HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

DEC 2021

PREPARATION OF A QUALITY SYSTEM DOSSIER

HSA
Health Sciences Authority

1. INTRODUCTION

Quality System Dossier (QSD) is a collation and collection of documents which contains information associated with the quality system of the pharmaceutical manufacturing operations carried out at the named overseas manufacturing site and any closely integrated operations at adjacent and nearby buildings.

QSD should be submitted by the manufacturer of therapeutic products and Cell Therapy and Gene Therapy (CTGTP) products to supplement the information provided in the application form requesting an overseas GMP audit. The information contained in the QSD should be comprehensive enough to provide an overview of the manufacturing site and its quality system so as to facilitate our assessment of the manufacturer's audit readiness prior to the arrangement of an on-site audit.

2. DEFINITIONS/ABBREVIATIONS

AHU	-	Air Handling Unit
BMR	-	Batch Manufacturing/Processing Record
BPR	-	Batch Packaging Record
CTGTP	-	Cell Therapy and Gene Therapy Products
GLC	-	Gel Layer Chromatography
GMP	-	Good Manufacturing Practice
HEPA	-	High Efficiency Particulate Air
HPLC	-	High Performance Liquid Chromatography
HSA	-	Health Sciences Authority, Singapore
HVAC	-	Heating, Ventilation and Air Conditioning
IQ	-	Installation Qualification
LAF	-	Laminar Air Flow
LAL	-	Limulus Amoebocyte Lysate
LVP	-	Large Volume Parenteral
OOS	-	Out of Specification
OQ	-	Operation Qualification
PIC/S	-	Pharmaceutical Inspection Co-operation Scheme
PLC	-	Programmable Logic Control
PQ	-	Performance Qualification
QA	-	Quality Assurance
QC	-	Quality Control
QSD	-	Quality System Dossier
QMS	-	Quality Management System (also known as PQS, Pharmaceutical Quality System)
SOP	-	Standard Operating Procedure
SVP	-	Small Volume Parenteral
VMP	-	Validation Master Plan

3. PURPOSE

The aim of this Guidance Notes is to guide the overseas manufacturer of therapeutic products and CTGTP in the preparation of a Quality System Dossier (QSD).

4. SCOPE

This Guidance Notes is applicable to overseas manufacturers of therapeutic products and CTGTP located outside of Singapore, whose products are registered or intended for registration in Singapore, but has not been previously audited and certified by a PIC/S member authority.

5. QUALITY SYSTEM DOSSIER (QSD)

5.1 GENERAL REQUIREMENTS FOR THE ORGANISATION OF QSD

5.1.1 The required documents stipulated in sections 6.1 to 6.7 should be submitted in the English language on individually numbered A4-size papers/sheets.

5.1.2 The sheets should be bound, preferably ring-bound, to ensure the integrity of the document.

5.1.3 Soft copy of the required documents may also be submitted in using specified electronic storage media, e.g. CD-ROM.

5.1.4 Documents scanned should maintain its legibility.

5.1.5 Floor plans, drawings, layout, flow-chart or schematics should be presented in a reasonably clear and legible format.

5.2 SECTIONS 6 TO 16 BELOW ELABORATE ON THE REQUIREMENT OF INFORMATION, DOCUMENTS/EVIDENCE THAT IS REQUIRED TO BE INCLUDED IN A QSD.

HSA reserves the right to request for other supporting documents, although HSA recognizes that the extent of quality system documentation may differ from one manufacturer to another, due to the types and number of dosage forms of therapeutic products as well as non- therapeutic products manufactured, size of the manufacturing facility, the competency of personnel, and the complexity and interactions of different manufacturing and/or packaging processes.

6. GENERAL INFORMATION ON COMPANY, MANUFACTURING SITE AND QUALITY MANAGEMENT SYSTEM (QMS), ALSO KNOWN AS PHARMACEUTICAL QUALITY SYSTEM

6.1 COMPANY / ORGANIZATION INFORMATION

Information on the company / organization and its related sites, particularly, any information relevant to understand the manufacturing operations. The following information should be included:

6.1.1 Company name and official address of the manufacturing site.

6.1.2 Name and designation of person(s) to be contacted.

6.1.3 Telephone and Fax Numbers.

6.1.4 24-hour contact Telephone Number in the case of product defects or recalls.

