Pharmaceutical production

An engineering guide

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Preface

The pharmaceutical industry aims to produce safe and effective medicines with efficiency and profitability. In order to achieve these aims, qualified personnel from many scientific and commercial disciplines are needed. The industry needs specialists with qualifications in biological, chemical, engineering and pharmaceutical sciences, but there is also a requirement for a wider knowledge of the integral parts of an innovative manufacturing company including research, development, manufacturing, distribution, marketing and sales. Chapter 1 sets the scene by introducing the essential stages, from the synthesis of a new chemical entity through to its development into a licensed medicine.

Further education and advanced training for staff in the industry is needed through in-house or external courses. However, there is a distinct lack of detailed texts written by industrial experts. This book overcomes this deficiency in the area of pharmaceutical engineering and provides detailed information in all principal areas relevant to the manufacture of medicines. It will be a useful reference book for information on topics selected from the vast range of material covered in Chapters 2 to 11. Comprehensive coverage of each major topic, written by experts, provides valuable information for both newcomers and experienced personnel working in the pharmaceutical industry.

Abbreviations and acronyms proliferate throughout the modern world and the pharmaceutical industry has its share. Fortunately, the editors have provided a list of acronyms and a glossary of terms most commonly used in the industry.

The book is divided into ten main chapters, each covering specialist areas with their principal sub-sections clearly set out in the comprehensive list of contents at the beginning of the book. This feature will be very useful for those who need rapid access to detailed information in a specific area.

Chapters 2 to 10 cover all the important aspects of the production of licensed medicines, as indicated in the following précis.

Chapters 5 and 6 cover in detail primary and secondary production from the preparation of bulk bioactive substance by chemical synthesis, biotechnology and extraction from natural products, through to modern packaging technologies

required for the finished medicine. Chapter 8 deals with the design of utilities and services, as well as the associated areas of cleaning and maintenance. The design of facilities is continued in Chapter 9 which covers the planning, furnishing and provision of services in laboratories, whereas the special requirements for process development and pilot plant are presented in Chapter 10.

Having provided an outline of the chapters dealing with production, we can turn towards the beginning of the book for coverage of regulatory matters and quality assurance. Chapter 2 is an outline of the main stages in the approval process, post-marketing evaluation and the European and US perspectives.

The concepts and practices embodied in Good Manufacturing Practice are covered concisely in Chapter 3 with special reference to engineering aspects of pharmaceutical production, whereas validation and safety issues are presented in great detail in Chapters 4 and 7.

Finally, in Chapter 11, the special requirements for the development and manufacture of modern bio-pharmaceutical products are dealt with in great detail with reference to small scale and pilot facilities.

After six years working in research and development in the pharmaceutical industry, the rest of my career has been in academic pharmacy. Close contact with the industry has been maintained through education, training, research, consultancy and involvement with the design, delivery, assessment and external examinership of postgraduate diploma and MSc courses for advanced training of personnel in the industry. Such courses by universities or independent consultants provide course material of a high standard, but this should be supplemented by texts written by experts working in the industry. The Engineering Guide to Pharmaceutical Production provides an authoritative and detailed treatment of all major aspects related to the manufacture of medicines.

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List of acronyms

The following is a list of acronyms used in this book. It is followed by a glossary of the more important validation terms.

ADR	Adverse Drug Reaction
AGMP	Automated Good Manufacturing Practice
AGV	Automated Guided Vehicles
AHU	Air Handling Unit
ALARP	As Low As Reasonably Practicable
ANDA	Abbreviated New Drug Application
ANSI	American National Standards Institute
API	Active Pharmaceutical Ingredient
ASME	American Society of Mechanical Engineers
BATNEEC	Best Available Techniques Not Entailing Excessive Costs
BL1	Biosafety Level 1
BL2	Biosafety Level 2
BL3	Biosafety Level 3
BL4	Biosafety Level 4
BMR	Batch Manufacturing Record
BMS	Building Management System
BOD	Biological Oxygen Demand
BP	British Pharmacopeia
BPC	Bulk Pharmaceutical Chemical
BPEO	Best Practicable Environmental Option
BS	British Standard
BSI	British Standards Institution
cAGMP	Current Automated Good Manufacturing Practice
CAMMS	Computer Aided Maintenance Management System
CCTV	Closed Circuit Television
CDER	Centre for Drug Evaluation and Research
CDM	Construction (Design and Management) regulations

