a summary of products manufactured for the year assessment from the receipt of the raw materials to the post-market surveillance. Its allocation in the first chapter of the guide signifies its importance to the overall quality management system. It is usually presented by means of statistical tools.

This review helps to;

- verify the consistency of the existing manufacturing process;
- determine the appropriateness of the current specifications of the starting materials and finished products;
- provide a trend which may identify deficiencies in recommending an improvement in the manufacturing process or materials used to manufacture the products.

OBJECTIVE

The guidance document is written to provide an interpretation and guidance to the Traditional Medicines and Health Supplement (TMHS) manufacturers in Malaysia in preparing the report for PQR. It also serves to facilitate compliance towards the regulatory requirements.

SCOPE OF THE REVIEW

Scope	:	All registered products including export only, both own and contract products ● For TMHS products that are inactively manufactured (e.g: less than 3 batches per year or statistically invalid), the PQR can be carried forward to the next cycle of PQR review. It is also acceptable for products with lesser than 3 batches per year, the number of batches can be combined to the next cycle of PQR. This also has to be properly justified. ● Registered products can be grouped based on particular characteristics/types, but it has to be scientifically justified. For example; products with the same active ingredients or same dosage form can be grouped for the review with proper justification. ● Registered products that are excluded from PQR have to be justified.
Duration	:	Normally every year of production or Fiscal Year as set by the manufacturer
Data collection	:	Each product manufactured in the previous year Any relevant reviews from last year PQR

Parameters for Review

Parameters below are the minimum review requirements as indicated in the guidelines. The manufacturer may use these recommendations. The description of each element is available in Appendix 2 – Report Sample.

i. A review of **starting materials and packaging materials** used for the product, especially those from new sources.

ii. A review of **critical in-process controls** and **finished product results**.

iii. A review of all **batches that failed** to meet established specification(s) and their **investigation**.

iv. A review of all **significant deviations or non-conformances**, their related investigations, and the effectiveness of resultant corrective and preventative actions taken.

v. A review of all **changes** carried out to the **processes or analytical** methods.

vi. A review of product registration requirement **variations** submitted/granted/refused, including those for third country (export only) dossiers.

vii. A review of the results of the **stability monitoring programme** and any adverse trends.

viii. A review of **all quality-related returns, complaints and recalls** and the **investigations** performed at the time.

ix. A review of **adequacy** of any other previous product process or equipment **corrective actions**.

x. The **verification status** of relevant **equipment** and **utilities**, e.g. air-conditioner/ventilation, water, compressed gases, etc.

xi. A review of **Technical Agreements** to ensure that they are up to date.

xii. For **new product registrations** and **variations** to product registrations, a review of post-marketing commitment.

DOCUMENTATION

Standard Operating Procedure (SOP) or equivalent document

A standard SOP contains the objectives of the PQR, personnel/department responsible for the activity and the procedure describing the data collection, review method, etc. The SOP should describe the method of conducting PQR clearly such as selection of products (each product or by grouping), product planning, the intended period of review, minimum of batches that allow for PQR to be conducted, parameters to review, reporting of the PQR and assessment whether corrective action and preventive action related to the PQR is required. The sample of the SOP is provided as **Appendix 1**.

Report of the review

The report (**Appendix 2**) is prepared using a controlled report template to ensure a standardised approach. It may include at least of these information;

1. Product name(s);
2. Batch size(s) and presentation(s);
3. Review date of the report;
4. Comparison of the review from previous PQRs;
5. Grouping of the products under review and its justification;
6. Data collection and analysis related to products under review as described in the Parameters For Review;
7. Identification of issues or trends entailing from the data collection and analysis;
8. Summary of findings, conclusions, and recommendations;
9. Proposed actions;
10. Name and signatures (with date) of the persons responsible in preparing, reviewing, and approving the report.

Approaches for Products Reviewed

It is notable that manufacturers may have many registered products with different starting materials, dosage forms, manufacturing processes, packaging materials, etc. So how does a manufacturer can manage PQR for all products?

There are many approaches to review products for PQR depending on the manufacturer capability and knowledge. For a starter; two approaches are **one report for each product** or the manufacturers may consider **grouping** several products with proper justification. The grouping may be those with similar dosage form, similar critical equipment, etc.

