BIOSIDUS
Quality for millions.

Integrated Management System Manual

Quality, environment and occupational health and safety.

December 2021

MATERIAL FOR INTERNAL USE


BIOSIDUS
Quality for millions.

CONTENTS OF THIS DOCUMENT

BIOSIDUS PRESENTATION

BIOSIDUS is an Argentine biotechnology company founded in 1983 that has since then developed a global business in the supply of biopharmaceuticals in Asia, Africa, Eastern Europe and Latin America.

BIOSIDUS has two production plants.

The Almagro plant, located in the Autonomous City of Buenos Aires, is involved in R&D activities and the production of active pharmaceutical ingredients, with production capacity in bacterial fermentation and large-scale cell culture.

Aseptic filling, lyophilization and packaging operations are carried out at the Bernal plant, located on the outskirts of Buenos Aires.

It was the first Latin American company to produce recombinant proteins for therapeutic use by bacterial fermentation or large-scale cell culture, having to date eight proteins in different products and dosage forms in the local and export markets, including human growth hormone, erythropoietin, granulocyte colony-stimulating factor, lenograstim, alpha and beta interferons, teriparatide.

HEADQUARTERS IN BUENOS AIRES, ARGENTINA
SALES IN 45 COUNTRIES WORLDWIDE
5 SALES OFFICES IN LATAM AND 3 IN OTHER CONTINENTS
PRESENCE IN ALMOST EVERY COUNTRY IN LATIN AMERICA
IN THE PROCESS OF OPENING A SUBSIDIARY IN URUGUAY
L&D AGREEMENTS IN 40 COUNTRIES
40 JOINT VENTURES UNDERWAY IN LATIN AMERICA
IMPLEMENTATION OF SEVERAL FILL & FINISH TECH TRANSFERS

ALGERIA	CAMEROON	ETHIOPIA	LIBYA	PAKISTAN	TOGO
ARGENTINA	CHILE	GABON	MALI	PANAMA	TUNISIA
AZERBAIJAN	COLOMBIA	GEORGIA	MOROCCO	PARAGUAY	UKRAINE
BANGLADESH	CONGO	GUATEMALA	MAURICIO	PERU	URUGUAY
BENIN	CÔTE D'IVOIRE	GUINEA	MAURITANIA	R. OF CONGO	UZBEKISTAN
BOLIVIA	COSTA RICA	HONDURAS	MEXICO	R. DOMINICANA	VENEZUELA
BOTSWANA	ECUADOR	IRAQ	NAMIBIA	SENEGAL	VIETNAM
BRAZIL	EGYPT	LEBANON	NICARAGUA	SRI LANKA	
BURKINA FASO	EL SALVADOR		NIGER	THAILAND	

Integrity Program

At **BIOSIDUS**, we are committed to providing the highest quality medicines while complying with the highest ethical standards. We believe that ethics and transparency are fundamental to the development of an open, honest and fair work environment. This is why we have an Integrity Program, which includes the Code of Conduct and several specific policies that establish the common values that must be used in our daily work and to carry out our commercial actions.

2. Leadership

THE MANAGEMENT OF BIOSIDUS ASSUMES ITS RESPONSIBILITY TO LEAD THE ORGANIZATION IN COMPLYING WITH THE PRINCIPLES SET OUT IN ITS INTEGRATED POLICY, WHICH IS BASED ON TRANSPARENT AND SOCIALLY RESPONSIBLE CONDUCT. THIS IS IN LINE WITH THE VALUES AND PRINCIPLES SET OUT IN THE COMPANY'S CODE OF ETHICS.

To this end, it establishes annual Objectives that contemplate and are compatible with the context in which its activities are carried out and with its strategic direction, and establishes mechanisms for periodic monitoring and follow-up of the progress of these objectives, constantly promoting improvement and increasing the positive perception of the company by customers and society.

The Management of **BIOSIDUS** regularly analyzes the context to detect changes that are generated or could be generated in order to establish strategies to either address risks and take preventive actions or take advantage of opportunities.

Periodically, the Management carries out a critical analysis of the performance of its Integrated Management System, assessing the degree of effectiveness in meeting the expectations established in the Objectives.

The Management develops its strategic planning taking into account the following:

- A consistent focus on its stakeholders (customers, shareholders, employees, suppliers and control bodies), for which we promote the maintenance of fluid and effective communications in order to be aware of their needs and expectations, their level of satisfaction and the opportunities to improve their consideration.
- The development of all its business activities under the concept of environmentally and socially responsible conduct, with an unrestricted respect for the legal requirements in force and placing special emphasis on pollution prevention, as well as on the safety and health of its employees.
- Maintain the certification of its Integrated Management System under recognized international standards.

The Management has established an Integrated Management Policy which is reproduced in this Manual and which has taken into account in its definition,

- Establish a performance framework for the Organization and the definition of objectives.
- Integrate the commitments with legal and stakeholder requirements.
- Uphold the importance of preventing and reducing the negative impact on the environment, avoiding or reducing the consumption of non-renewable natural resources.
- Preserve the safety and health of employees by providing safe and healthy working conditions to prevent injuries and adverse health effects.
- Ensure effective mechanisms for worker participation and consultation.

Ensure that this Policy is known and respected by all members of the Organization and is available to stakeholders upon request.

For the practical implementation of these management guidelines, **BIOSIDUS** Management has defined and maintains an organizational structure described below, assigning roles and responsibilities at different levels.

The Management is committed to defining and providing the necessary resources to maintain and improve the Integrated Management System on a continuous basis.

3. Integrated Management Policy

QUALITY, ENVIRONMENT, OCCUPATIONAL HEALTH AND SAFETY POLICY.

BIOSIDUS is a leading company that has been developing and manufacturing biotechnological pharmaceutical products based on recombinant proteins since 1984.

Due to our operational characteristics and the role that our activity imposes on us, we consider essential to promote and assume the commitment to comply with the **Quality, Environment and Health and Safety** requirements established by our company, in accordance with what has been agreed with our Customers and the applicable legal and regulatory requirements and others to which the company subscribes.

