An Analysis of Deficiencies Observed During On-Site Good Manufacturing Practice (GMP) Inspections of Local and Foreign Manufacturing Premise of Medicinal Registered Products in The Year 2022

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1.0 INTRODUCTION

As a secretariat of the Drug Control Authority (DCA), the National Pharmaceutical Regulatory Agency (NPRA), the Ministry of Health is responsible for ensuring the quality, safety, and efficacy of registered products and notified cosmetics.

The Good Manufacturing Practices (GMP) Section, Centre of Compliance and Quality Control (CCQC) is in charge of performing GMP inspections on local and foreign manufacturing facilities, which include:

- Pharmaceutical products (including scheduled poisons and over the counter products and medicinal gasses)
- Biologic products including Cell and Gene Therapy Products (CGTPs)
- Traditional/herbal products
- Health supplement products
- Cosmetics

The pharmaceutical products, Biologics products, Traditional/herbal products and Health supplements products are regulated as registered products. Hence, the manufacturers are required to apply for a license in order to conduct manufacturing activities. However, cosmetic products are regulated as notified products and do not require license prior to manufacturing activities.

For CGTPs, it is regulated under the listing programme until the year 2024 and requires full registration and license starting in 2025.

For medicinal gasses, it is regulated under voluntary registration until year 2022 and is required full registration and license starting in 2023.

The types of inspection that are performed by GMP Section includes:

Announced inspection:	Unannounced inspection:
● Pre-Licensing inspection ● Initial audit ● Pre-approval inspection ● Routine inspection ● Verification inspection ● Pre-certification inspection	Investigation inspection

For CGTPs, pre-certification inspection will be conducted until the year 2022. Pre-licensing inspection will only commence in 2023.

The main guidelines to be referred during GMP inspection are:

Type of products	Guideline
Pharmaceutical Products, Biologic Products, CGTPs, Medicinal Gas	PIC/S GMP Guide
Traditional/ Herbal products, Health supplements	Guideline on Good Manufacturing Practice for Traditional Medicines and Health Supplements
Cosmetic	Guidelines for Cosmetic Good Manufacturing Practice, Guidelines for Control of Cosmetic Products in Malaysia

The observation during an inspection (either good point or deficiencies) will be reported in the respective chapters:

- Pharmaceutical Quality System/ Quality Management System
- Personnel
- Premise and Equipment
- Documentation
- Production
- Quality Control
- Outsourced activities/ Contract manufacture and analysis
- Complaint and recall
- Internal audit
- Shipment and Distribution

Each deficiency will be classified as minor, major and critical based on the risk impact to the products manufactured.

2.0 PURPOSE

1. To comply with Indicator RI06 Mechanism exists to promote transparency, accountability and communication for the purpose of WHO Global Benchmarking Tool (GBT)

2. To promote transparency, accountability and communication within inspectors as well as inspectorate and industry

3. To improve mutual understanding and involvement of all manufacturers relevant to inspection activities by NPRA

3.0 SCOPE

1. Only applicable to routine inspections, conducted on-site towards local manufacturing premises of pharmaceutical products, biologic products, traditional/herbal medicines and health supplements.

2. Manufacturing premises of CGTPs and medicinal gasses are excluded as both products are currently under listing/voluntary registration program by NPRA.

3. Manufacturing premises of cosmetic products are excluded, as it is not considered as medicinal products under WHO GBT Benchmarking program.

4.0 DATA ANALYSIS AND DISCUSSION

a) Number of inspected premises with Acceptable/Unacceptable GMP compliance status and/or with regulatory action.