In order to describe the different approaches, using an example of Syarikat Ulik Mayang Sdn. Bhd. that has four registered TM products, which are;

a. Misai Kucing Tablet – Oral solid dosage
b. Red Cendawan Tablet – Oral solid dosage
c. Minyak Urut Belalang – External liquid
d. Minyak Urut Gamat – External liquid

1st Approach: One Report for Each Product

Under this approach, it is a straightforward approach whereby there will be total of four reports prepared for each product. Each report will review all the parameters. This approach can help the manufacturers to become familiarise on the concept of PQR and applicable to those with a small number of products registered.

2nd Approach: Grouping of products

Once the manufacturers are familiar with PQR, they may start to consider other approach. In this case, by grouping the products. Before they can begin, a proper justification is required to describe the grouping characteristics.

Products	Dosage forms	Common equipment	Other Equipment (Examples)
Misai Kucing Tablet	Tablets	Weighing balance	Direct contact: Blender, Fluid Bed Dryer, Miller, Compression Machine, Blister Indirect contact: Packaging
Red Cendawan Tablet			
Minyak Urut Belalang	External oil		Direct contact: External specific homogenizer, Filling Machine Indirect contact: Packaging
Minyak Urut Gamat			

With this approach, the manufacturer may consider to prepare two reports for each dosage forms.

EVALUATION OF PQR RESULTS

The collected data is evaluated in order to identify;

1. Any trends related to the parameters of the products.
   This is to illustrate the processes are in control or any deviations and Out of Specification (OOS) are justified. In order to do so, an appropriate statistical tool may be used to review the data collected. For example, the tools that may be used are process capability index (Cpk), charts, etc.

2. Any corrective and preventive action (CAPA) required.
   Based on the analysis interpreted, it is determined if any CAPA is required.

3. Any improvement in process, materials, etc.
   Whenever it is required, improvement in manufacturing process and materials is proposed and identified after the analysis and CAPA are finalised.

IMPLEMENTATION STRATEGY

It is understandable that the full implementation of PQR within a short period may overwhelm the manufacturers. Therefore, a timeline is prepared to provide guidance in implementing the PQR by stages. It is estimated that the manufacturers may be able to comply with the requirement within 4 years. This timeline is shown as below (**Figure 1**):