We will carry out our commitment as follows:

- Providing services with the highest quality standards, always seeking to exceed our customers' expectations by adding value to the satisfaction of their needs.
- Developing environmentally friendly processes, preventing and reducing negative impacts and promoting its protection.
- Promoting and facilitating the participation and consultation of our employees.
- Training and carrying out other preventive activities with the objective that our employees perform a safe work, preventing and reducing adverse effects on their own health, safety or physical condition, that of their colleagues, of our Customers and of any person who interacts with our operation.
- Optimizing our consumption of natural resources, thus actively participating in the preservation and protection of the environment for future generations.

Based on the commitments made and aware of the need to continue along the path of continuous improvement, the Management of **BIOSIDUS** has decided to:

ESTABLISH a Quality, Environment and Health and Safety Integrated Management System (IMS), with the aim of ensuring that the quality of our products, the reduction of environmental impacts, and the safety and health of our activities are in accordance with the commitments made in this document.

MAINTAIN the IMS effectively, ensuring that the principles and commitments of this Policy are shared, understood, developed and kept up to date at all levels of the organization.

ENSURE that all activities, products and services are carried out within the framework established by this Integrated Policy.

MINIMIZE and prevent harmful environmental impacts that our activities, products and/or services may cause, as well as undesired impacts or occupational risks and deviations regarding the quality of the service provided.

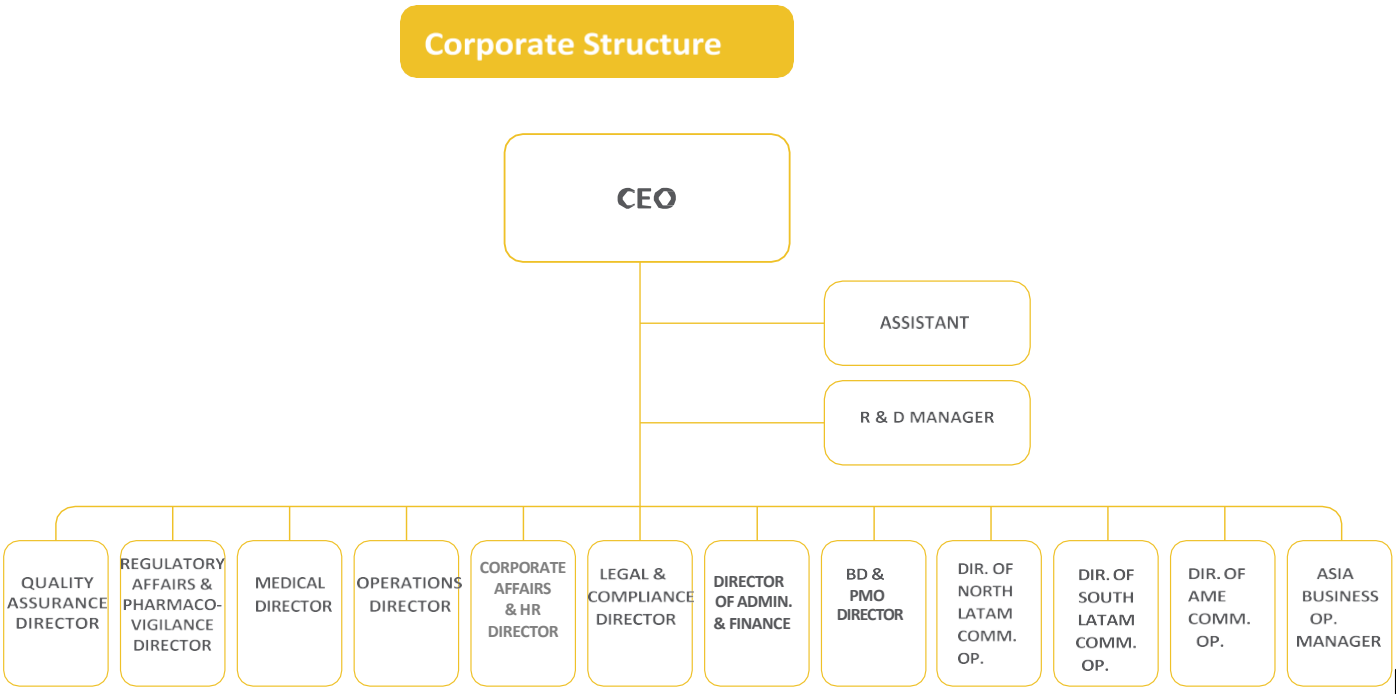
ADVANCE in the knowledge and awareness of quality requirements, reduction of environmental impacts and potential occupational risks as a tool for their prevention and/or minimization.

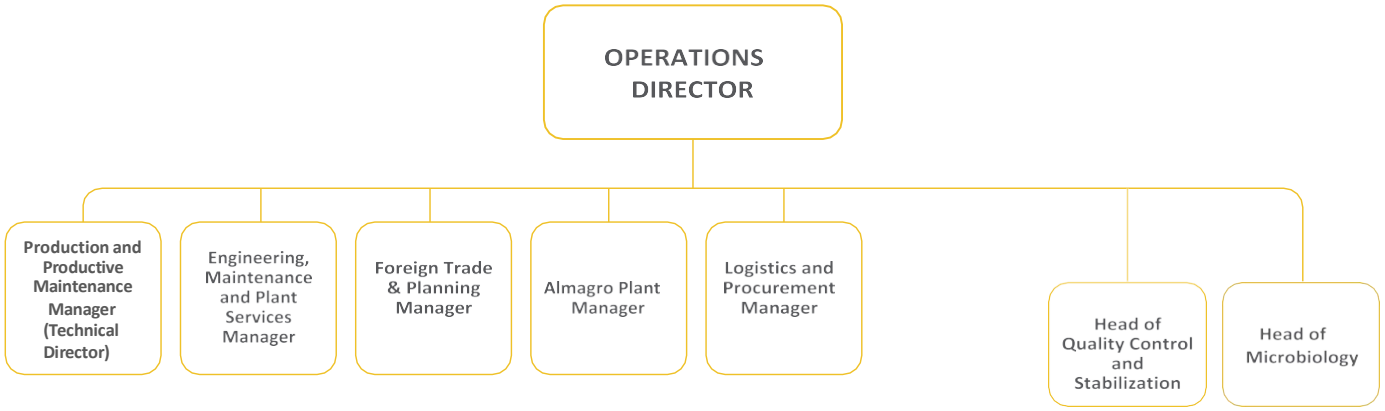
Mariano de Elizalde
CEO

COMPLEMENTARILY AND IN LINE WITH THIS CORPORATE INTEGRATED MANAGEMENT POLICY, BIODISUS HAS A QUALITY POLICY FOR ITS GMP SYSTEM IN FORCE IN BOTH PLANTS, WHICH IS PART OF THE DOCUMENTED INFORMATION IN FORCE.