CFC	Chlorofluorocarbons
CFR	Code of Federal Regulations
CFU	Colony Forming Unit
cGCP	Current Good Clinical Practice
cGLP	Current Good Laboratory Practice
cGMP	Current Good Manufacturing Practice
CHAZOP	Computer HAZOP
CHIP	Chemical Hazard Information and Packaging regulations
CIMAH	Control of Industrial Major Accident Hazards regulations
CIP	Clean In Place
CMH	Continuous Motion Horizontal
COD	Chemical Oxygen Demand
COMAH	Control Of Major Accident Hazards regulations
COSHH	Control Of Substances Hazardous to Health
CPMP	Committee on Proprietary Medicinal Products
CPU	Central Processing Unit
CSS	Continuous Sterilization System
CV	Curriculum Vitae
DAF	Dissolved Air Flotation
DIN	Deutsches Institüt für Normung
DMF	Drug Master File
DNA	Deoxyribonucleic Acid
DOP	Dioctyl Phthalate
DQ	Design Qualification
EC	European Community
EEC	European Economic Community
EMEA	European Agency for the Evaluation of Medical Products
EPA	Environmental Protection Agency
EPDM	Ethyl Propylene Diene Terapolymer
ERP	Enterprise Resource Planning
EU	European Union
FAT	Facility Acceptance Testing
FBD	Fluidized Bed Dryer
FDA	Food and Drug Administration
FMEA	Failure Mode Effects Analysis
FS	Functional Specification
GAMP	Good Automated Manufacturing Practice
GC	Gas Chromatograph
GCP	Good Clinical Practice
GLP	Good Laboratory Practice

GLSP	Good Large Scale Practice
GMP	Good Manufacturing Practice
GRP	Glass Reinforced Plastic
GSL	General Sales List
HAZOP	Hazard and Operability Study
HEPA	High Efficiency Particulate Arrestor
HFC	Hydrofluorocarbons
HIC	Hydrophobic Interaction Chromatography
HMAIP	Her Majesty's Inspectorate of Air Pollution (now defunct)
HMSO	Her Majesty's Stationery Office
HPLC	High Pressure Liquid Chromatograph
HS	Hazard Study
HSE	Health and Safety Executive
HSL	HAZOP Study Leader
HVAC	Heating Ventilation and Air Conditioning
IBC	Intermediate Bulk Container
ICH	International Conference on Harmonization
IDF	International Diary Foundation
IEC	Ion Exchange Chromatography
IEEE	Institute of Electrical and Electronics Engineers
IMV	Intermittent Motion Vehicle
IND	Investigational New Drug Application
I/O	Inputs and Outputs
IPA	Iso Propyl Alcohol
IPC	Integrated Pollution Control
IQ	Installation Qualification
ISO	International Standards Organization
ISPE	International Society for Pharmaceutical Engineering
LAAPC	Local Authority Air Pollution Control
LAF	Laminar Air Flow
LIMS	Laboratory Information Management System
LTHW	Low Temperature Hot Water
mAb	Monoclonal Antibody
MCA	Medicines Control Agency
MCB	Master Cell Bank
MCC	Motor Control Centre
MEL	Maximum Exposure Limit
MRA	Mutual Recognition Agreement
MRP	Manufacturing Resource Planning
MSDS	Material Safety Data Sheet

NCE	New Chemical Entity
NDA	New Drug Application
NDT	Non-Destructive Testing
NICE	National Institute for Chemical Excellence
NMR	Nuclear Magnetic Resonance
OEL	Occupational Exposure Limits
OES	Occupational Exposure Standards
OQ	Operational Qualification
OSHA	Occupational Safety & Health Administration
OTC	Over The Counter
P	Pharmacy only
PBTB	Polybutylene Teraphthalate
PC	Programmable Controller
PCB	Printed Circuit Board
PDA	Personal Digital Assistants
PEG	Polyethylene Glycol
PFD	Process Flow Diagram
PHA	Preliminary Hazard Assessment
Ph.Eur	European Pharmacopeia
PHS	Puck Handling Station
P&ID	Piping and Instrumentation Diagram
PLA	Product Licence Application
PMI	Positive Material Identification
POM	Prescription Only Medicines
PP	Polypropylene
PPE	Personal Protective Equipment
PQ	Performance Qualification
PSF	Performance Shaping Factors
PTFE	Polytetrafluoroethylene
PV	Process Validation
PVC	Polyvinyl Chloride
PVDF	Polyvinylidene Fluoride
PW	Purified Water
QA	Quality Assurance
QC	Quality Control
QRA	Quantitative Risk Assessment
R&D	Research and Development
RF	Radio Frequency
RH	Relative Humidity
RHS	Rolled Hollow Section