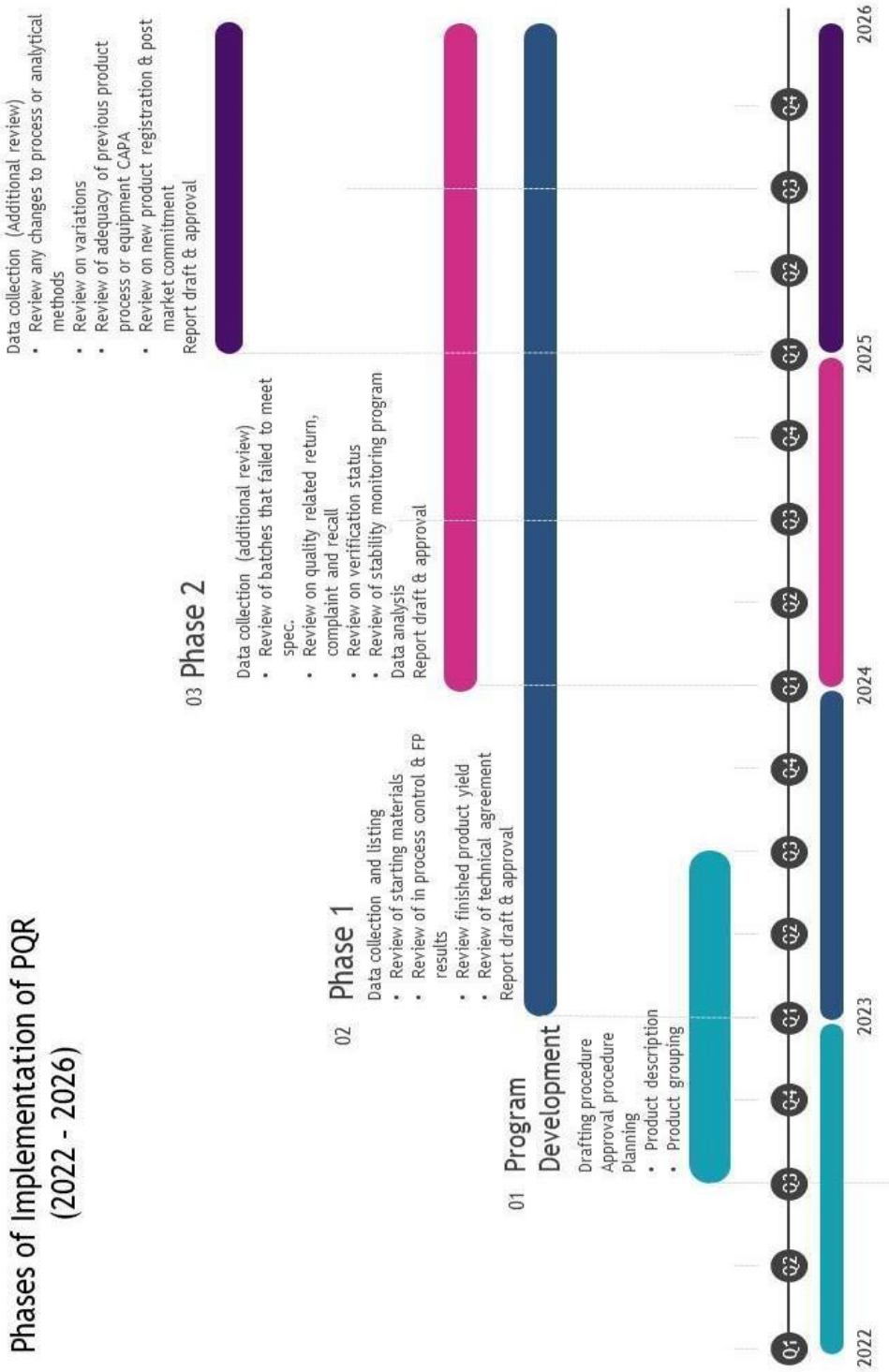

Figure 1: The phases for implementation of PQR

REFERENCES

1. Garis Panduan Amalan Perkilangan Baik (APB) bagi Ubat-ubatan Tradisional dan Suplemen Kesihatan (TMHS), Malaysia, Edisi Pertama, 2008.
2. ASEAN Guideline on Good Manufacturing Practice for Traditional Medicines (TM) and Health Supplements (HS).
3. Guidance for Industry: Product Quality Review Version 1.0, Drug Office, Department of Health, the Government of the Hong Kong Special Administrative Region
4. TGA Product Quality Reviews (PQRs) for listed and complementary medicines, Version 2.0, January 2019

Appendix 1

PROCEDURE SAMPLE

This sample for procedure serves **only** as a guide to begin the implementation of PQR.

Syarikat Ulik Mayang Sdn. Bhd.	Procedure for Product Quality Review (PQR)		SOP No.: QMS/PQR/01
Prepared by: Ms. Susan / 02/01/2022	Reviewed by: Ms. Lisa / 03/01/2022	Approved by: Mr. Alex / 04/01/2022	Effective date: 01/02/2022

1.0 PURPOSE

This document provides a procedure on the process in the preparation of Product Quality Review for registered traditional medicines and reviewing previous PQR in order to verify the process, material and product suitability and stability.

2.0 SCOPE

This SOP is applicable for all registered products manufactured, including third party contract and export only products manufactured by Syarikat Ulik Mayang Sdn. Bhd.

3.0 RESPONSIBILITIES

QA/QC department:

Responsible to collect data and review of relevant data of the products manufacturing from the management of materials, manufacturing processes and products, including any changes.

Responsible to ensure data retrieved from each relevant department for data collection. To coordinate the data collection, data review and the development of PQR report.

QA/QC Manager:

Responsible to ensure all provisions of this SOP are fulfilled and review of report.

QA/QC Head of Department:

Responsible to ensure that the activity is conducted in proper manner and approval of the report.

Manufacturing department:

Responsible to collect data and review of relevant data of the products manufacturing from the management of materials, manufacturing processes and products, including any changes. These data review is provided to QA for compilation and final review.

4.0 PROCEDURES

1. All the batches of products manufactured in a fiscal year shall be considered for PQR, in between January and December of the review year. However, for products that are manufactured for less than 3 batches per year, they can be considered for the next cycle of PQR.

2. There is a consideration to group the products and the justification of the grouping will be described in the PQR report. In case a product is grouped but was excluded from the review, it also must be supported by proper justification.

3. In order to facilitate the collection of required data, QA/QC personnel will prepare PQR template to identify appropriate PQR data parameters. Then, it is provided to the respective department for data collection. QA will provide a schedule for the reporting period to ensure the report can be prepared in a timely manner.

