ANNEX A
List of GMP Inspection Deficiencies

(The list is non-exhaustive and other observations may be added, removed, or re-classified as appropriate)

A. Quality Management System

1. *Critical*
   - Products are released and distributed with failed results for assay, micro
   - Products are approved for release with incomplete testing (assay, micro)
   - Production and release for distribution of unregistered products
   - Falsification or misrepresentation of manufacturing and QC records
2. *Major*
   - Absence or unimplemented procedure/s for change control system, batch release, PQR, CAPA, Deviation, OOS, Risk Management, document control, suppliers' qualification, and other significant SOPs.
   - Inconsistent implementation of significant SOPs
   - Deviation from the approved manufacturing authorization (LTO) or marketing authorization (CPR)
   - Products are released by an unauthorized person
   - Products are distributed without undergoing batch release but had passed laboratory testing
   - Products released with insufficient investigation/ deviations
   - Irreconcilable and untraceable records and documentation
   - Absence or incomplete Process Validation of released and distributed products
   - Absence of material/FG status tags
   - Distribution to unlicensed establishments/individuals
3. *Others*
   - Incomplete/inaccurate annual product review
   - Quality documents not updated
   - Change control, PQR, CAPA, Deviation, Risk Management or suppliers' qualification are implemented but no established program/procedure
   - No designated alternate authorized person

B. Personnel

1. *Critical*
   - No qualification (background, relevant experience and training) of QC & Production Managers
   - The QA Head acts as QC Head and Production Head, thus, independency of each division was not being practiced
   - Insufficient qualification and training of the person who is responsible to release for sale.
2. *Major*
   - Key personnel do not have sufficient practical experience in their responsibility area

- Insufficient qualification (lack of relevant experience and training) of QC & Production Managers
- 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
- Health requirements and or hygiene program not properly implemented or followed
- Responsibility of the person to release products for sale was not in the job description

3. *Others*
   - Inadequate training records
   - Insufficient written training program
   - Organizational Chart not updated
   - Health records not filed
   - Incomplete written sanitation procedure
   - Incomplete implementation of the written sanitation program
   - Incomplete records for the sanitation program

C. Premise

1. *Critical*
   - Generalized malfunctioning of the ventilation system(s) with evidence of widespread cross-contamination
   - Inadequate segregation (without study/evidence that cross-contamination does not occur) of manufacturing or testing areas from other manufacturing areas for high risk products
   - Manufacturing areas with evidence of contamination (mildew, mold, powder from previous productions, etc)
   - Evidence of widespread accumulation of residues / extraneous matter indicative of inadequate cleaning
   - Evidence of gross infestation
   - Evidence of contamination
2. *Major*
   - Malfunctioning of the ventilation system that could result in possible cross-contamination
   - Inadequate segregation (with risk of cross-contamination) of manufacturing or testing areas from other manufacturing areas for high risk products (↑)
   - Maintenance / periodic verification such as air filter replacement, monitoring of pressure differentials not performed. (↑)
   - Temperature and humidity not controlled and monitored when necessary (e.g. storage not in accordance with labelling requirements)
   - Heating, ventilation, air conditioning (HVAC) and purified water (PW) system not qualified. (↑)
   - Damage (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
   - Surfaces finish (floors, walls, and ceilings) that do not permit effective cleaning

- 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 (↑)
- Manufacturing or QC area serves as a passageway by personnel
- Toilet is directly located within the manufacturing area
- Illogical flow of personnel, materials, products, waste or process
- No separate area / insufficient precautions to prevent contamination or cross-contamination during RM sampling
- Non-production activities performed in production areas
- Doors giving direct access to exterior from manufacturing and packaging areas used by personnel
- No alert and action limits for microbial / environmental monitoring areas where products are manufactured
- Pressure differential gauges are not installed in critical production areas
- Monitoring of pressure differential for critical areas was not conducted/recorded during operation
- No Batch clearance/line clearance
- Corrugated boxes are brought inside clean rooms including hallways
- Doors are not well-fitted inside the production area
- Exposed light bulb inside clean rooms
- Unlabeled products are stored in close proximity without physical segregation
- Evidence of residues indicative of inadequate cleaning
- Compressed air not tested in compliance with acceptable standard