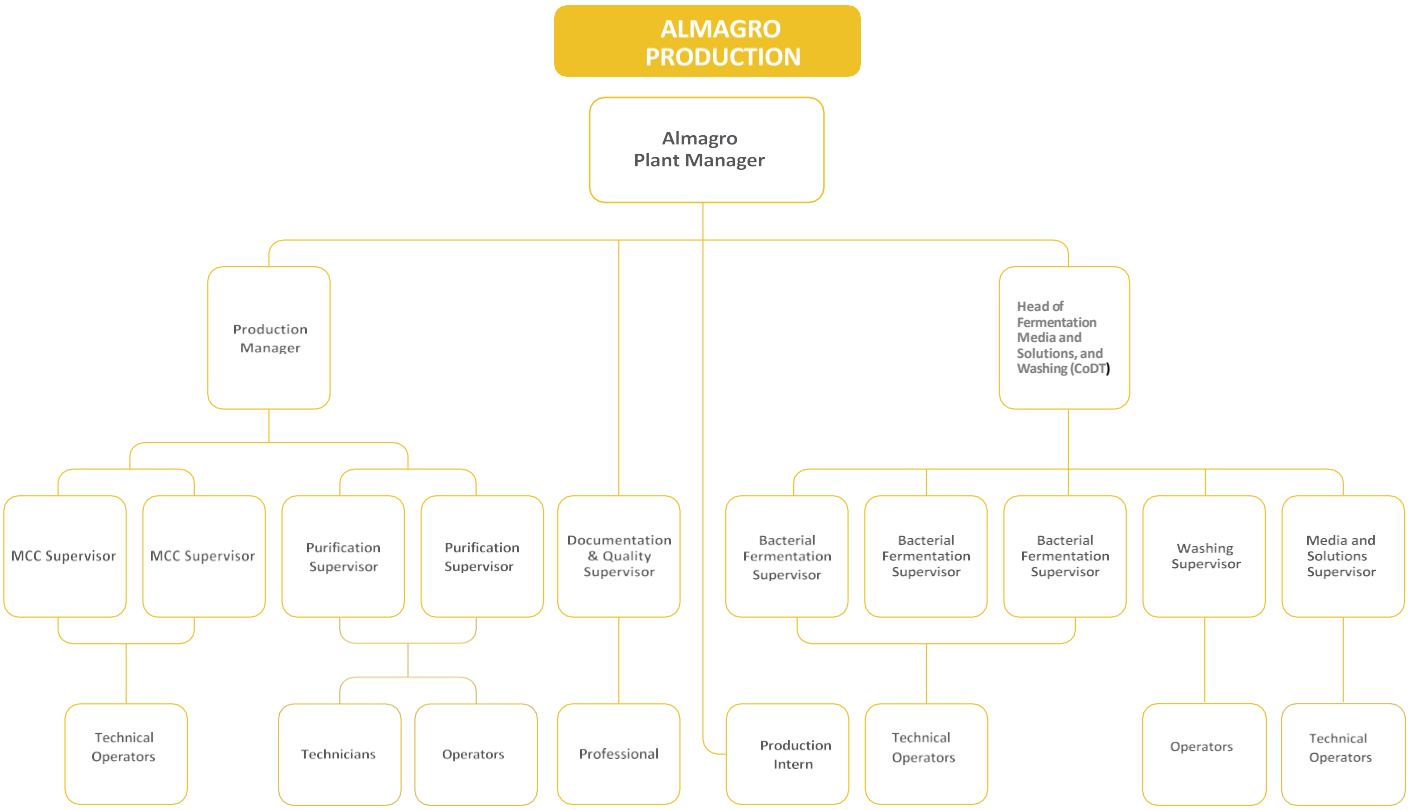
4. Organizational Structure

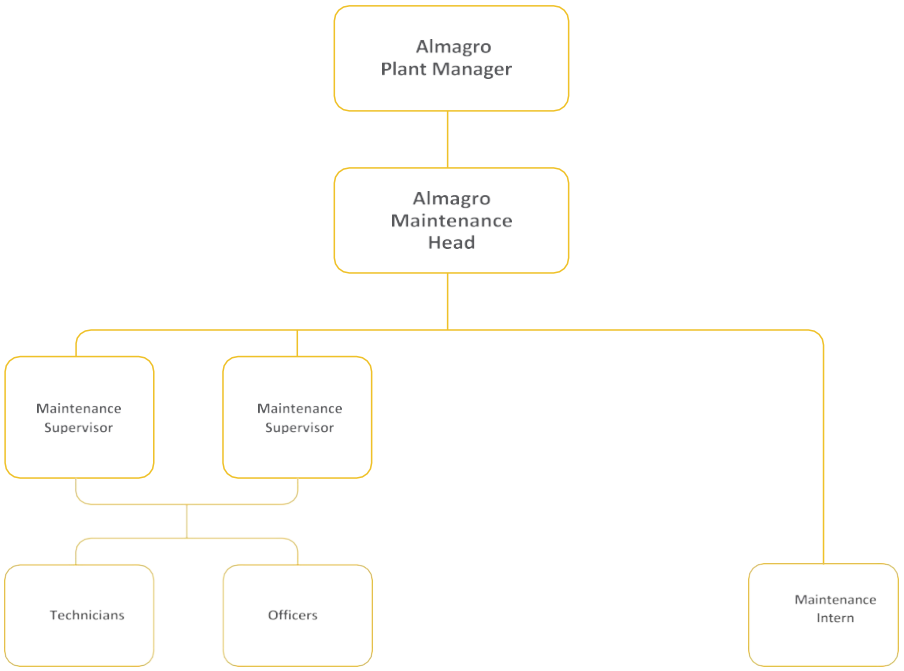
4.1 ORGANIZATION CHART – GENERAL MANAGEMENT

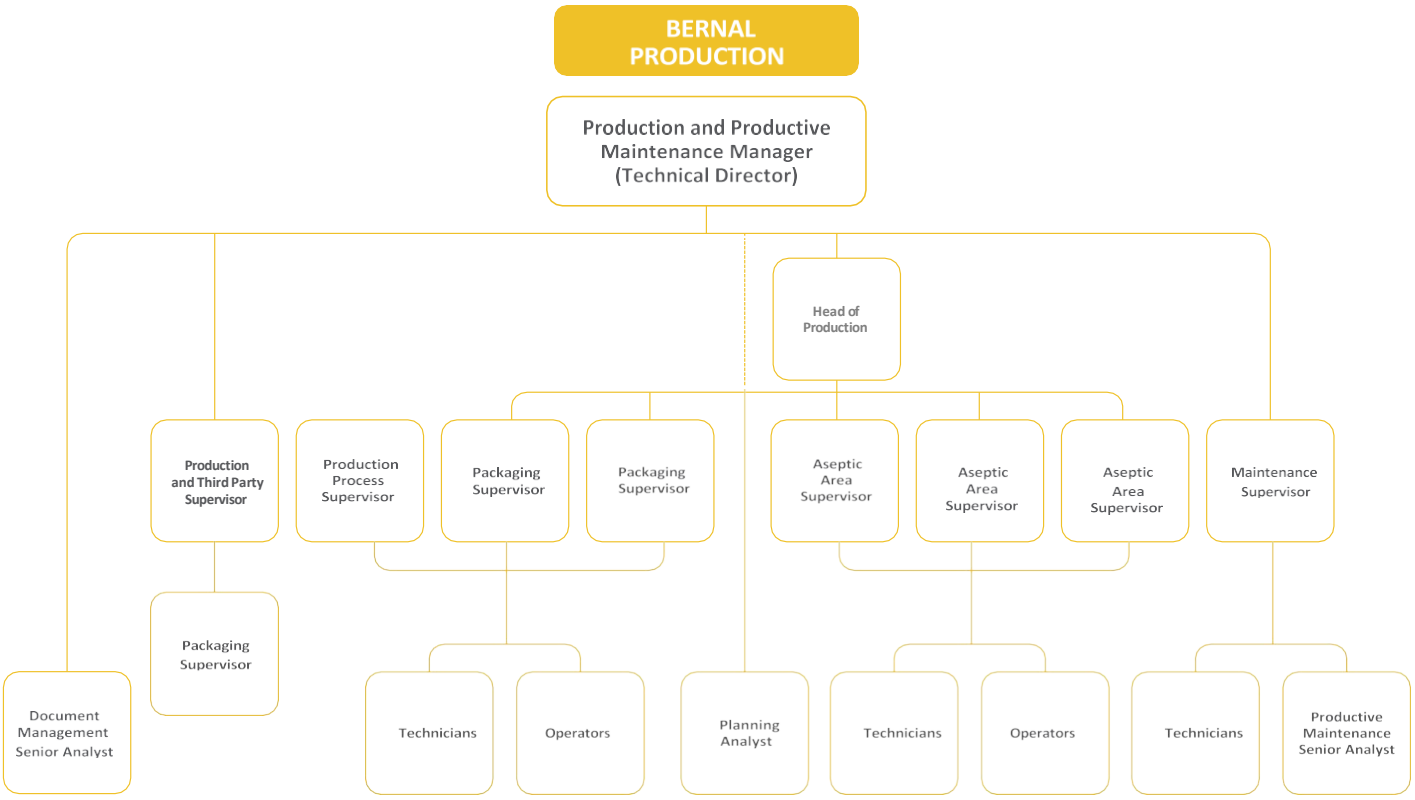




The Operations Management is the highest authority for the Integrated Management System, the scope of which is established in this Manual.






BERNAL PRODUCTION
Production and Productive Maintenance Manager (Technical Director)
Head of Production
Production and Third Party Supervisor
Production Process Supervisor
Packaging Supervisor
Packaging Supervisor
Aseptic Area Supervisor
Aseptic Area Supervisor
Aseptic Area Supervisor
Maintenance Supervisor
Document Management Senior Analyst
Packaging Supervisor
Technicians
Operators
Planning Analyst
Technicians
Operators
Technicians
Productive Maintenance Senior Analyst

4.2 ROLES AND RESPONSIBILITIES

BIOSIDUS recognizes the responsibilities as established in its Organizational Chart and in the other regulatory documents that make up the Integrated Management System. Employees may perform one or more of these tasks, being delegated the corresponding authority to fully exercise the tangible and intrinsic responsibilities of the position.

Their roles and responsibilities are defined in the job descriptions and in the different levels of the documented information of the IMS.

5. IMS General Requirements

BIOSIDUS HAS ESTABLISHED AND MAINTAINS AN INTEGRATED MANAGEMENT SYSTEM THAT MEETS THE REQUIREMENTS OF THE ISO 14001 AND ISO 45001 STANDARDS, TAKING INTO ACCOUNT THE BASIC PRINCIPLES OF A MANAGEMENT SYSTEM, AND IS DESCRIBED IN THIS IMS MANUAL.

These principles are:

- Customer focus
- Leadership
- Engagement and communication with people and stakeholders
- Process focus
- Evidence-based action taking
