REPLIGEN
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REPLIGEN
INSPIRING ADVANCES IN BIOPROCESSING

Quality Manual

Approvals/Date:

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Chief Executive Officer Date

20 Oct 17
VP of Global Operations Date

27 Oct 17
Sr. Director Quality Date

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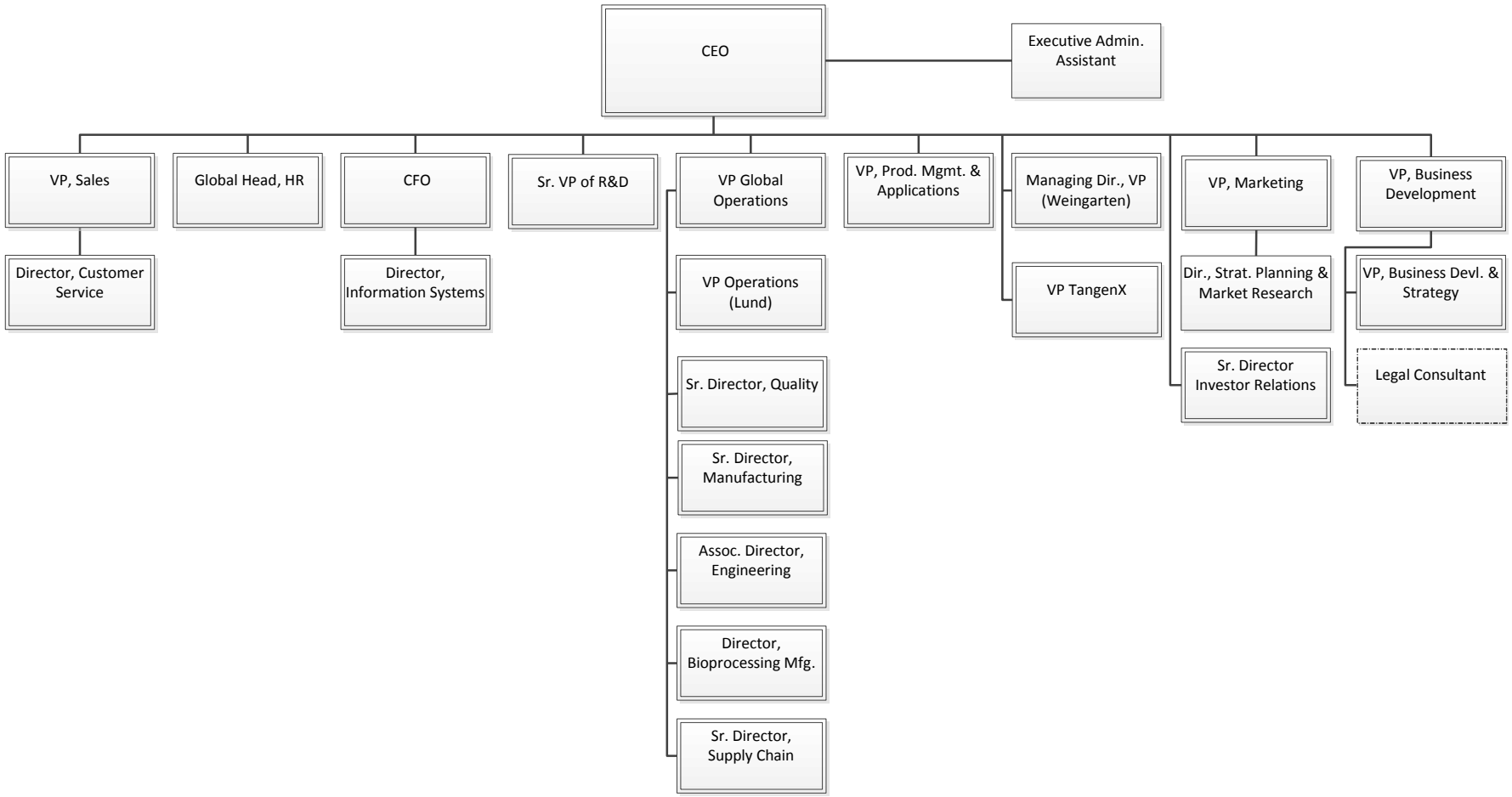
1. About the Organization

1.1. Organizational Structure



2. Purpose, Scope and Users

The Quality Manual documents the management system of Repligen Waltham and demonstrates the capability of Repligen to continuously provide products that address customer requirements.