6.1.5 Identification number of the site as e.g. GPS details, or any other geographic location system, D-U-N-S (Data Universal Numbering System) Number (a unique identification number provided by Dun & Bradstreet) of the manufacturing site.

6.1.6 Corresponding / Mailing address (if different from site address).

6.1.7 Additional warehouse / store address(es) (if different from the site address) including any off-site warehouse(s) used to store starting materials (raw materials) or packaging materials or intermediate bulk products or finished products.

6.1.8 Brief history of the company since its formation.

6.1.9 Information on whether any other company houses in the same manufacturing premises (i.e. different company name(s) but having the same address or more than one companies sharing the same manufacturing premises).

6.2 General Site Information

6.2.1 Description of the site [including the location, size (land area and floor area), type, age of buildings and other manufacturing activities on the site].

6.2.2 Description of the immediate environment (describe the surrounding area / industry).

6.2.3 Aerial View / Overview of Manufacturing Site showing the Main Buildings with its surrounding area. Please enclose a location map and photograph(s).

6.2.4 Indicate whether the site has been audited by your own national authority, or any foreign competent Authority (if the latter, state the name of authority and indicate clearly whether the audit is carried out for the same or different therapeutic products and CTGTP in the application).

6.2.5 Quote the relevant document (valid manufacturer's licence or valid manufacturing authorisation) issued by the Competent Authority. State the period of validity of licence document (if the validity of the document is given in the country concerned). Any conditions and/or restrictions should also be stated. If the Competent Authority does not issue manufacturing authorizations, this should also be stated.

6.2.6 Information on whether human and veterinary products are both prepared on the site.

6.2.7 Please specify whether the product is manufactured or part of manufacturing or packaging operation under a contractual agreement with another company. Either as a contract giver and/or contract acceptor.

6.2.8 Description of manufacturing activities on the site for the different categories of products (For example, API, traditional medicines (herbal medicinal products), cosmetic products, health supplements, investigational medicinal products etc.).

6.2.9 Information on whether any other manufacturing activities are carried out on the site. This covers both pharmaceutical and non-pharmaceutical activities.

6.2.10 List of GMP audits of the site within the last 5 years; including dates and name/country of the Competent Authority having performed the inspection.

6.2.11 Type of actual therapeutic products manufactured (as described at Appendix I) on the site. Please provide the following lists:

(a) List of dosage forms manufactured on the site,
(b) List of therapeutic products manufactured on the site, and
(c) List of non- therapeutic products manufactured on the site.

Please include both the product names and brand names and consider one brand as one product.

Please state the design production capacity and annual production volume of each product.

6.2.12 The total build-up area, floor area of each floor, floor area of each segregated areas or rooms including production areas, warehouse, quality control laboratories, weighing (dispensing) room, sampling room, changing room and other functional areas.

6.2.13 Information on how the toxic, hazardous substances and highly sensitizing substance are handled (e.g. in dedicated facilities or on a campaign basis).

6.3 Quality Management System (QMS)

(also known as Pharmaceutical Quality System, PQS)

6.3.1 Brief description of the Quality Management System (QMS) of the manufacturer i.e. Brief description of the quality management systems run by the company and reference to the standards used.

6.3.1.1 Responsibilities related to the maintaining of quality system including senior management.

6.3.1.2 Please provide a list of other licences, permits and/or certificates issued to the company by any agency, authority, accreditation body or conformity assessment body within the country or overseas. i.e. Information of activities for which the site is accredited and/or certified, including dates and contents/ scope of accreditations, names of accrediting bodies.

6.4 Release procedure of finished products

6.4.1 Detailed description of qualification requirements (education and work experience) of the Authorised Person(s) / Qualified Person(s) responsible for batch certification and releasing procedures.

6.4.2 General description of batch certification and releasing procedure.

6.4.3 Role of Authorised Person / Qualified Person in quarantine and release of finished products and in assessment of compliance with the Marketing Authorisation.

6.4.4 The arrangements between Authorised Persons / Qualified Persons when several Authorised Persons / Qualified Persons are involved.

6.4.5 Statement on whether the control strategy employs Process Analytical Technology (PAT) and/or Real Time Release or Parametric Release.

6.5 Management of suppliers and contractors

6.5.1 A brief summary of the establishment/knowledge of supply chain and the external audit program.

6.5.2 Brief description of the qualification system of contractors, manufacturers of active pharmaceutical ingredients (API) and other critical materials suppliers.