4. The parameters for review are as follows:

    i. A review of **starting materials and packaging materials** used for the product, especially those from new sources.

    ii. A review of **critical in-process controls** and **finished product results**.

    iii. A review of all **batches that failed** to meet established specification(s) and their **investigation**.

    iv. A review of all **significant deviations or non-conformances**, their related investigations, and the effectiveness of resultant corrective and preventative actions taken.

    v. A review of all **changes** carried out to the **processes or analytical** methods.

    vi. A review of product registration requirement **variations** submitted/granted/refused, including those for third country (export only) dossiers.

    vii. A review of the results of the **stability monitoring programme** and any adverse trends.

    viii. A review of **all quality-related returns, complaints and recalls** and the **investigations** performed at the time.

    ix. A review of **adequacy** of any other previous product process or equipment **corrective actions**.

x. The **verification status** of relevant **equipment** and **utilities**, e.g. air-conditioner/ventilation, water, compressed gases, etc.

xi. A review of **Technical Agreements** to ensure that they are up to date.

xii. For **new product registrations** and **variations** to product registrations, a review of post-marketing commitment.

5. Each department is responsible to prepare an analysis or interpretation of the data. Then, provides the information and its analysis to QA for the preparation of PQR. QA will follow up with the respective department, should the information does not reach the QA within stipulated time.

6. During the review, the assessment includes whether there is any CAPA required and comparing review from previous PQR, if applicable. If the report is satisfactory, the QA/QC Manager shall approve the PQR.

5.0 REFERENCE

Guidelines on Good Manufacturing Practice for Traditional Medicines and Health Supplements; Malaysia, 1st Edition, 2008

6.0 ATTACHMENT

Attachment 1 – Report Template

Appendix 2

REPORT SAMPLE

This report sample serves **only** as a guide to start preparing for the report.

Please refer to the explanatory notes (***in italic***) provided in each section below.

Syarikat Ulik Mayang Sdn. Bhd. Product Quality Review for 2020 (Review Period: 01 January – 31 December 2022)			
Document Reference:	APQR-20-XX-YY	Date of Review:	02/01/2021
Compiled by / Date:	Ms. Susan QA/QC Executive	Reviewed by / Date:	Ms. Lisa QA/QC Manager
Approved by / Date:	Mr. Alex CEO		

1.0 EXECUTIVE SUMMARY

1. *This part contains the summary of products being reviewed; which may include information such as*

    - *number of batches manufactured for the review period,*
    - *location of the manufacturing activity (if there are more than one production line),*
    - *batch sizes and dosage form*
    - *period of the report*

2. *It also can include a brief review on previous PQR for the products / group; if there is any.*
3. *The assessment includes the conclusion for the overall review of the products / group.*

2.0 DESCRIPTION OF PRODUCTS REVIEWED

1. *This part contains in detail products reviewed which shall include the product names, batch numbers, batch sizes, yield of each batch, date of manufacturing and date of release.*

2. *The justification on how the products grouping can be described under this para.*

3.0 REVIEW OF PARAMETERS

3.1 Review of Starting Materials and Packaging Materials

1. *This part contains all the starting materials – raw materials (both active and excipients) and packaging materials - used in the manufacturing of products under review. It includes;*

    a. *List of starting materials used with batch number*
    b. *List of the suppliers for starting materials.*
    c. *Qualification status of the supplier*
    d. *Compilation of analytical testing results conducted by the manufacturer.*
    e. *Any issue / problem occurs with any of the starting materials received during the review year.*

2. *Packaging materials are the packaging materials registered under the product registration. For example; blister, bottle, unit carton.*

3. *A summary of the overall performance / quality of the starting materials.*

3.2 Review of Critical In Process Control and Finished Product Results

1. *This part described any in-process test results (In-Process Quality Control), usually related with physical variation – e.g. weight / dimension, friability, hardness, disintegration time, fill volume / overage, uniformity of content.*

2. *As well as for finished products test results for both analytical, chemical and microbiological aspects. Tests such as;*

   - *Physical variation – e.g. weight / dimension, friability, hardness, disintegration time, fill volume / overage, uniformity of content*
   - *Chemical variables – e.g. active ingredient, specific ingredient, heavy metals, pH*
   - *Yield reconciliation*

3. *The data in this part may presented with suitable presentation of charts.*

4. *A summary of the overall performance of the IPQC, including any issues such as rejected batches due to foreign particles or microbial limit.*