RIDDOR	Reporting of Injuries, Disease and Dangerous Occurrences Regulations
RP-HPLC	Reverse Phase High Performance Liquid Chromatography
SCADA	Supervisory Control And Data Acquisition system
SEC	Size Exclusion Chromatography
SHE	Safety, Health and Environment
SIP	Sterilize In Place/Steam In Place
SOP	Standard Operating Procedure
SS	Suspended Solids
THERP	Technique for Human Error Rate Prediction
TOC	Total Organic Carbon
TWA	Time-Weighted Average
UK	United Kingdom
UPVC	Unplasticized Polyvinyl Chloride
URS	User Requirement Specification
USA	United States of America
USP	United States Pharmacopeia
UV	Ultra Violet
VDU	Visual Display Unit
VMP	Validation Master Plan
VOC	Volatile Organic Compound
WCB	Working Cell Bank
WFI	Water for Injection

Glossary

Acceptance criteria The product specifications and acceptance/rejection criteria, such as acceptable quality level and unacceptable quality level, with an associated sampling plan, that are necessary for making a decision to accept or reject a lot or batch (or any other convenient subgroups of manufactured units).

Action levels Levels or ranges that may be detrimental to end product quality, signalling a drift from normal operating conditions.

Alert levels Levels or ranges that signify a drift from normal operating conditions. These ranges are not perceived as being detrimental to end product quality, but corrective action should be taken to ensure that action levels are not obtained.

Audit An audit is a formal review of a product, manufacturing process, equipment, facility or system for conformance with regulations and quality standards.

Bulk drug substance Any substance that is represented for use in a drug and that, when used in the manufacturing, processing or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug. The term does not include intermediates used in the synthesis of such substances.

Bulk pharmaceutical chemical Any substance that is intended for use as a component in a 'Drug Product', or a substance that is repackaged or relabelled for drug use. Such chemicals are usually

made by chemical synthesis, by processes involving fermentation, or by recovery from natural (animal, mineral or plant) materials.

Calibration Comparison of a measurement standard or instrument of known accuracy with another standard or instrument to detect, correlate, report or eliminate by adjustment any variation in the accuracy of the item being compared.

Certification Documented statement by qualified authorities that a validation event has been done appropriately and that the results are acceptable. Certification is also used to denote the acceptance of the entire manufacturing facility as validated.

Change control A formal monitoring system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect validated status and take preventive or corrective action to ensure that the system retains its validated state of control.

Computer validation The validation of computers has been given a particular focus by the US FDA.

Three documents have been published for agency and industry guidance. In February 1983, the agency published the Guide to Inspection of Computerized Systems in Drug Processing; in April 1987, the Technical Reference in Software Development Activities was published; on 16 April, 1987, the agency published Compliance Policy Guide 7132 in Computerized Drug Processing: Source Codes for Process Control Application Programmes.

In the inspection guide, attention is called to both hardware and software; some key points being the quality of the location of the hardware unit as to extremes of environment, distances between CPU and peripheral devices, and proximity of input devices to the process being controlled; quality of signal conversion, for example, a signal converter may be sending inappropriate signals to a CPU; the need to

systematically calibrate and check for accuracy of I/O devices; the inappropriateness and compatibility within the distributed system of command overrides, for example, can an override in one computer controlled process inadvertently alter the cycle of another process within the distributed system? Maintenance procedures are another matter of interest to the agency during an inspection. Other matters of concern are methods by which unauthorized programme changes are prevented, as inadvertent erasures, as well as methods of physical security.

Hardware validation should include verification that the programme matches the assigned operational function. For example, the recording of multiple lot numbers of each component may not be within the programme, thus second or third lot numbers of one component may not be recorded. The hardware validation should also include worse case conditions; for example, the maximum number of alphanumeric code spaces should be long enough to accommodate the longest lot numbering system to be encountered. Software validation must be thoroughly documented — they should include the testing protocol, results, and persons responsible for reviewing and approving the validation. The FDA regards source code, i.e., the human readable form of the programme written in its original programming language, and its supporting documentation for application programmes used in any drug process control, to be part of the master production and control records within the meaning of 21CFR parts 210, 211 (Current Good Manufacturing Practice Regulations).

