UNVEILING GOOD MANUFACTURING PRACTICE (GMP) INSIGHT: DEFICIENCY ANALYSIS IN ON-SITE INSPECTIONS OF MANUFACTURERS FOR MEDICINAL PRODUCTS AND COSMETICS BY NATIONAL PHARMACEUTICAL REGULATORY AGENCY (NPRA), MINISTRY OF HEALTH MALAYSIA

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1.0 INTRODUCTION

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

Good Manufacturing Practice (GMP) Section, Centre of Compliance and Quality Control is responsible to perform GMP inspection towards local and foreign manufacturing premise consists of:

- Pharmaceutical products (including scheduled poisons, over the counter products and medicinal gases)
- Biologics 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 manufacturing licence in order to conduct manufacturing activities. Meanwhile, cosmetics are regulated as notified products and do not require a manufacturing licence prior to manufacturing activities.

For CGTPs, it is regulated by NPRA under the listing programme until the year 2024 and the product requires full registration and manufacturing licence starting in 2025.

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 has been conducted until the year 2022, followed by pre-licensing inspection commenced in 2023 and routine inspections initiated in 2024.

The main guidelines to be referred during GMP inspection are:

Type of products	**Guideline**
Pharmaceutical, Biologic, CGTPs, Medicinal Gases	PIC/S Guide to Good Manufacturing Practice for Medicinal Products and its Annexes
Traditional/ Herbal, Health supplements	Guidelines On Good Manufacturing Practice For Traditional Medicine And Health Supplements, First Edition; 2008
Cosmetic	Annex 1, Part 11: Guideline for Cosmetic Good Manufacturing Practice, Guidelines for Control of Cosmetic Products in Malaysia, Second Edition, August 2022

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

- Chapter 1: Pharmaceutical Quality System/ Quality Management System
- Chapter 2: Personnel
- Chapter 3: Premise and Equipment
- Chapter 4: Documentation
- Chapter 5: Production
- Chapter 6: Quality Control
- Chapter 7: Outsourced activities/ Contract manufacture and analysis
- Chapter 8: Complaint and recall
- Chapter 9: Internal audit
- Chapter 10: Shipment and Distribution

Each deficiency (findings) will be classified as Minor, Major and Critical based on the risk impact to the products manufactured.

2.0 PURPOSE/OBJECTIVE

1. To analyse major and critical deficiencies observed during routine inspection (local manufacturer) and non-routine inspection (foreign manufacturer) among manufacturers.

2. To identify the gap between industry practices and regulatory expectations.

3. To publish the outcome of the analysis for industry’s reference.

3.0 SCOPE

1. This study includes all manufacturing premises for registered product and notified cosmetics that covers:

   a) Routine on-site inspection towards local manufacturing facilities of pharmaceuticals, biologics, traditional/herbal medicines, health supplements and cosmetics and
   b) Non-routine on-site inspection towards foreign manufacturing facilities of pharmaceuticals.

2. Inspections conducted between January to December 2023.

3. Manufacturing premises of CGTPs is excluded from this study as the products are currently under listing/voluntary registration programme by NPRA.

4.0 DATA ANALYSIS

4.1 Outcomes of inspections

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

Compliance Status in Year 2023	Pharmaceutical	Traditional Medicine & Health Supplement	Cosmetics
Number of inspections conducted	72	142	130
Acceptable GMP status	70	138	125
Unacceptable GMP status	2	4	5
Regulatory action imposed	2	2	2

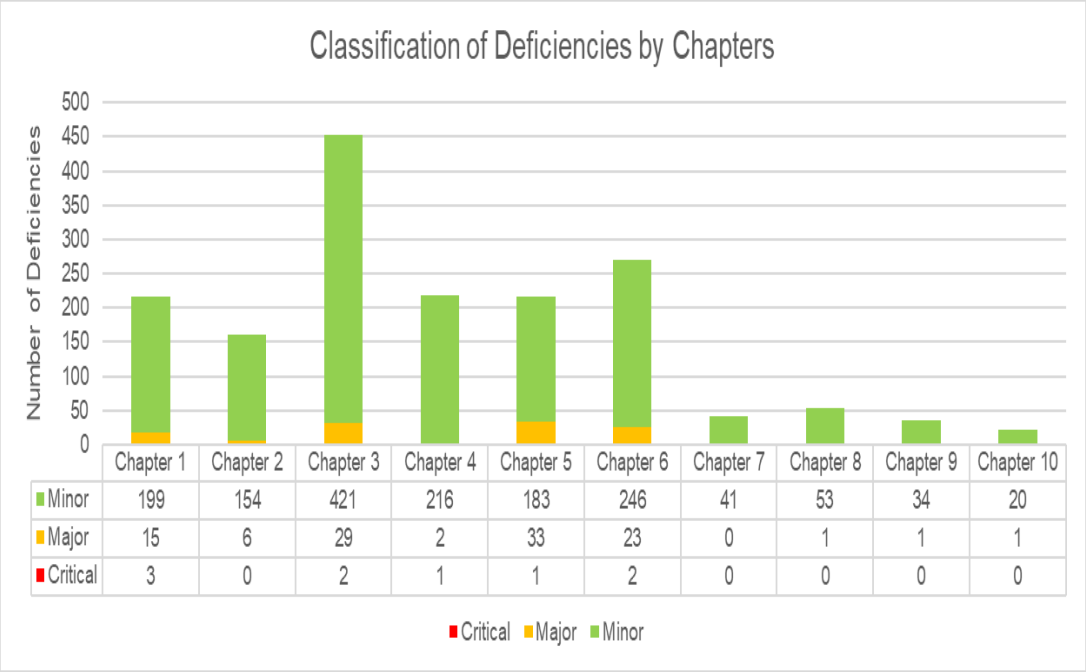
4.1.2 Total number of inspections in relative to type of inspections (routine and non-routine)

Types of Inspections	Pharmaceutical	Traditional Medicine & Health Supplement	Cosmetics
Routine Inspections	61	142	130
Non-Routine Inspection	11*	0	0