3. Terms and Definitions

For the purpose of this Quality Manual, Repligen references the terms and definitions listed in the current ISO 9000:2015 “Quality Management Systems Fundamentals and Vocabulary” document.

4. Context of the Organization

4.1. Understanding the Organization and its Context

Internal Issues	External Issues
Market Share	Customers Satisfaction
Employee Competency	Markets & Competitors
Organizational Performance	Regulatory & Statutory
Quality	Supplier Performance / Qualified Suppliers
Capacity	Overall Economic Climate
Communication	Technology Advances
Infrastructure	Cultural & Social
Intellectual Property	Health, Safety and Environmental Requirements
Internal Politics	Contracts/Agreements
Workforce Wellness	
Work-life balance	
Continual Improvement	
Business Continuity	

4.2. Understanding the Needs and Expectations of Interested Parties

Interested Parties	Needs and Expectations
External Providers	Prompt payment, health and safety, work relationship
Finance	Accurate inventory and sales data in the enterprise resource planning system, accurate financial reporting
IT	Equipment, qualified business analysts and network administrators, business applications
Sales	Product that meets intended use
Operations	Work toward established goals with the guidance of upper management, obtain the necessary resources to meet company goals and expectations, effective communication
Customers	Value for money, high quality product, expectations for design innovation, on time delivery, low cost, effective communication, technical support, supply continuity, defined lead times, defined points of contact
Distributors	Adherence to contractual agreements, prompt payment, product and price awareness, inventory supply
Contractors / Consultants	Adherence to contractual agreements, prompt payment, health and safety
Local, State and Federal Agencies	Adherence to standards and regulations, file permits and licenses on time, pay the fees on time
Affiliated Educational Institutions	Internship programs for students, support for research projects
Investors	Return on capital, transparency
Shareholders	Return on capital, transparency, effective communication
Competitors	None

Interested Parties	Needs and Expectations
Insurers	No claims, prompt payment, risk management
Board of Directors	Good financial performance, business strategy, legal compliance, avoidance of fines
Research and Development	Work in an environment that promotes the funding and support to continue research activities, new product and process development and product performance characterization
Registrars	Identification of applicable statutory and regulatory requirements for the products and services provided, understanding business strategy, application within the QMS, and update/maintenance of QMS
Field Service	Space, equipment, measurement tools to perform equipment/hardware maintenance and repair, tools for asset tracking
Field Applications	Training on product features, attributes, benefits, competitive analysis, access to sale information, tool for tracking product evaluations
Human Resources (employees)	Good and safe work environment, job security, recognition and award, training, effective communication
Marketing	Correct product branding, accurate product information and positioning
Product Management	Funnel, order and sale data; access to cost of goods sold (COG) information, technical support for product development and characterization; high quality product manufactured according to QMS; market and competitor analysis

4.3. Determining the Scope of the Quality Management System (QMS)

Repligen is a bioprocessing focused life science company capable of manufacturing Affinity ligands, Affinity resins, pre-packed chromatography columns, Alternating Tangential Flow systems and ELISA kits. Additionally Repligen performs new product development and executes product field service. Repligen's products and services are provided globally to customers developing and manufacturing biotherapeutics.