3.3 Review of all batches that failed to meet established specification(s) and their investigation

1. *This part contains if there is any failed batches for the products under review, which includes the reasons and investigation results. It may include any suggestion for improvement in process, materials, etc.*

3.4 Review of Significant Deviations or Non-Conformances

1. *This part summarises any deviation or non-conformances that occur to any of the batch under review. The reporting includes the root cause of deviation / non-conformance, investigations and any suggestion for CAPA.*

2. *It also will take into account any previous deviations from previous PQR on its status and effectiveness.*

3.5 Review of all changes carried out to the processes or analytical methods

1. *This part summarises any changes that occur in the manufacturing process or analytical testing of any affected batch under review. It has to include the justification of change, its impact to current processes and the effectiveness.*

Glossary

a. Change in this context defined as systematic approach to managing any changes to a product or system. It is to ensure the changes made are introduced into the system in a controlled and coordinated manner.

   For example; there is an improvement of mixing process that the manufacturer wish to incorporate into the existing process. Therefore, prior to the change, a request is made to the Quality Assurance. Upon evaluation by different department and the change is approved, the requester can proceed with the change.

3.6 Review of variations related to product registration requirement

1. *The part lists all the variation application submitted for products under review. Information such as*
   a. *number of product(s) submitted,*
   b. *status of registration,*
   c. *changes required from regulatory authority (RA), with status (granted or rejected)*
      **if rejected, should include reason of rejection*
   d. *any changes that are submitted to RA*

3.7 Review of stability monitoring programme and any adverse trends

1. *This part lists all batches number included under the stability programme during this review period. Information such as;*
   a. *Product involved with batch number, manufacturing date*
   b. *Packaging information – batch size, type*
2. *Elements for review including the real time data, on-going stability studies and OOS.*

3.8 Review of all quality related returns, complaints and recalls

1. *This part identified any returns, complaints or recalls for products under review. It also includes batches that are not included in the review period.*
2. *The information required such as*
   a. *Products involved and the batch number*
   b. *Reasons and classification of reasons of return, complaint or recall*
   c. *Associated investigation report reference*
   d. *Action taken and its status*
   e. *The extent of damage that may require further action on other batches*

3.9 Review of adequacy of the previous product process or equipment corrective actions

1. *This part will identify any previous Corrective Action Preventive Action (CAPA) on previous PQR on its implementation and effectiveness.*

3.10 Review of verification status of relevant equipment and utilities

1. *This part lists all equipment, laboratory instruments and utilities used in the manufacturing of the products under review. Information such as;*
    a. *Verification / re-verification status*
    b. *Next re-verification schedule*
    c. *Changes made to equipment, laboratory instruments and utilities that resulted in re-verification*

3.11 Review of technical agreements

1. *This part lists all contract acceptor / contract analytical service providers related to product under review. Information such as;*
    a. *Name & address*
    b. *Type of services provided*
    c. *Period of the validity of the contract*

3.12 Review on new product registration and variation & post-marketing commitment

1. *This part lists any variation or new registration involves the product under review, any post-market commitment such as market sampling, stability study program.*

4.0 CONCLUSIONS AND RECOMMENDATIONS

This part will summarise the PQR prepared with suggestions for improvement. A general statement on the overall performance of the product under review for the year.

Appendix 3

IMPLEMENTATION REPORT (based on Implementation Strategy)

Based on the implementation strategy, this schedule provides visualisation on the preparation of the PQR report at every stage of implementation.

Elements of the report / Parameters	Stages			
	Program Development	Phase 1	Phase 2	Phase 3
1.0 SOP				
• Drafting	√	-	-	-
• Approval		-		-
• PQR schedule / planning	√	-	-	-
○ Product description	√		√	
○ Product grouping (if applicable)				
• Review of SOP		√		√
	-		√	
2.0 Parameters for Review in the Report				
• Review of starting materials and packaging materials		√	√	√
• Review of in-process control & finished products results		√	√	√
• Review of finished product yields		√	√	√
• Review of technical agreements		√	√	√
		√	√	√
• Review of batches that failed to meet specification			√	√
• Review on quality related return, complaint and recall			√	√
• Review on verification status on equipment			√	√
• Review of stability monitoring program			√	√
			√	√
• Review of any changes to process or analytical methods				√
• Review on variation				
• Review on adequacy of previous product process or equipment CAPA				√

• Review on new product registration & post market commitment				√ √
3.0 Report Draft and Approval		√	√	√