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

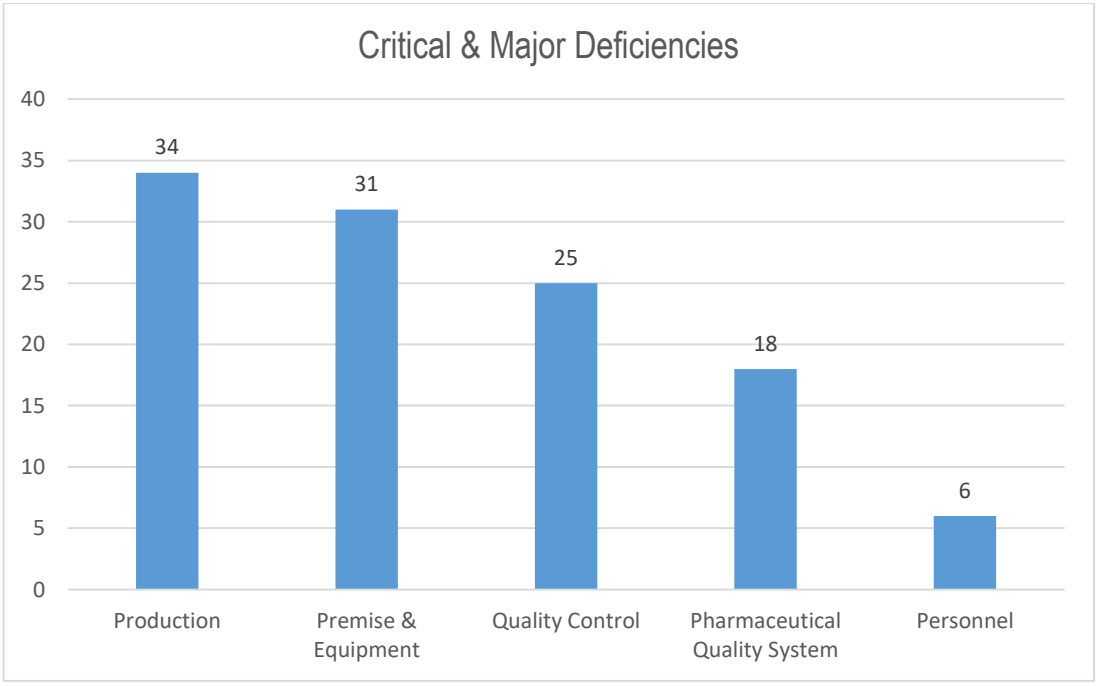
4.1.3 Number of deficiencies according to its classification (e.g. critical, major and minor) and inspection areas (e.g. Chapter 1 to 10)

Pharmaceutical



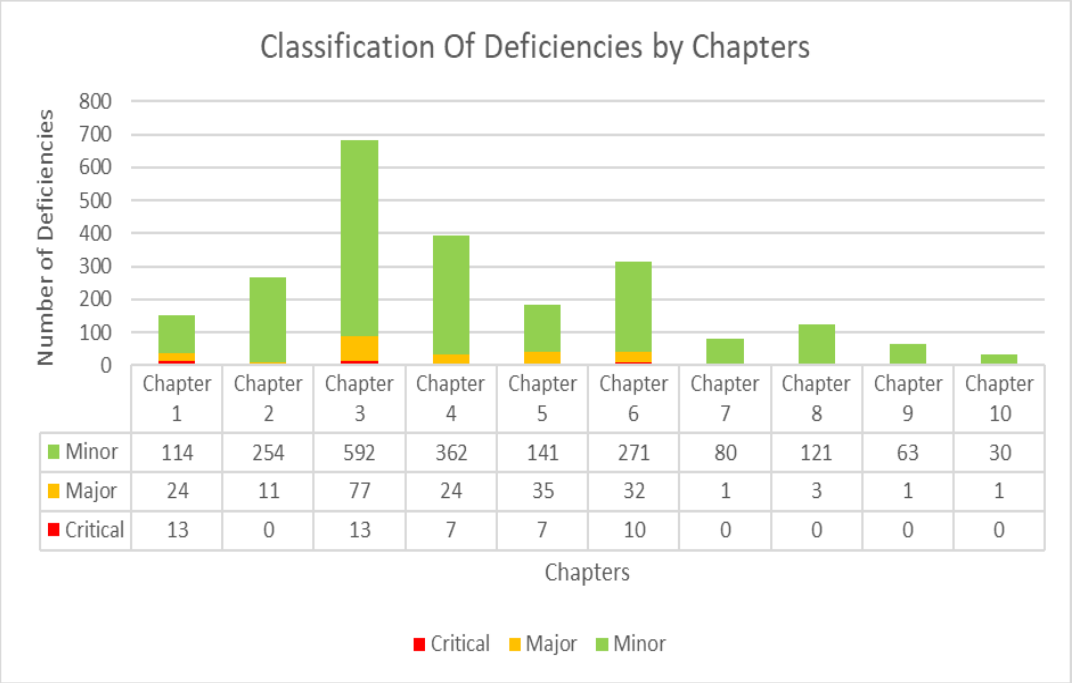
	Chapter 1	Chapter 2	Chapter 3	Chapter 4	Chapter 5	Chapter 6	Chapter 7	Chapter 8	Chapter 9	Chapter 10
Minor	199	154	421	216	183	246	41	53	34	20
Major	15	6	29	2	33	23	0	1	1	1
Critical	3	0	2	1	1	2	0	0	0	0

