**PHARMACY MANUFACTURING UNIT VALIDATION MASTER PLAN (VPM).**

**General Notes**

**Aims of Qualification and Validation**
Any significant changes to, premises, equipment or processes, which may affect the quality of the final product, directly or indirectly, should be qualified and validated.

The key elements of a qualification and validation program should be clearly defined and documented in a Validation Master Plan. The process should establish and provide documentary evidence that: premises, supporting utilities, equipment and processes have been designed in accordance with the requirements of GMP. This normally constitutes the Design Qualification or ‘DQ’ and includes confirmation that the premises, supporting utilities and equipment have been built and installed in compliance with their design specifications (this constitutes Installation Qualification or ‘IQ’) and that they operate in accordance with their design specifications (this constitutes Operational Qualification or OQ).

A specific process will consistently produce a product meeting its predetermined specifications and quality attributes (this constitutes Process Validation or PV. The term Performance Qualification or PQ may be used also).

**Purpose**
The VMP is intended to be a ‘live’ document that supports the design and construction of any production facility, its subsequent operation, maintenance and changes to the facility for its life span. The VMP should present an overview of the entire validation operation, its organisational structure, its content and planning. The core of the VMP is the list/inventory of items to be validated and the planning schedule.

The VMP should provide your organisation with the basis for validation and quality system activities required for cGMP compliance. This will enable any sterile or non-sterile medicinal product that is produced, processed, stored or distributed, by the manufacturing unit, to be validated under the control of an appropriate quality system.

The VMP should provide a cross-reference to other documents, such as SOP’s, validation protocols, validation reports, and design plans. A rationale for the inclusion or exclusion of validations, from the approach adopted should be included.

**VMP Document**
The VMP template is attached for completion as appropriate the document should be cross-referenced with design specifications, design plans and other relevant documentation. Appendices should contain all the relevant documentation referenced or stated in the VMP.
### Hospital Logo

**Hospital Name**

### VALIDATION MASTER PLAN

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APPENDICES

ANNEX 1 CLEANING VALIDATION MASTER PLAN
ANNEX 2 ANALYTICAL METHOD VALIDATION MASTER PLAN
1.0 LIST OF ABBREVIATIONS

AHU  Air Handling Unit  
BP   British Pharmacopoeia  
BS   British Standard  
CFR  Code of Federal Regulations  
cGMP Current Good Manufacturing Practice  
CIP  Clean In Place  
CIVA Centralised Intravenous Additives  
Comm. Commissioning  
CPU  Central Processing Unit  
DC   Direct Current  
DCC  Design Change Control  
DQ   Design Qualification  
DR   Design Review  
EDR  Enhanced Design Review  
EP   European Pharmacopoeia  
EU   European Union  
FAT  Factory Acceptance Test  
FDA  Food and Drug Administration  
FDS  Functional; Design Statement  
GA   General Arrangement  
GAMP Good Automated Manufacturing Practice  
GCP  Good Cleaning Practice  
GEP  Good Engineering Practice  
GLP  Good Laboratory Practice  
HACCP Hazard And Critical Control Point  
HS&E Health Safety And Environment  
HTM  Health Technical Memorandum  
HVAC Heating, Ventilation and Air Conditioning  
IA   Impact Assessment  
IQ   Installation Qualification  
ISO  International Standards Organisation  
ISPE International Society of Pharmaceutical Engineers  
LVF  Large Volume Fluids  
MCA Medicines Control Agency  

NHS  National Health Service  
O & M Operation and Maintenance  
OQ   Operational Qualification  
P&ID Piping and Instrumentation Diagram  
PCA  Patient Controlled Analgesia  
PFD  Process Flow Diagram  
PID  Proportional Integral and Derivative  
plc  Programmable logic controller  
PQ   Performance Qualification  
PV   Process Validation  
QA   Quality Assurance  
QC   Quality Control  
QMS  Quality Management System  
RA   Risk Assessment  
Rev. Revision  
SAT  Site Acceptance Test  
SIP  Sterilise/Sanitise In Place  
SOP  Standard Operating Procedure  
SVA  Small Volume Ampoules  
TPN  Total Parenteral Nutrition  
URS  User Requirement Statement  
VCC  Validation Change Control  
VMP  Validation Master Plan  
VSC  Validation Steering Committee  
VTF  Validation Technical File  
WFI  Water For Injection  

## 2.0 DOCUMENT REVISION HISTORY

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3.0 VALIDATION STEERING COMMITTEE

3.1 Membership of Validation Steering Committee

This Validation Master Plan has been compiled by a Validation Steering Committee (VSC) who will also manage its execution. The members of the VSC are listed below and by their signatures acknowledge their responsibilities to ensure that all validation activities are carried out as described in this Validation Master Plan (VMP) and its annexes.

