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Cobra Biologics

Pharmaceutical Quality Manual



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1 Introduction and Objectives

Cobra Biologics is dedicated to the contract manufacture and testing of biological medicinal products for development and clinical trial use.

Cobra's overall quality objective is to establish, implement and maintain a system that assures the delivery of products with the quality attributes appropriate to meet the needs of patients, health care professionals, regulatory authorities and both internal and external customers.

2 Scope

This manual applies to the provision of products and services subject to current Good Manufacturing Practices (cGMP) and is in line with the principles of International Conference on Harmonisation (ICH) Q10 "Pharmaceutical Quality System"

Such services encompass:

- Pharmaceutical Development:
 - o Process development;
 - o Manufacture of investigational products;
 - o Manufacturing process development and scale-up;
 - o Analytical method development.
- Technology Transfer:
 - o Transfer of processes from and to clients;
 - o Transfers within or between manufacturing and testing sites for investigational products.
- cGMP Manufacturing:
 - o Acquisition and control of materials;
 - o Provision of facilities, utilities, and equipment;
 - o Production (including packaging and labelling);
 - o Quality control and assurance;
 - o Release;
 - o Stability;
 - o Storage;
 - o Distribution.

3 Management Responsibility

Senior management within Cobra have the ultimate responsibility to ensure that an effective pharmaceutical quality system is in place to achieve the quality objectives, and



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that roles, responsibilities and authorities are defined, communicated and implemented throughout the company.

Cobra Management:

- Participate in the design, implementation, monitoring and maintenance of the quality system;
- Provide strong and visible support for the pharmaceutical quality system and ensure its implementation throughout the organisation;
- Ensure that a timely and effective communication and escalation process exists to raise quality issues to the appropriate levels of management;
- Defines individual and collective roles, responsibilities, authorities and inter-relationships of all organisational units related to the quality system and ensures that these interactions are communicated and understood at all levels of the organisation;
- Ensures that independent quality units exist with the authority to fulfil the requirements for quality systems as defined within both national and international regulations;
- Conducts management reviews of the pharmaceutical quality system utilizing performance indicators that measure progress against quality objectives.

Relevant Procedures:

SOP 029	Internal Auditing Policy
SOP 074	Reporting and Review of Quality Metrics within Cobra Biologics
G-153	Quality and Compliance Auditing

4 Quality Policy

Cobra Biologics quality policy is detailed in Appendix 1 of this manual.

This policy is approved by:

Director of Quality Assurance and Regulatory, Cobra Biologics AB
Site Manager, Cobra Biologics AB
Director of Quality, Biologics, Cobra Biologics
Chief Executive Officer, Cobra Biologics

Copies of this policy are displayed in each of the Company's facilities.

5 Quality System Processes

5.1 Documentation Systems

Good, detailed, precise, correctly completed and well controlled documentation is key to the successful and compliant manufacture of pharmaceutical products. Cobra Biologics utilize a comprehensive system of documentation for all GMP manufacturing and testing



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activities. All documentation is available for review by clients and regulatory authorities, and in the case of documentation relating to the manufacture of clinical materials, copies of key documents can be provided to clients.

Relevant Procedures:

- SOP000 The Preparation, Review, Approval and Control of Standard Operating Procedures
- SOP005 The Review, Approval and Archiving of Batch Manufacturing Records and Batch Folders
- SOP045 Policy for Completion of GMP Documentation
- G-060 Approval of GMP Documents
- G-061 Archiving
- G-093 Document management
- G-104 Review and Approval of Batch Manufacturing Records

5.1 Procedures and Methods:

All cGMP activities are detailed in procedures or analytical methods which have been reviewed and approved by relevant, qualified personnel as being fit for purpose and in compliance with regulatory requirements. The format of procedures and the methods of their review, approval and control are detailed in local Site controlling procedures.

Procedures are available for use at the place of work, in the language appropriate for their geographical location to ensure that they may be understood and followed. Additionally, all procedures are available as “read only” in electronic format via the company intranet. Procedures and methods also form the basis for training.