- Management of mutually beneficial relationships with suppliers
- Integration of Environmental and Health and Safety management into decision making
- Compliance with legal requirements
- Appropriate environmental protection practices and techniques
- Appropriate OSH risk prevention practices and techniques
- Self-management and performance evaluation
- Harmonization with other management systems

The **BIOSIDUS** Integrated Management System covers the main activities that affect the Quality of the company as well as the Environment with which it interacts and the Health and Safety of its workers.

In its design, the following has been taken into account:

- Ensure the ability to provide services that regularly meet customer requirements.
- Facilitate opportunities to improve customer satisfaction levels.
- Address risks and opportunities considering the context in which it operates.
- Generate evidence of performance that satisfies legal and relevant stakeholder requirements.

5.1 SCOPE OF THE INTEGRATED MANAGEMENT SYSTEM

Research, Development and Manufacture of Active Pharmaceutical Ingredients (API) of biotechnological origin, specifically recombinant proteins at its plant in the city of Buenos Aires.

Manufacture of Biotechnological Pharmaceutical Products, containing recombinant proteins as active ingredients, at its plant in Bernal, province of Buenos Aires.

5.2 PROCESS-ORIENTED APPROACH

The **BIOSIDUS** Integrated Management System has been developed favoring the process-oriented approach, taking into account an analysis of the risks identified in each process, in order to define the stages and management methods for each process, and to establish systematic measures for eliminating or reducing them to tolerable levels.