Overall Deficiencies by Chapter

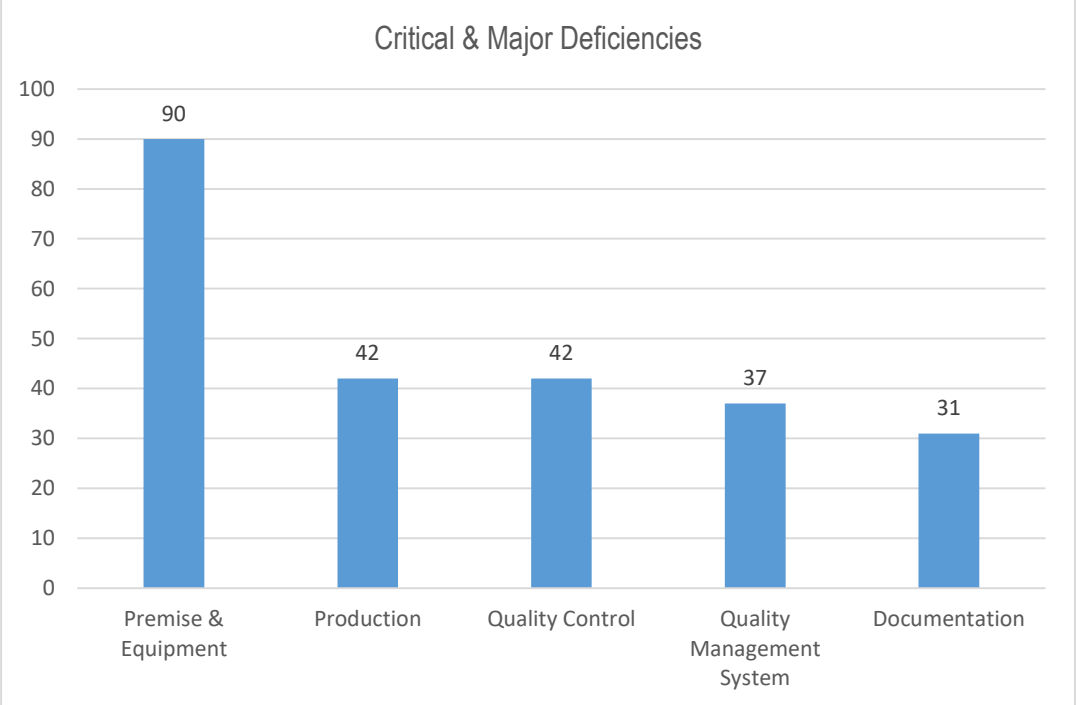


Top 5 Total Critical and Major Deficiencies

Traditional Medicine and Health Supplement

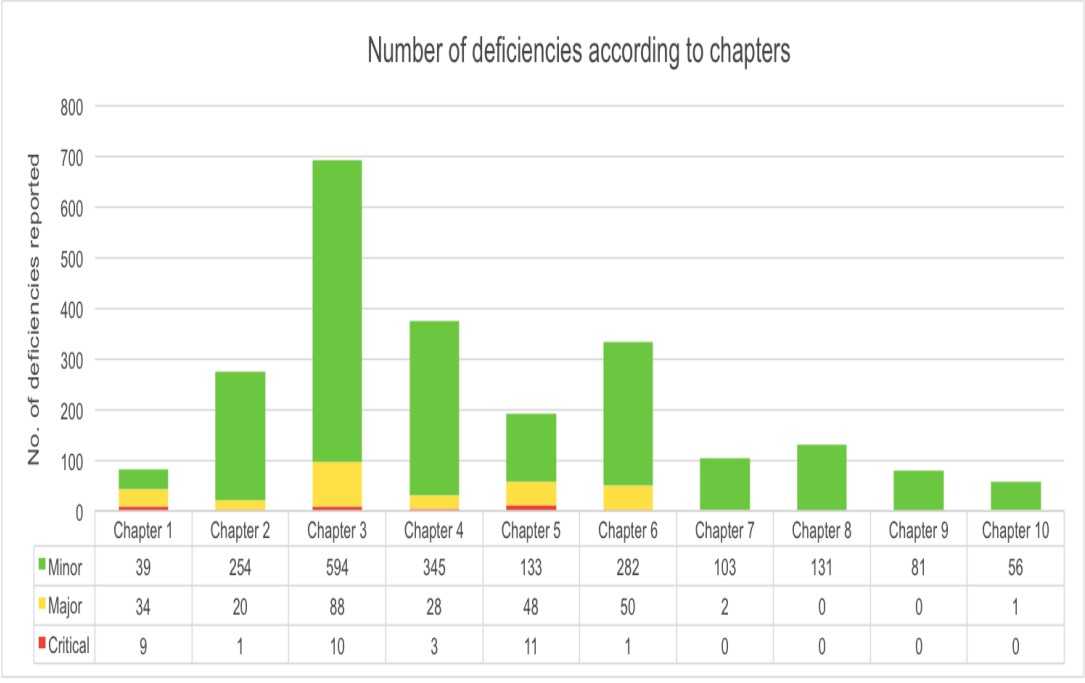


Overall Deficiencies by Chapter

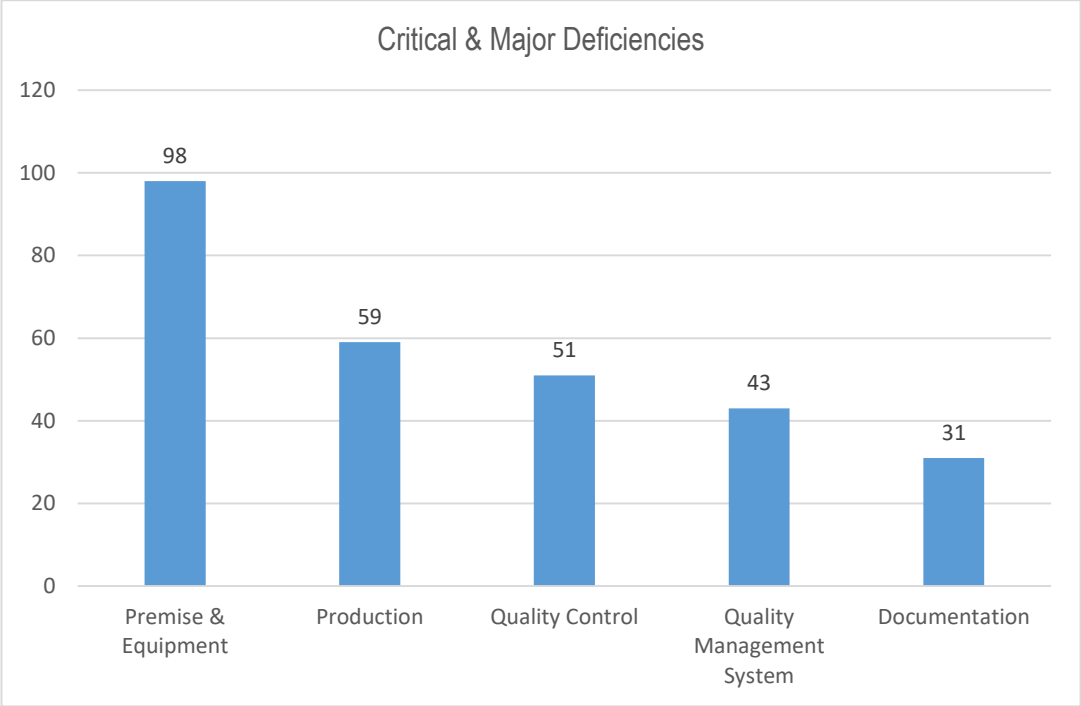


Top 5 Total Critical and Major Deficiencies

Cosmetics



Overall Deficiencies by Chapter



Top 5 Total Critical and Major Deficiencies

4.1.4 The number of frequently occurring observations pertaining to the relevant paragraph or clause in the guidelines to be referenced for critical and major deficiencies.

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

Refer Annexure 1 for details on the mentioned clauses.

5.0 DISCUSSION

5.1 Trend analysis

5.1.1 Comparison between percentage of deficiencies classification reported in year 2022 and 2023.

Pharmaceutical

Classification of Deficiencies	2022 (%)	2023 (%)
Critical	**0.69**	**0.53**
Major	**6.66**	**6.58**
Minor	**92.65**	**92.89**

The critical and major findings observed in the inspection of pharmaceutical premises demonstrate a slight decrease in percentage compared to last year, with a minor decrease from 6.66% in 2022 to 6.58% in 2023 for major findings. The consistently low percentage of critical findings suggests a strong commitment to upholding high standards of quality and safety within pharmaceutical premises.

Overall, the data indicates a relatively stable pattern of findings classifications over the two-year period, with minor fluctuations in percentages.

Traditional Medicine and Health Supplement

Classification of Deficiencies	2022 (%)	2023 (%)
Critical	**1.68**	**2.18**
Major	**14.32**	**9.14**
Minor	**84.00**	**88.68**

The trend in major findings witnessed a significant decrease, dropping from 14.32% in 2022 to 9.14% in 2023, whereas critical findings experienced a slight increase, rising

from 1.68% in 2022 to 2.18% in 2023. However, total percentage of critical and major deficiencies is reducing from 16% in 2022 to 11.32% in 2023, which may indicate an improvement for TMHS manufacturers.