It is recommended that the members of the VSC should include, but is not limited to the following areas of responsibility and expertise:

- Pharmacy Production Team Leader
- Pharmacy Senior Production Technician
- Trust Senior Engineer
- Pharmacy Quality Control Officer
- cGMP Consultant
- Validation Specialist

Additional members co-opted onto the VSC shall also sign below before undertaking any activities associated with this VMP.

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3.2 Responsibilities

With respect to the activities outlined in this VMP and its Annexes, including cleaning, manufacturing practices and analytical methods, the responsibilities of key VSC members are outlined below. Their responsibilities with respect to the overall operation are included where this may have an impact upon validation activities.

Approval of new or amended documentation should be accomplished with the minimum of delay, ideally within 2 working days, to facilitate the efficient operation of the facility.

3.2.1 Pharmacy Production Team Leader

The pharmacy production team leader is responsible for:
- Ensuring that appropriately qualified personnel are appointed.
- Ensuring production processes are in accordance with cGMP requirements.
- Facilitating validation activities.
- Training and management of personnel.
- Approval of user functional aspects of validation protocols.
- Approval of working production documents for overall content.

3.2.2 Pharmacy Senior Production Technician

The pharmacy operations representative is responsible for:
- Completion of batch records.
- Operating procedures.
- Training of personnel.

3.2.3 Trust Senior Engineer

- Ensuring that systems/equipment are appropriate for their purpose.
- Maintenance of systems/equipment.
- Maintenance procedures.
- Calibration policy and procedures.
- Revision of O & M manuals for equipment/systems.
- Approval of validation protocols for content relating to engineering content.

3.2.4 Pharmacy Quality Control Officer

- Ensuring appropriate Quality Control (QC) procedures are in place.
- Provision and maintenance of auditable document storage systems.
- Approval of validation protocols for quality aspects.
- Approval of all working QC and production documents.

3.2.5 Validation Engineer

- Identify and plan appropriate validation activities.
- Provide validation technical support and training.
- Ensure appropriate validation procedures are in place.
4.0 INTRODUCTION

4.1 Purposes of the VMP
The purposes of the VMP are to:

- Identify the members of the Validation Steering Committee.
- Identify Regulatory requirements.
- Identify and describe the facility, systems and equipment to be validated.
- Identify and describe products and processes to be validated.
- Identify the validation activities that will be undertaken.
- Identify the methods by which these activities will be undertaken.
- Identify the documentation requirements to support the above activities.

4.2 Overview of Project
This VMP relates to a new facility, to be known as the _______________________. In line with current GMP standards the new pharmacy will provide aseptically dispensed intravenous products and manufactured sterile and non-sterile products to ______________ Hospital patients.

4.3 Validation Philosophy
The VMP is intended to be a 'live' document that initially supports the design and construction of the facility and subsequently the operation, maintenance and change of the facility for its entire life. It will provide the basis for validation and quality system activities required for cGMP compliance. This will enable the validated production, processing, storage and distribution of a range of sterile and non-sterile medicinal products under the control of an appropriate quality system.

The VMP may be revised as appropriate to incorporate changes and/or additions to the facility and/or products.

Using current pharmaceutical industry guidelines, the validation steps and activities will be designed to address all critical product attributes and process steps whilst minimising unnecessary work. This will be achieved by employing techniques such as Impact Assessment and risk assessment, in order to focus validation activity onto those systems critical to product quality.

The validation process will follow these basic group headings:

- Quality Plan
- Design Reviews
- FAT/Commissioning
- Installation Qualification
- SAT/Operational/Performance Qualification
- Process Validation
- Cleaning Validation
- Analytical Method Validation

The validation activities will be incorporated into project design, construction programs and production schedules. The objective of this is to integrate similar activities, e.g. SAT with OQ, and thus reduce duplication of tests and checks to a minimum. Appendix D illustrates the relationship between project and validation stages.
5.0 REGULATORY STANDARDS AND GUIDELINES

The following is a list of standards and guidelines deemed to be appropriate for this project. This list is not exhaustive and further regulations and guidelines will be used where appropriate. The list will be reviewed and revised as necessary whenever a new revision of the VMP is issued.


