APPENDIX 27

INSPECTION

The related GMP and GDP guidelines referred are:

Guidelines	Product Type/ Category
PIC/S Guide to Good Manufacturing Practice for Medicinal Products * ** Refer to the Pharmaceutical Inspection Co-operation Scheme (PIC/S) website (www.picscheme.org)*	• Pharmaceuticals (Poison and Non-Poison) • Veterinary Medicinal Products • Investigational Medicinal Products • Active Pharmaceutical Ingredients
GMP Guideline for Traditional Medicines and Health Supplements, 1st Edition, 2008	• Traditional Products • Health Supplements
Guidelines on Good Manufacturing Practice (GMP) for Cosmetics (Annex 1, Part 10)	• Cosmetics
Guideline on Good Manufacturing Practice (GMP) for Veterinary Premixes, 1st Edition, January 2015	• Veterinary Products (Premixes)
Guidelines on Good Distribution Practice (GDP); 3rd Edition 2018 Supplementary Notes on Annex 1: Management of Time and Temperature Sensitive Products (TTSP) of Guideline on Good Distribution Practice	• For activities related to the storage and distribution of products/ cosmetics by manufacturers, importers and wholesalers (where applicable)

Refer to the NPRA website for the latest directives and circulars pertaining to GMP and GDP.

1. FOREIGN GMP INSPECTION

The PRH must provide acceptable evidence to prove that the manufacturer of the product follows an internationally accepted standard of GMP and recognized by the Authority in Malaysia.

The CDCR 1984 requires that the standard of manufacturing and quality control of medicinal products manufactured outside Malaysia be taken into consideration before the products are registered with the Authority. NPRA, as the secretariat to the DCA, is responsible for ensuring that all manufacturers of registered products in Malaysia provide acceptable evidence that the manufacturing premises conform to current GMP requirements. Hence, foreign manufacturers are also subjected to GMP conformity assessments through acceptable GMP evidence or GMP inspection.

For further details and forms, refer to the **Guidance Document Foreign GMP Inspection.**

2. MANAGING CHANGES OF MANUFACTURERS FACILITY

This section only focuses on changes related to manufacturing premises including quality control laboratories and storage/ warehouse facilities. For changes to product particulars, refer to Section E of Post Registration Process, which discusses Amendments to Particulars of a Registered Product.

Changes at the manufacturers' facility can potentially have a quality and safety impact. It is the responsibility of the site to assess information on the changes via a formal change control system and risk management, where applicable. Manufacturers, Importers and Wholesalers are recommended to have a system for categorizing types of changes. All changes to the facility shall be notified to the Centre of Compliance & Quality Control (PKKK) and/ or Centre of Regulatory Coordination & Strategic Planning (PKPSR).

Notification of changes will be reviewed to assess its significance and may be verified during the scheduled GMP inspection. PKKK will communicate further and arrange for an investigative/ for-cause inspection focusing on these changes, if deemed necessary.

Additional Information:

1. This section is applicable to local manufacturers only. For changes of importer or wholesaler particulars, refer to **Section E: Post-Registration Process**

2. For further details, refer to **Table A. Example of Immediate Notification** and **Table B. Example of Periodical Notification.**

Types of notification are immediate and periodical notification:

2.1 Immediate notification

This notification is applicable to manufacturers who plan/ undergo a major/ significant/ substantial change that could have an impact on the product quality and safety. Immediate Notification shall be made to and approved by the Centre of Compliance & Quality Control (PKKK) prior to its implementation.

Immediate Notification shall be submitted as follows:

a) Complete 'Borang Permohonan Penilaian Pelan Susun Atur Premis Pengilang' (NPRA/431/12) for changes related to manufacturing layout and process flow

OR

b) Official letter, which may include information (at the very least) such as;
   - Description of changes to the facility
   - Plan of changes (E.g. Gantt Chart, Validation Master Plan, etc.)
   - Details of the products affected, where applicable.