This consideration of risks is not limited to health, safety and environmental aspects, but is also extended to compliance with the service quality requirements agreed with the customer and, based on the context analysis carried out by the Management, to other aspects of the company's management that contribute to the success of the business and its expansion in the market.

This analysis not only allows us to identify risks that could affect our ability to operate effectively, but also helps us to detect opportunities to improve our management.

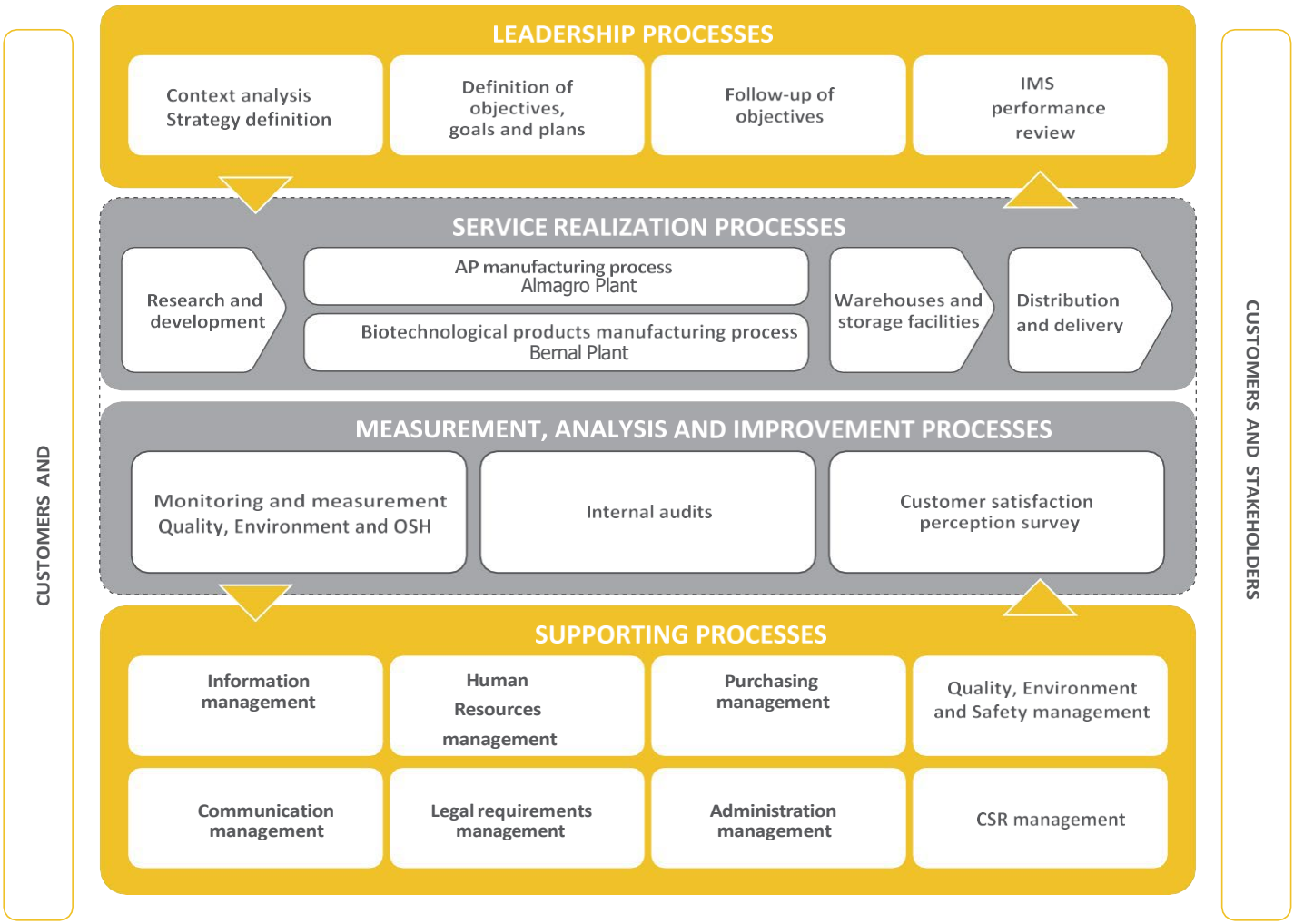
5.3 PROCESS MAP

BIOSIDUS has a process map that details all the processes within the scope of the IMS and the interactions between them.

BIOSIDUS manufactures biotechnological pharmaceutical products for therapeutic support in several pathologies. To this end, it has specific facilities entirely dedicated to the production of Active Pharmaceutical Ingredients (APIs) in its Almagro plant.

It also has specific facilities entirely dedicated to the production of Finished Products in its Bernal plant, using the APIs produced in the Almagro plant.

The general process map, which includes the processes common to both plants, is shown schematically, followed by the map of the manufacturing processes in each of these facilities.



API manufacturing process (Almagro Plant)	*See Annex 1*
Biotechnological products manufacturing process (Bernal Plant)	*See Annex 2*
Warehouse and Storage management processes	*See Annex 3*
Logistics and delivery processes	*See Annex 4*

5.4 PLANNING

In planning its Integrated Management System, BIOSIDUS has taken into account the following principles:

- Ensure that the IMS has the necessary elements to meet stakeholder requirements.
- Ensure that work is done to prevent undesirable effects and seek to increase desirable effects.
- Focus management on continuous improvement of processes, IMS performance, environmental performance, and occupational health and safety performance.

This planning takes into account actions to manage risks and opportunities. This includes not only taking action to reduce the likelihood or eliminate risks, but also addressing them when pursuing opportunities.

Associated documentation

»Context Analysis
»Risk and Opportunity Analysis (SWOT)
»Action plans
»Stakeholder Identification Matrix

5.5 ORGANIZATIONAL CONTEXT

BIOSIDUS regularly (at least once a year) carries out an analysis of the context in which it operates in order to identify those aspects that may affect its ability to provide services that meet the expectations of its customers and stakeholders.

This exercise, which focuses on risk and opportunity analysis, is intended to provide the information needed to guide the necessary changes, either to take preventive action if the risk assessed warrants it, or to take improvement action if opportunities are identified.

