DRUG ADMINISTRATION OF VIETNAM
DRUG QUALITY MANAGEMENT DIVISION

PROCEDURES FOR PREPARING, INSPECTING "GOOD MANUFACTURING PRACTICE" (GMP)

Code: QT.CL.01.05

	Prepared by	**Checked by**	**Approved by**
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Signature			

1. *The related people shall research and comply with contents stated in this Regulation.*
2. *Contents stated in this Regulation become effective as Direction of Director of Drug Aministration of Vietnam.*
3. *Each unit shall be delivered 01 orginal (affixed seal). When units wants to receive more documents, they shall request ISO Secretary to obtain the sealed version. The soft file is provided on Local Area Network to share information.*

RECIPIENTS *(clearly state the recipients and tick X in the next box)*

☐	DAV management board	☐	Drug registration dept.
☐	ISO committee	☐	Drug quality management dept.
☐	Oficial Administration dept.	☐	Drug price control dept.
☐	Pharm. Legislation & international Integration dept.	☐	Drug information and advertising dept.
☐	Planning & financial dept.	☐	Cosmetic management dept.
☐	Drug business management dept.	☐	Inspection dept.
☐	NRA committee	☐	Training Center
☐	Drug and Cosmetic magazine	☐	

REVISIONS HISTORY

No.	Date	Position	Revised content	Note
01	09/03/2015	5.2.6.c	Categorise GMP compliance level	
02	04/06/2015	5.2.8	Add content *"Special cases"*	
		5.5	Add content *"Risk rating and frequency of follow-up GMP inspection"*	
		5.6	Add content "Follow-up inspection plan"	
		BM.CL.01.05 /08	Revise GMP inspection format and add reference to WHO GMP Guideline for deficiencies	
		BM.CL.01.05 /15	Add form for *Risk assessment table*	
		Annex II	Add Annex II. *"Guidance on How to Score the Intrinsic Risk Factors"*	

1. PURPOSE

To describe the preparation steps for inspection, inspection steps on the basis of registering deployment of GMP in order to perform these in certain order so that:

- All inspection preparation, inspection periods of different companies and enterprises are conducted effectively in the same method.
- The inspection shall be always performed under GMP requirements and applicable regulations of Ministry of Health.
- It is easy for all members in Inspectors team to perform tasks.
- It is possible to change when forming new procedure.

2. SCOPE

Applied to inspection of issuing the GMP certificate of Drug and Cosmetics Quality Control Department of Drug Administration of Vietnam.

3. REFERENCES

- Drug Law issued dated 27 June 2005;
- Decision No. 1570/2000/QD-BYT dated 22 May 200 on promulgating regulations, standards of GLP of Ministry of Health
- Decision No. 2701/2001/QD-BYT dated 29 June 2001 on promulgating regulations, standards of GSP of Ministry of Health.
- Decision No. 3886/2004/QD-BYT dated 03 November 2004 on promulgating GMP recommended by World Health Organization.
- Decision No. 27/2007/QD-BYT dated 19 April 2007 on promulgating regulations, standards of GMP and regulations GSP.
- Decision No. 47/2007/QD-BYT dated 24 December 2007 on implementation of applying the regulations, standards of GMP, GLP, regulations of GSP and regulations of GDP for Companies of manufacturing, testing, trading, distributing, exporting, importing, storing and reserving vacine and medical biological products.
- Circular 45/2011/TT-BYT of the Ministry of Health dated 21/12/2011 amending and supplementing a number of articles of Decision 1570/2000/QD-BYT dated 22/05/2000 of the Ministry of Health on applying the principle of GLP; Decision 2701/2001/QD-BYT dated 29/6/2001 of the Minister of Health on applying the principle of GSP ; Circular 06/2004/TT-BYT dated 28/05/2004 guiding pharmaceutical toll processing ; Decision 3886/2004/QD-BYT dated 03/11/2004 of the Ministry of Health on applying the

principles and standards of GMP as recommended by the World Health Organization ; Circular 13/2009/TT-BYT dated 01/9/2009 of the Ministry of Health guiding on drug advertising activities; Circular 44/2014/TT-BYT dated 25/11/2014 of the Ministry of Health on drug registration; Circular 47/2010/TT-BYT dated 29/12/2010 guiding the export and import of drugs and primary packaging.

- Document No. 8071/QLD-CL dated 15 October 2004 on implementing simultaneously GMP, GLP and GSP of Director of Drug Administration of Vietnam.
- Decision No. 51/QLD-CL dated 05 May 2006 of Director of Drug Administration of Vietnam on promulgating the verification experts list of inspection registration document on GMP, GLP and GSP.

4. DEFINITIONS AND ABBREVIATIONS

4.1. Abbreviations

- GMP: Good Manufacturing Practice .
- GLP: Good Laboratory Practice
- GSP: Good Storage Practice
- SOP: Standard Operating Procedures
- DAV: Drug Administration of Vietnam
- QM Department: Drug Quality Management department

4.2. Terms

Routine Inspection	Refer to Quality Manual of Drug quality management division (#QM.CL.01.xx)
Follow-up Inspection	
Special Inspection	
Critical Deficiency	
Major Deficiency	
Minor Deficiency	

5. PROCEDURE

5.1. Process flow of routine inspection

Responsibilities	Implementation chart	Description/ Form
Company submission	GMP dossier aplication	
Administrative department	Receiving document (following checklist)	5.1.2.1 BM.CL.01.03/01 BM.CL.01.03/02
Drug Quality management dept Leaders	Assigning	5.1.2.2 BM.CL.01.03/03
Assigned officer	Dossiers evaluation	BM.CL.01.03/04 BM.CL.01.03/05
Drug Quality management dept Leaders	Reviewing	5.1.2.2
Leaders, officer of Drug Quality management dept	Set up inspection team and inspection schedule	5.1.2.3
Leaders of DAV	Reviewing	5.2.4
Leaders, officer of Drug Quality management dept	Completing inspection schedule	5.2.4
Leaders of DAV	Approving	5.2.5 BM.CL.01.03/06
Inspection team	Preparing GMP inspection	5.2.6 BM.CL.01.03/07
Inspection team	Conducting inspection	
Inspection team, Leaders of Drug Quality management dept	Prepare inspection report	5.2.7 BM.CL.01.03/08 BM.CL.01.03/09
Leaders, officer of Drug Quality management dept Leaders of DAV	Processing after inspecting	5.2.8 BM.CL.01.03/10 BM.CL.01.03/11 BM.CL.01.03/12 BM.CL.01.03/13
Inspection team	Keeping as archives	6

5.2. Regular inspection

5.2.1. Receiving application document

- Registration dossier for GMP ceritication is submitted to Administrative department. The dossier is verified following the checklist for new registration dossier (BM.CL.01.03/01) for new established company or the checklist for re registration dossier (BM.CL.01.03/02) for Recertification Company. The Administrative department log in documents archives history then delivery to Quality Drug Management department.
- Quality Drug Management department log in to documents archives history and update in List of registered company for GMP inspection (BM.CL.01.03/03).
- Managers of department shall assign officer to review GMP registration dossier

5.2.2. Reviewing application document

a) Time frame:

Within 05 days from receiving dossier from Administrative department, assigned officer shall handover evaluation sheet and dossier to experts for reviewing, evaluation of dossier.

+ GMP new registration dossier evaluation sheet - BM.CL.01.03/04
+ GMP re-registration dossier evaluation sheet – BM.CL.01.03/05

b) The document evaluation shall be performed in accordance to regulations specified in Decision:

- Decision No. 1570/2000/QD-BYT dated 22 May 200 of Ministry of Health on promulgating regulations, standards of "Good Laboratory Practice”
- Decision No. 2701/2001/QD-BYT dated 29 June 2001 of Ministry of Health on promulgating regulations, standards of "Good Storage Practice”
- Decision No. 3886/2004/QD-BYT dated 03 November 2004 of Ministry of Health on promulgating "Good Manufacturing Practice“ as recommended by World Health Organization
- Decision No. 47/2007/QD-BYT dated 24 December 2007 on implementation of applying the regulations, standards of "Good Manufacturing Practice", "Good Laboratory Practice", regulations of “Good Storage Practice" and regulations of "Good Distribution Practice" for Companies of manufacturing, testing, trading, distributing, exporting, importing, storing and reserving vaccine and medical biological products.

c) Experts for GMP dossier evaluation: has been appointed by the Director of DAV.

d) Evaluation results:

- In case, the dossier is complete as required: Assigned officer will send the Evaluation sheet and dossier to Head of QM department; this activity will be recorded in the List of registered company for GMP inspection (BM.CL.01.03/03).
- In case, the dossier is not complete: Assigned officer has to coordinate with the manufacturer by phone to update and correct the dossier; this activity will be recorded in the monitoring of GMP inspection form. The manufacturer has to submit a complete dossier within 30 days to QM department or assigned officer for reviewing again. If the dossier is update and contain enough required information, the process will follow e).