6.5.3 Measures taken to ensure that products manufactured are compliant with TSE (Transmitting animal spongiform encephalopathy) guidelines.

6.5.4 Measures adopted where counterfeit/falsified products, bulk products (i.e. unpacked tablets), active pharmaceutical ingredients or excipients are suspected or identified.

6.5.5 Written procedures:

6.5.5.1 Procurement of starting materials including raw materials, packaging materials, intermediate and bulk products.

6.5.5.2 Qualification and approval of suppliers.

6.5.5.3 Receipt, quarantine, sampling, QC testing, storage and release of starting materials including raw materials, packaging materials, intermediate, bulk products as well as finished products.

6.6 Quality Risk Management (QRM)

6.6.1 Brief description of QRM methodologies used by the manufacturer.

6.6.2 Scope and focus of QRM including brief description of any activities which are performed at corporate level, and those which are performed locally. Any application of the QRM system to assess continuity of supply should be mentioned.

6.6.3 Written procedures: SOP on QRM or any other document(s) in connection to QRM.

6.6.4 Records/Reports: An example on application of QRM (if any).

6.7 Product Quality Reviews (PQR)

6.7.1 Brief description of methodologies used
Please enclose the following written procedures, supporting documents, records and photographs:

6.7.2 Written procedures: SOP on PQR or a policy document related to PQR

6.7.3 Records/Reports: Records of PQR (one typical product per dosage form)

7. PERSONNEL

7.1 Please provide an updated detailed organisation chart down to production operators and laboratory technicians level incorporating names and designation of staff in the following departments:

Warehouse, Production, QA, QC, Technical/Engineering Support, and Sales/Distribution departments.

7.2 Please state the total number of head count (overall) employed and working at the manufacturing site. Number of employees (i.e. head counts including all part-time / full-time, temporary / contract service workers engaged) engaged in each of the following functioning departments: quality assurance, production, quality control, storage & distribution, technical and engineering support services.

7.3 Operating hours and number of shifts.

7.4 Job description, qualification and experience of key personnel including Head of Production and Head of QA/QC.

7.5 Personnel flow diagram.

7.6 Personnel hygiene requirements, including gowning.

7.7 Pre-employment and periodic medical / health examinations policies.

7.8 GMP training programme for production, QC/QA, warehousing personnel.

Please enclose the following written procedures, supporting documents, records and photographs:

7.9 Written procedures:

7.9.1 Gowning procedure (for Clean Rooms and Environmentally Controlled Areas)

7.9.2 Personal Hygiene

7.9.3 Pre- and Post- Employment Health Examination

7.9.4 GMP Training Programme for manufacturing and QC/QA laboratory personnel

7.10 Supporting documents

7.10.1 Training schedule

7.10.2 Health examination schedule

7.10.3 Samples of a job specification

7.11 Records:

7.11.1 A sample of Health Examination Record for a production personnel.

7.11.2 Samples of GMP Training Record of an operator, a production supervisor, head of production and head of QA/QC.

7.12 Photographs: Changing room.

8. PREMISES, UTILITIES AND EQUIPMENT

8.1 Premises

8.1.1 Short description of plant; size of the site and list of buildings. If the production for different markets, i.e. for local, EU, USA etc takes place in different buildings on the site, the buildings should be listed with destined markets identified (if this has not been described above)

8.1.2 Floor layout plans and description of manufacturing areas with indication of scale and annotate each plan with name.

Please enclose the following floor layout plans:

8.1.2.1 A floor layout plan highlighting all production areas, warehouses, laboratories, weighing (dispensing) room, sampling room and other functional areas including the floor area of each segregated areas (rooms).

8.1.2.2 A floor layout plan indicating locations of all the production equipment, and utilities including location of water treatment plant, air receiver/dryer, chiller, AHU or HVAC system.

8.1.2.3 A floor layout plan indicating clean / non-cleaned areas or controlled / non-controlled areas.

8.1.2.4 A floor plan of the warehouse indicating the following areas:

i. storage areas for different categories of materials including raw materials, packaging materials such as containers, printed packaging materials such as labels, product inserts and unit boxes, intermediate bulk and finished products
ii. receiving bay
iii. dispatch bay
iv. quarantine areas
v. rejected area
vi. recalled or returned materials or product areas
vii. storage area for storing highly active or sensitizing materials or products
viii. storage area for storing highly toxic, hazard and/or sensitizing materials or products
ix. storage area for storing highly flammable materials or products

x. Cold chain (2°C to 8°C) storage room and/or room dedicated for materials or products required specific storage condition (If any)

8.1.3 Storage condition including temperature and relative humidity and their acceptance criteria.

8.1.4 Nature of construction and finishes of the walls, floor, ceiling, door and window. This should include all processing areas, packaging areas and critical storage areas.