Although a documented systematic approach has not been formally implemented, context analyses are usually carried out at Management meetings with the participation of the management teams, following the logic of a SWOT scheme. Opportunities and risks are assessed, and action plans are developed based on the conclusions of these analyses. This approach is extended to all IMS processes both in the plants and in the warehouse.

The evolution of the defined objectives and plans is regularly monitored, both at the operational level of each plant (more frequently) and at the strategic level, the latter involving the direct participation of the Management.

Although summary minutes of the issues discussed are prepared in all cases, access to the contents of these minutes is generally reserved and, in some cases, confidential, given their strategic nature.

Associated documentation

»Context Analysis
»Risk and Opportunity Analysis (SWOT)
»Objectives / Action plans

5.6 UNDERSTANDING STAKEHOLDERS NEEDS AND EXPECTATIONS

Fort the analysis of the context mentioned in the previous paragraph, **BIOSIDUS** considers the following stakeholders, which are relevant for the effective performance of the IMS, taking into account their expectations and needs.

- **External customers:**
  Since they can be companies, agencies or others that interact with the company.
- **Internal customers:**
  People who make up the work team of our company, operational and administrative.
- **Suppliers:**
  Both of supplies and services contracted by our company.
- **Control bodies:**
  Both in terms of limits and regulatory controls of our activity, as well as the management of authorizations and permits.
- **Other stakeholders:**
  Municipalities, trade unions, foundations, chambers, etc.

Associated documentation

»Stakeholder Identification Matrix

5.7 IDENTIFICATION OF PRODUCT AND PROCESS REQUIREMENTS

When identifying the requirements for products and services, the following are taken into account:

- Those agreed with the customer in the offer, the order or the purchase order or in any other document in which the customer describes the conditions of presentation and delivery of the product.
- The national and international standards that regulate the quality requirements of the product.
- Legal and/or regulatory requirements.
- The requirements that BIOSIDUS deems necessary for the proper manufacture, storage, preservation and shipment of its products, even if they have not been expressly mentioned by the customer.

The manufacture of pharmaceutical products in any activity that is regulated by health control agencies, in our case ANMAT (National Administration of Drugs, Food and Medical Devices) and its enforcement agency INAME (National Institute of Medicines).
According to the legislation in force, the authorization to manufacture and sell pharmaceutical products requires the obtaining of the corresponding certificate, which is granted after the submission of all the documentation that supports the development of the product, the manufacturing process, the specifications to be met and the studies that support the safety and efficacy of its use.
The applicable legislation requires the application of **GMP** (Good Manufacturing Practice) standards for this activity and the obtaining of the corresponding GMP certificate by the manufacturing facilities.
GMP standards describe the requirements for the facilities, equipment, processes and employees involved in the tasks related to the manufacture of medicines, covering aspects from the purchase of inputs through each and every stage of the manufacture of products, including their shipment and distribution to customers.

The products are manufactured according to carefully designed and validated processes, where all operations are documented.

The **BIOSIDUS** Integrated Management System is responsible for ensuring the application and compliance with all requirements defined in the GMP guidelines and other specific guidelines related to the manufacture of pharmaceutical products to demonstrate that the processes are compliant, robust and capable of consistently producing pharmaceutical products that meet their respective specifications.

The main documents supporting this activity are as follows:

»CGGZ-242/** Quality Assurance Program
»VMP-001/** Validation Master Plan
»CGGZ-241/** Supplier Selection and Qualification
»CGGZ-093/** Internal Audits Program
»CGGZ-003/** GMP Training Program
»CGGZ-346/** Periodic Product Reviews
»Aspect Identification and Environmental Impact Assessment Matrix
»Hazard Identification and Risk Assessment Matrix
»CHWZ-013/** Operational Controls, Hazards, Risks, Aspects, and Environmental Impacts

5.8 IDENTIFICATION OF LEGAL REQUIREMENTS

BIOSIDUS identifies and determines how to manage the applicable legal requirements and other requirements to which it subscribes in relation to its environmental, energy efficiency, occupational health and safety aspects.

This information is documented and updated as part of the Integrated Management System processes, and the necessary activities are implemented to ensure compliance.

The company periodically reviews and documents its compliance with legal requirements.

Associated documentation

»SOP identification, update of the assessment of compliance with legal requirements
»Regulatory Requirements Identification Matrix
»Regulatory Compliance Verification Report

5.9 IDENTIFICATION OF ENVIRONMENTAL ASPECTS AND IMPACT ASSESSMENT

BIOSIDUS identifies the aspects and assesses the impacts to determine which of its activities and processes are significant, taking into account those that it can control and influence. This identification takes into account the life cycle perspective.

This information is documented and kept up to date. It considers not only normal operating situations, but also abnormal situations and emergencies that may occur.
Based on the results of these analyses, the necessary operational control measures are implemented to eliminate the negative impacts or reduce them to tolerable levels and, where possible, to increase the positive impacts.

Associated documentation

»CHWZ-012/** Identification and updating of aspects and environmental impact assessment
»Aspect Identification and Environmental Impact Assessment Matrix
»CHWZ-013/** Operational Controls, Hazards, Risks, Aspects, and Environmental Impacts

5.10 HAZARD IDENTIFICATION AND RISK ASSESSMENT

BIOSIDUS identifies the hazards arising from the analysis of its activities and processes and carries out a risk assessment in order to implement control measures to eliminate them, where possible, or reduce them to a tolerable level.

This information is documented and updated as part of the Integrated Management System processes, and the necessary activities are implemented to keep the risks under control.
The information arising from these identification activities is integrated to be taken into account in the operation control measures implemented on the processes and formally established in the different levels of documentation that make up the IMS.

These operational control measures are applied in our facilities, both to our employees and to third parties who have to perform tasks in our facilities, through the definition of specifications and an active interaction with them.

Associated documentation

»Hazard Identification and Risk Assessment Matrix
»CHWZ-013/** Operational Controls, Hazards, Risks, Aspects, and Environmental Impacts

5.11 ACTIONS TO ADDRESS RISKS AND OPPORTUNITIES

BIOSIDUS takes into account its knowledge of the context in which it operates, as well as the identification and understanding of the needs of its customers and stakeholders, in order to determine the actions necessary to address the risks and/or opportunities that arise.