4. PIC/S Guide to Good Manufacturing Practice for Medicinal Products, 15th Jan 02


7. AS/NZS 14644.2:2002 : Cleanrooms and associated controlled environments – Part 2: Specifications for testing and monitoring to prove continued compliance with ISO 14644.1


13. ISPE Baseline Guide Volume 3, Sterile Manufacturing Facilities

14. ISPE Baseline Guide Volume 4, Water and Steam Systems

15. ISPE Baseline Guide Volume 5, Commissioning and Qualification

16. BS 5295 Environmental Cleanliness in Enclosed Spaces

17. European Pharmacopeia

18. British Pharmacopeia


20. Good Automated Manufacturing Practice.

21. Good Laboratory Practice.
6.0 DESCRIPTION OF PRODUCTS AND PROCESSES

6.1 Introduction
The pharmacy produces and issues a large number of products to in-patients, out-patients and other group hospitals/clinics.
This VMP applies to all production processes in the pharmacy.

6.2 Product Groups
Products with similar characteristics and/or manufacturing processes have been placed into seven groups. A general process flow diagram (PFD) has been generated for each group (found in Annex A). Where significant differences occur within a group, these are identified in sub-sections within the PFD for the group.
The seven product groups are:
- Cytotoxics (dispensed, unlicensed manufacture)
- TPN (dispensed, unlicensed)
- CIVA (dispensed, unlicensed)
- Terminally sterilised products (licensed manufacture)
- Non-Sterile Products (unlicensed manufacture)
- Repacking (dispensed)
- Other (unlicensed manufacture)

Please refer to schedule of products, product group descriptions and associated process flow charts located in appendix A.
Whenever new products are to be processed by the pharmacy, then each will be assessed for inclusion into an existing group. Where this is inappropriate, e.g. a significant new process is introduced, then a new group will be added, with supporting PFD and process descriptions.

6.3 Processes
For each product group, the manufacturing processes and the specific equipment utilised will be described in detail. Specifically, these will include all processes critical to product quality. Processes that involve ‘standard’ operation of equipment, e.g. weighing of product materials, may be simply listed and referenced to appropriate equipment SOPs.

6.4 Product Storage and Distribution
Generally for compounded products, product storage time is relatively short, as most products are manufactured to meet prescription orders and in some cases have a short shelf life. When batch production is employed, batch size is managed to meet anticipated short-term demand and hence avoid the need for long-term storage. Batch products with a prolonged expiry, raw materials and repacked products will be stored in a quarantine area before release for use, which will be a designated site in the cold room or storage area that is inaccessible.

Products will be stored within a dedicated storage area. Where necessary, products will be stored in refrigerators or a cold room.
There is a paper system for Inventory control.
Products are delivered by a variety of routes dependant upon product and intended use. Generally they will be delivered in small lots, carried by hand, trolley, etc. to the end user. Returnable cold boxes will be used when a cold chain delivery is required.
7.0 PROJECT DESCRIPTION

Note: All drawings referenced in this section are located in Appendix C.

7.1 Site Location
The new pharmacy is located on the site of the __________________. Its position with respect to other facilities on the same site is shown on layout drawing no. _____________.

7.2 Facility Design and Layout.
The facility consists of a ___________________. Please refer to drawing no. _____________.

The facility contains the production area. This is divided into 2 discrete clean room production suites termed zones 1, 2 and 3 according to the HVAC zoning.

- Zone 1 _____________.

Please refer to drawing no. _____________.

There is a walk-on ceiling level above the clean rooms within which piped services, HVAC ducting and electrical services are located.

The plant room within which equipment such as Air Handling Units (AHUs), Water for Injections (WFI) generation, storage and circulation equipment, clean steam generator and control panels is situated in _____________. Please refer to drawing no. _____________.

7.3 Production Suites

7.3.1 Zone 1, Non-Sterile Manufacturing

All rooms classified GMP grade D. Please refer to schedule of room data sheets located in Appendix C. Served by HVAC zone 1. Please refer to drawing no. _____________.

Processes undertaken in this area include:
- Non-sterile manufacture of creams, ointments, suppositories, oral suspensions, oral liquids and capsules.
- Extemporaneous preparation of creams, ointments and oral suspensions

Please refer to process flow diagrams located in Appendix A.