Examples of changes are listed in **Table A. Example of Immediate Notification**

2.2 Periodical Notification

This notification is applicable to manufacturers that plan/ undergo a minor change that would not give any impact to the product quality and safety. Periodical Notification can be submitted in the form of official letter, which may include information (at the very least) such as;

- Description of changes
- Plan of changes (E.g. Gantt Chart, Validation Master Plan, etc.)

Examples of changes that require Periodical Notification are as per **Table B. Example of Periodical Notification**

Note: Both ***Table A. Example of Immediate Notification*** *and* ***Table B. Example of Periodical Notification*** *are examples for both regulator and the industry. Requirement for further action is still subject to the evaluation by PKKK based on the risk of the changes proposed/ implemented by the manufacturer.*

Table A. Examples of Immediate Notification

Items	Example	Description	Requirement of NPRA/431/12	Type of Application under NPRA/431/12	Documentation Required	Remarks (if any)
1.	Change of Manufacturing site (including drug substance if any)	Require submission of new layout plan E.g. New lot	YES	New premises layout (Processing Fee= RM1000.00)	As per NPRA/431/12 requirement	Verification of information via GMP inspection, if necessary. Please refer further to Section E.
2.	Introduction of new line/ upgrading clean room	a. Addition of new manufacturing/ packaging line	YES	Revision of existing premises layout (Processing fee: RM 500.00)	As per NPRA/431/12 requirement	Verification of information via GMP inspection, if necessary. Please refer further to Section E.

Items	Example	Description	Requirement of NPRA/431/12	Type of Application under NPRA/431/12	Documentation Required	Remarks (if any)
		b. New Production Block	YES	Revision of existing premises layout (no changes of premises address) (Processing fee: RM 500.00)	As per NPRA/431/12 requirement	Verification of information via GMP inspection, if necessary. Please refer further to Section E.
		c. Upgrading to clean room E.g. Renovation of the production floor according to clean room requirement	YES	Revision of existing premises layout (Processing fee: RM 500.00)	As per NPRA/431/12 requirement	Verification of information via GMP inspection, if necessary.

Items	Example	Description	Requirement of NPRA/431/12	Type of Application under NPRA/431/12	Documentation Required	Remarks (if any)
3.	Change of Manufacturing/ Packaging Rooms (including manufacturing/ packaging room located in warehouse facility e.g. Centralized dispensing room in warehouse)	a. Relocate or add manufacturing rooms, which affect the process flow	YES	Revision of existing premises layout (Processing fee: RM 500.00)	As per NPRA/431/12 requirement	Verification of information via GMP inspection, if necessary.
		b. Change of room function	YES	Revision of existing premises layout (Processing fee: RM 500.00)	As per NPRA/431/12 requirement	
		c. Resizing of the room (without affecting existing process flow)	NO	Not applicable	Notification to PKKK, NPRA	
4.	Change of equipment, or manufacturing process or	Addition of critical equipment	NO	Not applicable	Notification to PKKK, NPRA	Verification of

Items	Example	Description	Requirement of NPRA/431/12	Type of Application under NPRA/431/12	Documentation Required	Remarks (if any)
	utility					information via GMP inspection, if necessary.
		Changes/ addition of critical steps in manufacturing (including packaging) process	NO	Not applicable	Notification to PKKK, NPRA	Verification of information via GMP inspection, if necessary. May involve product variation (Refer to CPCE, NPRA)
		Changes/ addition of critical utility, such as water system, pharmaceutical gases and HVAC, etc	NO	Not applicable	Notification to PKKK, NPRA	Verification of information via GMP inspection, if necessary.
5.	Sharing of manufacturing facilities between traditional medicines and health supplements	No changes in manufacturing facility	NO	Not applicable	Notification to PKKK, NPRA.	Verification of information via GMP inspection, if necessary.