3. *Others*
   - Un-screened/un-trapped floor drains
   - Outlets for liquids (PW) and gases not identified
   - Damages to surfaces not directly adjacent or above exposed to products
   - Inadequate rest, change, wash-up and toilet facilities

D. Equipment

1. *Critical*
   - Equipment used for complex manufacturing operations of critical products not qualified and with evidence of malfunctioning or lack of appropriate monitoring
   - Foreign materials such as grease, oil, rust and particles inside the production equipment which have contact with the product
2. *Major*
   - Equipment used during critical steps of manufacture, packaging/labelling, and testing, including computerized system is not qualified (↑)
   - Equipment do not operate within its specifications. (↑)
   - Stored equipment not protected from contamination
   - Inappropriate equipment for production: surface porous and non-cleanable / material to shed 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 (↑)
- PW 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
- Outdated equipment calibration
- No equipment usage logbooks
- No preventative maintenance program for major equipment / no records maintained
- Cleaning Validation was not conducted (↑)
- Use of temporary means or devices for repair with contact with the product.
- Unsecured or Inadequate labeling / storage of rejected materials and products that could generate mix-ups
- Non-conduct of qualification
- Use of inappropriate materials (e.g. PVC) and valves (e.g. ball valves) for the pharmacopeial water distribution system
- Presence of dead legs
- Records of sanitization of pharmacopeial water distribution system was not available
- Non-conduct of water system sanitization
- Poor preventive maintenance program for the pharmacopeial water system
- Pharmacopeial water not tested according to phamacopoeial requirements
- Unreadable labels on the water distribution pipelines (e.g. faucet for the hot & cold water & tap water)
- Preventive maintenance for HVAC lacks critical testing (e.g. integrity testing, pressure differential)
- Uncorrected failed PM results for HVAC system or Water System
- Common HVAC for Production and Micro Laboratory
- Inconsistent conduct of Preventive Maintenance of facilities

3. *Others*
   - 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 without contact with the product
   - Defective or unused equipment not removed or appropriately labelled
   - Minor equipment used for non-critical products not qualified
   - Presence of leaks in water system
   - No records of testing/maintenance for utilities (ie integrity tesing-HEPA)

E. Documentation

1. *Critical*
   - Evidence of falsification or misrepresentation of records
   - Evidence of falsification or misrepresentation of manufacturing and packaging orders

2. *Major*
    - Lack of or incomplete Master Production Documents
    - Unavailability of documentation from suppliers in a timely manner
    - Lack, inconsistent or incomplete distribution records
    - Insufficient retention time for evidence and records to be maintained
    - Poor or untraceable records
    - Inconsistencies in records
    - Products released for distribution without or with incomplete of Process Validation
    - Unsigned process documents (e.g. BMR, Line Clearance)
    - Incomplete data in process documents
    - Use of scrap paper, correction fluids and/or pencil for recording raw data
    - Unsigned corrections and erasures
    - Absence of pertinent records and documents
    - Poor record control (e.g. no document number, no pagination, poor records retrieval)
    - Absence of back-up for electronic records
3. *Others*
    - No organization charts
    - Incomplete plans and specifications for the manufacturing buildings
    - Forms, records not cross referenced in the procedure

F. Production

1. *Critical*
    - Production commenced with no written Master Formula
    - Master formula or manufacturing batch record showing gross deviations or significant calculation errors
    - Evidence of falsification or misrepresentation of manufacturing & packaging orders
2. *Major*
    - Master Formula prepared/verified by unqualified personnel
    - Lack of or incomplete validation studies/reports for critical process (lack of evaluation/approval) (↑)
    - Inadequate validation of change over 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, not documented or not adequately implemented
    - 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 and packaging materials not held in quarantine until released by QC