Relevant Procedures:

- SOP 000 The Preparation, Review, Approval and Control of Standard Operating Procedures
- SOP 072 Policy for Harmonisation of Cobra Quality Control Procedures with Pharmacopoeial Monographs and other Regulatory Guidelines.
- G-001 Recipharm Biologics’ Quality System
- A-054 Analytical Procedures

5.2 Training:

All staff engaged in cGMP activities undergo initial training in the principles and practices of GMP prior to undertaking unsupervised work in a cGMP area. Staff also undergo annual refresher training in GMP.

All staff engaged in cGMP activities are fully trained in the procedures or methods relevant to their activities in accordance with the site’s training procedure. Additionally, all staff carrying out cGMP batch manufacture or testing are trained in the associated batch manufacturing records, analytical methods and associated documentation prior to the manufacture or testing of the batch.

Relevant Procedures:

- SOP 036 Training of Staff within Cobra Biologics



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G-008	Documentation of Training
G-044	Introductory Training
G-144	Practical Training at RBA

5.3 Validation;

As a manufacturer of active pharmaceutical ingredients or intermediates for development or clinical trial use, the manufacturing processes and analytical methods used are not usually capable of being validated. There are exceptions to this however for safety related processes (for example, aseptic manufacture of whole cell live vaccines).

All equipment used for cGMP manufacture and analysis, together with the facilities and utilities associated with these activities, are fully validated, calibrated and maintained in order to ensure their reliability and fitness for purpose. Validation documentation includes (as appropriate): validation master plans, user requirement specifications, design qualification, installation qualification, operational qualification and performance qualification.

Relevant Procedures:

SOP 063	Policy for Cleaning, Cleaning Verification and Cleaning Validation
SOP 064	Validation Overview at Cobra
SOP 076	Preparation of User Requirements Specifications
SOP 077	Procedure for Performing Design Qualification
SOP 078	Procedure for Performing Installation and Operational Qualification
SOP 079	The Use and Management of Vendor Supplied Validation Documentation
SOP 080	Procedure for performing PQ
SOP 085	Procedure for the Generation and Approval of a Validation Project Plan
SOP 086	Computer System Validation Policy and Guidance
G-105	Validation



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5.4 Analytical Testing, Qualification and Out of Specification Results;

The requirements for analytical testing are detailed in a target analytical profile document and/or a specification. (see also Section 5.7, below.)

As a manufacturer of active pharmaceutical ingredients or intermediates for development or clinical trial use, analytical methods used for early phase trials are not usually capable of being fully validated due to lack of material or lack of reference standards. There are exceptions to this however for certain safety related methods which (as detailed in individual quality agreements) can undergo full validation in accordance with cGMP or pharmacopoeial requirements and methods. As knowledge of the product and associated testing increases (usually for later phase II and phase III trials) it is appropriate to validate the analytical testing methods.

Where non-validated analytical methods are employed for cGMP testing, they are “scientifically sound” in accordance with Section 19.8 of “The Rules Governing Medicinal Products in the European Union Volume 4, Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Part II: Basic Requirements for Active Substances used as Starting Materials”

Non - conforming analytical results are assessed in accordance with a formal Out of Specification procedure.

Relevant Procedures:

- | | |
|---------|---|
| SOP 015 | Out of Specification (OOS) Investigation Procedure |
| SOP 082 | Policy for Assay Qualification and Validation |
| A-053 | Qualification and Validation of Analytical Procedures |
| A-175 | Laboratory Investigation of Unexpected Analytical Results |

5.5 Change Control

All changes potentially impacting quality relating to a GMP facility, system, process, method, procedure or equipment are carefully controlled by the use of a formal change control system. This ensures that all potential benefits and risks are assessed in a controlled manner prior to a change being implemented. It also defines and tracks the actions required for successful implementation and closure of the change, together, where appropriate, with an assessment of the outcome. Depending on the requirements of the quality agreement (see Quality Agreements below) client approval of a change may be required.