Outcomes of inspections

Compliance Status in Year 2022	Pharmaceutical	Traditional Medicine & Health Supplement
Number of inspections conducted	52	47
Acceptable GMP status	50	45
Unacceptable GMP status	2	2
Regulatory action imposed	2	2

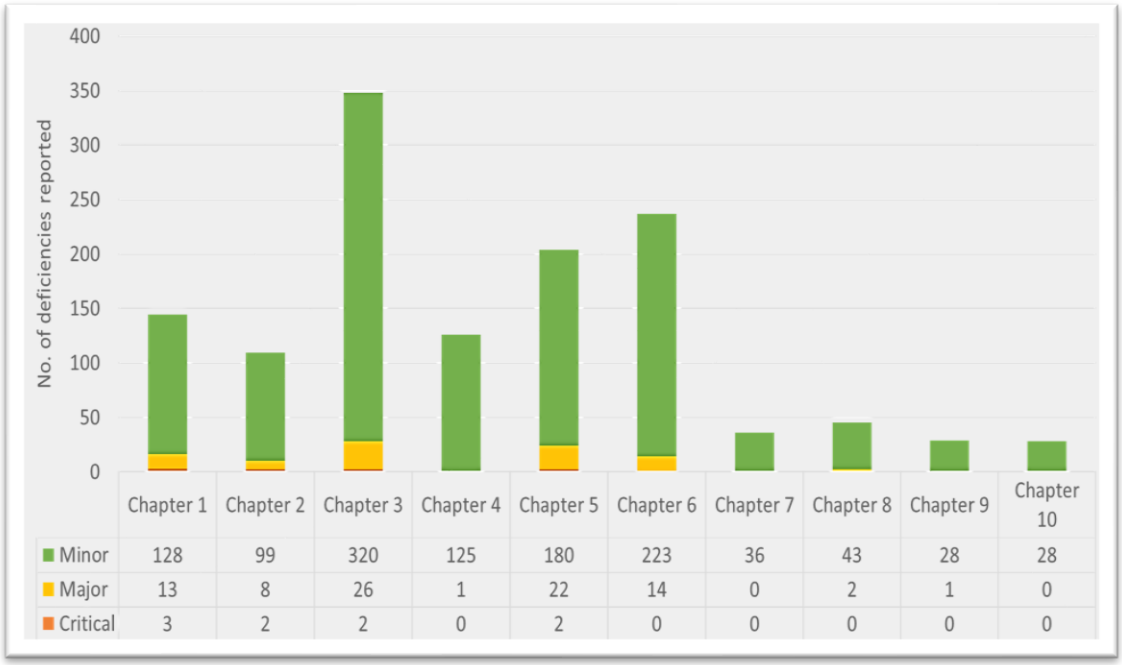
b) Total number of inspections relative proportion of each type of inspections (e.g. routine, pre-licensing, pre-approval inspection, etc.)

Types of Inspections	Pharmaceutical	Traditional Medicine & Health Supplement
Routine Inspections	43	47
Non-Routine Inspection	9*	0

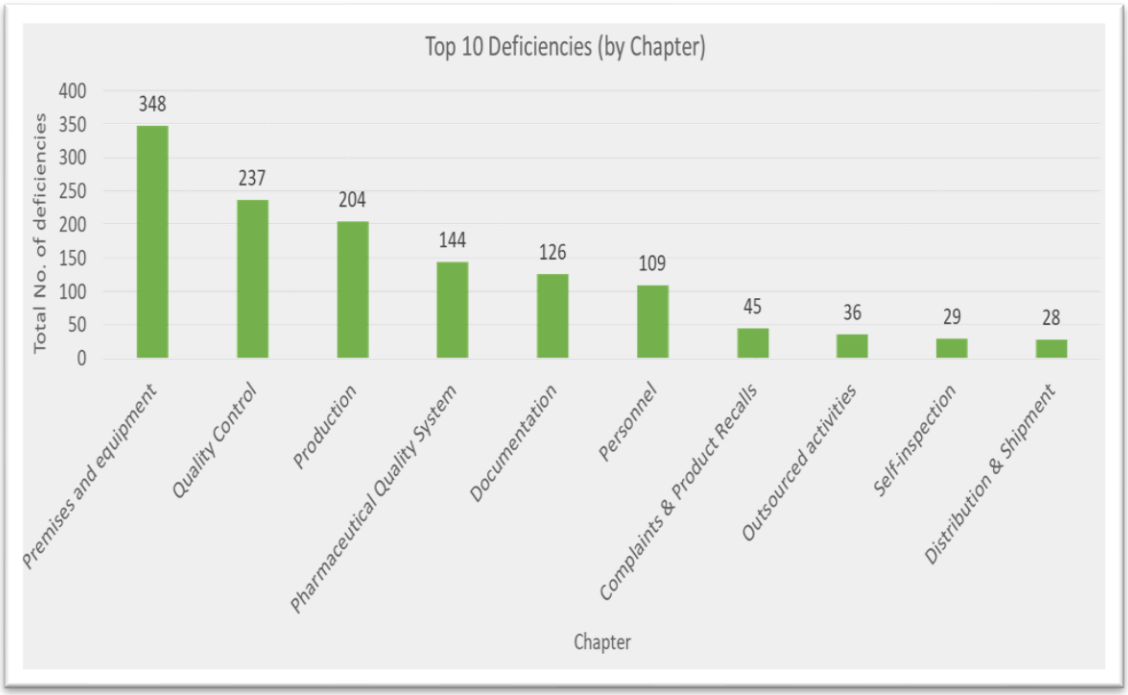
*9 non-routine inspections were pre-certification inspections of foreign manufacturers