The zone is divided into 3 discrete areas and accessed by dedicated personnel change airlock number _____________.

- Hazardous non-sterile product manufacture, including Dithranol/Coal Tar, flammables and cytotoxics.
- Prep 1, 2 and 3. Non-sterile product manufacture (non-hazardous).
- Equipment and bottle wash area. Pass boxes provide access for materials to local storage areas within preparation areas.

Please refer to typical personnel, material, product and waste flow diagrams located in Appendix A.

7.3.2 Zone 2, Preparation of Cytotoxic and Parental Nutrition Products

Rooms classified EU grades B, C and D served by HVAC zone 2. Additionally there is a small equipment store. Please refer to schedule of room data sheets located in Appendix C, and to drawing no. _____________.

Processes undertaken in this area include:
- Aseptic dispensing of parenteral nutrition products and aseptic dispensing of other parenteral items.
- Aseptic dispensing of cytotoxic chemotherapy
- Aseptic manufacture of cytotoxic chemotherapy

Please refer to process flow diagrams located in Appendix A.

The zone is divided into 4 discrete areas:

- Grade D cytotoxic compounding area. Accessed by dedicated personnel change airlock number ______. Compounding of Cytotoxic products in grade A isolator.
- Grade D cytotoxic materials disinfection and final check area, access……etc..
- Grade D check and disinfection area, serving grade B compounding room. Personnel access via …… Materials access via corridor and trolley transfer airlock.
- Grade B area for compounding of Total Parenteral Nutrition (TPN) products in grade A laminar flow cabinet. Personnel access via cascading grade B change. Materials access via hatch.

Please refer to typical personnel, material, product and waste flow diagrams located in Appendix A.
8.0  EQUIPMENT AND SERVICES TO BE VALIDATED

8.1  Impact Assessment
In order to simplify the validation and minimise unnecessary qualification activities, an Impact Assessment (IA) exercise will be carried out, following an approved procedure. This will encompass all equipment and services installed within the facility. It will define the validation requirements for equipment and services that are found to be critical to product quality and risk to patient.

It is expected that equipment and services that are deemed non-critical will be installed, operated and maintained subject to Good Engineering Practice (GEP).

Data from the IA should be used to provide information for use in the qualification protocols, such as critical instrument listings and acceptance criteria.

IA will be considered for any change to established equipment and/or services in order to help define validation or re-validation requirements.

Validation activities appropriate to the equipment and services may be considered at IA.

The location of the IA results will be recorded and the data entered in a validation matrix attached to this VMP in appendix B.

8.2  Risk Assessment
Appropriate Risk Assessments (RAs) will be carried out to identify and challenge all installation, operation, cleaning and maintenance processes.

Processes that are identified as critical to product quality and risk to patient will be subject to Process Validation.

Some processes may be identified as hazardous with respect to Health, Safety and Environmental (HS&E) considerations. In such cases, appropriate HS&E activities will be carried out. Generally this activity is outside the scope of this document. It is recognised, however, that some hazardous processes will involve validatable processes, items of validatable equipment and/or services.

Where it is logical to do so, the qualification protocols may include HS&E tests. A simple example of this is the qualification of operation of emergency stops.

Data from the RA should be used to provide information for use in the operation and maintenance SOPs. These must include sufficient information to ensure that HS&E requirements are satisfied.

Data from the RA should be used to provide information for use in the qualification protocols, such as critical instrument operational limits and acceptance criteria.

RA will be completed for any change to established processes.

8.3  Validation Matrix
A comprehensive list of equipment, services and processes will be generated from IA and RA results. Appropriate validation activities from, but not limited to, the listings in section 9.1 will be entered against all validatable entries to create a matrix of validation activities. This matrix will be attached to this VMP in appendix B and updated as necessary through the life-cycle of the facility.
9.0 VALIDATION ACTIVITIES

Validation activities will be carried out in accordance with this Validation Master Plan and the completed documentation will be indexed in the Validation History Files.

9.1 Validation Activities

All prospective and concurrent validation activities will be performed according to previously agreed protocols. Any retrospective validation activities will comprise of a review and collation of existing data to demonstrate conformance to predetermined acceptance criteria. Details of the specific tests and methodology that will be used to determine validation compliance will be found in the validation protocols for each item.