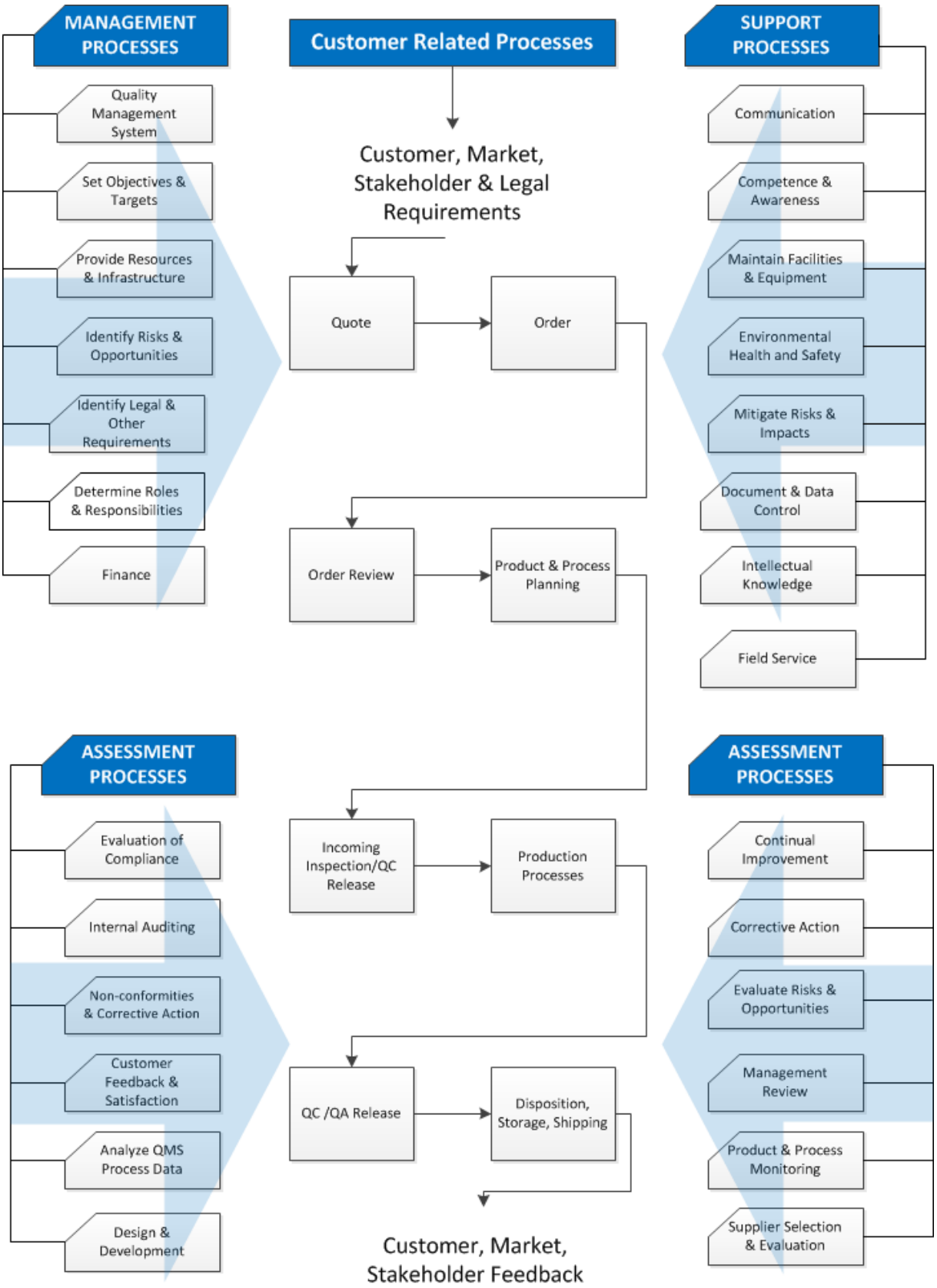
4.4. Quality Management System and its Processes

Repligen has established and implemented the QMS, which is maintained and continually improved according to the requirements of the ISO 9001:2015 standard including processes needed and their interactions.

Repligen determined required inputs and desired outputs of the processes, criteria and methods needed for effective operation and control of these processes, as well as resources needed and responsibilities and authorities for processes. Sequences and interactions between the processes are described in Figure 1: Process Map.

During management review, Top Management of Repligen evaluates business performance and evaluates the QMS for continual improvement. Reference Attachment 1 for specific documents supporting ISO 9001:2015 clauses.

Figure 1: Process Map



5. Leadership

5.1. Leadership and Commitment

5.1.1 General

The Top Management of Repligen is accountable for the effectiveness of the QMS and providing resources to ensure that the Quality Policy is compatible with the strategic direction and the context of the organization.

The Top Management ensures that QMS requirements are integrated into Repligen's business processes, and that the QMS is achieving the intended results.

The Top Management communicates the importance of an effective QMS, promotes continual improvement, a process approach, risk-based thinking, and supports relevant management roles to demonstrate leadership to their areas of responsibility.