c) Number of each category of deficiencies (e.g. critical, major and minor) for each chapter (e.g. Chapter 1 to 10)

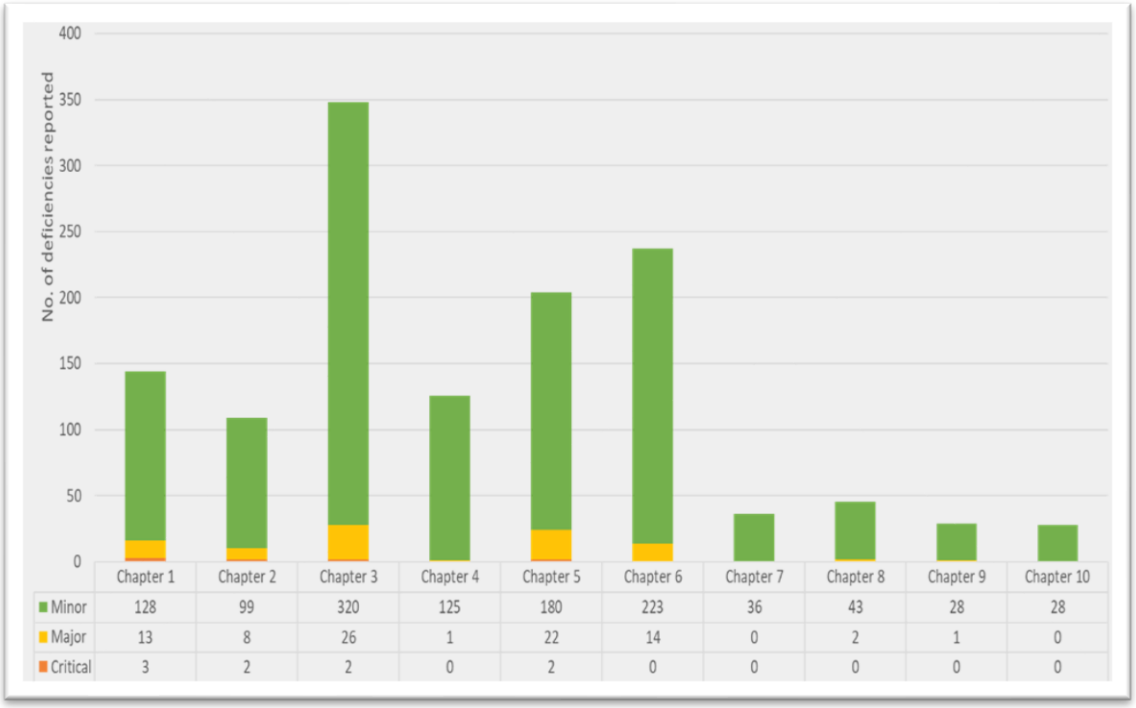
i. Pharmaceutical



	Chapter 1	Chapter 2	Chapter 3	Chapter 4	Chapter 5	Chapter 6	Chapter 7	Chapter 8	Chapter 9	Chapter 10
Minor	128	99	320	125	180	223	36	43	28	28
Major	13	8	26	1	22	14	0	2	1	0
Critical	3	2	2	0	2	0	0	0	0	0