- Labels not properly controlled
- Starting and in-process materials are used without prior authorization by QC
- Inadequate/inaccurate labeling of bulk/in-process/finished drugs, raw & packaging materials
- Raw material dispensing not done by qualified persons, according to SOP.
- Changes in batch size not prepared/verified by qualified personnel.
- Inaccurate/incomplete information in master /manufacturing /packaging batch documents
- No written procedure for packaging operations.
- Non-standard occurrences during packaging not investigated by qualified personnel
- Master production records not in compliance with marketing authorization
- Inadequate control of coded and non-coded printed packaging material (including storage, dispensing, printing, disposal)
- Inadequate handling of outdated/obsolete packaging material
- Holding time study was not conducted

3. *Others*
   - Incomplete SOPs for handling materials and products
   - Access to production areas not restricted to authorized personnel
   - Inadequate checks for incoming materials
   - Written procedures incomplete for packaging operations
   - No agreed tolerance for yield/ reconciliation

G. Quality Control

1. *Critical*
   - No person in charge of QC
   - QC department not a distinct and independent unit.
2. *Major*
   - Inadequate facilities, personnel and testing equipment
   - No authority to enter production areas
   - No SOPs approved and available for sampling, inspection and testing of materials
   - Out of specification test results, deviations and borderline conformances not properly investigated and documented, according to SOP
   - Reprocessing / reworking / re-sale of returned products done without prior aseessment/approval of QC.
   - Inadequate evidence to demonstrate that storage and transportation conditions are appropriate
3. *Others*
   - Investigations of non-conformances not completed in a timely manner

H. Raw Material Testing

1. *Critical*
   - Evidence of falsification or misrepresentation of analytical results
   - No evidence of COA available from supplier and no testing done by the manufacturer
   - Use of raw material (API) after expiration date

- Testing for DEG and other impurities for glycerin, propylene glycol, and solutions of sorbitol used for oral preparations was not conducted by both the company and the supplier

2. *Major*
   - 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/inadequate specifications of RM, PM & FG
   - Specifications of RM, PM and FG not approved by QC
   - Test methods not validated
   - Use of raw material (API) after the retest without proper testing.
   - Multiple lots comprising one receipt were not considered as separate for sampling, testing and release
   - No SOP for conditions for transportation and storage
   - Testing for identity not done on each containers for starting materials or after manipulation or repackaging by third party
   - No SOPs approved and available for sampling, inspection and testing of materials
   - RM / PM used in production without prior approval of QC
   - Significant SOPs were not implemented
   - Deviations and action limits are not properly investigated and documented according to the SOP
   - No action taken for OOS raw materials
3. *Others*
   - Lots identified for confirmatory testing used in production without QC approval
   - Incomplete validation/verication of test methods

I. Packaging Material Testing

1. *Major*
   - Reduce testing program in place without adequate certification of the vendors/ suppliers
   - Lack of or insufficient testing of PM
   - Inadequate specification
   - Specs not approved by QC
   - RM / PM used in production without prior approval of QC
2. *Others*
   - Inadequate procedures of storage
   - Inappropriate environment and or precautions to prevent contamination of packaging material during sampling

J. Finished Goods Testing

1. *Critical*
   - Finished product not tested for compliance with applicable specifications prior to release

- Evidence of falsification or misrepresentation of testing & stability results/ forgery of COA

2. *Major*
   - Incomplete/inadequate specifications
   - FG specs not approved by QC
   - Incomplete testing
   - Lack of or insufficient validation of test methods
   - No SOP for conditions for transportation and storage
   - Products not in finished form tested and considered as result for FG testing
   - Conduct of trial runs
3. *Others*
   - Inadequate method transfers for a validated analytical method
   - Method validation report does not specify the revision of the analytical method used at the time of validation