5.1.2 Customer Focus

The Top Management of Repligen demonstrates leadership and commitment with respect to customer focus through ensuring:

- that customer and statutory and regulatory requirements are defined, understood, and consistently met
- the risks and opportunities that can affect conformity of products and services and the ability to enhance customer satisfaction are determined and addressed
- the focus on enhancing customer satisfaction is maintained

5.2. Policy

Repligen has defined the Quality Policy and is available to employees and the public.

This Policy represents the framework for continually improving the QMS and ensuring customer requirements are met.

5.3. Organizational Roles, Responsibilities and Authorities

Top Management is ultimately responsible for the quality of Repligen Waltham's products and services since they control the resources, systems and processes by which quality products are produced. Top Management is authorized and responsible for business planning, development and the communication of our policies, QMS, establishment and deployment of quality objectives, the provision of resources needed to implement and improve the QMS and attending annual management reviews.

Responsibilities and authorities for relevant roles are assigned by the Top Management and communicated within Repligen to:

a. Ensure that the QMS conforms to ISO 9001:2015;
b. Report on the operation of the QMS and any opportunities;
c. Ensure that continuous improvement is taking place;
d. Ensure that customer focus is promoted throughout the organization;
e. Ensure the integrity of the QMS is maintained during changes;
f. Ensure that responsibilities and authorities related to the QMS are communicated and understood.

All managers demonstrate their commitment to the development and improvement of the QMS through the provision of necessary resources, through their involvement in the internal audit process and through their proactive involvement in continual improvement activities. Emphasis is placed on improving both the effectiveness and efficiency of key system processes.

All managers are authorized and responsible for the execution of the business plan and the implementation of the policies, processes, and systems described in this manual. All managers are responsible for planning and controlling the management system processes within their area of responsibility, including the establishment and deployment of operational level objectives needed to implement and improve these processes.

All employees are responsible for the quality of their work and implementation of the policies and procedures applicable to the processes they perform. Employees are motivated and empowered to identify and report any known or potential problems and to recommend related solutions to aid the corrective action process. Employees are required to perform training for their job function. Employees are required to focus on customer satisfaction.

The Management Representative (Sr. Director of Quality) is responsible for ensuring that processes needed for the QMS are maintained, performance and required improvement of the QMS are reported into the Top Management, and to promote awareness of customer requirements throughout the organization. The Management Representative is authorized to perform a yearly review of the QMS with the Top Management.

6. Planning

6.1. Actions to Address Risks and Opportunities

While planning the QMS, Repligen considers the context of the organization, needs and expectations of interested parties, and the scope of the QMS.

Repligen determines risks and opportunities that ensure the QMS can achieve intended results, enhance desirable results, prevent or reduce undesired effects, are compatible with the context of the organization, and can achieve continual improvement.

6.2. Quality Objectives and Planning to Achieve Them

Departmental Management continuously defines measurable and timed quality objectives for the relevant functions and levels within the organization. The objectives are monitored by each Departmental Head in the context of monitoring and measurement as well as during management review.

Quality objectives are consistent with the Quality Policy and prescribed to all levels and functions in Repligen, taking into account applicable requirements, relevance to conformity of products and services, and enhancement of customer satisfaction.

Activities in the plans to achieve quality objectives, responsibilities, deadlines, and resources for the realization of the objectives are defined and documented as Quality Objectives. Realization of the plans is regularly reviewed by Top Management in order to monitor realization and to include new or modified situations, or at least during regular management review meetings.

6.3. Planning Changes

The Management Representative (Sr. Director of Quality) plans changes to the QMS considering the purpose of the changes and potential consequences, integrity of the QMS, and allocation or relocation of responsibilities and authorities.

7. Resources

7.1. Resources

Repligen determines and provides resources needed for establishment, implementation, maintenance, and continual improvement of the Quality Management System.

7.2. Competence

Repligen provides the necessary staff with the needed knowledge and skills, organizational infrastructure, and financial resources for establishing, implementation, maintenance, and improvement of the QMS.

In cases where it is deemed necessary and justified, Repligen will hire competent external personnel and organizations from relevant fields for realization of activities for which the organization does not have adequate resources.

Managers are responsible for identifying the needs and conducting professional training of employees who carry out activities that may have a significant impact on the quality of product, service and customer satisfaction.

Each organizational department manager /process owner is responsible for the suitable competency of his/her workers, on the basis of education, training, and/or work experience, in accordance with the requirements of their work.