  In case the document is not submitted within 30 days, QM department or assigned officer will cancel the inspection in monitoring of GMP inspection form and details reasons for cancellation. If the manufacturer requires to be inspected, the manufacturer must submit new dossier registration.

e) Reviewing:

QM department's managers shall review GMP dossier and evaluation sheet.

- If need adding, back to previous step
- If approved, managers shall approve and forward to next step.

5.2.3. Preparing inspection schedule

a) Every month, QM department manager assign an officer to prepare monthly inspection schedule, in which include:

+ List of applied manufacturer having dossier reviewed and passed.
+ Tentative inspection schedule
+ Member of inspection team *
+ Fee and mean of transportation

* Members of inspection team: are selected following SOP of Qualification of GMP Inspector (QT.CL.16.02), QM.CL.01.XX Quality Manual of Drug Quality Management Division and considering based on type of products, number of products and size of each Manufacturer.

b) QM Department's manager reviews the monthly schedule and submits to Head of DAV for approval.

c) Head of DAV reviews the monthly schedule:

- If not appropriate, return back to QM department for ajustment.
- If appropriate, Head of DAV approves the schedule.

5.2.4. Set up inspection team

- QM Department's manager asign an oficer to prepare:
  + Draft of Decision to set up inspection team
  + Collect all material for the ínpection
- Submit to Head ò DAV for reviewing and approval of Decision to set up inspection team
- In case of necessary, member of inspection team may change. The decision will be forward to Administration office for stamping and archive in QM dept.

5.2.5. Prepare of GMP inspection

a) Officer in charge of application dossier should handout all material for inspection to secretary of inspection team, which include:
   + Decision to set up inspection team
   + GMP application dossier
   + Reviewing record of GMP application dossier

b) Secretary of inspection team is in charge of:
   + Sending Decision of inspection to all members of inspection team and applied manufacturer.
   + Provide necessary documents and information to members of inspection team
   + Coordinate between inspection team and applied manufacturer to conclude the inspection date.
   + Inform applied manufacturer the final concluded inspection date.
   + Draft the inspection plan (BM.CL.01.04/06)
   + Lead Inspector has to arrange the meeting or coordinating with inspectors in inspection team to prepare the inspection plan, assign works and remind notice points during inspection.

The inspection period is about 2-5 working days (in which the last day is for preparing inspection report), that depend on scope of inspection, number of inspector in the Inspection Team, type of product, size of the company, and other related issues should be taken into consideration.

Factors that increase inspection time, as examples;

- Complicated logistics involving more than one building or location where work is carried out.
- Inspected manufcturer having staff speaking foreign language (requiring interpreters)
- System covers highly complex processes or relatively high number of unique activities

Factors that decrease inspection time, as examples;

- Inspection initiated by complaint or suspect of quality violation
- No/ low risk product/ process
- Small site carryout only some parts of manufacturing process
- High percentage of employees doing the same, simple tasks

c) Inspection plan at company need to sure that inspection activity cover all facility activity and main system, manufaturing, quality control, storage, maintenance, calibration/validation procedures, which potentiate high affect for product in the acceptable time. Inspection plan should clarify about work assignment for each inspector. Inspection plan include some main contents:

- Scope and purpose of inspection;
- List products are producing in facility;
- Information of company: recall product, ADR reported products, violated record in regulations and GMP standard (if any)…
- List inspectors of inspection team;
- Timeline and location for meeting with manufacturer;
- The areas, units will be inspected;
- The draft timeline for each inspector activity;
- The schedule and location for meeting (kick-off meeting, routine meeting, final meeting);
- List of documents should be reviewed (may be attached with inspection plan);

d) After inspection plan was united, team secretary inform to manufacturer time of inspection.

Inspection plan might be changed during inspection period if have any deficiency is detected which should be further inspected. Need to review inspection progress and compare with inspection plan to have appropriate adjustment. Announce to company about any change in inspection plan.

5.2.6. Onsite inspection

a) Opening meeting

* Lead Inspector introduce:
  + Legal bases and members of inspection team
  + Objective, scope of inspection
  + Inspection plan
* The Manufacturer should make a brief presentation about their operation and GMP application activities (total not more than 60 minutes), including:
  + Organization structure
  + Production situation
  + Summary on GMP training operation and results
  + Layout of production area
  + Personnel flow, Materials/ intermediates/ packaging materials/ finished products flow
  + HVAC system
  + Water system and waste treatment
  + Firefighting system and labor safety
  + Dosage form of products produced
  + IPC
  + Supplier qualification
  + For QC activities: following SOP QT.CL.02.xx
  + For warehouse activities: following SOP QT.CL.03.xx.
  + Self inspection

After brief presentation of Manufacturer, inspection team can pose questions to clarify unclear point in registration document or on presentation of Manufacturer before performing mock inspection.

b) Field inspection

- After the opening meeting, inspection team shall conduct the inspection by following the Aide-Memoire as a guideline. Inspector can gather data by:
  + Ask questions or make an interview directly to supervisor or operator
  + Review the existing documents
  + Observe the operation
- Inspectors should inform his/her findings or observations to Manufacturer's staff before leaving that area and write down those findings or observations into Inspection Note (following Form of inspection note: **BM.CL.01.03/07**) using unerase-able pen. Inspectors shall write down all deficiencies they encountered during inspection even though Manufacturer can correct such deficiency immediately**.**
- During the inspection, inspectors should take samples and send for analysis whenever there is any doubt on the quality of the product(s).
- The inspectors can get access to all areas, documentation relate to the production and quality control of product including SOPs, protocol, diagram, records, data and design of premises during the inspection. If needed, the inspectors can ask to make copies of documents or to take photographs of premises and equipment.
- In case a Critical deficiency is found, Lead Inspector shall record, evaluate the risk and order the Manufacturer to stop production/ activities related to the deficiency (order must be informed at closing meeting of inspection and written in inspection report). Lead Inspector shall rapidly submit such record to Head of DAV for consideration and inform the Manufacturer right after Head of DAV makes a decision.
- At the end of working time of each day:
  + The inspection team should make an informal meeting to report progress of inspection, exchange findings or observations, and obstacles found during inspection.
  + Lead Inspector summarize these information, prepare the List of deficiencies and inform to manufacturer. This inform may delay to the next morning. Manufacturer may submit additional evidence to explain about these deficiencies.

c) Inspection team meeting at the end of inspection

At the final inspection day, secretary team will collect all findings or observations during the inspection. Inspection team will review, discuss and classify found deficiencies (refer to Annex 1.Classification of GMP deficiencies) and conclude level of GMP compliance for manufacturer.

Level of GMP compliance is defined in QM.CL.01.XX Quality Manual of Drug Quality Management Division:

A - Good GMP compliance: Manufacturer has no critical or major deficiency.

B - Sastified GMP compliance: Manufacturer has no critical deficiency and 1 - 6 major deficiencies.

C - Basic GMP compliance: Manufacturer has no critical deficiency and 7-14 major deficiencies.

D - GMP Non-Compliance: Manufacturer has 1 or more critical deficiencies and/or more than 14 major deficiencies.

d) Closing meeting

On behalf of the inspection team, Inspection leader:

- Repeat the objective and scope of inspection
- Summarize the observations found during the inspection in both strength and weakness, and final conclusion of GMP comliance level of company
- Explain to company if having unclear point and adding the company's comments if appropriate;

5.2.7. Finalize inspection report

- The secretary of team finalizes the inspection report (**BM.CL.01.03/08**) then submit to QM department manager for independently review, if the manager is member of inspection team, he should assign another officer to do it. Inspection report must attach list of defficiencies which should be described clearly & in detail. All defficiencies must be listed, classified and refered to relevant reference to the WHO, PICs GMP guide.
- The inspection report should be completed and send to company within 30 work days since finished inspection date. The list of participant in inspection should be attached to the inspection report (BM.CL.01.03/10).

- The secretary of team is responsible for inspection report archive, receiving and handling Corrective and Preventive action **(**CAPA) of manufacturer and drafting Decision of granting Certification for manufacturer.

5.2.8. Processing after inspecting

Processing after inspection will depend on the level of GMP compliance:

a) Good (A) and Sastified (B) GMP compliance manufacturer:

QM Department submits the inspection report attached with draft decision and GMP certificate (form BM.CL.01.03/10, BM.CL.01.03/11) to Head of DAV for approval.