K. Samples

1. *Major*
   - Retained samples not kept for finished products
   - Failure to submit retained samples when alternative sample retention granted
2. *Others*
   - Samples of raw material not available
   - Insufficient quantity for finished products or API
   - Improper storage conditions

L. Stability Testing

1. *Critical*
   - No data available to establish shelf-life of products
   - Evidence of falsification or misrepresentation of stability data / forgery of COA
2. *Major*
   - Insufficient data to establish shelf-life
   - Insufficient number of lots 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 materials / reworked or reprocessed lots
   - Testing methods not validated
   - In-process materials were used for time zero for stability
   - Inappropriate storage conditions for stability samples
3. *Others*
   - Stability testing not performed at the time required by the written program
   - Review of stability data not performed in a timely manner

M. Reference Standard

1. *Critical*
   - Use of expired secondary standard for testing
2. *Major*
   - No appropriate monitoring device provided
   - There were noted expired reference standards and/or volumetric reagents kept in the cabinet
   - Logbook and inventory for primary and secondary reference standards were not provided
   - Secondary reference standards were not standardized against the primary reference standard
   - There was no potency result indicated on the label of secondary reference standards
   - Volumetric reagents were not standardized
3. *Others*
   - Incomplete information on labels
   - Primary reference standards were not checked for its validity and expiry in the USP catalog
   - There were no provided inventory records for reference standards
   - No records/evidence of destruction of expired standards

N. Computer System Validation

1. *Major*
   - Audit trail function was not enabled
   - There was no designated system administrator
   - Back-up for data was not provided
   - Process controls to ensure data integrity in the computerized system were not fully in place
   - Time and date of the computer used can be changed
   - Non conduct of CSV
   - Common username and password
   - Access levels of analysts were not defined

O. Microbiological Laboratory

1. *Major*
   - Growth Promotion Test was not performed/conducted on the prepared media
   - Non-use of positive control
   - Reference Microorganisms were not available in the microbiology laboratory
   - Inappropriate storage of media
   - Incomplete testing
   - Insufficient incubation period
   - Alert and action limit was not established

P. Contract Manufacturing Agreement

1. *Major*
   - Agreement not in accordance with PIC/S requirements

- There is no assurance that the results and conclusions generated by third party are accurate, premise and reliable

2. *Others*
   - Expired agreement
   - Absence of agreement

Q. Complaints and Recalls

1. *Major*
   - Ineffective / inadequate recall procedure
   - Improper quarantine and disposal practices that would allow recalled / rejected units to be returned for sale
   - No system, or Lack of or inadequate system for complaint handling and returned goods
   - Lack of or incomplete records of complaints received relative to the quality of product complaint
2. *Others*
   - Incomplete recall procedure
   - No agreement between the wholesaler, the importer and distributor relative to a recall process
   - No SOP on Handling Product Complaints
   - Effectivity of recall procedure was not validated

R. Self-Inspection

1. *Major*
   - No or inadequate self-inspection program. Program does not address all applicable sections of GMPs. Records incomplete or not maintained
2. *Others*
   - Internal audit was not regularly conducted
   - Unsigned inspection reports

ANNEX B

ACRONYMS

API - Active Pharmaceutical Ingredient

BMR – Batch Manufacturing Record

CAPA – Corrective Action-Preventive Action

COA – Certificate of Analysis

CPR – Certificate of Product Registration

CSV – Computer System Validation

DEG –Diethylene glycol

FG – Finished Goods

GMP – Good Manufacturing Practice

HEPA – High Efficiency Particulate Air

HVAC – Heating, Ventilation and Air-conditioning

LTO – License to Operate

OOS – Out-of-Specifications

PIC/S – Pharmaceutical Inspection Cooperation Scheme

PM – Packaging Material

PQR – Product Quality Review

PVC – Polyvinyl chloride

PW – Pharmaceutical Water

QA – Quality Assurance

QC – Quality Control

RM – Raw Material

SOP – Standard Operating Procedure