In most cases, the protocols for major new equipment will be produced and executed by the equipment suppliers, with review of the documentation and witnessing of the practical activities being performed by RVI or their agents. RVI will, however, produce ‘header’ protocols that will verify that protocols produced and executed by others conform to the requirements defined in this VMP.

9.1.1 User Requirement Specification (URS)

An approved statement of the users' requirements in terms of function, throughput, operatability and applicable local standards must be obtained for each new item.

9.1.2 Technical Specification

An approved document translating the URS into a specification detailing how the requirements are to be achieved. Together with the URS, this will provide the objectives and acceptance criteria for the subsequent validation protocols.

9.1.3 Impact Assessment

The criticality of systems, equipment and components with respect to product quality will be assessed using appropriate tools such as Impact Assessment (as described in the ISPE Baseline® Guide, Commissioning and Qualification). Appropriately qualified personnel will conduct the assessments. The results will be formally recorded and approved and will be used to provide information for the generation of appropriate validation protocols and qualification tests within the validation protocols. Subsequent activities e.g. cGMP Review will focus on the systems and equipment defined as critical and having a direct impact on product quality.

9.1.4 Design Review/Qualification

A review of the developed designs will be performed for critical or bespoke items to ensure:

- Compliance with the User’s Requirement
- Compliance of design details with cGMP requirements
- Practical validation tests will be possible

The findings of the Design Reviews will be recorded in written reports, which will be included in the validation report, together with a record of any follow-up actions.

9.1.5 Factory Acceptance Tests

Some items of new or refurbished equipment may be subject to acceptance tests at the supplier’s
premises. The data gained may be referenced in subsequent validation documentation provided that:

- These tests are pre-approved by the VSC
- Witnessed by the VSC or their agents
- Critical instruments are calibrated to appropriate standards
- The equipment is not dismantled for transport to site
- The manufacturer can certify that no subsequent changes have been made to the construction or control systems. Summary reports of the Factory Acceptance Tests and any follow up actions will be included in the validation documentation.

### 9.1.6 Commissioning

Relevant items will be fully commissioned prior to Installation Qualification. This is to ensure as a minimum:

- That all items of equipment, utilities and processes are safe to validate.
- All mechanical assembly and pre-qualification checks have been completed.
- Items of equipment, utilities and processes have been operated and shown to be fully functional.
- Documentation is completed and provided.

Commissioning records may form part of the qualification data to support the validation study provided that they are traceable and have been audited by appropriate members of the VSC and prepared by appropriately qualified personnel nominated by the VSC.

### 9.1.7 Installation Qualification

Installation Qualification (IQ) of items will be carried out to ensure that as a minimum:

- The installation has been carried out according to specification and design intentions.
- A record of the principal features of the item and its components as installed is available.
- There is sufficient information available to enable the item to be operated and maintained safely, effectively and consistently.

Each protocol will contain a rationale stating the validation requirements for the item of equipment/system and will challenge items such as: materials of construction, lubrication, spare parts, change parts, calibration, operations and maintenance manuals, training and standard operating procedures.

If specified, the item or system shall be subjected to a Factory Acceptance Test (FAT) at the vendors works before executing of IQ.

### 9.1.8 Calibration

All instruments deemed critical for product quality or safety must be calibrated according to approved Standard Operating Procedures before commencing Operational Qualification of that item. Generally this will be verified at IQ stage.
9.1.9 Operational Qualification

Operational Qualification (OQ) test methodology will encompass testing, as close as possible to production conditions, and where practical, “worst case” conditions.

The Operational Qualification will be carried out to determine as a minimum that:

- All critical instruments have been calibrated to allow subsequent validation work to be performed safely and with repeatable results.
- The facility environments can be controlled in accordance with their specification.
- Each item of process equipment operates as specified throughout its anticipated operating range.
- Each utility operates reliably as specified.

Each protocol will contain a rationale stating the validation requirements and methodology for the item of equipment/system. The protocol will use commissioning documentation wherever possible to prove the equipment/system meets the criteria set out for it. At this stage it will also be ensured that draft standard operating and maintenance SOPs and training programmes identified in the installation qualification documents are in place.

If specified, the item or system shall be subjected to a Site Acceptance Test (SAT) before executing of OQ. Verified results from the SAT may be used to complete OQ tests where appropriate.