As part of all validation efforts, conditions for revalidations are a requirement.

Concurrent validation

Establishing documented evidence that the process being implemented can consistently produce a product meeting its predetermined specifications and quality attributes. This phase of validation activities typically involves careful monitoring/recording of the

process parameters and extensive sampling/testing of the in-process and finished product during the initial implementation of the process.

Construction qualification The documented evaluation of the construction or assembly of a piece of equipment, process or system to assure that construction or assembly agrees with the approved specifications, applicable codes and regulations, and good engineering practices. The conclusion of the evaluation should decidedly state that the equipment, process or system was or was not constructed in conformance with the specifications.

Critical process variables Those process variables that are deemed important to the quality of the product being produced.

Design review A 'design review' is performed by a group of specialists (such as an Architect, a Quality Assurance Scientist, a HVAC Engineer, a Process Engineer, a Validation Specialist, a Civil Engineer and a Regulatory Affairs Specialist) to review engineering documents to ensure that the engineering design complies with the cGMPs for the facility. The thoroughness of the design review depends upon whether the engineering project is a feasibility study, a conceptual design, preliminary engineering, or detailed engineering. Minutes of all meetings for design review will be sent to team members and the client to show the compliance of the design to cGMPs.

Drug Substances recognized in the official USP; substances intended for use in the diagnosis, cure, mitigation or prevention of disease in man or other animals; substances (other than food) intended to affect the structure or any function of the body of man or other animals; substances intended for use as a component of any substances specified above but does not include devices or their components, parts or accessories.

Dynamic attributes Dynamic attributes are classified into functional, operational and quality attributes, which are identified,

monitored, inspected and controlled during actual operation of the system.

Edge of failure A control or operating parameter value that, if exceeded, may have adverse effects on the state of control of the process and/or on the quality of the product.

Facilities Facilities are areas, rooms, spaces, such as receiving/shipping, quarantine, rejected materials, approved materials warehouse, staging areas, process areas, etc.

Functional attributes Functional attributes are such criteria as controls, instruments, interlocks, indicators, monitors, etc., that operate properly, are pointing in the correct direction, and valves that allow flow in the correct sequence.

Good manufacturing practice (GMP) The minimum requirements by law for the manufacture, processing, packaging, holding or distribution of a material as established in Title 21 of the Code of Federal Regulations.

Installation qualification protocol An installation qualification protocol (IQ) contains the documented plans and details of procedures that are intended to verify specific static attributes of a facility, utility/system, or process equipment. Installation qualification (IQ), when executed, is also a documented verification that all key aspects of the installation adhere to the approved design intentions and that the manufacturer's recommendations are suitably considered.

Intermediate (drug/chemical) Any substance, whether isolated or not, which is produced by chemical, physical, or biological action at some stage in the production of a bulk pharmaceutical chemical and subsequently used at another stage in the production of that chemical.

Life-cycle The time-frame from early stages of development until commercial use of the product or process is discontinued.

Master plan

The purpose of a master plan is to demonstrate a company's intent to comply with cGMPs and itemizes the elements that will be completed between the design of engineering and plant start-up. A typical master plan may contain, but is not limited to, the following elements: approvals, introduction, scope, glossary of terms, preliminary drawings/facility design, process description, list of utilities, process equipment list, list of protocols, list of SOPs, equipment matrices, validation schedule, protocol summaries, recommended tests, calibration, training, manpower estimate, key personnel (organization chart and resumes), protocol examples, SOP examples.

Medical devices

A medical device is defined in the Federal Food Drug and Cosmetic Act Section 201(h) as:
An instrument, apparatus, implement or contrivance intended for use in diagnosis, cure, mitigation, prevention or other treatment of disease in man or other animals, or intended to alter a bodily function or structure of man or other animal.
This is the definition used in the code of Federal Regulations 21 parts 800 to 1299. Medical Devices.

Operational attributes

Operational attributes are such criteria as a utility/system's capability to operate at rated ranges, capacities, intensities, such as: revolutions per minute, kg per square cm, temperature range, kg of steam per second, etc.