- Inspection team explains and clarifies the related contents if having any request from Head of DAV.
- Manufacturer must submit CAPA plan for found deficiencies. CAPA evaluation result (form BM.CL.01.03/12) will be an input for follow-up inspection plan of the following year.

b) Basic GMP compliance manufacturer

- Company must submit CAPA to address deficiencies within 2 months from the finished inspection date (at closing meeting). When received, within 10 days, secretary and leader of the inspection team should evaluate the CAPA and notes in CAPA evaluation sheet (BM.CL.01.03/12).
  + If the CAPA is satisfied (number of major deficiencies which have not been corrected is less than 10 and the company has detail plan to address them), QM Department submits the inspection report attached with draft decision and certificate GPs (form BM.CL.01.03/10, BM.CL.01.03/11) to Head of DAV for approval (as handling in section a)).
  + If the CAPA is not satisfied, inspection team request manufacturer to submit additional CAPA within 2 months by sending the CAPA evaluation result to email of Head of QM in manufacturer. Out of this timeframe, or the additional CAPA is not satisfied, DAV issue Decision to stop production activity in the company (form BM.CL.01.03/13). The company has to resubmit its application. The company could only continue production after the next inspection is satisfied.

- Inspection team explains and clarifies the related contents if having any request from Head of DAV.

c) GMP Non –Compliance:

DAV issue Decision to stop production activity in the company (form BM.CL.01.03/13). The company must carry out CAPA and submit GMP registration again when the corrective action is complete. The company could only continue production after the next inspection is satisfied.

d) Special cases:

In the following special circumstance case, Drug Quality Management Division will propose to Lead of DAV/MOH to consider risk-benefit evaluation to alow the manufacturer which was considered as GMP non-compliance to continute production one or some determined products in a determined period of time:

+ The manufacturer supplies vaccines, medicines for urgent need to prevent outbreak disease, overcome consequences of natural disasters, catastrophes;

+ Alternative product is not available or not enough or could not be supplied on time;

+ Having effective measures for strictly monitoring, testing and inspection in order to assure and minimize risk for product quality and to solve problems timely incase having issues on quality of vaccines

5.3. Follow-up inspection

Using the same instruction as clause 5.2.3, 5.2.4, 5.2.5, 5.2.6, 5.2.7, 5.2.8 as of Regular Inspection, detail in proposed Corrective Action shall be taken into consideration.

5.4. Special inspection

- Using the same instruction as clause 5.2.3, 5.2.4, 5.2.5, 5.2.6, 5.2.7 as of Regular Inspection, cause of the concise inspection shall be taken into consideration.
- QM Department’s managers set up the Inspection Team and Inspection time, submit to General Director of DAV for issuing Decision for conduct inspection. The decision will be informed to manufacturer within 24-48h.
- Depend on the cause of the concise inspection, the inspection shall be:

  * **Product-based:** focus on the development of product from raw

materials to the secondary packaging, including the following matters:

+ Specification of the raw materials and packaging materials
+ SOPs
+ Manufacturing instruction/ records
+ Equipment logs
+ Sampling procedure
+ IPC of intermediates products and bulks
+ Testing procedure/ records
+ Release procedure

*** Procedure-based:** example:

+ Inward transfer and discharging staff from clean rooms
+ Sampling of raw materials
+ Manual cleaning of equipment
+ Transfer of rejected goods
+ Manual packaging of small batches
+ Initial weight of raw materials
+ Integrity tests of product-carrying sterile filters

*** Area- based:** focus on high-risk area suspected:

+ Hygiene and cleanliness status of the room and facilities
+ Status of floors, walls and ceillings
+ Labeling of materials, equipment and pipes
+ Provisions zones and materials movement
+ Machine log books (calibrations, maintenance, malfunction)
+ Prevention of cross-contaminations
+ Required instructions or on-site records
+ Responsibility regulations of the area
+ Clothing and conduct of the employees and their place of work
+ Staff training documents

5.5. Risk rating and frequency of follow-up GMP inspection

The risk ratings is a content of GMP inspection using risk approche. Risk rating that are assigned to sites are based on an assessment of two different kinds of risk - an intrinsic risk and a compliance-related risk.

The intrinsic risk estimated for a site reflects the complexity of the site, its processes and products as well as the criticality of the products or services provided by the site including from a supply perspective.

The compliance-related risk that is estimated for the site reflects the GMP compliance status of the site immediately following the most recent routine inspection at the site. When this risk is being estimated, the classification and number of deficiencies identified at the last inspection are taken into account.

Once the intrinsic risk and the compliance-related risk associated with the site have been estimated (after GMP inspection completion), those two risks are then combined using a simple matrix to generate a relative risk rating for the site. It is this risk rating that is considered when deciding the frequency of GMP follow-up inspection at the site. The worksheet for risk score and Guidance on how to assess the intrinsic risk are provided in Apendix 2 and Appendix 3.

5.6. Annual inspection plan

- Every December each year, QM manager shall assigne an officier to establish annual inspection plan for the following year. QM manager reviews and put this plan in Plan of QM department Activity for the following year.
- The annual inspection plan includes:
    + Routine inspection plan: base on the frequency for GMP recertification is 3 years
    + Follow-up inspection plan: base on Risk rating and frequency of follow-up GMP inspection, information on Quality, ADR of products.

5.7. Dosage form format

General principle: Content in the inspection report, issuance decision and GMP certificate include dosage form and active principle group.

- **Dosage form:**

    - Solid dosage form: tablet, effervescent tablet, film-coated tablet, sugar-coated tablet, powder (powder for suspension, powder for solution, effervescent powder), granules (granules for suspension, granules for solution, effervescent granules), hard capsule, soft capsule.
    - Injectables: powder for injection, infusion (solution for infusion, oil in water emulsion , etc...), small volume injection, suspension

for injection, emulsion for injection, lyophilized powder for injection, concentrate solution for injection, etc...

- Ointment, cream, gel, pasta
- Liquid for external use, Oral liquid, Oral syrup, lotion, suspension, emulsion, oral gel.
- Implant
- Nanomedicine
- Transdermal Patch
- Suppositoire: Rectal Suppositoire, Vaginal Suppositoire, urethral suppositoire.
- Eye drops, eye ointment
- Nasal drop, ear drop: nasal spray, Ear spray, "nasal drops, suspension", "ear drops, suspension" nasal spray, suspension", "ear spray, suspension"; "nasal drops, emulsion", "ear drops, emulsion"; "nasal spray, emulsion", "ear spray, emulsion";
- Inhalation: aerosol for inhaler, "inhalation vapour, ointment", inhalation vapour
- Nebuliser
- Medicated sponge
- Liquid Extract, viscous extract, dry extract
- Tincture
- Elixir/ Alcoolaturae (Cồn thuốc)
- Medicinal Parcel (Thuốc thang)
- Herbal Tea, Tea, solute tea, cake tea
- And other chemist forms

- **The API groups:**
  - Products containing Beta-lactam antibiotic.
  - Products containing Penicillin antibiotic.
  - Products containing Cephalosporin antibiotic.
  - Products containing hormones
  - Antineoplastic medicine.
  - Radioactive products.
  - Products containing micro-organism.
  - Others ....
- **For vaccines and biological products:**

Name of vaccine, biological products (according to international name, not to write brand name).

- **For pharmaceutical materials:**
  To write international name of each material.
- **For the Company doing packing activities:**
  To write the process/stage of packing.

6. DOCUMENTS STORAGE

All Documents and Archives of this SOP would be storaged in accordance with DAV's regulation:

- Registration dossier of company
- Registration dossier evaluation sheet
- Decision for establishing inspection team
- GMP inspection report
- Submitted CAPA of company
- CAPA evaluation sheet
- Decision of issuing certificate and certificate of inspected Companies.
- Document submitted to Heads of DAV
- Decision to stop production activity in the company

7. APPENDIX

BM.CL.01.05/01	Checklist for GMP new registration dossier
BM.CL.01.05/02	Checklist for GMP re- registration dossier
BM.CL.01.05/03	List of registered company for GMP inspection
BM.CL.01.05/04	GMP new registration dossier evaluation sheet
BM.CL.01.05/05	GMP re registration dossier evaluation sheet
BM.CL.01.05/06	Inspection plan at company form
BM.CL.01.05/07	Inspection note form
BM.CL.01.05/08	Inspection report form
BM.CL.01.05/09	The list of participant in inspection
BM.CL.01.05/10	Decision for granting GMP certificate
BM.CL.01.05/11	GMP certificate
BM.CL.01.05/12	CAPA evaluation sheet
BM.CL.01.05/13	Decision to stop production activity in the company

BM.CL.01.05/14	Annual GMP inspection plan
BM.CL.01.05/15	Risk assessment table
Annex I	Classification of GMP deficiencies
Annex II	Guidance on How to Score the Intrinsic Risk Factors