8.1.5 Maintenance of premise and fittings (description of planned preventive maintenance programmes; breakdown and repair activities and its documentation).

8.2 Utilities

8.2.1 Heating, Ventilation & Air Conditioning (HVAC) System

8.2.1.1 Description of HVAC system.

8.2.1.1.1 State the airflow design criteria, indicate the specification of the air supply, temperature, humidity, pressure differentials and air change rate and single pass or recirculation (%).

8.2.1.1.2 State the Filter design and efficiency (e.g. Bag 99% efficiency, HEPA 99.997% efficiency) and the number of filters. Details of any alarms on the HVAC system should be given.

8.2.1.1.3 More details should be given for critical areas with potential risks of airborne contamination. This will include sterile product areas or areas for processing powders, granulation and tableting.

8.2.1.1.4 Description of the mechanism of air monitoring system and its documentation.

8.2.1.1.5 Please enclose the following documents:

8.2.1.1.5.1 Number of AHU(s), supplying to which area(s) / room(s) and their capacities.

8.2.1.1.5.2 A floor layout plan indicating location and number of HEPA filters.

8.2.1.1.5.3 An airflow diagram / drawings of the manufacturing facility. Indicating the air supply from AHU(s) and

return air, pressure differentials between adjoining areas.

8.2.1.1.5.4 A floor layout plan indicating, if applicable, air classification of the rooms/areas (according to air classification stipulated in Annex 1 of the PIC/S Guide To GMP For Medicinal Products) used for manufacture and packaging operations including weighing (dispensing) room, changing room(s) and sampling room.

8.2.2 Water Treatment / Purification System

8.2.2.1 Description of the water quality, water purification systems, including cleaning, maintenance, sanitation, monitoring of quality of water and its documentation.

8.2.2.2 Please enclose schematic drawings of the water purification system including the location of the valves, direction of flow, sampling points and the following information:

- Material of construction;
- Types of valve used;
- Type of Pipe works;
- Filters;
- UV Sterilizers;
- Pressure Gauges

8.2.3 Gases (E.g. Nitrogen)

8.2.3.1 Compressed air
8.2.3.2 Other gases used in production / QC Lab

8.2.4 **Steam** (if any)

Please enclose the following written procedures, supporting documents, records and photographs:

8.2.5 Written procedures

8.2.5.1 Cleaning of premises (warehouse, production area / packaging areas).

8.2.5.2 Maintenance & cleaning of HVAC system & other critical pharmaceutical utilities.

8.2.5.3 Maintenance, cleaning and sanitation of water purification system.

8.2.5.4 Microbiological (environmental) monitoring programme for manufacturing and primary packaging areas.

8.2.5.5 Monitoring/testing of water quality including the type and frequency of test.

8.2.5.6 Pest Control programme.

8.2.5.7 Temperature and relative humidity monitoring (for warehouse / storage area).

8.2.5.8 Storage of highly active materials, flammables, corrosives and other hazardous substances.

8.2.6 Supporting documents

8.2.6.1 Material flow diagram (From incoming starting and packaging materials receiving, quarantine & storage, issued to production, finished products storage and release).

8.2.6.2 Pest control programme schedule.

8.2.6.3 Microbiological (Environmental) monitoring programme schedule.

8.2.6.4 Location of baits (mapping) for pest control programme.

8.2.6.5 Storage condition (temperature) mapping of warehouse (storage areas).

8.2.6.6 Number and location of temperature measuring/monitoring devices or temperature recording sensors in warehouse, production areas and/or primary assembly area(s).