Relevant Procedures:

- | | |
|---------|--|
| SOP 030 | Procedure for the Management of Change |
| G-178 | Management of Change |



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5.6 Deviations

Deviations are raised for failures in validated equipment and systems, and where approved procedures have not been followed. Deviations are fully investigated in a timely manner in order to determine root causes and the associated actions to prevent recurrence. Client notification requirements are detailed in the relevant project Quality Agreement (see Section 5.8)

Relevant Procedures:

SOP 046	Deviation Reporting
SOP 003	The Preparation, Approval, Use, Issuing and Review of Batch Records
G-186	Deviations

5.7 Manufacturing Specifications

The manufacturing specification is a key, critical document which details:

- All manufacturing steps
- Sampling and testing requirements
- Target analytical profile(s) and/or specification(s) of the intermediate, bulk or final product
- Environmental monitoring requirements

for a manufacturing operation. The manufacturing specification is generated by the operations group using information from clients, Production, Quality Assurance and Quality Control. It is the defining document from which the detailed batch manufacturing documents are generated. The manufacturing specification is approved by the client as well as QC, QA and Operations groups. Compliance of the BMR with the approved manufacturing specification is audited by the QA group.

A draft manufacturing specification may be drawn up for the execution of engineering runs. This draft record is written by the Operations group with inputs from development and QC. This document is used to write the draft Batch Manufacturing Records (BMR). Draft manufacturing specifications and BMRs are not audited by the Quality Assurance group.

The manufacturing specification is used in conjunction with the quality agreement. These two documents along with the client approved contract define the overall deliverables for manufacture.

Relevant Procedures:

SOP 089	Generation of Manufacturing Specifications
SOP 050	Environmental Monitoring Policy
G-197	Environmental Monitoring Programme, Clean room B841
G-143	Generation of Specifications

5.8 Quality Agreements

It is an EU requirement that a quality agreement must be in place prior to commencement of cGMP activities. The agreement defines the quality requirements and the split of responsibilities between Cobra and the client.



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It is the responsibility of Quality Assurance to ensure that the quality agreement is in place before cGMP works commence and it is the responsibility of the operations group to not start cGMP work until the quality agreement and manufacturing specification are in place.

Where clients have their own quality agreement document, this may be used instead of the Cobra quality agreement.

All quality agreements are approved by a Cobra Site Head of Quality Assurance or QP and by a senior designate of the client Quality/Regulatory organisation.

Relevant Procedures:

SOP 053 The Preparation And Approval of Quality Agreement Documents

5.9 Vendor Assurance and Raw Material Release

The quality of all raw materials and contracted services is appropriately assured depending on the use and criticality of the material or service being employed.

Additionally, all production materials are inspected and released by the quality unit in accordance with the relevant material specification.

Relevant Procedures:

SOP 034 Choosing and Working with Contractors and Consultants
SOP 059 Vendor Assurance
SOP 051 Clearance of Raw Materials Destined for Use in Manufacturing
G-127 Release of Raw Materials
G-193 Vendor Assurance



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5.10 Stability testing

No material for clinical use may be released to a clinic without adequate determination of the material's stability. Stability studies may also be performed on bulk drug substances and some raw materials or key intermediates if for example, it is known that the materials are temperature sensitive or subject to degradation over time. It is essential for a client to consider performing stability studies as early as possible in the product's development cycle to ensure that enough data is available to allow trial registration and product release to the clinic.

Relevant Procedures:

SOP 025 Stability Testing Policy
A-124 Guidelines for Stability Studies

5.11 Product Release

Depending on the nature of the product, its regulatory status and the commercial and quality agreements between the client and Cobra, manufactured or imported products may be released for further GMP manufacture (in the case of bulk drug substances or intermediates) or directly to clinic (for final formulated drug products which have been filled at an appropriately licensed facility.)

Intermediates and bulk drug substances may be approved for further GMP manufacture by an appropriately experienced and qualified member of the site Quality Assurance unit.

Where release to a clinic is required, this is performed by a Qualified Person (QP) listed on the site's Manufacturing Authorisation. Where multiple sites of manufacture are used, such as for the manufacture of the bulk drug substance and the fill - finishing operations, QP agreements are employed in accordance with Annex 16 of the EU Rules and Guidance for Pharmaceutical Manufacturers and Distributors.