Cosmetic

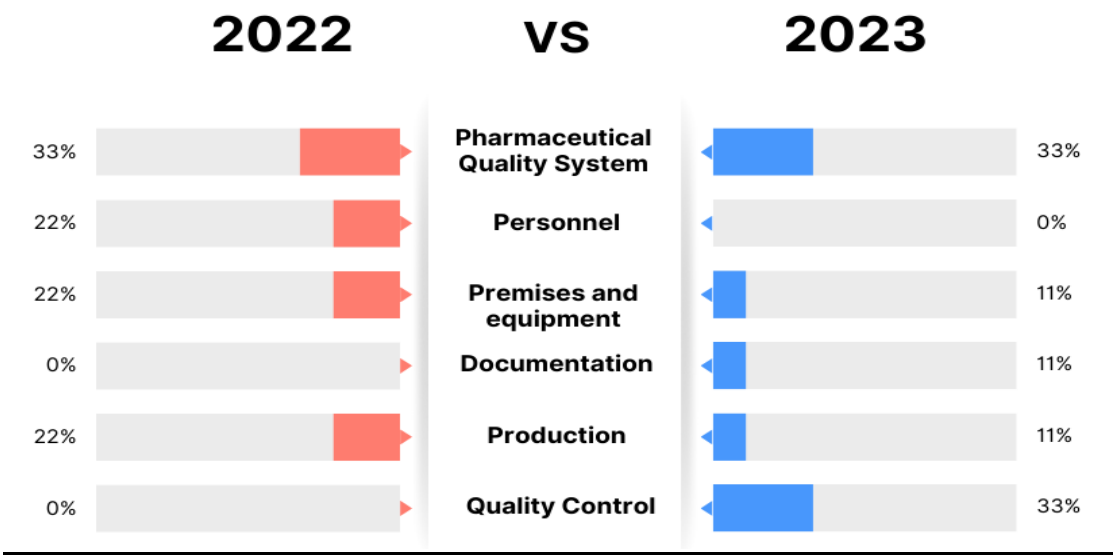
Classification of Deficiencies	2023 (%)
Critical	**1.5**
Major	**11.7**
Minor	**86.8**

No comparison was conducted as the data was not reported in the previous study. In 2023, critical findings accounted for 1.5%, major findings for 11.7%, followed by minor findings at 86.8%.

5.1.2 Comparison of critical and major deficiencies reported in year 2022 and 2023.

Pharmaceutical

Comparative chart on Critical deficiencies reported for pharmaceutical manufacturers in 2022 and 2023

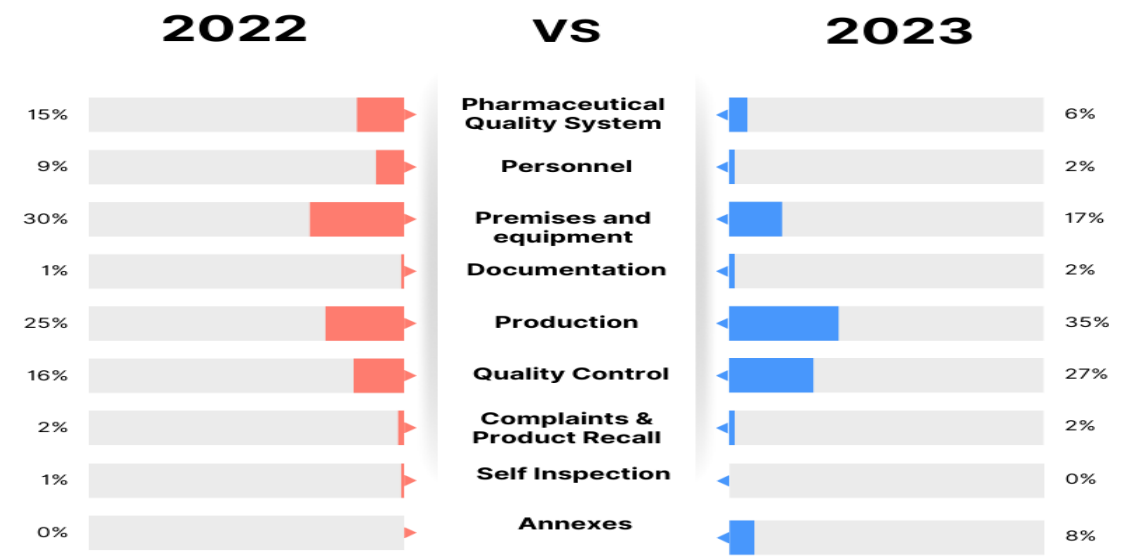


The chart shows significant reduction of critical findings from aspect Personnel with 22%, Premises and Equipment with 11%, and Production with 11% from the year 2022 to 2023. In 2023, element such as Pharmaceutical Quality System retained the same

percentage of critical findings as the previous year, accounting for 33% of total critical findings.

Conversely, both aspects Documentation and Quality Control reported no critical findings in 2022 compared to 11% and 33% respectively in 2023.This signifies that an emphasis needs to be given on aspects related to good documentation practices and quality control.

Comparative chart on Major deficiencies reported for pharmaceutical manufacturers in 2022 and 2023



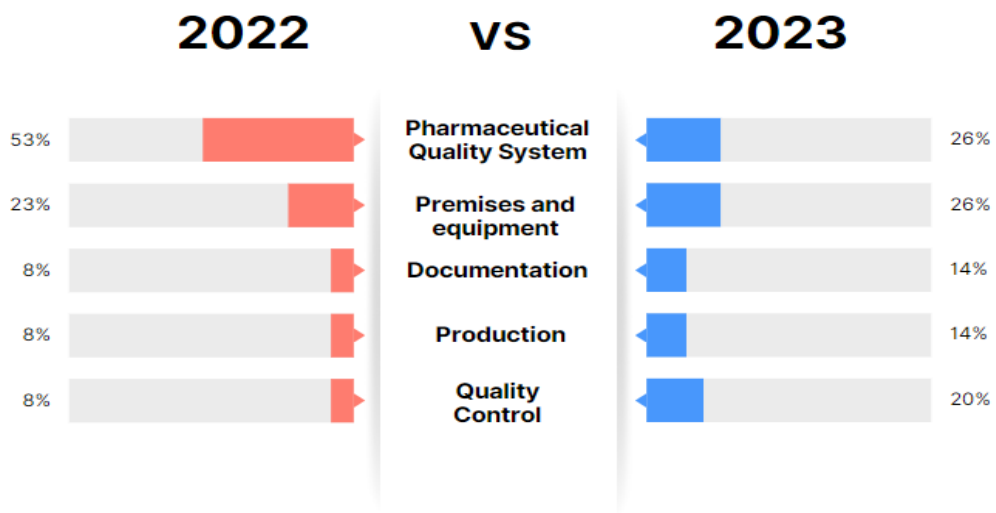
Overall, major findings were identified across various elements such as Pharmaceutical Quality System, Personnel, Premises and Equipment, Documentation, Production, Quality Control and Complaints and Product Recall in both 2022 and 2023. Notably, there was a notable absence of major findings in the self-inspection chapter in 2023, contrasting with a mere 1% in 2022. Conversely, 2023 witnessed an increase in major findings under PIC/S annexes, with 8% reported, compared to no findings in 2022.

A discernible downtrend in major findings was observed in 2023 across the initial three elements of PIC/S guidelines which is Pharmaceutical Quality System, Personnel, and Premises and Equipment. Pharmaceutical Quality System is deemed to be one of the key indicators to assess the overall performance of the pharmaceutical facility in terms of manufacturing product that is of quality, safety and efficacy and reduction of major findings from this chapter highlighting an enhanced adherence of the pharmaceutical manufacturers to Good Manufacturing Practice (GMP) principles.

Conversely, an escalation in major findings was noted in the Production and Quality Control chapters from 2022 to 2023, signalling a pressing need for heightened emphasis and bolstered knowledge, competency, and training within the industry in these areas to ensure adherence to regulatory standards.