These actions are implemented and monitored in order to ensure that the expected results are achieved, to increase the desired effects, to reduce the likelihood of undesired effects and to encourage improvement. The monitoring of these actions shall allow, whenever possible, timely corrective action to be taken in the event of deviations.

To ensure their effective implementation, they will be integrated into the current processes of the IMS and may include the modification of these processes and the documented information related to them, if necessary.

When the need for changes to the IMS becomes apparent, the management will ensure that they are implemented in an orderly and planned manner, taking into account:

- What will be the impacts of these changes
- What resources will be needed
- To what extent will the IMS be affected

Associated documentation

»Risk and Opportunity Analysis (SWOT)
»Action plans
»Stakeholder Identification Matrix

5.12 OBJECTIVES, TARGETS AND PROGRAMS

Based on its analysis of the context, the Management establishes annual performance objectives and prepares programs for the different processes included in the Integrated Management System to define actions for their fulfillment.

The objectives are consistent with the Integrated Management Policy, are measurable whenever possible, and include a commitment to continuous improvement of IMS performance.

The definition of objectives takes into account what is to be done, who is responsible, what resources are required, in what time frame the result is expected to be achieved, and how the results will be evaluated to define effectiveness.

Once defined, the objectives are documented, communicated, and monitored and evaluated through a management dashboard during periodic management control meetings. Finally, their fulfillment is evaluated in the Management System Performance Review carried out by the Management.

Associated documentation

»IMS Objectives – Year 2021
»CPZZ-541/** "Project management"
»IMS Performance Review Report

5.13 OPERATIONAL PLANNING

BIOSIDUS plans, implements and controls the processes necessary to meet the requirements of its Management System and the performance objectives defined by the Management. For this purpose:

- It determines the requirements related to the services, including legal and other requirements, environmental, safety and health aspects that affect the operation.
- It establishes criteria for the implementation of processes and for the acceptance of their results.
- It determines the resources required.
- It defines the nature and extent of controls to ensure the effectiveness of the processes.
- It defines the amount and scope of documented information needed to ensure the reliability of the processes and to provide evidence of compliance with the requirements established for their implementation.
- Control over change is maintained.
- Where third party services are required as part of the service, control over these operations and their performance is ensured.

5.14 CHANGE PLANNING

Changes to the IMS are planned and may have the following origins:

- Management review.
- External or internal audits of the IMS.
- Customer complaints and claims.
- Satisfaction surveys.
- Improvements in production, storage and shipping processes.
- Identification of failures or opportunities for improvement in the development of processes.
- Changes in applicable regulations.
- Information obtained from usual market analysis of competitors, customers and suppliers.
- Changes suggested by stakeholders.

Regarding the manufacturing processes of its products, and in accordance with GMP requirements, it is fundamental to demonstrate the reproducibility of the processes, and in this sense, the implementation of changes is a reason that could potentially affect the processes or the products manufactured.

For this reason, **BIOSIDUS** has developed a specific documented procedure for evaluating and approving changes to facilities, equipment, procedures and processes.
This procedure describes an in-depth multidisciplinary evaluation to cover different concepts and needs, involving specialists in each of these disciplines, with the aim of identifying possible impacts, using different tools to develop an analysis of potential risks and define the necessary actions to minimize them.

The Quality Assurance department is responsible for managing all proposed changes, authorizing the implementation of only those that have been proven safe and do not affect the processes and products involved.

Associated documentation

»CGGZ-005/** "Change Control"
»Change Record

6. Supporting processes

INFORMATION MANAGEMENT

BIOSIDUS, which has adapted its Management System to the new approaches of international standards, is aware of the following variations in the information necessary for its Integrated Management System to effectively meet the performance expectations of its stakeholders.

Documented information

It is the information that must be maintained and controlled, regardless of its medium (paper, digital) and its origin (this includes external documentation), that is necessary to support the proper execution of the processes (manual, procedures, instructions) and that generates evidence of the results obtained (records).

To this end, there are documented procedures to ensure that the documented information is approved by the established levels of responsibility, distributed in a controlled manner so that it is available when and where it is needed, and maintained intact and protected from inappropriate use while it is in force.

These controls are extended to internal documentation, with different methodologies depending on the type of documentation and its use within the organization.

The documented information of the Management System shall be provided by the person in charge of the IMS.
The control and distribution of the documented information is carried out in accordance with the Quality Assurance area and the digital records are archived in the "Integrated Management System" digital folder within the Biosidus SharePoint.

Undocumented information

BIOSIDUS has other internal and external sources of information that contribute to its knowledge of its development environment, its relationship with stakeholders and its strategic decisions, which are not necessarily documented but are monitored to ensure their reliability.

The Management decides to what extent this information may be documented according to its use in the IMS.

General documentation requirements

The Integrated Management System has been implemented on the basis of documenting the information necessary to ensure the relevance, applicability and consistency of the methodologies that ensure compliance with expectations regarding its performance.

This documented information includes that which is required by the applicable regulatory framework and that which the organization has defined as necessary to regulate and organize its processes and to provide evidence of compliance.

One of the fundamental aspects on which the Integrated Management System is based is the management of the documentation that supports all the activity that BIOSIDUS performs for its drug manufacturing process.

The structure that ensures the consistency of the BIOSIDUS Integrated Management System is as follows:

IMS Policy
It establishes the first level of policy with respect to Quality, Environment, Energy Efficiency and Occupational Health and Safety. It is available to the public through the website, signs and delivery to those stakeholders who request a copy.

Integrated Management System Manual
It identifies the elements of the IMS and how they interact. It is the document that states the policy of the Integrated Management System and describes the way in which its operating mechanisms are implemented, responding to the requirements of the standards that define its frame of reference.

General procedures
These documents define, at a general level, the responsibilities, methodologies and associated procedures that are normally associated with a main process and raise the interaction with other processes of the IMS.

Specific procedures / Work instructions / Forms
These documents, as the name implies, define responsibilities, methods and associated records at a specific level. They are usually derived from a general procedure.
In the case of instructions, they define in a practical way the steps to be followed or the criteria for performing tasks, as well as the information to be left in an associated record. Forms are the formats provided for keeping the company's operating records.

Technical documentation
The technical documentation is all supporting documentation of the processes that appear necessary to complete definitions of technical aspects of the process or products. This level of documented information can be both internal and external.

Records
These are documents that provide objective evidence of the degree of compliance with Quality, Environmental, Health and Safety and Hygiene requirements.