8.2.7 Records:

8.2.7.1 A sample of cleaning record for premise (e.g. warehouse and production area).

8.2.7.2 A sample of pest control record.

8.2.7.3 A sample of test report of water & trend analysis data incorporating at least 20 data.

8.2.7.4 A sample of temperature and relative humidity monitoring record of warehouse.

8.2.7.5 A sample of microbiological (environmental) monitoring record of manufacturing area.

8.2.8 Photographs:

8.2.8.1 Receiving area for incoming materials.

8.2.8.2 Storage area for raw materials, packaging materials, printed materials such as labels, finished products.

8.2.8.3 Quarantine area for starting materials and finished product.

8.2.8.4 Storage area for flammable, narcotics or high-risk materials.

8.2.8.5 Reject area

8.2.8.6 Returned goods area.

8.3 Equipment

8.3.1 Description of major production and quality control laboratories equipment. If the equipment has additional devices, these should be recorded e.g. automatic weighing machines with a printer; a labeler incorporating a bar code reader for the label; a lot number and expiry date over printer; a freeze drier equipped with a steam sterilization facility.

8.3.2 In the quality control laboratory, general descriptions such as pH meters, chromatographic equipment GLC, HPLC with computer systems, particle size analysers is required.

8.3.3 In microbiology laboratory, descriptions such as incubators (temperature ranges), facilities for LAL testing, membrane filtration, sterility testing etc.

8.3.4 Information on the use of computers, microprocessors, PLC and etc. in the premise.

Describe the following:

8.3.5 Maintenance programmes (including planned preventive maintenance and break down maintenance) for equipment and its documentation.

8.3.6 Calibration programme for measuring equipment and recording instrument.

8.3.7 Means/Methods for tracking scheduling of calibration.

Please enclose the following written procedures, records and supporting documents:

8.3.8 Written procedures

8.3.8.1 Maintenance of manufacturing equipment.

8.3.8.2 Cleaning of manufacturing equipment.

8.3.8.3 Cleaning of production vessel and connecting pipes.

8.3.8.4 Calibration of weighing balances and other measuring/ monitoring equipment.

8.3.9 Records:

8.3.9.1 A sample of calibration record of a weighing balance.

8.3.9.2 A sample of cleaning record of a production equipment.

8.3.10 Supporting documents

8.3.10.1 A list of manufacturing equipment with number of unit, age and output capacity.

8.3.10.2 A list of packaging equipment with number of unit and age.

8.3.10.3 A list of quality control instrument with number of unit and age.

8.3.10.4 A list of weighing balances with range and accuracy.

8.3.10.5 A list of computer software systems.

8.3.10.6 A sample of weighing balances and other measuring / monitoring equipment calibration schedule.

8.3.10.7 A sample of production / quality control instrument maintenance schedule.

9. DOCUMENTATION

9.1 Description of documentation control system. Good documentation constitutes an essential part of the quality assurance system and is key to operating in compliance with GMP requirements. The various types and/or variety forms of documents and media used including paper-based, electronic or photographic media or hybrid (i.e. combination of both electronic and manual /paper based) should be fully defined. Appropriate good documentation practice should be applied with respect to the type of document. Type of documentation used refers to: instructions (directions, or requirements such as Specifications, Manufacturing Formulae, Processing, Packaging and Testing

Instructions, Procedures and Protocols, Technical Agreements) and records/reports such as Records, Certificates of Analysis and Reports.

The main objective of the system of documentation utilised must be to establish, control, monitor and record all activities which directly or indirectly impact on all aspects of the quality of therapeutic products. The Quality Management System should include sufficient instructional detail to facilitate a common understanding of the requirements, in addition to providing for sufficient recording of the various processes and evaluation of any observations, so that ongoing application of the requirements may be demonstrated.

Relationships and control measures for master documents, official copies, data handling and records need to be stated for both hybrid and homogenous systems. Appropriate controls for electronic documents such as templates, forms, and master documents should be implemented. Appropriate controls should be in place to ensure the integrity of the record throughout the clearly defined retention period.

It should be clearly defined which record is related to each manufacturing activity and where this record is located. Secure controls must be in place to ensure the integrity of the record throughout the retention period and validated where appropriate.

When documents and records are stored or archived off-site (including pharmacovigilance data, when applicable): List of types of documents/records; Name and address of storage site and an estimate of time required retrieving documents from the off-site archive.

Please enclose the following written procedures, records and supporting documents:

9.2 Written procedures

9.2.1 Standard operating procedure of documentation system.

9.2.2 Document control procedure (including the design, preparation, approval, revision distribution and retention of documents).

9.2.3 Document change control procedure.

9.2.4 Control, storage and the period of retention for documents (including master documents and batch related documents).