ii. Traditional Medicine and Health Supplement



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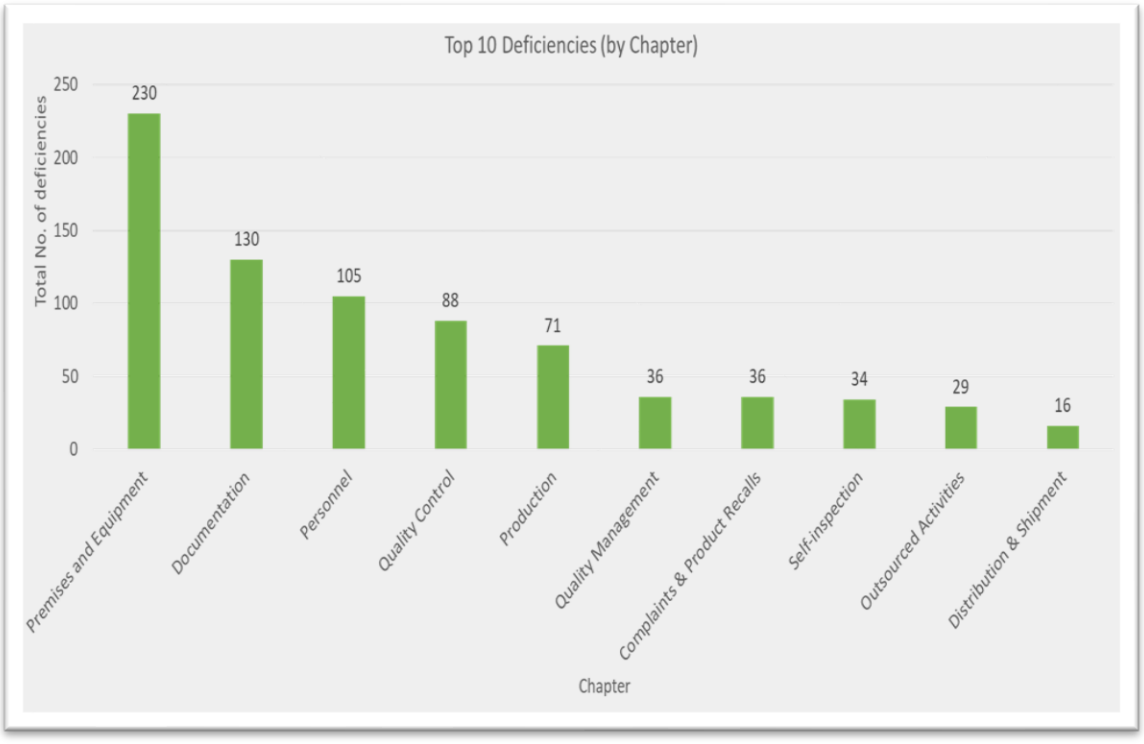

d) Number of frequently occurring observations (in regards to relevant para/ clause in the guidelines to be referred) for critical and major deficiencies.

Both critical and major findings for each chapter are further categorized according to the para/clause of the relevant guideline and reported in a table format and further analysed using appropriate statistical tools. This is to identify the most frequently reported finding during inspection.