Checklist for GMP new registration dossier

No	Items	Number	Yes	No	Comments
1	GMP registration form	01	☐	☐	
2	Copies documents with signature of authorized person and stamp of company: - Manufacturer estabishment authorization, or - Business license, or - Investiment authorisation;	01	 ☐ ☐ ☐	 ☐ ☐ ☐	
3	Organizational chart	01	☐	☐	
4	Personnel training: programme, documents, synthesis report	01	☐	☐	
5	Manufacturing areas (design, location: + Layout of production area: + Personnel flow + Materials/intermediates/ packaging materials/finished products +Water system + HAVC system + Clean room arrangement + Waste treatment	 01 01 01 01 01 01 01	 ☐ ☐ ☐ ☐ ☐ ☐ ☐	 ☐ ☐ ☐ ☐ ☐ ☐ ☐	
6	List of equipments	01	☐	☐	

Checklist for GMP re registration dossier

No	Items	Number	Yes	No	Comments
1	GMP re registration form	01	☐	☐	
2	Copies documents with signature of authorized person and stamp of company: - Manufacturer estabishment authorization, or - Business license, or - Investiment authorisation;	01	☐ ☐ ☐	☐ ☐ ☐	
3	Report on corrective action for defficiencies in last inspection	01	☐	☐	
4	Report on production activity of company during 3 year since last inspection	01	☐	☐	
5	Report on changement of company related to GMP implementation during 3 year since last inspection and other documents (if any)	01	☐	☐	

(Form Excel)

DANH SÁCH CƠ SỞ ĐANG ĐĂNG KÝ CHỨNG NHẬN GMP

Cập nhật: 05-03-15

TT	COMPANY CODE	COMPANY NAME	SITE CODE	LOCATION	LINE CODE	LINE / DOSSAGE FORM	LAST APPLICATION						CERTIFICATE			INSPECTION PLAN	PROGRESS	NOTE
							APPLICATION			INSPECTION	CAPA	CONCLUSION	Code	Date	Exp.	Date	Detail	
							GPs	Type	Date	Date	Date							

DRUG ADMINISTRATION OF VIETNAM
Department of drug and cosmetic quality management

Socialist Republic of Vietnam
Independence – Freedom -Happiness

GMP NEW REGISTRATION DOSSIER EVALUATION SHEET

- Name of enterprise:
- Director:
- Location:
- Chain for registration of GMP inspection:

I. Content of evaluation

1.1. Legality of GMP registration dossier

	Yes	No
+ Legality of GMP registration form	☐	☐
+ Manufacturer estabishment authorization, or - Business license, or Investiment authorisation;	☐	☐
Note: (Meet requirements or not)	.....	.....

1.2. GMP Training document can represent:

	Yes	No
+ Subject of training course	☐	☐
+ Trainer	☐	☐
+ Trainee	☐	☐
+ Objective of training	☐	☐
+ Training time	☐	☐
+ Training result	☐	☐
Note: (Meet requirements or not)	.....	.....

1.3. Organizational structure:

+ Organizational structure:	☐	☐
+ Write clearly function, realtion of the departments	☐	☐
+ Write clearly title, qualification of managers	☐	☐
Note: (meet the requirement or not)	☐	☐

1.4. Location map of Company:

+ In city: ☐ + In industrial zone: ☐ + Other: ☐

1.5. Are here layout of:

+ Direction of material	☐	☐
+ Way for worker	☐	☐
+ have airlock at nessessary positions	☐	☐
+ Schem of supplying clean air	☐	☐
+ Diagram of pressure difference	☐	☐
+ Supply clean of production region	☐	☐

Note: (meet requirement or not)

1.6. Catalogue of manufactured products (or in expection for manufacturing) ☐ ☐

II. COMMENT OF EXPERT AND THE REMARKS DURING INSPECTION

III SIGNATURE OF THE EVALUATION EXPERTS

IV. CONCLUSION AND RECOMMENDATION OF DEPARTMENT MANAGER

DRUG ADMINISTRATION OF VIETNAM
Department of drug and cosmetic quality management

Socialist Republic of Vietnam
Independence – Freedom -Happiness

GMP RE REGISTRATION DOSSIER EVALUATION SHEET

- Name of enterprise:
- Director:
- Location:
- Chain for registration of GMP inspection:

I. Content of evaluation

1.1.Legality of GMP registration form	Yes ☐	No ☐
Note: (meet requirement or not)	.....	.....

1.2. Are there these reports?

+ Report on production activity of company during 3 year since last inspection	Yes ☐	No ☐
+ Report on corrective action for defficiencies in last inspection		
- Any changes in personal?	Yes ☐	No ☐
- Any changes in premises?	Yes ☐	No ☐
- Any changes in equipements?	Yes ☐	No ☐
- Other changes?	Yes ☐	No ☐

Note: (meet requirement or not)

II. COMMENT OF EXPERT AND THE REMARKS DURING INSPECTION

III SIGNATURE OF THE EVALUATION EXPERTS

IV. CONCLUSION AND RECOMMENDATION OF DEPARTMENT MANAGER

MINISTRY OF HEALTH
DRUG ADMINISTRATION OF VIETNAM

SOCIALIST REPUBLIC OF VIETNAM
Independence - Freedom - Happiness

Date :

AGENDA FOR GMP INSPECTION

I. General information:

1. **Manufacturer:**
2. **Site Address:**
3. **Inspection Type:**

   □ **First inspection** □**Re-inspection** □ **Follow-up inspection**
4. **Scope of inspection:**

   - Production line:

   - Product name:
5. **Requirement of GMP standard: GMP-WHO, Specific GMP.**
6. **Inspectors:**

II. Agenda For GMP Inspection:

Timeline	Content	Responsible person
Day 1		
….-…..	***Opening meeting*** **1. Audit team leader:** - Introduce the purpose, scope inspection; - Announce the inspection decision, audit team members; - Introduce the inspection agenda. **2. Brief presentation of company:**	
….-….	Doing inspection	
….-….	**Final meeting: Announce to company about detected deficiencies during inspection.**	
Agenda inspection can be changed during inspection period for being suitable with production situation.		

INSPECTION NOTE

Date	Name of manufacturer	Inspectors	Page
		(Sign)	
(Area to be inspected)	(Details of evidence found during the inspection)		

DRUG ADMINISTRATION OF VIETNAM

INSPECTION REPORT
"GOOD MANUFACTURING PRACTICES "

Name of company:.....

Date ../.../....

MINISTRY OF HEALTH
DRUG ADMINISTRATION OF VIETNAM

Socialist Republic of Vietnam
Independence – Freedom – Happiness

……, date ... month ... year ...

GMP INSPECTION REPORT

I. Manufacturer

- Name of inspected manufacturer.
- Address of inspected manufacturer (including telephone, fax)
- Address of manufacturing site if different from that given above.
- Site number (e.g. site master file or number allocated by the responsible authority).
- Manufacturing license number, if applicable.
- Activities.
- Pharmaceutical products manufactured.
- Key personnel.

II. Inspection details

- Date(s) of inspection(s).
- Previous inspection date.
- Type of inspection.
- Scope of inspection.
- The regulatory authority.
- GMP guidelines used for assessing compliance.
- For foreign inspections state whether, the national regulatory authority (NRA) of the country where the inspection took place was informed and whether it took part in the inspection.
- Brief report of inspection activities undertaken.
- Samples taken and results obtained.
- Assessment of the site master file.
- GMP-related recalls from the market of any product in the last 2 years.

III. Inspector(s)

- Decision No…… dated ….. of DAV on establishment of GMP inspection team at …(manufacturer name)……, the members of the inspection team include :

  1…..... – Team leader.

  2..... - Secretary.

  3.....

  4…….

IV. Inpection findings

Describing following relevant headings from the WHO GMP Guide. This section can link the findings to the deficiencies and used to explain classification

1. **Quality assurance**

(a) Quality system and documented quality policy of the manufacturer, e.g. as described in the quality manual.

2. **Organization and personnel**

(a) Organizational chart showing the arrangements for quality assurance, including production and quality control.

(b) Qualifications, experience and responsibilities of key personnel.

(c) Outline of arrangements for basic and in-service training and method of keeping records.

(d) Health requirements for personnel engaged in production. (e) Personnel hygiene requirements, including clothing.

3. **Premises**

(a) Manufacturing areas (design, location etc.) used e.g. for storage and manufacturing (e.g. weighing, production, packaging) and flow of personnel and material.

(b) Special areas for the handling of highly toxic, hazardous and sensitizing materials.

(c) Nature of construction and finishes.

(d) Systems such as drainage, ventilation, air conditioning, and sup-ply of steam and gas. Detailed description of critical areas with potential risks of contamination and cross-contamination.

(e) Classification of the rooms used for the manufacture of products, including clean rooms.

(f) Water systems.

(g) Planned preventative maintenance programme.

(h) Qualification of premises and systems as appropriate.

4. **Equipment**

(a) Design, location and adaptation of equipment used in production and control laboratories.

(b) Planned preventative maintenance programmes for equipment and records.

(c) Qualification and calibration, including records.

5. Materials

- Sourcing of materials, supplier qualification

- Control, storage and handling of materials, including: starting materials; packaging materials; intermediate and bulk products; finished products; returned

and rejected materials; reagents and culture media; reference standards; waste material.