9.2.5 Arrangement for electronic or microfilmed records.

9.2.6 Handling of process (manufacturing) deviations.

9.2.7 Handling of OOS and failure investigation.

9.3 Supporting documents

9.3.1 Document flow (From design, generation including prepare, review and distribute, till stored or archived).

9.3.2 SOP index

9.3.3 Manufacturing deviation index (last 24 months).

9.3.4 OOS and failure investigation index (last 24 months).

9.3.5 Change control index (last 24 months).

9.3.6 Sample of specifications for:

9.3.6.1 A raw material (active ingredient)

9.3.6.2 A raw material (excipient)

9.3.6.3 A packaging material [e.g. container (vial) and etc.]

9.3.6.4 A printed packaging material (e.g. label, product insert and etc.)

9.3.6.5 A finished product

9.4 Records:

9.4.1 A sample of approved supplier list, specifying supplier name, manufacturing site address, material (including raw materials and packaging materials) and date of approval.

9.4.2 A sample of manufacturing deviation record

9.4.3 A sample of OOS and failure investigation record

9.4.4 A sample of change control record

9.4.5 Inventory record of a typical starting material

10. PRODUCTION

10.1 Describe the production operations using flow charts specifying critical production and in-process control parameters.

10.2 Describe the operations being carried out at the site with the existing facilities and specify the types of pharmaceutical products, also explain the role of the Authorized Person(s).

10.3 If penicillin / cephaloporin, cytotoxic or radioactive substances are handled, give details of the handling of these products.

10.4 Describe how products are identified during production and how in-process control and storage are organized.

10.5 When only packaging is undertaken, give a description particular on the operations related to labeling, filling etc. Describe the nature of containers used e.g. sachets, tamper proof glass containers.

10.6 Arrangements for reprocessing or rework.

10.7 Arrangements for the handling of rejected materials and products.

10.8 Describe the company's general policy for validation / qualification programme for clean room, laminar flow hood, critical production equipment and critical quality control instrument, and their revalidation. The validation programme should include the arrangements of cleaning, process, analytical method, water system, container closure, computerized systems validation and etc.

Please enclose the following written procedures, records, supporting documents and photographs:

10.9 Written procedures

10.9.1 Control and issuance of approved raw materials (from warehouse to production).

10.9.2 Control and issuance of approved packaging materials (from warehouse to production) and coded/printed labels for packaging operation.

10.9.3 Control and handling of raw material dispensing (weighing).

10.9.4 Control measures to prevent contamination, cross contamination, adulteration and mix-up.

10.9.5 Preparation, approval and handling of master formula, batch manufacturing (processing) records (BMR) and batch packaging records (BPR).

10.9.6 Batch numbering system.

10.9.7 Batch re-processing/Re-working.

10.10 Supporting documents

10.10.1 A list of raw materials used.

10.10.2 A list of packaging materials used (including containers, caps, stoppers, labels, product inserts, unit boxes and outer cartons and etc.).

10.10.3 Material flow (i.e. movement of materials from receiving of incoming starting materials at the receiving bay, release from store to production, movement of intermediate bulk and finished products from production to warehouse, storage and dispatch for distribution) (Same as 8.2.6.1, no need to provide if it has already been provided in 8.2.6.1).

10.10.4 Waste flow (movement and disposal of waste materials).

10.10.5 Master production log (last 24 months).

10.10.6 Validation Master Plan (VMP).

10.10.7 Qualification protocol of clean room and/or LAF (if any).

10.10.8 Aseptic validation protocol (if any).

10.10.9 IQ, OQ and PQ protocol of a typical production equipment

10.10.10 Installation, Operational and Performance Qualification protocol of a typical quality control instrument.

10.10.11 Cleaning Validation Protocol of a typical production equipment.

10.10.12 Computer validation protocol of a typical software used in production and/or QC laboratory or warehouse.

10.10.13 Validation protocol of a container closure system (if any).

10.10.14 Validation protocol of water purification system.

10.10.15 Process Validation Protocol (A sample per dosage form).

10.10.16 Analytical Method Validation Protocol (A sample) (if any).

10.10.17 Clean Room qualification / re-qualification Protocol (if any).

10.10.18 Autoclave qualification / re-qualification Protocol (if any).

10.10.19 Lyophilizer qualification / re-qualification Protocol (if any).

10.11 Records:

10.11.1 A complete set of batch manufacturing records.

10.11.2 A complete set of batch packaging records.

10.11.3 A sample of maintenance / servicing / repair record of a production equipment (i.e. equipment log).

10.12 Photographs:

10.12.1 Sampling area.

10.12.2 Changing area.

10.12.3 Weighing area

10.13.4 Production area (including all critical processing areas).

10.12.5 Filling area/primary packaging area/secondary packaging area.

11. QUALITY CONTROL (QC)

11.1 Description of the QC system and of the activities of the QC department, including elements of QC system e.g. test methods, analytical testing, packaging component testing, biological and microbiological testing.