i. Pharmaceutical

Finding Classification	Area	Clause in GMP Guidelines
Critical findings	Pharmaceutical Quality System	1.1 Quality Management is a wide-ranging concept, which covers all matters, which individually or collectively influence the quality of a product. It is the sum total of the organised arrangements made with the objective of ensuring that medicinal products are of the quality required for their intended use. Quality Management therefore incorporates Good Manufacturing Practice.
	Personnel	2.10 The manufacturer should provide training for all the personnel whose duties take them into production and storage areas or into control laboratories (including the technical, maintenance and cleaning personnel), and for other personnel whose activities could affect the quality of the product.
		2.18 Every person entering the manufacturing areas should wear protective garments appropriate to the operations to be carried out.
	Production	5.19 Cross-contamination should be prevented by attention to design of the premises and equipment as described in Chapter 3. This should be supported by attention to process design and implementation of any relevant technical or organizational measures, including effective and reproducible cleaning processes to control risk of cross-contamination.
Major findings	Annex 15	Qualification and validation
	Pharmaceutical Quality System	1.8 Good Manufacturing Practice is that part of Quality Management which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorisation, Clinical Trial Authorisation or product specification. Good Manufacturing Practice is concerned with both production and quality control. The basic requirements of GMP are that….
	Production	5.25 Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or the reproducibility of the process, should be validated.
	Premises and equipment	3.2 Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They should be cleaned and, where applicable, disinfected according to detailed written procedures.

ii. Traditional Medicine and Health Supplement

Finding Classification	Area	Clause in GMP Guidelines
Critical findings	Quality Management	1.2 Quality Assurance is a wide-ranging concept which covers all matters which individually or collectively influence the quality of a product. It is the sum total of the organized arrangements made with the object of ensuring the medicinal product are of the quality required for their intended use. Quality Assurance therefore incorporates Good Manufacturing Practice plus other factors outside the scope of this Guide. The system of Quality Assurance appropriate for the manufacture of traditional medicines and health supplements should ensure that…
		1.3 Good Manufacturing Practice is that part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Product Registration or product specification. Good Manufacturing Practice is concerned with both production and quality control. The basic requirements of GMP are that…
	Premises and equipment	3.41 Manufacturing equipment should be adequate for the operations performed and should be designed, constructed, placed and maintained in such a way to…
Major findings	Quality Management	1.2 Quality Assurance is a wide-ranging concept which covers all matters which individually or collectively influence the quality of a product. It is the sum total of the organized arrangements made with the object of ensuring the medicinal product are of the quality required for their intended use. Quality Assurance therefore incorporates Good Manufacturing Practice plus other factors outside the scope of this Guide. The system of Quality Assurance appropriate for the manufacture of traditional medicines and health supplements should ensure that…
	Premises and equipment	3.13 Buildings should be effectively lit and ventilated with air control facilities (including temperature, humidity and filtration), appropriate both to the operations undertaken within them and to the external environment.
	Production	5.12 At all time during processing, all materials, bulk containers, major items of equipment and where appropriate rooms used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and batch number. Where applicable, this indication should also mention the stage of production.
	Quality Control	6.16 All testing operations described in the Product Registration dossier should be carried out according to the approved methods.

5.0 RECOMMENDATION AND AREAS OF IMPROVEMENT

According to PIC/S Guidance on Classification on GMP Deficiencies (PI 040-1 3 Appendices, 1 January 2019), Critical deficiency means:

i. A deficiency which has produced, or leads to a significant risk of producing either a product which is harmful to the human or veterinary patient or a product which could result in a harmful residue in a food producing animal.
ii. A "Critical" deficiency also occurs when it is observed that the manufacturer has engaged in fraud, misrepresentation or falsification of products or data.
iii. A "Critical" deficiency may consist of several related deficiencies, none of which on its own may be "Critical", but which may together represent a" Critical" deficiency, or systems' failure where a risk of harm was identified and should be explained and reported as such. The critical deficiency defined as a deficiency which has produced, or leads to a significant risk of producing either a product which is harmful to the human.

Based on the study, the top 3 critical deficiencies reported were clause 1.1 under Chapter 1 Pharmaceutical Quality System (PQS), clause 2.10 & 2.18 under Chapter 2 Personnel and clause 5.29 under Chapter 5 Production.

a) Chapter 1 Pharmaceutical Quality System (PQS)

1.1 Quality Management is a wide-ranging concept, which covers all matters, which individually or collectively influence the quality of a product. It is the sum total of the organised arrangements made with the objective of ensuring that medicinal products are of the quality required for their intended use. Quality Management therefore incorporates Good Manufacturing Practice.