Before setting the item or system in motion, the following will be necessary:

- The required SOPs (usually manufacturer’s operating instructions) necessary for the safe operation of the item or system will have been identified.
- Site pressure testing will have been completed and documented.
- Correct personal protection equipment and training in its use will have been provided.
- HS&E risk assessments and method statements will have been completed where appropriate.

9.1.10 Standard Operating Procedures

Standard Operating Procedures (SOPs) must be in place to enable the items and systems to be operated consistently as intended during Performance Qualification testing. These may include, but are not limited to:

- Operation
- Cleaning
- Testing
- Sampling
- Maintenance
- Calibration
- Production processes
- QA/QC/Monitoring
- Training
9.1.11 Performance Qualification

Performance Qualification (PQ) test methodology will encompass testing as close as possible to production conditions, and where practical, “worst case” conditions.

Performance Qualification will determine whether the items, either in isolation or in combination with other items, can process defined standard loads or batches of a representative product, placebo, components or packaging consistently and repeatably to specification when operated according to approved procedures and under normal production conditions.

9.1.12 Combined Qualifications (I/OQ & O/PQ)

In the case of items which are of simple construction and have few functions, Installation Qualification checks and Operational Qualification tests (I/OQ) may be described in combined Installation and Operational Qualification protocols. Similarly, Operational Qualification tests and Performance Qualification (O/PQ) tests may be described in combined protocols.

The resulting protocols may be as brief as is necessary to adequately verify all aspects that impact upon product quality.

Examples of equipment for which I/OQ may be appropriate are simple mobile vessels, balances, suppository moulds, measuring glassware, etc.

Examples of equipment for which O/PQ might be appropriate are fridges, mixers, cooling coil, etc.

9.1.13 Process Validation (PV)

The purpose of process validation is to provide documented evidence that the process and facility can consistently produce product that will satisfy a predetermined quality standard and comply with the relative Regulatory Standards and, if applicable, meet or exceed previous recorded quality levels.

PV requires three consecutive product batches to meet all acceptance criteria for in-process and product testing and will involve enhanced sampling and testing using validated methods.

Any changes to equipment and/or systems critical to product quality will require PV to be repeated.

New products/processes will be subject to PV.

9.1.14 Cleaning Validation

Cleaning validation, which will be controlled through a separate validation plan (please refer to Annex 1 of this document), will provide documented evidence that a cleaning procedure is effective in reducing, to pre-defined maximum allowable limits, all chemical and microbiological contamination from an item of equipment or a manufacturing area following processing. The means of evaluating the effectiveness of cleaning will involve sampling cleaned and sanitised surfaces and verifying the absence of product residues, cleaning residues and bacterial contamination.

The installation and mechanical functionality of cleaning equipment and clean in place (CIP) systems will be covered by equipment IQ and OQ protocols. The term cleaning validation is to be used to describe the analytical investigation and subsequent verification of a cleaning procedure or cycle. The cleaning validation protocols should reference background documentation relating to the rationale for “worst case” testing, where this is proposed. It should also explain the development of the acceptance criteria, including chemical and microbial specifications, limits of detection and the selection of sampling methods.
Particular note will be taken of the requirements of section 3.6 of the “Rules and Guidance for Pharmaceutical Manufacturers and Distributors, 2002”, where potent or sensitising products such as penicillins or cephalosporins are to be processed.

9.1.15 Analytical Method and Laboratory Equipment Validation

Analytical method validation and the associated laboratory equipment qualification, which will be the subject of a separate validation plan, (please refer to Annex 2 of this document), provide documented evidence that test methods are effective, reproducible and repeatable. The validation protocols should reference background documentation relating to the rationale for the determination of limits of detection and method sensitivity.

Validation of the analytical methods will be a pre-requisite for any analytical testing associated with, for example, QC checks and cleaning validation assessments. It should be demonstrated that the laboratory activities meet the requirements of GLP.

9.1.16 Product Storage and Distribution Validation

It is recognised that there is a very diverse requirement for storage and distribution due to:

- The large number of products.
- The limited shelf life of some products.
- The temperature sensitivity of some products.
- The requirement to manufacture ‘on demand’ to meet specific patients’ needs.
- The economic need to produce maximum batch size wherever possible.

The storage and distribution processes will be controlled by appropriate SOPs and validated where necessary. Appropriate RAs will be conducted to focus the validation activity upon those products that are particularly susceptible to environmental conditions during storage and distribution and have limited shelf life. The validation protocol(s) will be designed to verify that the product(s) are maintained at specified environmental conditions during storage and during distribution to the patient.