The method of ensuring the necessary competencies for roles, responsibilities, and authorities for implementation and control activities within the QMS was established.

7.3. Awareness

Repligen ensures that people doing work under its control are aware of the Quality Policy, relevant quality objectives, their contribution to the effectiveness of the QMS, and implications of nonconformance with the QMS requirements.

7.4. Communication

External Communication

Product Management, Marketing and Investor Relations are responsible for determining external communications relevant to the QMS, product specific documentation and shareholder information.

Internal Communication

Meeting	Host	Site	Global
Quarterly All Hands Meeting	CEO/COO		X
Monthly Operations Meeting	VP		X
Annual Management Review	Sr. Director of Quality	X	
Departmental Staff Meeting	Departments Heads	X	
Daily Pulse Boards	Departments Managers	X	

7.5. Documented Information

Documented information of the Quality Management System is carried out through the following documents:

- Quality Policy, Quality Objectives
- Quality Manual
- Procedures for Document and Record Control
- Documented information, including records, is documented in Attachment 1.

8. Operation

8.1. Organizational Planning and Control

Repligen's Research and Development organization is responsible for planning and developing processes needed for product realization.

8.2. Requirements for Products and Services

Repligen's Product Management organization defines the communication with customers, the process of determining and reviewing the requirements related to product and services, and changes to requirements for product and services.

8.3. Design and Development of Products and Services

Top Management appoints persons responsible for planning, realization, and management of product design and development and project management.

8.4. Control of Externally Provided Processes, Products and Services

Repligen ensures that delivered product is compliant with specified purchasing requests by documenting an adequate method for evaluation and selection of suppliers.

8.5. Production and Service Provision

Repligen defines activities of planning and executing the product realization process under controlled conditions, in order to ensure full capability of the process and to prevent nonconformities.

8.6. Release of Products and Services

Repligen performs product release testing at the appropriate stage to verify that the product and service requirements are met.

8.7. Control of Nonconforming Outputs

The organization ensures that nonconforming outputs are identified and controlled to prevent their unintended use or delivery.

9. Performance Evaluation

9.1. Monitoring, Measurement, Analysis and Evaluation

9.1.1 General

Departmental Management in Repligen defines what will be monitored and measured, as well as the methods and timing for monitoring and measuring. Results of the monitoring and measuring will be evaluated at appropriate levels and functions in the organization and the Top Management will evaluate the performance of the QMS during monthly operations meetings and management review.

9.1.2 Customer Satisfaction

Repligen monitors customers' perceptions and feedback to which their needs and expectations have been fulfilled.

9.1.3 Analysis and Evaluation

Repligen analyzes and evaluates appropriate data and information arising from monitoring and measurement.

The results of the analysis are used to evaluate:

- conformity of products and services;
- the degree of customer satisfaction;
- the performance and effectiveness of the Quality Management System;
- if planning has been implemented effectively;
- the effectiveness of actions taken to address risks and opportunities;
- the performance of external providers;
- the need for improvements to the Quality Management System.

9.2. Internal audit

Repligen conducts internal audits at planned intervals to demonstrate conformance and effectiveness of the Quality Management System.

9.3. Management Review

Top Management of Repligen conducts regular reviews of the QMS, at least once a year. Operations meetings are conducted for providing monthly trending of the QMS between management review meetings.

10. Improvement

10.1. General

Repligen determines and selects opportunities for improvement and implements any necessary actions to meet customer requirements and enhance customer satisfaction.

These include:

- improving products and services to meet requirements, as well as to address future needs and expectations;
- correcting, preventing, or reducing undesired effects;
- improving the performance and effectiveness of the Quality Management System.

10.2. Nonconformity and Corrective Action

Repligen handles nonconformities in order to assess the impact, control, and implement corrective actions.

Repligen has established a corrective action system to investigate and document the root cause and actions to correct supplier, internal, and customer-reported nonconformities. Corrective actions are assigned to a responsible individual and tracked by number and completion date.

10.3. Continual Improvement

Repligen continually improves the suitability, adequacy, and effectiveness of the Quality Management System.

The organization considers the results of analysis and evaluation, and the outputs from management review, internal audits and operations meetings, to determine if there are needs or opportunities to be addressed as part of continual improvement.