Items	Example	Description	Requirement of NPRA/431/12	Type of Application under NPRA/431/12	Documentation Required	Remarks (if any)
6.	Sharing of manufacturing facilities between notified cosmetics and other non-cosmetics (e.g. household products, insect repellent or veterinary cosmetic)	No changes in manufacturing facility	NO	Not applicable	Notification to PKKK, NPRA.	Verification of information via GMP inspection, if necessary.

Table B. Examples of Periodical Notification

Items	Example	Description	Requirement of NPRA/431/12	Type of Application under NPRA/431/12	Documentation Required	Remarks (if any)
1.	Change or addition of warehouse facility	Renovation or addition of new warehouse or alternative warehouse	NO	Not applicable	Notification to PKKK & PKPSR, NPRA	Verification of information via GMP inspection, if necessary. The new warehouse needs to be licensed by NPRA before commencing operation. New Manufacturer's License application is required
2.	Change or addition of QC facility	Renovation or addition of QC facility E.g. Retention sample store, microbiological laboratory, stability chamber etc.	NO	Not applicable	Notification to PKKK, NPRA	Verification of information via GMP inspection, if necessary.
3.	Other renovation (without affecting existing manufacturing layout)	Other renovation E.g. Change of flooring, ceiling, door and wall.	NO	Not applicable	Notification to PKKK, NPRA	Verification of information via GMP inspection, if necessary.

Items	Example	Description	Requirement of NPRA/431/12	Type of Application under NPRA/431/12	Documentation Required	Remarks (if any)
4.	Change of key personnel	Applicable to QA/QC Manager, Head of production, Production Pharmacist	NO	Not applicable	Notification to PKKK & PKPSR, NPRA	May involved change of holder of Manufacturer's License.
5.	Addition or replacement of manufacturing equipment, without affecting existing manufacturing layout	a. Replacement of old equipment with new equipment in existing designated room E.g. Replace the old tableting machine with new tableting machine in existing tableting room.	NO	Not applicable	Notification to PKKK, NPRA	Verification of information via GMP inspection, if necessary.

Items	Example	Description	Requirement of NPRA/431/12	Type of Application under NPRA/431/12	Documentation Required	Remarks (if any)
		b. Installation of new equipment in existing room E.g. New encapsulation or tableting machine in the existing room.	NO	Not applicable	Notification to PKKK, NPRA	Verification of information via GMP inspection, if necessary.
6.	Change of manufacturer address with no changes in manufacturing site	Changes of building number, postal code, street name, etc.	NO	Not applicable	Notification to PKKK, NPRA Business License from local authority	New Manufacturer's License application is required Please refer to Section E. May involve variation application to update the company details.

Items	Example	Description	Requirement of NPRA/431/12	Type of Application under NPRA/431/12	Documentation Required	Remarks (if any)
7.	Change of manufacturer name	Company SSM registration number remain unchanged. No changes on manufacturing facility	NO	Not Appplicable	Notification to PKKK, NPRA SSM Certificate	New Manufacturer's License application is required Please refer to Section E. May involve variation application to update the company details.
8.	Change of manufacturer SSM registration number.	No changes in manufacturing facility	NO	Not applicable	Notification to PKKK, NPRA SSM Certificate	Pre-licensing GMP inspection Please refer to Section E. May involve variation application to update the company details.

Items	Example	Description	Requirement of NPRA/431/12	Type of Application under NPRA/431/12	Documentation Required	Remarks (if any)
9.	Cessation of manufacturing operation	Example: • Relocation to new site. • Cessation of business activity	NO	Not Applicable	Notification to PKKK, NPRA Manufacturer's License to be returned to NPRA	Verification of information by PKKK if necessary.
10.	Sharing of manufacturing facilities between medical devices and medicinal products	No changes in manufacturing facility	NO	Not Applicable	1. Notification to PKKK, NPRA. 2. Establishment Licence from MDA	Verification of information via GMP inspection, if necessary