6. Production

(a) Transport, handling and use of starting materials, packaging ma-terials, and bulk and finished products.

(b) Production operations and important parameters (e.g. sampling, quarantine, weighing, process operations and conditions, accep-tance limits).

(c) Validation (e.g. process).

(d) Change control and deviation reporting.

7. Sanitation and hygiene

(a) Procedures for sanitation and/or cleaning (e.g. of premises and equipment) and records.

(b) Personal hygiene.

8. Quality control

(a) Activities of quality control (including quarantine control, sam-pling, chemical and microbial analysis).

(b) Organization and personnel.

(c) Premises.

(d) Equipment and instrumentation.

(e) Materials.

(f) Documentation (e.g. specifications, procedures, reports, records).

9. Storage

(a) Changing room

(b) Materials warehouse: sampling area, quarantine area, intermediates, bulk and finished products storage, release, rejected, returned or recalled products storage, packaging materials storage

10. Documentation

(a) Documentation (e.g. specifications, procedures, records, proto-cols, reports).

(b) Preparation, revision and distribution of documentation.

(c) Reports on production, quality control (including environmental control), engineering and other relevant areas.

11. Validaton

(a) Validation master plan.

(b) Validation and qualification protocols and reports for qualification and validation (e.g. of premises, systems, equipment, process, computer, cleaning, analytical methods).

(c) Stages of validation.

(d) Types of validation.

12 Contract production and analysis

(a) Responsibilities of contract giver.

(b) Responsibilities of contract accepter.

(c) Contract (containing clearly defined responsibilities).

(d) GMP compliance of the contract accepter (initial assessment and continued compliance audited at regular intervals).

13 Complaints and Product recalls

(a) Procedure, records and investigation.

14 Self-inspection and quality audits

(a) Procedure, programme and compliance.
(b) Items for self-inspection.
(c) Self-inspection team.
(d) Frequency of self-inspection.
(e) Self-inspection report.
(f) Follow-up action.
(g) Quality audit.
(h) Suppliers' audits.

V. List of defficiencies

No	Defficiencies	References	Classification
1.	***Quality assurance***		
1.1			
1.2			
2.	***Personnel and training***		
3.	***Premises***		
	……		

All defficiencies must be listed, classified (e.g. as "critical", "major" and "minor") and refered to relevant reference to the WHO, PICs GMP guide.

VI. Conclusions

.....

Inspection report was announced, argeed between Inspection team and the firm. Inspection report is prepared in 03 copies. The company kept 01 copy and DAV kept 02 copies./.

Inspection team		**Representative of Company**
Secretary	***Leader***	***Director***

……

LIST OF PARTICIPANTS IN GMP INSPECTION

1. Name of company
2. Address
3. Time of inspection
   - Begin:
   - End:

I. Inspection team

No	Name	Sign	Title

II. Manufacturer:

No	Name	Sign	Title

Inspection team

Signature

Name
Title

Manufacturer

Signature

Name
Title

MINISTRY OF HEALTH
DRUG ADMINISTRATION OF VIETNAM

Socialist Republic of Vietnam
Independence – Freedom – Happiness

No…../QD-QLD

Hanoi, date ... month ... year ...

DECISION

On issuance of certificate of conformity to the requirements of "Good Manufacturing Practices", "Good Laboratory Practices" and "Good Storage Practices" certificate for Company……..

HEAD OF DRUG ADMINISTRATION OF VIETNAM

Pursuant to Decision No. 3861/QD-BYT dated 30/9/2013 of Minister of Health on providing functions, tasks and powers of Departments, bureaus, offices, Inspector of Health Ministry;

Pursuant to Decision No. 3886/2004/QD-BYT dated 03/11/2004 of Minister of Health on implementation of applying the principles, standards "Good Manufacturing Practices" according to counseling of World Health Organization (GMP – WHO);

Pursuant to Decision No. 1570/2000/QD-BYT dated 22/5/2000 of Minister of Health on implementation of applying the principles of "Good Laboratory Practices";

Pursuant to Decision No. 2701/2001/QD-BYT dated 29/6/2001 of Minister of Health on implementation of applying principles of "Good Storage Practices";

Pursuant to Inspection report date …. at company……

According to request of Department of Drug quality management,

Decides:

Article 1. To issue for Company……the certificate of conformity to the requirements of Good Manufacturing Practices as recommended by the World Health Organization, of Good Laboratory Practices and of Good Storage Practices for the following dosage forms:

Location of factory:

This certificate is valid for three years from the date of approval.

Article 2. This decision is effective from the date of approval.

Article 3. Mr, Mrs: Head of the: Administrative department, Drug quality management department, Drug registration department – Business Management department - DAV, Director of Company….. have responsibility to execute this decision.

Recipients:
- As article 3;
- Archived: VT, CL (02 copies).

Director -General

BỘ Y TẾ
MINISTRY OF HEALTH
CỤC QUẢN LÝ DƯỢC
DRUG ADMINISTRATION OF VIETNAM

Số: /GCN-QLD

CỘNG HÒA XÃ HỘI CHỦ NGHĨA VIỆT NAM
SOCIALIST REPUBLIC OF VIETNAM
Độc lập – Tự do – Hạnh phúc
Independence – Freedom – Happiness

GIẤY CHỨNG NHẬN

ĐẠT TIÊU CHUẨN "THỰC HÀNH TỐT SẢN XUẤT THUỐC"

CERTIFICATE OF GOOD MANUFACTURING PRACTICES (GMP)

CỤC TRƯỞNG CỤC QUẢN LÝ DƯỢC CHỨNG NHẬN

Director - General of Drug Administration of Viet Nam certifies that

Name of company

Location of Factory

đạt yêu cầu "Thực hành tốt sản xuất thuốc" theo khuyến cáo của Tổ chức Y tế thế giới, "Thực hành tốt phòng kiểm nghiệm thuốc" và "Thực hành tốt bảo quản thuốc" đối với các dạng thuốc thành phẩm sau:

conforms to the requirements of Good Manufacturing Practices as recommended by the World Health Organization, of Good Laboratory Practices and of Good Storage Practices for the following dosage forms:

Dosage forms

Hà Nội, ngày tháng năm
CỤC TRƯỞNG
Director - General

Giấy chứng nhận này có giá trị trong ba năm kể từ ngày ký

This certificate is valid for three years from the date of approval.

Trương Quốc Cường

CAPA EVALUATION SHEET

No	Defficiency	Corrective action	Plan of Corrective action	Inspection team's Comment

Conclusion: **Sastified**
Not - Sastified

Evaluator

(Signature, Name)

MINISTRY OF HEALTH
DRUG ADMINISTRATION OF VIETNAM

SOCIALIST REPUBLIC OF VIETNAM
Independence - Freedom - Happiness

No: 702/QD-QLD

Hanoi, December 22nd 2014

DECISION
On stopping production …….in …(name of manufacturer)

DIRECTOR-GENERAL OF DRUG ADMINISTRATION OF VIETNAM

Pursuant to current pharmaceutical regulation;

Pursuant to Decision No. 3861/QD-BYT dated September 30th 2013 of the Minister of Health on defining functions, tasks, powers and organizational structure of Drug Administration of Vietnam - Ministry of Health;

Considering the proposal in the inspection report dated …. of DAV inspection team at manufacturer….

Considering the proposal of Drug Quality Management department,

HEREBY DECIDES

Article 1: To stop vaccine production …….in …(name of manufacturer)
at address: ……

Article 2: Suspending or Revising the GMP certificate issuing with the Decision ….

Article 3: This Decision shall come into full force and effect since the date of signing.

Article 4: Chief of Office, Head of Departments: Drug quality management, Drug business management of Drug Administration of Vietnam and Director of …(name of manufacturer) shall be responsible for implementing this Decision.

Recipients:
- As Article 4;
- Archived: VT, CL.