11. Revision History

REVISION	INITIATED BY/COMMENTS	DATE	DIR/OCR NO.
01	John Tuttle / Company Quality Manual – Initial Release	04/2008	DIR080123
02	John Tuttle / Company Quality Manual: Updated by ISO 9001 Stage I Audit.	10/2008	DCR080312
03	John Tuttle / Company Quality Manual: Document updated to reflect current business practices	11/2008	DCR080338
04	Maiysha Laguerre: Document updated to reflect current revisions to ISO 9001:2008 standard, business practices and address audit findings	10/2009	DCR080363
05	Deirdre Georgoudis: Rewrite to reflect change in scope and reflect ISO requirements for a QM.	09/2011	DCR11225
06	Deirdre Georgoudis: Added Appendix 1 Repligen Document Reference to ISO standard and new process flow charts; added relevant ATF per CC14015	10/2014	DCR14446
07	Noelia Ortiz: Updated Appendix 1. Updated the hierarchy for Repligen documentation. Updated Section 2 “Scope”. Included reference to SOP-10069 “Product Design and Commercialization Process”.	09/2016	DCR16674
08	N. Ortiz: Removed exclusions from Section 2. Corrected SOP # for Product Development document from SOP-10028 to SOP-10069. Added note “The numbers in the figure below are the ISO 9001 clause number” in section 6.1.2. Added ‘Affinity Resins” in section 7.1.1.	12/2016	DCR17122
09	N.Ortiz: Complete re-write to align with ISO 9001:2015. CAPA # 16025.	06/2017	DCR17671
Effective Date	**Revision Number**	**Author**	**Description**
See Effective Date in Overlay	10	N. Ortiz	Added in section 7.4 a table to document the internal communication. Added responsibilities section. Corrected procedure numbers in Attachment 1. Added the needs and expectations for interested parties.

Attachment 1

ISO 9001:2015 Clause		Repligen Procedure
4. Context of Organization		
4.1	Understanding the organization and its context	CAP-1004, Quality Manual
4.2	Understanding the needs and expectations of interested parties	
4.3	Determining the scope of the quality management system	
4.4	Quality management system and its processes	
5. Leadership		
5.1	Leadership and commitment	SOP-1488, Management Review
		SOP-10117, Ensuring and Evaluating Customer Satisfaction
		SOP-10047, Recall Procedure
5.2	Policy	CAP-1005, Repligen Corporate Quality Policy
5.3	Organization roles, responsibilities and authorities	SOP-1488, Management Review
		SOP-1490, Internal Audit Procedure
		SOP-1496, Supplier Management Program
6. Planning		
6.1	Actions to address risks and opportunities	SOP-10079, Corrective Action Procedure
		SOP-10108, Risk Management
6.2	Quality objectives and planning to achieve them	SOP-1488, Management Review Monthly Operation Meetings
6.3	Planning of changes	SOP-1447, Product and Process Change Management
7. Support		
7.1	Resources	SOP-1488, Management Review
		SOP-1501, Preventive Maintenance Program
		SOP-1171, Equipment Control
		SOP-MFG-1205, Pest Control
		SOP-MFG-1207, Environmental Monitoring of the Seyon Manufacturing Suites
		SOP-MFG-1209, RO/DI Monitoring
		SOP-MFG-1264, Manufacturing General Housekeeping
		SOP-QC-1264, General Housekeeping Procedure
		SOP-MFG-1350, Gowning and Personnel Flow for the Manufacturing and QC Facilities
		SOP-MFG-1330, Equipment Flow within the Waltham Manufacturing Facility
		SOP-MFG-1351, Cleaning Procedure for the Repligen Manufacturing Facilities
		SOP-MFG-10009, Maintenance of the OPUS ISO 7 and ISO 8 cleanrooms
		SOP-1181, Calibration Program
		Repligen Biosafety Plan
		Repligen Chemical Hygiene Plan