The point at which the responsibility for the product passes from the Pharmacy to intermediate agents or the end user should be clearly defined. It will be verified that products are only delivered to recognised persons or organisations who have the appropriate facilities and understanding to maintain product quality.

9.1.17 Relocated Equipment

A significant number of existing equipment items will be transferred to the new facility from other pharmacies. All aspects of the relocation will be effectively managed and controlled by means of an equipment re-location procedure. The procedure will, as a minimum, control all aspects of the re-location that may impact upon cGMP. The procedure will include a model document that can be adapted to suit all types of equipment. It should be completed in sufficient detail to ensure that any required retrospective validation can be completed successfully.

The evidence of validation and associated documentation that exists for relocated equipment should be reviewed and the scope of the validation exercise subsequently defined.

The relocated equipment will be subject to the IA procedure as defined in section 9.1.3. Where the equipment is deemed to be of direct impact, then it will be subject to the same qualification process as new items. However, it is recognised that the quantity and/or quality of the supporting documentation may be limited. In such cases, the criticality of components should be taken into consideration and steps taken to establish documented evidence that cGMP requirements are
satisfied. The methodology used should be described in the rationale section of the respective qualification protocols.

Typical activities may include:

- Non-destructive testing to establish nature of product contact materials.
- Review of process and batch data to provide appropriate OQ and PQ acceptance criteria.
- Modification of existing SOPs to reflect use of the equipment in the new facility, with subsequent testing using the modified SOPs.
- Review of maintenance records to establish planned maintenance programme.
- Re-calibration of critical instruments.
- Annotated digital photography of equipment to provide pictorial evidence of component layout and identification.
- Tagging of components.
- Review of training records to establish re-training requirements.

A copy of the equipment re-location procedure and model document will be placed in Appendix B.

9.1.18 Computer Validation Testing

Only to be included if any items of equipment have a programmable logic controller (plc).

9.2 Validation Reports

At the end of any validation activity a validation report will be completed. This report will summarise the results of the validation activity and highlight any issues such as deviations that have arisen. The purpose of the report is to enable others, e.g. licensing inspectors, to understand the key aspects of the activity without having to read sometimes extremely lengthy documents.

9.3 Validation History File

The Validation History File will contain all relevant documentation associated with the design, construction, installation, commissioning and operation of the facility, equipment and services. All qualification activities will challenge this documentation for cGMP compliance.

The documentation will be held in a secure location with controlled access. It will be stored in an orderly manner, supported by an effective indexing system, e.g. a searchable database, allowing prompt retrieval of any document.

Simplified History Files will be maintained for no impact and non-GMP systems and equipment in line with GEP expectations.

A master Validation History File document list will be placed in Appendix B of this document.
10.0 CHANGE CONTROL

10.1 VMP Revisions
During the course of the facility validation lifecycle, this Validation Master Plan and its annexes may be subject to amendment. Details of the amendments with reasons will be recorded in section 1.0, Revision History, and the revised VMP re-approved by the signing of a revised cover page.

10.2 Change Control Initiation
At an appropriate stage, e.g. completion of detailed design, the design will be approved by completion and approval of a cGMP Review. Following approval of the cGMP Review, the design will be 'fixed' and any subsequent significant changes will be controlled by the use of an appropriate change control procedure.

10.3 Definition of Change
The objective is to minimise the quantity of documentation whilst retaining the audit trail of validation activities, hence the impact of proposed changes on the validation process will be assessed. Techniques such risk assessment, impact assessment, etc will be used as appropriate. Generally, indications of significant changes will be, but are not limited to:

- Direct impact on product
- Indirect impact on product
- Changes required to test methods and/or acceptance criteria of protocols
- Test data in validation reports will require revision.
- cGMP and/or regulatory requirements have been compromised.

Some examples of significant Changes:
- Specification of critical instruments.
- Product contact materials of construction.
- Replacement of critical instrument after IQ and before OQ
- Acceptance criteria for a critical process have been re-defined.

10.4 Change Control Procedure
The Change Control Procedure(s) will be approved by the VSC prior to use and will define as a minimum:

- The proposer of the change.
- Equipment/systems affected by the change.
- Validation protocols/reports affected by the change.
- Validation support documentation affected by the change.