DIRECTOR
(Signed and stamped)
Truong Quoc Cuong

MINISTRY OF HEALTH
DRUG ADMINISTRATION

SOCIALIST REPUBLIC OF VIETNAM
Independence - Freedom - Happiness

Ha Noi, day … month … year ……

ANNUAL INSPECTION PLAN OF ……

No.	COMPANY NAME	LOCATION	LINE / DOSAGE FORM	CERTIFICATE EXP.	FOLLOW-UP PLAN	2015												Inspectors	Date of inspection	Type of inspection
						1	2	3	4	5	6	7	8	9	10	11	12			
1					-															
2					-															

DIRECTOR
(Signed and stamped)
Truong Quoc Cuong

Risk Assessment Table

PART A – Manufacturer information	
Site Name	
Site Address	
Licence Number (if any)	
FP or API Manufacturer?	
Last Inspection Date	
Name of previous lead inspector	

PART B – The Intrinsic Risk Associated with the Site

Risk Factor	Risk Score	Matrix for Estimating the Intrinsic Risk
The Complexity of the site, its processes and products, is regarded as:	**1 2 3** **Circle one**	
The Criticality of the products manufactured by the site, or the criticality of the analytical testing or other service offered provided by the site, is regarded as:	**1 2 3** **Circle one**	

	Criticality		
Complexity	**1**	**2**	**3**
1	1 (Low)	2 (Low)	3 (Med)
2	2 (Low)	4 (Med)	6 (High)
3	3 (Med)	6 (High)	9 (High)

Use the above matrix and record the Intrinsic Risk associated with the site below:

Low □ Medium □ High □

PART C - The Compliance-related Risk based on the last Inspection

The compliance risk indicated by the most recent deficiency profile of the site is:	**Low □** **Medium □** **High □**	- No Major or Critical Deficiencies, 1-6 major deficiences - 7 to 14 Major Deficiencies: *Number of Majors* = ____ -1 or more Critical and/or more than 14 Majors deficiencies

PART D – The Risk-Rating assigned to the Site

Complete the matrix below by combining the Intrinsic risk score and the Compliance-related risk score to determine the Risk Rating for the site.:

	Intrinsic Risk		
Compliance Risk	**Low**	**Medium**	**High**
Low	Risk Rating = A	Risk Rating = A	Risk Rating = B
Medium	Risk Rating = A	Risk Rating = B	Risk Rating = C
High	Risk Rating = B	Risk Rating = C	Risk Rating = C

The Risk Rating associated with this site is: A □ B □ C □

PART E – The Recommended Frequency for Routine Inspections at the Site

A	Reduced Freq. 3 years
B	Moderate Freq. 1.5 years
C	Increased Freq. 1 year

Using the Risk Rating, the recommended frequency for follow-up inspections at the site is an inspection every: ……..

PART F – Recommended Scope of the next Routine Inspection

Note: This Part should be periodically updated if new information is received about the site before the next routine inspection that may warrant a change in the scope of that inspection.

For example, information can be received relating to, Quality Defects, Recalls, Market Surveillance Test Results, Enforcement Investigations, and other indicators of non-compliance, such as the failure to implement a variation to an MA, that might require the scope of the next inspection to be changed. Information may also relate to major changes at the site (indicated perhaps via an MA variation or a manufacturing authorisation variation submission) and this may warrant a change in scope.

Document on the right the **recommended focus & depth** of the next routine inspection. ***Note**: Take into account the following:* • The areas in which deficiencies were identified during the most recent inspection at the site, particularly major and critical deficiencies; • The areas that were not inspected (or that were not inspected in detail) during the most recent inspection at the site; • The areas that were considered inadequately resourced at last inspection; • Planned changes at the site that may alter the complexity or criticality risk ratings associated with the site • Any other area that the inspector feels warrants review at the next inspection.	
Document on the right the required duration of the next routine inspection:	
Document on the right the required number of inspectors that should be assigned to the next routine inspection:	
Document on the right any specific competence or expertise that will be required on the inspection team when performing the next routine inspection of the site:	

PART G – Signatures & Dates

Record here the names of the persons who completed this quality Risk management exercise, and sign and date this form:

Name: Name: __
Name: Name: __

Signed: Date:

Annex I. Classification of GMP Deficiencies

Glossary:

Critical deficiency: A deficiency which has produced, or leads to a significant risk of producing either a product which is harmful to the human.

Major deficiency: A non-critical deficiency: which has produced or may produce a product, which does not comply with its marketing authorisation; or which indicates a major deviation from GMP; or which indicates a major deviation from the terms of the manufacturing authorisation; or which indicates a failure to carry out satisfactory procedures for release of batches; or a combination of several "other'' deficiencies, none of which on their own may be major, but which may together represent a major deficiency and should be explained and reported as such.

Minor deficiency: A deficiency which cannot be classified as either critical or major, but which indicates a departure from good manufacturing practice. A deficiency may be "other" either because it is judged as minor, or because there is insufficient information to classify it as major or critical.

Critical Product - A critical product is one for which any of the following criteria may apply:

- narrow therapeutic window
- high toxicity
- sterile product
- biological drug

High Risk Product - Any product that may trigger a health risk even at low levels, following cross-contamination. Those include but are not limited to penicillins, certain cytotoxic and biological products.

Low Risk Product - Products such as certain topical non prescription.

Complex manufacturing process: process for which slight deviations in the control of parameters could result in a non-uniform product or product not meeting its specifications. As examples, powder mixing or granulation for low dosage solid forms, long acting/delayed action products, sterile products.

Note: Certain Major deficiencies may be upgraded to a Critical deficiency. They are indicated with an arrow (↑)

1. Premises

1.1. Critical Deficiencies

- No air filtration system to eliminate airborne contaminants that are likely to be generated during fabrication or packaging.
- Generalized malfunctioning of the ventilation system(s) with evidence of widespread cross-contamination.
- Inadequate segregation of manufacturing or testing areas from other manufacturing areas for high risk products.

1.2. Major Deficiencies

- Malfunctioning of the ventilation system that could result in possible localized or occasional cross-contamination.
- Maintenance/periodic verification such as air filter replacement, monitoring of pressure differentials not performed. (↑)
- Accessory supplies (steam, air, nitrogen, dust collection, etc.) not qualified.
- Heat, Ventilation, Air Conditioning (HVAC) and purified water system not qualified. (↑)
- Temperature and humidity not controlled or monitored when necessary (for example, storage not in accordance with labelling requirements).
- Damages (holes, cracks or peeling paint) to walls/ceilings immediately adjacent or above manufacturing areas or equipment where the product is exposed.
- Un-cleanable surfaces created by pipes, fixtures or ducts directly above products or manufacturing equipment.
- Surfaces finish (floors, walls and ceilings) that do not permit effective cleaning.
- Unsealed porous finish in manufacturing areas with evidence of contamination (mildew, mould, powder from previous productions, etc.). (↑)
- Insufficient manufacturing space that could lead to mix-ups. (↑)
- Physical and electronic quarantine accessible to unauthorized personnel/ Physical quarantine area not well marked and/or not respected when used. (↑)
- No separate area/Insufficient precautions to prevent contamination or cross-contamination during raw material sampling.

1.3. Minor Deficiencies

- Doors giving direct access to exterior from manufacturing and packaging areas used by personnel.

- Un-screened/Un-trapped floor drains.
- Outlets for liquids and gases not identified.
- Damages to surfaces not directly adjacent or above exposed products.
- Non-production activities performed in production areas.
- Inadequate rest, change, wash-up and toilet facilities.

2. Equipment

2.1. Critical Deficiencies

- Equipment used for complex manufacturing operations of critical products not qualified and with evidence of malfunctioning or lack of appropriate monitoring.

2.2. Major Deficiencies

- Equipment does not operate within its specifications. (↑)
- Equipment used during the critical steps of fabrication, packaging /labelling, and testing, including computerized systems, is not qualified. (↑)
- Tanks for manufacturing of liquids and ointments not equipped with sanitary clamps.
- Stored equipment not protected from contamination. (↑)
- Inappropriate equipment for production: surfaces porous and non-cleanable/material sheds particles. (↑)
- Evidence of contamination of products by foreign materials such as grease, oil, rust and particles from the equipment. (↑)
- No covers for tanks, hoppers or similar manufacturing equipment.
- No inadequate precautions taken when equipment such as oven or autoclave contains more than one product (possibility of cross-contamination or mix-ups). (↑)
- Equipment location does not prevent cross-contamination or possible mix-ups for operations performed in common area. (↑)
- Purified water system not maintained or operated to provide water of adequate quality. (↑)
- Leaking gaskets with potential impact on product quality. (↑)
- No calibration program for automatic, mechanical, electronic or measuring equipment/no records maintained.
- No preventative maintenance program for major equipment/no records maintained.
- No equipment usage logs.

2.3. Minor Deficiencies

- Insufficient distance between equipment and walls to permit cleaning.
- Base of immovable equipment not adequately sealed at points of contact.
- Use of temporary means or devices for repair.
- Defective or unused equipment not removed or appropriately labelled.
- Minor equipment used for non critical products not qualified.

3. Personnel

3.1. Critical Deficiencies

- Individual in charge of Quality Control (QC) or production for a fabricator of critical/high risk products does not hold a university degree in a science related to the work being conducted and does not have sufficient practical experience in their responsibility area.

3.2. Major Deficiencies

- Individual in charge of QC or Production for a fabricator, packager/ labeller, importer, distributor or tester does not hold a university degree in a science related to the work being conducted.
- Individual in charge of QC or Production for a fabricator, packager/ labeller, importer, distributor or tester does not have sufficient practical experience in their responsibility area.
- Individual in charge of QC for a wholesaler or secondary labeller is not qualified by academic training and experience.
- Delegation of responsibilities for QC or Production to insufficiently qualified persons.
- Insufficient personnel for QC or Production operations resulting in a high probability of error.
- Insufficient training for personnel involved in production and QC resulting in related GMP deviations.