Release of product to clinic is performed in accordance with Annex 13 of the EU Rules and Guidance for Pharmaceutical Manufacturers and Distributors, together with any specific requirements of the country into which the product is to be released.

Relevant Procedures:

SOP 020 Procedure for the Release of Pre-Clinical and Clinical Materials by Quality Assurance
G-126 Disposition of Drug Substance Batches



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5.12 Complaints and Recall

All complaints are dealt with promptly by appropriately experienced members of the Quality Assurance department. Whilst Cobra can and does release investigational products to clinics, the monitoring of the trials and adverse reactions exhibited by patients is performed by the trial sponsor and associated clinicians. As these materials are of an investigational nature, reactions of patients to them can be extremely unpredictable and variable. As such, information leading to a recall, and the need for a recall is normally detailed in quality agreements as the responsibility of the client and therefore does not follow the normal commercial pharmaceutical recall process. However, Cobra recognize the relationship between complaints and recall and has procedures to link these.

Relevant Procedures:

SOP 031	Complaints, Recalls, Returns and destruction of Materials
G-059	Customer Complaints, Recalls or Other Urgent Quality Events



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Appendix 1 Quality Policy

Cobra Biologics Quality Policy.

Cobra Biologics, Keele and Recipharm Biologics AB, Södertälje (together, Cobra) are holders of relevant national authorisations for the manufacture and import of Investigational Medicinal Products.

Cobra comply with the Recipharm global quality policies and manual together with all relevant European and UK national regulations and guidelines relating to the manufacture of biological pharmaceuticals for clinical use. The facilities are routinely inspected by the UK MHRA (Keele) and Swedish MPA (Södertälje) to assure that all current Good Manufacturing Practices (cGMP) are followed.

As an international supplier of clinical materials, Cobra also complies with all international cGMP requirements, including those of the International Conference on Harmonisation (ICH), US Code of Federal Regulations (in particular CFRs 210, 211 and 600) and where appropriate, those of the World Health Organisation.

Cobra's Quality Management System includes the following elements:

People:

The Quality Assurance units are separate from Manufacturing.

All staff have job descriptions and are suitably qualified and trained to carry out their allocated duties.

Premises:

All premises and equipment used for the manufacture and testing of clinical materials are constructed, validated, cleaned, classified and maintained in order to ensure that products are adequately protected, minimizing the possibility of contamination.

Equipment:

All equipment used for manufacturing and testing of clinical materials is validated, maintained and calibrated to ensure both reliability and reproducibility of operations.

Processes:

All manufacturing processes follow a Manufacturing Specification agreed between the Client and Cobra. All manufacturing follows, and is recorded on, approved Batch Manufacturing Records (BMRs) such that full traceability of manufacturing operations and conditions are maintained. BMRs are reviewed and approved by both manufacturing and QA both prior to issue and after completion of manufacturing operations.

Products:



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Cobra has no products of its own. There is therefore no conflict between Cobra's own products and those of its clients. The list of product types that Cobra is licensed to produce is listed within the relevant Site Manufacturing Authorisations.

Procedures:

All cGMP manufacturing and testing activities are described in approved procedures and analytical methods. Key quality system procedures include: Training; Validation; Change Control; Deviations; Complaints and Recall; Vendor Assurance; Quality Agreements; Manufacturing Specifications; Analytical Method Qualification; Out Of Specification; Product Release.

Product Release and Client Deliverables:

Bulk Drug Substances are released by appropriately experienced and qualified senior members of the QA departments. Drug Products, where authorized, are released by EU Qualified Persons named on the relevant Site Manufacturing Authorizations. In addition to the manufactured material, (where specified in the Quality Agreement) Cobra can supply a comprehensive package of documentation covering all activities pertinent to the manufacture of the batch.

Date:	Date:
Maria Krook Director of Quality Assurance and Regulatory, Cobra Biologics AB	Paul Stockbridge Director of Quality, Biologics Cobra Biologics
Date:	Date:
Ulrika Ljungkvist Site Manager Cobra Biologics AB	Peter Coleman Chief Executive Officer Cobra Biologics



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Appendix II Quality System Flowchart