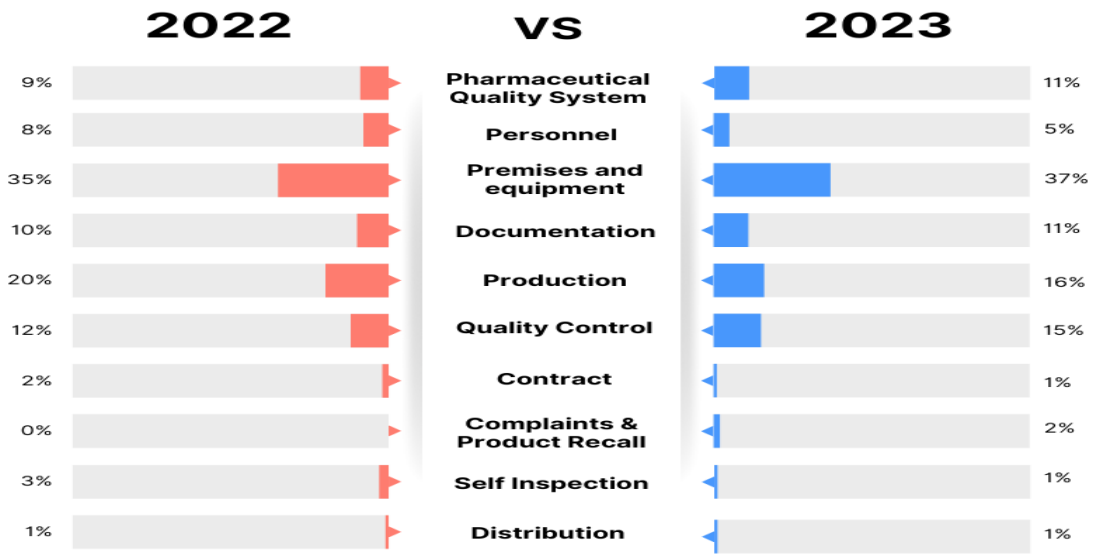
Traditional Medicine and Health Supplement

Comparative chart on Critical deficiencies reported for TMHS manufacturers in 2022 and 2023



The chart illustrates a significant reduction in critical findings for the Quality System aspect, decreasing from 53% in 2022 to 26% in 2023, while showing slight increases in other aspects such as Premises and Equipment, rising from 23% in 2022 to 26% in 2023, Documentation from 8% to 14%, Production from 8% to 14%, and Quality Control from 8% to 20%. These data suggest that attention should be focused on the aspects of Premises and Equipment, Documentation, Production, and Quality Control, as there is a noticeable trend shift indicating an increase in findings compared to the Quality System aspect.

Comparative chart on Major deficiencies reported for TMHS manufacturers in 2022 and 2023

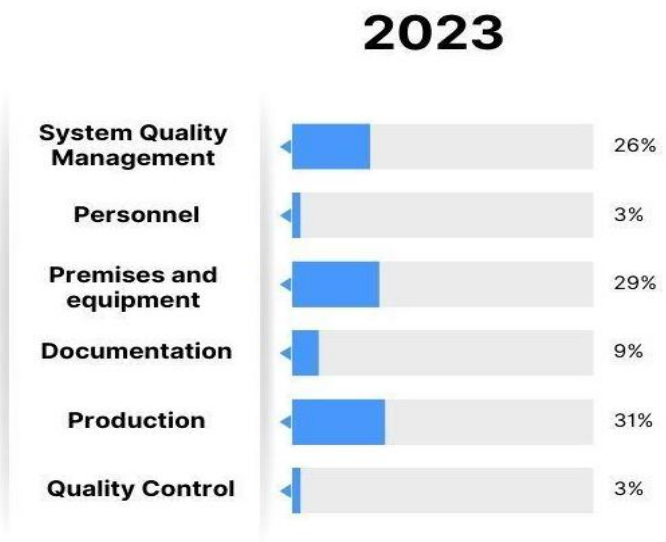


Major findings were observed in all aspects of GMP elements in 2023, contrasting with 2022, where only the Complaint & Recall aspect did not contribute to major findings. Overall, the data for both years exhibited a consistent pattern of major findings across all aspects of GMP. Premises & Equipment consistently demonstrated the highest contribution to major findings in both 2022 and 2023.

Cosmetic

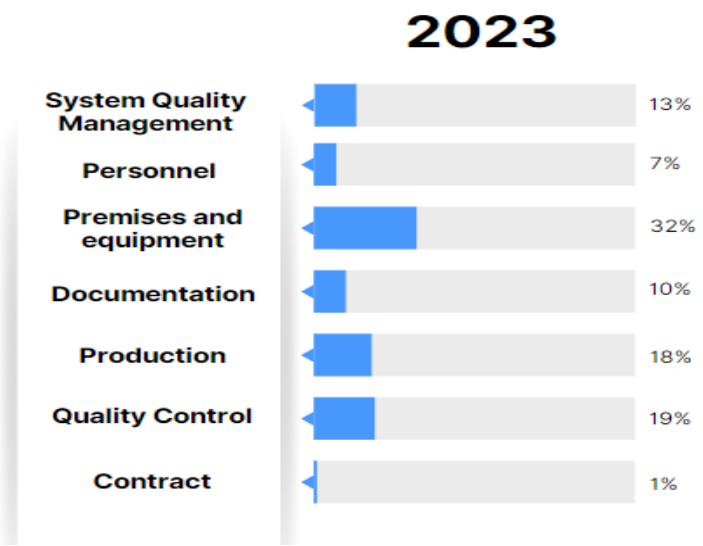
No comparison data done as data was not reported in year 2022.

Critical deficiencies reported for cosmetic manufacturers in 2023



The data shows aspects System Quality, Premise and Equipment and Production play a significant role in contribution of critical findings with Production portrays the highest with 31%, Premise and Equipment with 29% and followed by Quality System with 26%.

Major deficiencies reported for cosmetic manufacturers in 2023



In 2023, 7 out of 13 elements in the guidelines significantly contributed, with 32% of the findings attributed to the Premise and Equipment aspect. Quality Control accounted for the second-highest percentage at 19%, followed by Production and System Quality at 18% and 13% respectively. Personnel and Contract aspects contributed less than 10% to the findings.

5.1.3 Comparison of most repeated clauses in critical and major deficiencies.

Pharmaceutical

Classification of Deficiencies	2022	2023
Critical	1.1	1.8
	2.18	6.15
	5.29	-
Major	Annex 15	5.23
	1.8	6.15
	5.25 & 3.20	6.16

The top critical clauses observed in 2022, such as 1.1 (Quality Management), 2.18 (suitable clean room garments), and 5.29 (prevention of cross-contamination), were not repeated in 2023. Instead, in 2023, the top critical clauses were 1.8 (basic principles of GMP) and 6.15 (testing method validation). Additionally, the primary major clauses in 2023 were focused on the Production aspect, particularly clause 5.23 (validation of manufacturing process), which was also evident in 2022 under clause 5.25. Furthermore, clauses related to Quality Control predominated in 2023, exemplified by clauses 6.15 (testing method validation) and 6.16 (testing record).

Traditional Medicine and Health Supplement

Classification of Deficiencies	2022	2023
Critical	1.2	1.2
	1.3	1.3
	3.41	3.41
Major	1.2	3.51
	3.13	3.16
	5.12	1.2

The data shows for both 2022 and 2023 highlighted that clauses 1.2 (Quality management on Quality Assurance (QA)), 1.3 (Quality management on manufacturing process), and 3.41 (Suitability of manufacturing equipment) were the most frequently repeated for critical deficiencies. These clauses maintained their prevalence across both years.