3.3. Minor Deficiencies

- Inadequate training records.
- Insufficient written training program

4. Sanitation

4.1. Critical Deficiencies

- Evidence of widespread accumulation of residues/extraneous matter indicative of inadequate cleaning.
- Evidence of gross infestation.

4.2. Major Deficiencies

- Sanitation program not in writing but premises in acceptable state of cleanliness.
- No standard operating procedures (SOP) for microbial/environmental monitoring, no action limits for areas where susceptible non-sterile products are manufactured.
- Cleaning procedures for production equipment not validated (including analytical methods). (↑)
- Inadequate written health requirements and/or hygiene program.
- Health requirements and/or hygiene program not properly implemented or followed.

4.3. Minor Deficiencies

- Incomplete written sanitation procedure.
- Incomplete implementation of the written sanitation program.

5. Raw Material Testing

5.1. Critical Deficiencies

- Evidence of falsification or misrepresentation of analytical results.
- No evidence of testing Certificate of Analysis (COA) available from the supplier/synthesizer and no testing done by the Canadian fabricator

5.2. Major Deficiencies

- Reduced testing program in place without adequate certification of the vendors/suppliers.
- Water used in the formulation is not of acceptable quality.
- Insufficient testing of raw material.
- Incomplete specifications.
- Specifications not approved by QC.
- Test methods not validated.
- Use of raw material after retest date without proper retesting.
- Use of raw material after the expiration date.
- Multiple lots of the same raw material, comprising of one reception, are not considered as separate for sampling, testing and release.
- No SOP for conditions of transportation and storage.
- Certification of brokers or wholesalers allowed without proper documentation.

5.3. Minor Deficiencies

- Lots identified for confirmatory testing used in production without QC approval.
- Incomplete validation of test methods.

6. Manufacturing Control

6.1. Critical Deficiencies

- No written Master Formula.
- Master Formula or manufacturing batch document showing gross deviations or significant calculation errors.
- Evidence of falsification or misrepresentation of manufacturing and packaging orders.

6.2. Major Deficiencies

- Master Formula prepared/verified by unqualified personnel.
- Lack of or incomplete validation studies/reports for critical manufacturing process (lack of evaluation/approval). (↑)
- Inadequate validation of changeover procedures. (↑)
- Unapproved/undocumented major changes compared to Master Production Documents. (↑)
- Deviations from instructions during production not documented and not approved by QC.
- Discrepancies in yield or reconciliation following production not investigated.
- Line clearance between production of different products not covered by SOP and not documented.
- No regular checks for measuring devices/no records.
- Lack of proper identification of in-process materials and production rooms resulting in a high probability of mix-ups.
- Inadequate labelling/storage of rejected materials and products that could generate mix-ups.
- Upon receipt, bulk and in-process drugs, raw material and packaging material not held in quarantine until released by QC.
- Labels are not properly controlled. (↑)
- Production personnel using bulk and in-process drugs, raw material and packaging material without prior authorization by QC. (↑)
- Inadequate/inaccurate labelling of bulk/in-process drugs, raw material and packaging material

- Raw material dispensing not done by qualified persons, according to an SOP.
- Master Formula incomplete or showing inaccuracies in the processing operations.
- Changes in batch size not prepared/verified by qualified personnel.
- Inaccurate/incomplete information in manufacturing/packaging batch documents.
- Although documented, combination of batches done without QC approval/not covered by SOP.
- No written procedures for packaging operations.
- Non-standard occurrences during packaging not investigated by qualified personnel.
- Inadequate control of coded and non-coded printed packaging material (including storage, dispensing, printing, disposal).
- Inadequate handling of outdated/obsolete packaging material.
- No or inadequate self-inspection program/Program does not address all applicable sections of GMPs/Records incomplete or not maintained.
- Fabrication, packaging/labelling and testing operations carried out at a unlicenced site. (↑)
- No agreement between the contractor, the importer and the distributor covering the fabrication and packaging/labelling operations.
- Recall: Absence of recall procedure combined with distribution practices that would not permit an adequate recall (distribution records unavailable or not kept). Improper quarantine and disposal practices that would allow recalled/rejected units to be returned for sale.

6.3. Minor Deficiencies

- Incomplete SOPs for handling of materials and products.
- Access to production areas not restricted to authorized personnel.
- Inadequate checks for incoming materials.
- Written procedures incomplete for packaging operations.
- Incomplete recall procedure.
- No agreement between the wholesaler, the importer and the distributor relative to a recall of a drug when the importer or distributor assumes wholesaler's responsibilities with respect to recalls.
- Incomplete/inaccurate annual product quality review.

7. Quality Control Department

7.1. Critical Deficiencies

- No person in charge of QC available on premises.
- Quality Control department is not a distinct and independent unit, lacking real decisional power, with evidence that QC decisions are often overruled by production department or management.

7.2. Major Deficiencies

- Inadequate facilities, personnel and testing equipment.
- No authority to enter production areas. (↑)
- No SOPs approved and available for sampling, inspection and testing of materials.
- Products made available for sale without approval of QC department. (↑)
- Products released for sale by QC without proper verification of manufacturing and packaging documentation.
- Master production documents not in compliance with marketing authorization. (↑).
- Out of specification test results, deviations and borderline conformances not properly investigated and documented, according to a SOP. (↑)
- Raw material/packaging material used in production without prior approval of QC.
- Reprocessing/Reworking done without prior approval of QC department. (↑)
- Lack of or inadequate system for complaint handling.
- Returned goods are made available for sale without assessment and/or approval by QC.
- SOPs covering operations that can affect the quality of a product such as transportation, storage, etc... not approved by QC department/not implemented.
- Inadequate evidence to demonstrate that storage and transportation conditions are appropriate.
- Lack of or insufficient change control system.
- For testing laboratories (in house or contract), the systems and controls in place for the proper qualification, operation, calibration and maintenance of equipment, standards, solutions, and records keeping do not assure that the results and conclusions generated are accurate, precise and reliable. (↑)
- Products tested at a unlicensed site. (↑)
- Sterility testing not performed in a Grade A environment within a Grade B background or in an isolator of a Grade A within an appropriate background and limited access to non-essential personnel.

7.3. Minor Deficiencies

- No agreement between the contract laboratory and the establishment covering the testing activities.
- Investigations of non-conformances not completed in timely manner.

8. Packaging Material Testing

8.1. Major Deficiencies

- Reduced testing program in place without adequate certification of vendors/suppliers.
- Lack of or insufficient testing of packaging material. (↑)
- Inadequate specifications.
- Specifications not approved by QC.
- No identity test done by the packager/labeller after receipt on its premises
- Certification of brokers or wholesalers done without proper documentation.

8.2. Minor Deficiencies

- Inadequate procedures of transportation and storage.
- Inappropriate environment and/or precautions to prevent contamination of packaging material during sampling.

9. Finished Product Testing

9.1. Risk 1 (Critical)

- Finished product not tested for compliance with applicable specifications by the importer/distributor before release for sale and no evidence is available that the products have been tested by the fabricator.
- Evidence of falsification or misrepresentation of testing results/forgery of COA.

9.2. Major Deficiencies

- Non-compliant products made available for sale. (↑)
- Incomplete/inadequate specifications.
- Finished product specifications not approved by QC.
- Incomplete testing. (↑) .
- Lack of or insufficient validation of test methods. (↑)
- No SOP for conditions of transportation and storage.
- Use of unique identifier principles not meeting the acceptable options.

9.3. Minor Deficiencies

- Inadequate method transfer for a validated analytical method.
- Method validation report does not specify the revision of the analytical method used at the time of validation.

10. Records

10.1. Critical Deficiencies

- Evidence of falsification or misrepresentation of records.

10.2. Major Deficiencies

- Lack of or incomplete Master Production Documents.
- Unavailability of documentation from suppliers in a timely manner.
- Lack of or incomplete records of sale.
- Lack of or incomplete records of complaints received respecting the quality of a drug.

10.3. Minor Deficiencies

- Incomplete plans and specifications for the manufacturing buildings
- Insufficient retention time for evidence and records to be maintained.
- No organization charts.
- Incomplete records for the sanitation program.

11. Samples

11.1. Major Deficiencies

- Retained samples not kept for finished products.
- Failure to submit retained samples when alternative sample retention granted.

11.2. Minor Deficiencies

- Samples of raw material not available.
- Insufficient quantity for finished products or active pharmaceutical ingredients (API).
- Improper storage conditions.

12. Stability

12.1. Critical Deficiencies

- No data available to establish the shelf-life of products.
- Evidence of falsification or misrepresentation of stability data/forgery of COA.