Generally, manufacturers need to pay attention on the design and implementation of PQS which incorporating Good Manufacturing Practice and Quality Risk Management in order to ensure the medicinal products produced are fit for their intended use, comply with the requirements of Marketing Authorization and do not place patients at risk due to inadequate safety, quality and efficacy.

The PQS consisted of the elements below:

- Sufficiently qualified personnel to carry out all the tasks
- individual responsibilities clearly understood by individuals and recorded
- personnel should receive initial and continuing training including hygiene instructions.
- Premise and equipment properly located, designed, constructed, adapted and maintained to suit the operations to be carried out.
- Layout and design must aim to minimize risk of errors and permit effective cleaning and maintenance in order to avoid cross contamination, build-up of dust or dirt and adverse effect on the quality of product
- Good Documentation including sufficient instructional details to facilitate common understanding of the requirements in addition to providing sufficient recording of the various processes and evaluation of any observations.
- Production Operations follow clearly defined procedures

- Quality control which includes sampling, specifications, and testing as well as organisation, documentation and release procedure which ensure that the necessary and relevant tests are carried out and that materials are not released for use nor product release for sale for supply until their quality has been judged satisfactory.
- The independence of Quality Control from Production.
- any outsourced activities should be appropriately defined, agreed and controlled in order to avoid misunderstandings which could result in a product or operation of unsatisfactory quality
- A system and appropriate procedures should be in place to record, assess, investigate and review complaints including potential quality defects and if necessary, to effectively and promptly recall medicinal products from the distribution network.
- To conduct self-inspection in order to monitor the implementation and compliance and to propose necessary corrective measures.

In addition, the evaluation of PQS also involved aspects such as handling of change control, deviation, product quality review, quality risk management, CAPA and management review.

b) Chapter 2 Personnel

2.10 The manufacturer should provide training for all the personnel whose duties take them into production and storage areas or into control laboratories (including the technical, maintenance and cleaning personnel), and for other personnel whose activities could affect the quality of the product.

2.18 Every person entering the manufacturing areas should wear protective garments appropriate to the operations to be carried out.

Generally, training activities should be well planned and executed to ensure personnel receive sufficient training relevant to their task so that they can perform their duties well.

In addition, manufacturers need to pay attention to the protective garments provided for the operator and ensure the garments are suitable for the operations to be carried out. The availability, suitability and the cleanliness of the garments should be emphasized.

The handling of used garments and laundry activities also need to be improved to ensure the garments used will not pose any risk of contamination to the operations and products.

Manufacturers involved in sterile manufacturing activities should also ensure the integrity of sterile garments used.

c) Chapter 5 Production

5.29 Cross-contamination should be prevented by attention to design of the premises and equipment as described in Chapter 3. This should be supported by attention to process design and implementation of any relevant technical or

organizational measures, including effective and reproducible cleaning processes to control risk of cross-contamination.

Manufacturers need to pay attention to the measures taken for controlling the risk of contamination. The measure taken should take into consideration the outcome of the Quality Risk Management Process. The measure could be taken but not limited to:

- dedicating the whole manufacturing activities or self-contained production area on campaign basis followed by a validated cleaning process
- Cleaning verification after each product campaign
- Validated cleaning process of equipment
- Proper cleaning and disinfection of premise
- environmental monitoring within manufacturing area
- Proper handling of waste handling, contaminated rinsing water and soiled gowning
- Handling of spills and accidental event or deviation from procedures
- Supervision of working behaviours to ensure personnel are comply with the procedure

Based on the study on THMS manufacturers, the top 3 critical deficiencies reported were clause 1.2 & 1.3 under Chapter 1 Quality Management, clause 3.1 under Chapter 3 Premises and Equipment and clause 4.1 under Chapter 4 Documentation.

d) Chapter 1 Quality Management

1.2 Quality Assurance is a wide-ranging concept which covers all matters which individually or collectively influence the quality of a product. It is the sum total of the organized arrangements made with the object of ensuring the medicinal product are of the quality required for their intended use. Quality Assurance therefore incorporates Good Manufacturing Practice plus other factors outside the scope of this Guide.