Meanwhile, the top major clauses in 2023 were identified as clause 3.51 (cleaning of equipment and utensils), 3.16 (maintenance of building/production area), and 1.2 (Quality management on Quality Assurance (QA)), in contrast to clause 1.2 (Quality

management on Quality Assurance (QA)), 3.13 (condition in production areas (temperature/humidity)), and 5.12 (labelling of equipment/materials/rooms) in 2022.

The Premises and Equipment aspect, along with Production, remained the top aspects for major findings, consistent with 2022. This emphasizes that these aspects should be the primary focus for improvement.

Cosmetic

Classification of Deficiencies	2023
Critical	**1.2.1**
	6.4.5
	8.3.2
Major	**7.1.2**
	8.3.2
	3.1

The most frequent clauses reported as critical and major deficiencies in year 2023 are tabulated as above with respective number of findings. No comparisons data done as there was no data reported in the previous study.

5.2 Recommendation and Area 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 is defined as a deficiency which has produced, or leads to a significant risk of producing a product which is harmful to the human.

Conversely, Major Deficiency means a deficiency that is not a “Critical” deficiency, but which:

i. Has produced or may produce a product which does not comply with its Marketing Authorisation, Clinical Trial Authorisation, product specification; pharmacopoeia requirements or dossier.
ii. Does not ensure effective implementation of the required GMP control measures.

iii. Indicates a major deviation from the terms of the manufacturing authorisation.
iv. Indicates a failure to carry out satisfactory procedures for release of batches or (within PIC/S) failure of the authorised person to fulfil his/her duties.
v. Consists of several “Other” related deficiencies, none of which on its own may be “Major”, but which may together represent a “Major” deficiency or systems failure and should be explained and reported as such.

Pharmaceutical

Based on the study, the top 2 critical deficiencies reported were clause 1.8 under Chapter 1 Pharmaceutical Quality System (PQS), and clause 6.15 under Chapter 6 Quality Control while the top 3 major deficiencies reported were clause 5.23 under Chapter 5 Production as well as clause 6.15 and 6.16 under Chapter 6 Quality Control. It should be noted that clause 6.15 is second in terms of the most reported deficiency for both critical and major classification.

Chapter 1: Pharmaceutical Quality System (PQS)

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:

(i)All manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing medicinal products of the required quality and complying with their specifications; (ii) Critical steps of manufacturing processes and significant changes to the process are validated; (iii) All necessary facilities for GMP are provided including: Appropriately qualified and trained personnel; Adequate premises and space; Suitable equipment and services; Correct materials, containers and labels; Approved procedures and instructions, in accordance with the Pharmaceutical Quality System; Suitable storage and transport. (iv) Instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided; (v) Procedures are carried out correctly and operators are trained to do so; (vi) Records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected; (vii) Any significant deviations are fully recorded, investigated with the objective of determining the root cause and appropriate corrective and preventive action implemented; (viii) Records of manufacture including distribution which enable the complete history of a batch to be traced are retained in a comprehensible and accessible form; (ix) The distribution of the products minimises any risk to their quality and takes account of good distribution practice; (x) A system is available to recall any batch of product, from sale or supply; (xi) Complaints about products are examined, the causes of quality defects investigated and appropriate measures taken in

respect of the defective products and to prevent reoccurrence.

Clause 1.8 encapsulates the essential requirements for maintaining GMP compliance.

Chapter 5: Production

> *5.23 Validation studies should reinforce Good Manufacturing Practice and be conducted in accordance with defined procedures. Results and conclusions should be recorded*

Clause 5.23 emphasises the importance of validation studies in reinforcing GMP standards within pharmaceutical manufacturing. Validation serves as a critical component in ensuring the reliability, consistency and compliance of manufacturing processes.

Chapter 6 Quality Control

> *6.15 Testing methods should be validated. A laboratory that is using a testing method and which did not perform the original validation, should verify the appropriateness of the testing method. All testing operations described in the Marketing Authorisation or technical dossier should be carried out according to the approved methods*.

Clause 6.15 which relates to validation of testing methods is one of the most common deficiency in both critical and major categories that was found in pharmaceutical premises inspected in 2023. The prevalence of this finding highlights its critical importance in the context of GMP compliance and product quality assurance. Non-compliance with validation requirements for testing methods can lead to inaccurate or unreliable test results, compromising the safety, efficacy and quality of pharmaceutical products.

Furthermore, deviations from approved testing methods may trigger regulatory scrutiny and enforcement actions, potentially jeopardising market access and patient trust. The root causes of the deficiency may stem from various factors, including inadequate validation or verification protocols, lack of expertise or resources, insufficient documentation practices or discrepancies between laboratory practices and regulatory expectations. Manufacturers should have comprehensive validation and verification protocols for testing methods to ensure accuracy, reliability and compliance with regulatory requirements.

> *6.16 The results obtained should be recorded. Results of parameters identified as critical quality attributes should be trended and checked to make sure that they are consistent with each other. Any calculations should be critically examined.*

It is important that all results obtained through quality control testing be recorded accordingly to allow for cross checks.

Traditional Medicine & Health Supplement

Based on the study on Traditional Medicine & Health Supplement manufacturers, the top 3 critical deficiencies reported were clause 1.2 and 1.3 under Chapter 1 Quality Management and clause 3.41 under Chapter 3 Premises and Equipment while the top 3 major deficiencies reported were clause 3.51 and 3.16 under Chapter 3 Premises and Equipment and clause 1.2 under Chapter 1 Quality Management.

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 organised arrangements made with the object of ensuring the medicinal product is 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 organised 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 authorised 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.

Chapter 3 Premises and Equipment

> *3.16 The condition of buildings should be reviewed regularly, and repaired where necessary. Special care should be exercised to ensure that building repair or maintenance operations do not adversely affect, directly or indirectly, either the traditional medicines or health supplements during their manufacture and storage, or the accurate functioning of equipment.*

The condition of the buildings should be reviewed periodically and repaired as needed. Building repair and maintenance operations conducted should not adversely affect the manufacturing and storage of the traditional medicines and/or health supplements and the function of the 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…*

Manufacturing equipment should be adequate for the operations performed. Manufacturing equipment should be designed, constructed, placed and maintained:

- To be suitable for its intended use.
- To be easily dismantled for inspection or to demonstrate that routine cleaning procedures can eliminate the possibility of contamination.
- To minimise any contamination, risk of confusion or the omission of a processing step during manufacturing.
- At a distance from other equipment sufficient to avoid congestion and cross-contamination

> *3.51 Equipment and utensils should be cleaned both inside and outside after use according to established procedures and should be kept or stored in a clean condition and be checked for cleanliness prior to each use to ensure that all products or materials from the previous batch are removed.*

Equipment and utensils used after the manufacturing process should be cleaned thoroughly in accordance with the procedure in place and kept in a clean condition. The cleanliness of the equipment and utensils should be checked before use to prevent cross-contamination.

Cosmetic

Based on the study on Cosmetic manufacturers, the top 3 critical deficiencies reported were clause 1.2.1 with 4 findings; clauses 6.4.5 and 8.3.2 with 3 findings each.

Meanwhile, clause 7.1.2, 8.3.2 and 3.1 were reported as most frequent major deficiencies with number of deficiencies of 18, 17 and 12 respectively.