Please enclose the following written procedures, supporting document, records and photographs:

11.2 Written procedures

11.2.1 Quarantine and release of raw materials, packaging materials, intermediate bulk and finished products.

11.2.2 Preparation, approval and issuance of status labels including ‘quarantine’, ‘sampled’, ‘passed’ or ‘released’, ‘rejected’, ‘cleaned’, ‘not in use’ and etc.

11.2.3 Control of re-test of raw materials.

11.2.4 Handling and disposal of rejected incoming / production raw materials, packaging materials, intermediate bulk product and finished products.

11.2.5 Procurement, storage, handling and use of reference standards and laboratory reagents.

11.2.6 Storage and handling of retention samples including raw materials, packaging materials and finished products.

11.2.7 Sampling method and sampling plan of raw materials, packaging materials, intermediate bulk and finished products.

11.2.8 On-going stability testing programme.

11.2.9 Supporting documents

11.2.9.1 A list of reagents

11.2.9.2 A list of reference standards

11.2.9.3 Product/equipment status labels:

11.2.9.3.1 A sample of “quarantine” label
11.2.9.3.2 A sample of “sampled” label
11.2.9.3.3 A sample of “passed/approved/released” label
11.2.9.3.4 A sample of “rejected” label
11.2.9.3.5 A sample of “cleaned” label

11.2.9.4 Stability study schedule

11.2.10 Records:

11.2.10.1 A sample of QC testing/analytical record.
11.2.10.2 A sample of incoming raw material check list.

11.2.11 Photographs:

11.2.11.1 A photograph showing different areas of QC laboratories.

12. CONTRACT MANUFACTURE AND ANALYSIS (i.e. Outsourced Activities)

12.1 Description of the methods in which the GMP compliance of a contract manufacture / assembly or contract analysis (contract testing laboratory), contract acceptor is assessed.

12.2 Details of the technical contract including the scope and responsibility between the contract giver and acceptor and the way in which the GMP compliance, or compliance with other appropriate standards, is assessed to ensure product compliance with the Marketing Authorisation / Product Licence.

12.3 The selected standards should be assessed for the suitability of its application. The type of products manufactured by the contract acceptor should also be specified.

12.4 Use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis.

12.5 List of contract manufacturers and laboratories including the addresses and contact information and flow charts of supply-chains for outsourced

manufacturing and Quality Control activities; e.g. sterilization of primary packaging material for aseptic processes, testing of starting raw-materials etc.

12.6 Brief overview of the responsibility sharing between the contract giver and acceptor with respect to compliance with the Marketing Authorization.

Please enclose the following written procedure and supporting documents:

12.7 Written procedures:

12.7.1 Contract manufacturing and analysis (Use of external, scientific, analytical or other technical assistance in relation to manufacture and analysis).

12.7.2 Qualification / approval of a contract acceptor.

12.8 Supporting documents

12.8.1 A list of contract manufacturers / assemblers / contract testing laboratories engaged with scopes of the contract(s) i.e. For each external service provider, please provide the Name, Address, Telephone no., Fax no and briefly outline the service provided. For each external contract manufacturer, please also provide short description of its quality system, quality policy and audit programme (self-inspection or audit by external organization undertaken).

12.8.2 A sample of an accreditation certificate or supplier audit report of a contract acceptor.

12.8.3 A sample of the contract agreement.

13. DISTRIBUTION, COMPLAINTS AND PRODUCT RECALLS

13.1 Description on arrangements and recording system for distribution.

Please enclose the following written procedures and records.

13.2 Written procedures

13.2.1 Handling of product complaints

13.2.2 Handling of returned goods

13.2.3 Handling of product recalls

13.2.4 Distribution/Export of finished products including security and safety of shipment, ex-factory to end user (both local market and overseas market).