Operation qualification protocol

An operation qualification (OQ) contains the plan and details of procedures to verify specific dynamic attributes of a utility/system or process equipment throughout its operated range, including worse case conditions. Operation qualification (OQ) when executed is documented verification that the system or subsystem performs as intended throughout all anticipated operating ranges.

Operating range

A range of values for a given process parameter that lie at or below a specified maximum operating value and/or at or above a specified minimum operating

value, and are specified on the production worksheet or the standard operating instruction.

Overkill sterilization process A process which is sufficient to provide at least a 12 log reduction of microorganisms having a minimum D-Value of 1 minute.

Process parameters Process parameters are the properties or features that can be assigned values that are used as control levels or operating limits. Process parameters assure the product meets the desired specifications and quality. Examples might be: pressure at 5.2 psig, temperature at $37°C \pm 0.5°C$, flow rate at $10 \pm 1.0 \, l \, min^{-1}$, pH at 7.0 ± 0.2.

Process variables Process variables are the properties or features of a process which are not controlled or which change in time or by demand; process variables do not change product specifications or quality.

Process validation Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.

Process validation protocol Process validation protocol (PV) is a documented plan, and detailed procedures to verify specific capabilities of a process equipment/system through the use of simulation material, such as the use of a nutrient broth in the validation of an aseptic filling process.

Product validation A product is considered validated after completion of three successive successful lot size attempts. These validation lots are saleable.

Prospective validation Validation conducted prior to the distribution of either a new product or a product made under a revised manufacturing process, where the revisions may have affected the product's characteristics, to ensure that the finished product meets all release requirements for functionality and safety.

Protocol A protocol is defined in this book as a written plan stating how validation will be conducted.

Quality assurance The activity of providing evidence that all the information necessary to determine that the product is fit for the intended use is gathered, evaluated and approved.

Quality attributes Quality attributes refer to those measurable properties of a utility, system, device, process or product such as resistivity, impurities, particulate matter, microbial and endotoxin limits, chemical constituents and moisture content.

Quality control The activity of measuring process and product parameters for comparison with specified standards to assure that they are within predetermined limits and, therefore, the product is acceptable for use.

Retrospective validation Validation of a process for a product already in distribution based upon establishing documented evidence through review/analysis of historical manufacturing and product testing data, to verify that a specific process can consistently produce a product meeting its predetermined specifications and quality attributes. In some cases a product may have been on the market without sufficient pre-market process validation.

Retrospective validation can also be useful to augment initial pre-market prospective validation for new products or changed processes.

Revalidation Repetition of the validation process or a specific portion of it.

Specifications Document that defines what something is by quantitatively measured values. Specifications are used to define raw materials, in-process materials, products, equipment and systems.

Standard operating procedure (SOP) Written procedures followed by trained operators to perform a step, operation, process, compounding or other discrete function in the manufacture or produc-

	tion of a bulk pharmaceutical chemical, biologic, drug or drug product.
State of control	A condition in which all process parameters that can affect performance remain within such ranges that the process performs consistently and as intended.
Static attributes	Static attributes may include conformance to a concept, design, code, practice, material/finish/ installation specifications and absence of unauthorized modifications.
Utilities/systems	Utilities/systems are building mechanical equipment and include such things as heating, ventilation and air conditioning (HVAC) systems, process water, product water (purified water, water for injection), clean steam, process air, vacuum, gases, etc. Utilities/ systems include electro-mechanical or computer-assisted instruments, controls, monitors, recorders, alarms, displays, interlocks, etc., which are associated with them.
Validation	Establishing documented evidence to provide a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality.
Validation programme	The collective activities related to validation.
Validation protocols	Validation protocols are written plans stating how validation will be conducted, including test parameters, product characteristics, production equipment, and decision points on what constitutes acceptable test results. There are protocols for installation qualification, operation qualification, process validation and product validation. When the protocols have been executed it is intended to produce documented evidence that the system has been validated.
Validation scope	The scope identifies what is to be validated. In the instance of the manufacturing plant, this would include the elements that impact critically on the

quality of the product. The elements requiring validation are facilities, utilities/systems, process equipment, process and product.

Worst case A set of conditions (encompassing upper and lower processing limits and circumstances including those within standard operating procedures), which pose the greatest chance of process or product failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.

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