Chapter 1.2 Quality Management System

> *1.2.1 A quality system should be developed, established and implemented as a means by which stated policies and objectives will be achieved. It should define the organisational structure, functions, responsibilities, procedures, instructions, processes and resources for implementing the quality management.*

Inspections reported on the failing overall quality system. Areas contributing to this failure mainly related to poor GMP understanding, maintenance and cleaning for premises and equipment, document traceability, control on risk of contamination sources and release activity. Manufacturers should develop an established quality system and maintain a good manufacturing practice throughout the whole manufacturing activity by personnel from all divisions.

Chapter 3 Premises

> *3.1 Effective measures should be taken to avoid any contamination from the surrounding environment and from pests*

All surfaces exposed to the processing activities may pose risks of contaminating the product, therefore cleanliness is vital in any manufacturing facility. Facility should be designed for easy cleaning, sanitising activity and must have proper segregation.

Chapter 6.4 Procedure and Processing

> *6.4.5 Particular attention should be paid to problem of cross- contamination in all stages of processing.*

Risks of cross-contamination may occur during processing, packaging and storage activity. Manufacturers should ensure no cross contamination may occur by proper segregation of production activities and detailed labelling of rooms, equipment, materials, documents and others. Proper planning is also important to optimise resources and minimise cross contamination as well as wastage.

Chapter 7 Quality Control

> *7.1.2 Quality control involves sampling, inspecting and testing of starting materials, in process, intermediate, bulk, and finished products. It also includes where applicable, environmental monitoring programs, review of batch documentation, sample retention program, stability studies and maintaining correct specifications of materials and products.*

Quality control is a critical aspect throughout and after the manufacturing process. Prior to product release, manufacturers must ensure that cosmetics meet standards through activities such as sampling, inspecting, and testing starting materials, as well as in-process, intermediate, bulk, and finished products.

Chapter 8.3 Documents for Production

> *8.3.2 Batch Manufacturing Record (BMR)*
>
> *(a) Batch Manufacturing Records should be prepared for each batch of product.*
> *(b) Each BMR should include the following:*
>
> i. *Name of product*
> ii. *Batch formula*
> iii. *Brief manufacturing process*
> iv. *Batch or code number*
> v. *Date of the start and finish of processing and packaging*
> vi. *Identity of individual major equipment and lines or location used*
> vii. *Records of cleaning of equipment used for processing as appropriate*
> viii. *In-process control and laboratory results, such as pH and temperature test records*
> ix. *Packaging line clearance inspection records*
> x. *Any sampling performed during various steps of processing*
> xi. *Any investigation of specific failure or discrepancies*
> xii. *Results of examinations on packed and labelled products*

BMR provides a valuable audit trail to ensure that the product meets all regulatory requirements and standards. Therefore, manufacturers must make the batch records available and legible for all products manufactured in their facility. BMR will also enable manufacturers to track the production process and enable them to make necessary adjustments for future batches. Information listed above is expected to be included in BMR.

6.0 CONCLUSION

In conclusion, among the 72 pharmaceutical product manufacturing premises analysed, Chapter 3, which focuses on Premises and Equipment, had the most significant overall findings, totalling 452 across critical, major, and minor categories. However, when considering only critical and major findings, Chapter 5 had the highest count at 34. These two aspects of GMP should be the focus for improvement, as they are crucial aspects in the manufacturing process.

For TMHS manufacturers, Chapter 3, which focuses on Premises and Equipment, exhibited the most significant overall findings, totalling 682 across critical, major, and minor categories. Even when considering only critical and major findings, Chapter 3 still had the highest count with 90 findings. Additionally, clause in Chapter 3 has consistently been one of the top areas of concern in both 2022 and 2023, along with Chapter 1 on Quality Management. These two aspects of GMP should be prioritized for improvement, particularly Chapter 3 regarding Premises and Equipment.

For cosmetic manufacturers, the Premises and Equipment aspect had the most overall findings, followed by the Documentation aspect. When considering only critical and major findings, Premises and Equipment still had the most, followed by Production and Quality Control. Therefore, the Premises and Equipment and Documentation aspects should be prioritized for improvement, in addition to the aspects of Production and Quality Control.

7.0 LIMITATION

1. This study does not cover the entire scope of GMP inspections in 2023, as it excludes non-routine inspections for local manufacturer. To provide more precise information, future analyses should include all GMP inspections.
2. There are no data comparison made on cosmetics manufacturing as such data was not analysed in previous study. Further comparison can be made in the next study if applicable.

8.0 REFERENCES

Report on ‘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’.

Pharmaceuticals

Deficiencies Classification	Area	Clause in GMP Guidelines
Critical	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 …(3)
	Premises and equipment	3.7 Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels. (1)
	Documentation	4.8 Records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of medicinal products are traceable.(1)
	Production	5.42 Critical processes should be validated (see "Validation" in this Chapter).(1)
	Quality Control	6.15 Testing methods should be validated. A laboratory that is using a testing method and which did not perform the original validation, should verify the appropriateness of the testing method. All testing operations described in the Marketing Authorisation or technical dossier should be carried out according to the approved methods.(2)
Major	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 …(3)
	Personnel	2.6 The duties of the Authorised Person(s) are described in the national requirements and can be summarised as follows: a) An Authorised Person must ensure that each batch of medicinal products has been manufactured and checked in compliance with the laws in force in that country and in accordance with the requirements of the Marketing Authorisation; b) The Authorised Person(s) must meet the qualification requirements laid down in the national legislation, they shall be permanently and continuously at the disposal of the holder of the Manufacturing Authorisation to carry out their responsibilities; c) The responsibilities of an Authorised Person may be delegated, but only to other Authorised Person(s).(1)

		2.20 Direct contact should be avoided between the operator's hands and the exposed product as well as with any part of the equipment that comes into contact with the products.(1)
	Premises and equipment	3.34 Manufacturing equipment should be designed, located and maintained to suit its intended purpose.(3)
	Documentation	4.18 The Processing Instructions should include …(1)
	Production	5.23 Finished Validation studies should reinforce Good Manufacturing Practice and be conducted in accordance with defined procedures. Results and conclusions should be recorded.(5)
	Quality Control	6.15 Testing methods should be validated. A laboratory that is using a testing method and which did not perform the original validation, should verify the appropriateness of the testing method. All testing operations described in the Marketing Authorisation or technical dossier should be carried out according to the approved methods.(5)
	Complaints and Product Recall	8.11 If a quality defect is discovered or suspected in a batch, consideration should be given to checking other batches and in some cases other products, in order to determine whether they are also affected. In particular, other batches which may contain portions of the defective batch or defective components should be investigated.(1)
	Annex 1 (Manufacture of sterile medicinal products)	Clause 41 Changing and washing should follow a written procedure designed to minimise contamination of clean area clothing or carry-through of contaminants to the clean areas.(1)
	Annex 8 (Sampling of starting and packaging materials)	Clause 2 The identity of a complete batch of starting materials can normally only be ensured if individual samples are taken from all the containers and an identity test performed on each sample. It is permissible to sample only a proportion of the containers where a validated procedure has been established to ensure that no single container of starting material will be incorrectly identified on its label.(1)
	Annex 15 (Qualification and validation)	Clause 4.2 Where re-qualification is necessary and performed at a specific time period, the period should be justified and the criteria for evaluation defined. Furthermore, the possibility of small changes over time should be assessed.(1)
		Clause 9.2 Where microbial testing of product is carried out, the method should be validated to confirm that the product does not influence the recovery of microorganisms.(1)