13.2.5 Mode of delivery, shipment and storage condition.

13.3 Records

13.3.1 A sample of sales (distribution) record of a typical finished product.

13.3.2 A sample of deviation and/or out of specification (OOS) record.

13.3.3 A sample of product complaint record

13.3.4 A sample of returned goods record

13.3.5 A sample of product recall record

13.3.6 A sample of disposal record

14. SELF INSPECTION

14.1 Description on the self-inspection system including the composition of self-inspection team, frequency and scope in conducting self-inspection.

Please enclose the following written procedures, supporting documents and records.

14.2 Written procedures

14.2.1 Self-inspection programme

14.3 Supporting documents

14.3.1 Self-inspection schedule

14.4 Records

14.4.1 A record format of self-inspection (a blank format only)

15. MANUFACTURE OF STERILE THERAPEUTIC PRODUCTS AND CTGTP

Additional information should be provided to illustrate control strategies used to minimise risks of microbiological contamination, and of particulate and pyrogen contamination. Quality Assurance is particularly important, and this type of manufacture must strictly follow carefully

established and validated methods of preparation and procedure. Sole reliance for sterility or other quality aspects must not be placed on any terminal process or finished product test.

15.1 Clean rooms and clean air devices classification

15.2 Routine monitoring of clean rooms and clean air devices during operation and the monitoring locations based on a formal risk analysis study and the results obtained during the classification of rooms and/or clean air devices.

15.3 Isolator or Blow/fill/seal units or Restricted access barriers system used (if any)

15.4 Description and control of terminal sterilisation cycle

15.5 Description and control of aseptic preparations (if any)

15.6 Medial fill or process simulation test (if abovementioned 15.5 is applicable)

15.7 Personnel training and gowning

15.8 Sanitation programme for clean areas

15.9 Description of location and type of filter used e.g. filter through a sterile filter of nominal pore size of 0.22 micron (or less), (if the process is a filtration method for sterilisation in the final container).

15.10 Holding time of bulk products

15.11 Bioburden monitoring programme

15.12 Description of vial capping process – as an aseptic process using sterilised caps or as a clean process outside the aseptic core. (If applicable).

15.13 Describe whether filled containers of parenteral products inspected individually for extraneous contamination or other defects.

15.14 Any other relevant information

16. Appendix TO THIS GUIDANCE NOTE

Appendix 1: TYPE OF PRODUCTS MANUFACTURED

17. REFERENCE DOCUMENTS

- GUIDE-MQA-20: Guidance Notes on GMP Conformity Assessment of an Overseas Manufacturer

END OF DOCUMENT

APPENDIX 1: TYPE OF PRODUCTS MANUFACTURED

A. Sterile products

A.1 Liquid dosage forms (large volume solutions, including LVP and rinsing solutions)

A.1.1 Aseptically prepared
A.1.2 Terminally sterilized

A.2 Liquid dosage forms (small volume solutions, including SVP and eye drops)

A.2.1 Aseptically prepared
A.2.2 Terminally sterilized

A.3 Semi-solid dosage forms

A.4 Solid dosage forms

A.4.1 Solid fill
A.4.2 Freeze-dried

B. Non-sterile products

B.1 Liquid dosage forms

B.2 Semi-solid dosage forms

B.3 Solid dosage forms

B.3.1 Unit dose form (eg tablets, capsules, suppositories, pessaries)
B.3.2 Multi dose form (eg powders, granules)

C. Biological products

C.1 Vaccines

C.2 Sera

C.3 Blood products

C.4 Others (describe) (Example: monoclonal antibodies, mAb)

D. Specifically toxic and hazardous substances

D.1 Penicillins

D.2 Cephalosporins

D.3 Hormones

D.4 Cytostatics

D.5 Others (describe)

E. Packaging only

E.1 Liquid dosage forms

E.2 Semi-solid dosage forms

E.3 Solid dosage forms

F. Contract manufacturing (kind of products)

Company reported upon is:

F.1 Acceptor

F.2 Giver

G. Drugs for clinical trials

H. Others
Including products not subjected to registration/licensing by the Competent Authorities (e.g. veterinary products, cosmetics, health/dietary supplements, etc).

HEALTH SCIENCES AUTHORITY

Health Products Regulation Group
Blood Services Group
Applied Sciences Group

www.hsa.gov.sg

Contact Information:

For further information, please contact:

Overseas Audit Unit
Audit Branch
Audit & Licensing Division
Health Products Regulation Group
Health Sciences Authority

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For feedback, please go to:
https://www.hsa.gov.sg/contact-us

HSA
Health Sciences Authority