The system of Quality Assurance appropriate for the manufacture of traditional medicines and health supplements should ensure that…

Manufacturers should have an organized Quality Assurance system appropriate for manufacturing activities of traditional medicines and health supplements that are of quality essential for their intended use. The system established should include the following:

- Good Manufacturing Practice requirements are considered
- Responsibilities of managerial positions are defined
- Measures are taken to ensure supply and use of correct starting and packaging materials and manufacturing activities
- Intermediate products and any in-process activities are controlled
- Processing and checking of finished products are conducted in accordance with specified procedures.

- Products manufactured are not released for supply before authorized personnel have certified that each production batch has been manufactured and controlled according to the requirements of the Product Registration and any other procedures relevant to the production, control and release of products.
- Measures taken to ensure products are stored, distributed and handled appropriately to maintain its quality throughout their shelf life.
- Regularly appraise the effectiveness and applicability of the Quality Assurance system according to procedures for Self-Inspection and/or quality audit.

1.3 Good Manufacturing Practice is that part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Product Registration or product specification.

Good Manufacturing Practice is concerned with both production and quality control. The basic requirements of GMP are that…
Manufacturers should adopt Good Manufacturing Practice to produce products consistently of standard quality appropriate for their intended use and as required by the Product Registration or product specification. The basic requirements of Good Manufacturing Practice include:

- Manufacturing processes are clearly defined and reviewed, subsequently shown to be able to manufacture products consistently with quality while complying with their specifications
- Personnel/ operators are qualified and trained to carry out procedures correctly
- Adequate premises and suitable equipment
- Correct materials, containers and labels
- Approved procedures and instructions
- Records are made during production and any significant deviations are recorded and investigated accordingly
- Suitable storage and transportation
- Distribution records are made to enable the history of a batch to be traced
- Establish a system to conduct recall of any batch of product
- Complaints on marketed products are investigated including the cause of quality defects and appropriate measures taken to prevent reoccurrence

e) Chapter 3 Premises and Equipment

3.1 The premises for manufacturing should be of suitable size, design, construction and location to facilitate proper operation, cleaning and maintenance. The individual working areas must be adequate so that any risk of confusion, cross-contamination and other mistakes that could adversely affect the quality of the products could be avoided.

Manufacturing premises should be suitably designed and constructed for the manufacturing activities of traditional medicines and health supplements. Regular cleaning and review of the condition of premises and equipment should be conducted and premises repaired where necessary to ensure the production areas,

laboratories and stores are well maintained in a clean and proper condition.

f) Chapter 4 Documentation

4.1 The system of documentation should be able to record the complete history of each batch. It should be adequate to permit investigation and tracing of defective products.

A clearly written documentation system should be prepared to permit tracing of batch history of traditional medicines and health supplements manufactured. This includes records of activities conducted for starting materials received, storage, maintenance, quality control, distribution and related activities.

6.0 CONCLUSION

In conclusion, chapter 3—which is about Premise and Equipment—shows the most significant overall findings, as well as the top major and minor findings, for manufacturers of pharmaceutical products. It demonstrates that the area requires some attention and improvement activity from the manufacturer in order to avoid any risk to the products. Besides, Chapters 5 and 6 are two additional areas for the manufacturers to look at.

The area that has to be looked at for Traditional Medicine and Health Supplement manufacturers is also chapter 3, which shows the highest overall findings, highest major and minor findings. The other focus is on the manufacturer's documentation and quality control activities which has been analysed as an area that recorded frequent findings.

7.0 LIMITATION

This study does not include the whole GMP inspection in 2022, as non-routine and off-site inspections are not included. As a result of an improvement, the entire GMP inspection should be included in the analysis in order to offer more precise information.

8.0 REFERENCES

WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory systems of medical products, revision VI. Geneva: World Health Organization; 2021.