Traditional Medicine and Health Supplements

Deficiencies Classification	Area	Clause in GMP Guidelines
Critical	Quality Management System	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 organised arrangements made with the object of ensuring the medicinal product is 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…(5)
		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…(5)
	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…(4)
	Documentation	4.10 The records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of traditional medicines and health supplements products are traceable. They should be retained for at least one year after the expiry date of the finished product.(2)
		4.35 The standard operating procedures for batch numbering should assure that the same batch numbers will not be repeatedly used; this applies also to reprocessing.(2)
	Production	5.19 Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross contamination arises from the uncontrolled release of dust, gases, vapours, sprays or organisms from materials and products in process, from residues on equipment, and from operators' clothing. The significance of this risk varies with the type of contaminant and of product being contaminated. Cross-contamination should be avoided by appropriate technical or organisational measures….(2)
	Quality Control	6.8 The identity and quality of starting materials and finished products should be tested.(3)
		6.16 Sample containers should bear a label indicating the contents, with the batch number, the date of sampling and the containers from which samples have been drawn.(3)

	Complaints and Product Recalls	8.12 Responsibility and procedures for recall of traditional medicines and health supplements should be established by the manufacturer to facilitate the recall of a batch from any link of the distribution chain when this becomes necessary.(1)
Major	Quality Management System	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 organised arrangements made with the object of ensuring the medicinal product is 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…(11)
	Personnel	2.6 All personnel who are directly engaged in the manufacturing activities should be trained in the operations and in the principles of Good Manufacturing Practice. (3)
		2.7 Training in Good Manufacturing Practice should be on a continuing basis and with adequate frequency to assure that employees remain familiar with Good Manufacturing Practices requirements relevant to their functions. Training in Good Manufacturing Practice should be in accordance with written programmes approved by the head of the Production Department and the head of the Quality Control Department. (3)
	Premises and equipment	3.51 Equipment and utensils should be cleaned both inside and outside after use according to established procedures and should be kept or stored in a clean condition and be checked for cleanliness prior to each use to ensure that all products or materials from the previous batch are removed. (14)
	Documentation	4.26 During processing, the following information should be recorded at the time each action is taken and, after completion, the record should be dated and signed in agreement by the person responsible for the processing operations…(8)
	Production	5.58 The evaluation of finished products and documentation which is necessary before release of product for sale are described in Chapter 6 (Quality Control)….(8)
	Quality Control	6.1 Quality control is concerned with sampling, specifications, testing, organisation, documentation and release procedures which ensure that the necessary tests are in fact carried out, and that the materials are not released for use, nor products released for sale and supply until their quality has been assessed to be satisfactory.(7)
	Complaints and Product Recalls	8.12 Responsibility and procedures for recall of traditional medicines and health supplements should be established by the manufacturer to facilitate the recall of a batch from any

		link of the distribution chain when this becomes necessary.(1)
		8.15 There should be established written procedures, regularly checked and updated, when necessary, in order to organise any recall activity.(1)
		8.20 The progress of the recall process should be recorded, and a final report issued, including reconciliation between the delivered and recovered quantities of the products.(1)
	Self-Inspection	9.4 Self inspection should be conducted in an independent and detailed way by a designated competent person(s) from the company. Independent audits by external experts may also be useful.(1)

Cosmetic

Deficiencies Classification	**Area**	**Clause in GMP Guidelines**
Critical	Quality Management System	1.2.1 A quality system should be developed, established and implemented as a means by which stated policies and objectives will be achieved. It should define the organisational structure, functions, responsibilities, procedures, instructions, processes and resources for implementing the quality management. (4)
	Personnel	2.1.1 The organisational structure of the company shall be such that the production and the quality control sections are headed by different persons, neither of whom shall be responsible to the other. (1)
		2.1.4 The responsibilities and authority of key personnel should be clearly defined. (1)
	Premises and equipment	3.6 Wall and ceiling, where applicable should be smooth and easy to maintain. The floor in processing areas should have a surface that is easy to clean and sanitise. (2)
		3.12 Storage areas should be of adequate space provided with suitable lighting, arranged and equipped to allow dry, clean and orderly placement of stored materials and products. (2)
		5.3.1 Equipment and utensils should be kept clean. (2)
	Documentation	8.3.2 Batch Manufacturing Record (BMR) (a) Batch Manufacturing Records should be prepared for each batch of product. (b) Each BMR should include the following: i. Name of product ii. Batch formula iii. Brief manufacturing process iv. Batch or code number v. Date of the start and finish of processing and packaging vi. Identity of individual major equipment and lines or location used vii. Records of cleaning of equipment used for processing as appropriate

		viii. In-process control and laboratory results, such as pH and temperature test records ix. Packaging line clearance inspection records x. Any sampling performed during various steps of processing xi. Any investigation of specific failure or discrepancies xii. Results of examinations on packed and labelled products (3)
	Production	6.4.5 Particular attention should be paid to problem of cross-contamination in all stages of processing. (3)
	Quality Control	7.1.1 A quality control system should be established to ensure that products contain the correct materials of specified quality and quantity and are manufactured under proper conditions according to standard operating procedures. (1)
Major	Quality Management	1.1.1 In the manufacture of cosmetic products, overall control and monitoring is essential to ensure that the consumer receives products of specified quality. (8)
		1.2.1 A quality system should be developed, established and implemented as a means by which stated policies and objectives will be achieved. It should define the organisational structure, functions, responsibilities, procedures, instructions, processes and resources for implementing the quality management. (8)
	Personnel	2.2.1 All personnel directly involved in the manufacturing activities should be appropriately trained in manufacturing operations in accordance to GMP principles. Special attention should be given to training of personnel working with any hazardous materials. (5)
	Premises	3.1 Effective measures should be taken to avoid any contamination from the surrounding environment and from pests. (12)
	Documentation	8.3.2 Batch Manufacturing Record (BMR) (a) Batch Manufacturing Records should be prepared for each batch of product. (b) Each BMR should include the following: i. Name of product ii. Batch formula iii. Brief manufacturing process iv. Batch or code number v. Date of the start and finish of processing and packaging vi. Identity of individual major equipment and lines or location used vii. Records of cleaning of equipment used for processing as appropriate viii. In-process control and laboratory results, such as pH and temperature test records ix. Packaging line clearance inspection records x. Any sampling performed during various steps of processing xi. Any investigation of specific failure or discrepancies

		xii. Results of examinations on packed and labelled products (17)
	Production	6.4.4 Bulk products should be properly labelled until approved by Quality Control, where applicable. (6)
		6.4.5 Particular attention should be paid to problem of cross-contamination in all stages of processing. (6)
	Quality Control	7.1.2 Quality control involves sampling, inspecting and testing of starting materials, in process, intermediate, bulk, and finished products. It also includes where applicable, environmental monitoring programs, review of batch documentation, sample retention program, stability studies and maintaining correct specifications of materials and products. (18)
	Storage	10.1.2 Storage areas should be designed or adapted to ensure good storage conditions. They should be clean, dry and well- maintained. Where special storage conditions are required (temperature and humidity) these should be provided, checked and monitored. (4)