ISO 9001:2015 Clause		Repligen Procedure
		Emergency Action Plan
		Incident Reporting
		Information Security Program
		IT Retention Policy
7.2	Competence	SOP-10112, HR Job Description and Resume Procedure
		SOP-QC-1036, Quality Control Training Program
		SOP-MFG-1349, Manufacturing Training Program
7.3	Awareness	SOP-1489, Training Procedure
7.4	Communication	Company Meetings
7.5	Documented information	SOP-1150, Control of Records
		SOP-1098, Control of Documents
		SOP-1302, Using, Completing and Reviewing Repligen Documentation
		EQ-9000, Installation, Operation, and Maintenance of the Repligen Electronic Management System
		EQ-9001, Training and Development Module Procedure
8. Operation		
8.1	Operational planning and control	SOP-1488, Management Review
		SOP-1447, Product and Process Change Management
		SOP-1449, Quality Systems Oversight of US Biologics (USBL)
		Component Specification (CS), Analytical Reagent (AR), Raw Material (RM), Component Production Record (CPR), Bottling Production Record (BPR)
8.2	Requirements for products and services	SOP-10117, Ensuring and Evaluating Customer Satisfaction
		SOP-10035, Customer Property
		SOP-10106, Product Design and Development Procedure
		Customer Requirements (CR) documents
		SOP-10015, Processing OPUS Custom Orders
		SOP-1134, Processing of Customer Complaints
		SOP-1496, Supplier Management Program
		SOP-1447, Product and Process Change Management
		Supply and Quality Agreements
8.3	Design and development of products and services	SOP-1378, Repligen Validation Program
		SOP-10110, Design History Files Management
		SOP-10108, Risk Management
		SOP-10106, Product Design and Development Procedure
		SOP-10069, Product Development and Commercialization Process (PDCP)
		SOP-1447, Product and Process Change Management
8.4	Control of externally provided processes, products and services	SOP-1496, Supplier Management Program
		SOP-10091, New Supplier Procedure
		SOP-10090, Supplier Corrective Action Request
		SOP-1495, Receiving Procedure

ISO 9001:2015 Clause		Repligen Procedure
		SOP-1094, Control of Incoming Raw Materials and Analytical Reagents
		SOP-1488, Management Review
		SOP-10042, Control of Incoming Components
		SOP-1449, Quality Systems Oversight of US Biologics (USBL)
8.5	Production and service provisions	SOP-1378, Repligen Validation Program
		SOP-1501, Preventive Maintenance Program
		SOP-1181, Calibration Program
		SOP-10079, Corrective Action Procedure
		SOP-1097, Identification System
		SOP-10035, Customer Property
		SOP-MFG-10006, Aseptic Technique
		SOP-10093, Shipping Procedure
		SOP-MFG-1351, Cleaning Procedure for the Repligen Manufacturing Facility
		SOP-1134, Processing of Customer Complaints
		SOP-10047, Recall Procedure
		SOP-1447, Product and Process Change Management
		SOP-10117, Ensuring and Evaluating Customer Satisfaction
8.6	Release of products and services	Component Batch Records, Bottling Batch Records
		Certificate of Analysis
		SOP-10048, Repligen ATF Factory Acceptance Test (FAT)
		SOP-10093, Shipping Procedure
		SOP-10042, Control of Incoming Components
		QC Release Testing SOPs
8.7	Control of nonconforming outputs	SOP-1188, Nonconforming Material Procedure
		SOP-10047, Recall Procedure
9. Performance Evaluation		
9.1	Monitoring, measurement, analysis and evaluation	SOP-10079, Corrective Action Procedure
		SOP-10117, Ensuring and Evaluating Customer Satisfaction
		SOP-1501, Preventive Maintenance Program
		SOP-1181, Calibration Program
		SOP-1134, Processing Customer Complaints
9.2	Internal audit	SOP-1490, Internal Audit Procedure
9.3	Management Review	SOP-1488, Management Review
		Operation Meetings
10. Improvement		
10.1	General	SOP-1488, Management Review
10.2	Nonconformity and Corrective Action	SOP-10078, Root Cause Analysis Procedure
		SOP-1188, Nonconforming Material Procedure
		SOP-10079, Corrective Action Procedure
		SOP-1496, Supplier Management Program
		SOP-10090, Supplier Corrective Action Request

ISO 9001:2015 Clause		Repligen Procedure
		SOP-1487, Out of Specification (OOS) Results
		SOP-1050, Documenting Planned and Unplanned Deviations
10.3	Continual improvement	SOP-1490, Internal Audit Procedure
		SOP-10079, Corrective Action Procedure
		SOP-1496, Supplier Management Program
		SOP-1488, Management Review