12.2. Major Deficiencies

- Insufficient number of lots to establish shelf-life.
- Insufficient data to establish shelf-life.
- No action taken when data shows that the products do not meet their specifications prior to the expiry date. (↑)
- Lack of or inadequate continuing stability program.
- No stability studies pertaining to changes in manufacturing (formulation)/packaging material.
- Testing methods not validated.
- No consideration given to enroll worst case scenarios (for example, reworked/reprocessed lots).
- Inappropriate storage conditions for stability samples.

12.3. Minor Deficiencies

- Stability testing not performed at the time required by the written program.
- Review of stability data not performed in a timely manner.

13. Sterile Products

13.1. Critical Deficiencies

- Lack of or inadequate validation of critical sterilization cycles.
- Water for Injection (WFI) systems not validated with evidence of problems such as microbial/endotoxin counts not within specifications.
- No media fills performed to demonstrate the validity of aseptic filling operations.
- No environmental controls/No monitoring for viable microorganisms during filling for aseptically filled products.
- Aseptic filling operations continued following unsatisfactory media fill results obtained.
- Batches failing initial sterility test released for sale on the basis of a second test without proper investigation.
- Inadequate environmental conditions for aseptic operations.
- Absence of leak test for ampules

13.2. Major Deficiencies

- Aqueous-based products not subject to terminal steam sterilization without proper justification or approval through the marketing authorization.
- Inadequate room classification for processing/filling operations. (↑)

- Aseptic manufacturing suites under negative pressure compared to clean areas (C-D). Clean areas (C-D) under negative pressure to unclassified areas. (↑)
- Insufficient number of samples taken for environmental monitoring/ inadequate sampling methods. (↑)
- Insufficient environmental controls/Insufficient monitoring for viable microorganisms during filling for aseptically filled products. (↑)
- Premises and equipment not designed or maintained to minimize contamination/generation of particles. (↑)
- Inadequate maintenance of purified water and WFI systems.
- Inadequate re-validation of purified water and WFI systems after maintenance, upgrading, out-of-specs trends.
- Inadequate training of personnel.
- Personnel involved in aseptic filling prior to completing successful media fill.
- Inadequate gowning practices for clean and aseptic areas.
- Inadequate sanitation/disinfection program.
- Inadequate practices/precautions to minimize contamination or prevent mix-ups.
- Non-validated time lapse between cleaning, sterilization, and use of components, containers and equipment.
- No consideration given to bioburden prior to sterilization.
- Non-validated time lapse between start of manufacturing and sterilization or filtration.
- Inadequate program for media fill.
- Capability of media to grow a wide spectrum of microorganisms not demonstrated.
- Misinterpretation of results for media fill.
- Samples for sterility testing insufficient in number or not representative of the entire production run.
- Each sterilizer load not considered as a separate lot for sterility testing.
- Purified water is not used as the feed water for the WFI system and the clean steam generator.
- Inadequate testing program for WFI. (↑)
- The WFI used for the final rinsing of containers and components used for parenteral drugs is not tested for endotoxins when those containers and components are not depyrogenated subsequently.

- Inappropriate environment/controls for crimping following aseptic filling.
- Inadequate inspection for particles and defects. (↑)
- Gases used to purge solutions or blanket products not passed through a sterilizing filter. (↑)
- Inadequate integrity testing of sterilizing or vent filters. (↑)

13.3. Minor Deficiencies

- Steam used for sterilization not monitored to assure suitable quality.
- Inadequate control on the maximum number of personnel present in clean and aseptic areas.

Appendix II. Guidance on How to Score the Intrinsic Risk Factors

1. Complexity

This concerns the complexity of the site, its processes and its products.

Note: The Site Master File (if available) and the last GMP inspection report can be useful sources of information on which to assign the Complexity score.

There are three possible scores here, 1, 2 and 3.

Sites with a low risk factor score in this area are known to have a low level of complexity in the design of the site, in its products and processes. When scoring this Risk Factor, it is useful to consider the following:

- General but useful indicators of **site complexity** are:
  - The size of the site – large sites are rated more complex than smaller sites
  - The number of different manufacturing or distribution processes that are in use at the site – larger numbers generally give rise to more complexity
  - The level of dedication of equipment and facilities (e.g. Air Handling Units) that is in place at the site – sites with a low level of dedication are considered more complex than other sites
  - The number of staff at the site – larger numbers generally give rise to more complexity
  - The number of commercial markets/countries supplied by the site - larger numbers generally give rise to more complexity
  - The number of customers supplied by the site - larger numbers generally give rise to more complexity
  - If the site is a contract manufacturer or contract laboratory, the site can be regarded as being relatively complex

- General but useful indicators of **process complexity** are:
  - Sterile and aseptic manufacturing processes – these are always considered highly complex processes.
  - Parametric release activities – these are usually considered highly complex processes.
  - The number of critical steps that must be controlled within a process – generally, processes with a high number of critical steps can be considered to be more complex processes.
  - The type of products manufactured – some product types such as low-concentration/high potency dosage forms and sustained released dosage forms can be more complex to manufacture than other types of products (such as immediate release tablets) and the complexity of their manufacturing process should be rated more highly here.
  - The number of unit operations in a non-sterile manufacturing process - larger numbers generally give rise to more complexity.
  - Repackaging activities - repackaging an already packaged batch can be considered a moderately to highly complex process.
  - The extent of reprocessing or reworking taking place at the site: these activities can add complexity to the process
  - Biological processes
  - The extent of subcontracting in use by the site - a significant use of contract manufacturers, off-site distribution sites or contract laboratories generally gives rise to complexity.

- In case of importers, the complexity of importation, batch release and product distribution processes – sometimes the arrangements in place for importation can be quite complex.

➢ General but useful indicators of **product complexity** are:

- The number of components that make up any one product pack - larger numbers of components in a pack generally give rise to more product complexity. For example, a pack of an injectable product may have 4 components within it (a lyophilised vial, a diluent vial, a transfer needle and a technical leaflet, whereas a pack of a tablet product may have just a blister strip and a patient information leaflet within it.)
- Products requiring special storage and distribution: (e.g. cold chain products and short-shelf-life products such as radiopharmaceuticals can be complex to manage.)

Tip: *When considering product complexity, it is useful to imagine that you are holding a pack of the product in your hand and are asked: "What aspects of this product render is a complex product?"*

Scoring Guideline:

Assign a score of 1 to sites with a low overall level of Complexity.
Assign a score of 2 to sites with a moderate overall level of Complexity.
Assign a score of 3 to sites with a high overall level of Complexity.

Note: When assigning the overall complexity rating, the rating (1, 2 or 3) which most reflects the various individual complexity ratings that were assigned to site, process and product complexity should be chosen. This is similar to taking an average of all of the individual complexity ratings that were assigned.

In cases where there is insufficient information or knowledge about the complexity associated with the site, its processes and products, a medium score of 2 should be assigned.

2. Criticality

This concerns how critical the availability of the products manufactured by the site are from a supply perspective, or how critical the services provided by the site are. An example of a critical service provided by a site may be an analytical testing service performed for several other companies.

(Note: The Site Master File (if available) and the last GMP inspection report can be useful sources of information on which to assign the Criticality score)

There are three possible scores here, 1, 2 and 3.

Scoring Guideline:

➢ Assign a high score (of 3) to sites that are known to manufacture essential products or that are known to be sites that provide an essential service that is not readily available elsewhere:

- These may be sites that are the major or sole supplier of an essential product (such as an important vaccine, a critical blood product, etc.). Note: it is recognised that being the major or the sole supplier of an essential product does not present any risk to product quality; rather, it presents a risk to product availability.
- The test methods (and related equipment) used by these sites cannot easily or readily be performed or used by other laboratories.

- These may be sites that provide a contract manufacturing or testing service to a number of other manufacturers and a disruption in such services would have a significant impact on product availability.

➢ Assign a low score (of 1) to sites that are known to manufacture only non-essential products or that are known to be sites that do not provide an essential service:

- These may be sites that are not the sole supplier of any important products (such as an important vaccine, a critical blood product, etc.).
- The test methods (and related equipment) used by these sites are not such that they cannot be readily performed or used by other laboratories.
- These are not sites that provide a contract manufacturing or testing service to many other manufacturers, where a disruption in such services would have a significant impact on product availability.

➢ Assign a medium score (of 2) to sites that are in between the above types of sites

Note: *In cases where there is insufficient information or knowledge about the criticality associated with the site, a medium score of 2 should be assigned.*

Risks of specific products:

Products	Risk score		
	High	Medium	Low
Injection, infusion products Injection vaccines and biologicals	H		
Small-volume injection products Oral vaccines and biologicals	H		
Eye-drop, sterile ointment	H		
Solid oral medicine of hormones, betalactam antibiotics		M	
Solid or liquid oral medicine		M	
Topical, herbal medicine			L