The proposer of the change will be responsible for:

- Obtaining all the necessary approvals prior to carrying out the change.
- Managing the activities necessary to expedite the change
- Obtaining the necessary approvals of the completed change.

The Change Control may logically include other non-validation data such as budget approvals and HS&E implications.
11.0 QUALITY MANAGEMENT

It is a requirement of cGMP that an effective quality management system (QMS) is in place. This QMS will provide the basis for all SOPs that are utilised within the facility.

The VMP will support and be referenced from a QMS established for the Pharmacy.

It is the responsibility of the QA/QC Department to assure the maintenance of cGMP standards, as described by the VMP, for the all processes associated with the manufacture and/or dispensing of the products described in Appendix A.

The VMP and associated documents will be updated as necessary to include any new product or process. Any new product or process will be subject to IA and/or RA as appropriate to define the appropriate activities necessary to maintain the required quality standards and cGMP compliance.
12.0 SCHEDULE OF STANDARD OPERATING PROCEDURES

It is a requirement of cGMP that effective operating procedures are in place for all equipment, systems and processes that may have an effect upon product quality and that they are followed correctly.

The validation activities (program and protocols) will ensure that these procedures are in place and approved.

A schedule of all standard operating procedures shall be prepared and maintained to support the facility during its life cycle.

Appropriate procedures will be qualified during OQ and PQ validations.

A list of all operating procedures will be indexed or referenced in Appendix B.
13.0 PREVENTATIVE MAINTENANCE

It is a requirement of cGMP that effective preventative maintenance procedures are in place and are followed correctly.

The validation activities will ensure that these procedures are developed and approved. The procedures will apply to all equipment and systems that may have a direct or indirect impact upon product quality.

Maintenance activities will be scheduled such that the minimum requirements for maintenance are met and will be integrated with production activities.

Only approved methods and materials will be used during maintenance activities.

A schedule of all maintenance procedures shall be prepared and maintained to support the facility during its life cycle. Appropriate procedures will be cross-referenced in the validation protocols.

A list of all maintenance procedures will be indexed or referenced in Appendix B.
14.0 SCHEDULE OF WORK PACKAGES

It may be necessary to place certain equipment and systems into logical groups termed work packages, particularly during design, installation and commissioning phases of the new facility. A schedule of work packages will be placed in appendix B.
15.0 TRAINING

Procedures for the training of personnel will be established. These procedures will ensure that:

- The appropriate level of training and education is provided for all personnel employed within the facility.
- Training records are established and maintained for all personnel employed within the facility.

The training will be referenced to all the SOPs identified or referenced in Appendix B.
16.0 RESPONSIBILITIES AND APPROVAL OF PROTOCOLS AND DOCUMENTATION

16.1 Protocol Responsibility
It is recognised that there will be protocols addressing a diverse range of equipment and systems. Each protocol and its associated report will be assigned to a relevantly qualified person (the document ‘sponsor’). Typically the document ‘sponsor’ will be the author of the protocol. He/she will be responsible for:

- Ensuring that appropriate protocol/report approvers are nominated.
- Authorising each page of protocol after approval.
- Checking and approving each completed report test page and completion of test progress checklist.
- Completion of summary report.
- Ensuring that any deviations are progressed (in conjunction with validation manager).
- Presentation of report for interim and final approvals.

16.2 Approval of Protocols and Reports
In order to expedite the approval process, the following guidelines may be applied:

- The number of reviewers will be kept to the minimum necessary to ensure that critical aspects of document content are covered.
- The document ‘sponsor’ will ensure that copies of the document are distributed to all reviewers.
- Copies of the document will be reviewed simultaneously by all reviewers. Each reviewer will only comment on items relevant his/her particular expertise.
- After a predefined time, say 5 working days, the comments will be collated by the sponsor who, within a further predefined time, will resolve conflicting comments and amend the document. The document will be re-issued with appropriate revision number for approval.

16.3 Approval Of Validation Documentation
Validation support documentation will be provided in accordance with history file indexes prepared specifically for each system, equipment item groups, work packages, etc. The history file indexes will define responsibility for supply and expected delivery schedule for the individual documents.

On receipt, the documents will be reviewed for content by appropriate members of the VSC or by suitably qualified personnel nominated by the VSC. If the content is satisfactory, the documents will be placed in the validation history file.
## Appendix A

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