Their content is defined not only to provide evidence of activities performed, but more importantly, to provide data analysis for decision making and improvement, as well as to ensure traceability and reproducibility of processes.

All management records are kept in accordance with legal or contractual requirements and are available to any supervisor or auditing body that may require them, with prior authorization from BIOSIDUS Management.

BIOSIDUS uses international guidelines and standards for the drafting and preparation of these documents, on the basis of which it develops its activities and the specific supporting documents.

Associated documentation

»CGGZ-353/** Documentation Structure of the Quality System
»CGGZ-001/** Preparation and Organization of Procedural Standards
»CGGZ-131/** Change of documents
»CGGZ-174/** Format and preparation of Master Batch Record (MBR)

The procedure CGGZ-174/** "Format and preparation of Master Batch Record (MBR)" describes the procedure for drafting the most important activity performed by the company and refers to the preparation of production batches of active ingredients and finished products.

INFORMATION MANAGEMENT

BIOSIDUS ensures internal communication between the different levels and functions involved in the Integrated Management System processes.

This communication takes place through various mechanisms that are discussed and described in the current procedure. These include training, meetings and events, e-mails, bulletin boards, etc.

This document also addresses the mechanisms through which external communication with stakeholders, contractors and visitors is ensured for the purpose of communicating or responding in a timely manner.

Associated documentation

»Internal and External Communications Policy

BIOSUDUS STATES THAT IT WILL NOT COMUNICATE ITS SIGNIFICANT ENVIRONMENTAL ASPECTS EXTERNALLY UNLESS EXPRESSLY REQUESTED IN WRITING BY A STAKEHOLDER. COMMUNICATION WILL ONLY TAKE PLACE WITH THE EXPRESS APPROVAL OF THE MANAGEMENT, WHICH WILL ASSESS THE RELEVANCE OF THE REQUEST.

PARTICIPATION AND CONSULTATION

BIOSIDUS has different areas that facilitate the participation and consultation of workers at all levels, either through their representatives, as in the case of the Joint Health and Safety Committee and the periodic meetings held by the Human Resources area with union representatives, or directly and personally, in response to the Open Door Policy promoted by the Management.

A very relevant aspect of participation takes place in the planning process, when the opinions of all areas of both plants are surveyed using a SWOT approach, analyzing the context from their perspective and providing their opinions and comments.

In the Joint Committee, specific health, safety and environmental protection issues are analyzed by the representatives.

Associated documentation

»Minutes of Joint Committee Meeting
»Minutes of Meetings with the Union
»CRRZ-015/** "Internal regulations of the Health, Hygiene, Safety and Environment Committee"

7. Resource management

BIOSIDUS MANAGEMENT ENSURES THAT ADEQUATE RESOURCES ARE PROVIDED FOR THE EFFECTIVE OPERATION AND IMPROVEMENT OF ITS INTEGRATED MANAGEMENT SYSTEM.

To this end, it has identified resource requirements, including the designation of trained staff to manage, perform and verify IMS-related activities, organizational infrastructure, and financial and technological resources.

This analysis assesses the capabilities and limitations of internal resources and the need to supplement them with external resources operating within the IMS control framework.

People

The staff designated with the responsibilities defined in the BIOSIDUS Integrated Management System have been appointed to each position according to their competence, based on their level of education, training, practical skills and experience.

BIOSIDUS Management pays special attention and care to all members of the organization or third parties working with the company who perform tasks that may potentially cause significant environmental impacts and/or occupational health and safety risks.

BIOSIDUS has established and ensures that all employees receive adequate training to perform their activities, and has established general guidelines for the coordination and implementation of training activities, taking into account the following criteria:

- It identifies employee competency needs for activities that affect quality, the environment, and occupational health and safety.
- It provides training to staff in order to meet these needs.
- It evaluates the effectiveness of the training provided.
- It ensures achievement of management objectives.
- It maintains appropriate records of Education, Experience, Training and Qualifications.

Periodic activities are carried out to ensure awareness of IMS Policy, IMS requirements and procedures, significant environmental, energy efficiency and occupational health and safety issues, roles and responsibilities, achievement of objectives and consequences of deviation from established procedures.

Competence

BIOSIDUS selects its staff and identifies their training needs in order to ensure that they can competently carry out the activities assigned to them and that affect the quality of the services.

The Management allocates resources to ensure that these requirements are met, reviews and approves a Training Plan according to the needs identified in each area, and verifies compliance.

To this end, each Management must identify the training needs of the employees under its responsibility and communicate them to the HR area (the GMP Training Plan is managed by the Quality Assurance area) in order to design the Training Plan with this information.

All staff in the organization undergoes:

- An introductory training (induction), including the contents of the Code of Ethics and the Integrity Program.
- Specific training for the assigned function, organized by the area manager and carried out by experienced and qualified staff.
- Ongoing training in health and safety and responsible care of the environment.

Additional training is carried out when the need is identified by the person in charge of the area. This training may take the form of:

- Internal courses conducted by external and/or internal staff.
- External training courses.
- Practical test.
- All training courses are recorded in a file managed by the Human Resources area.

Records are kept to evaluate the effectiveness of the training.

Associated documentation

»SOP CGGZ-132/** Job Description
»Annual Comprehensive Training Plan

Awareness

The Management of **BIOSIDUS** ensures that all persons involved in the company, regardless of their level of responsibility in the IMS, know and are aware of the Integrated Policy, the complementary policies, the objectives assigned to their function, the importance and impact of their daily tasks on the effectiveness of the company's operations, the environmental aspects and impacts, as well as the hazards and risks in their work area, and compliance with the requirements of customers and stakeholders.

Awareness is raised through training of all employees, regular work meetings, communication and individual discussions.

The context conditions are taken into account in order to work and develop actions related to disease prevention and the promotion of healthy habits.

Associated documentation

»Internal communications (mailings, signs, messages on social networks)
»Material from lectures and meetings to configure the Training Plan with this information.

Infrastructure

The Management of **BIOSIDUS** provides and maintains the necessary facilities, equipment, materials and supplies to achieve product conformity, to ensure compliance with legal requirements, to ensure environmental performance in accordance with its objectives, and to provide a safe and healthy work environment to prevent injuries and damage to health.

BIOSIDUS has and allocates resources to provide its employees with all the tools, supplies and equipment they need to perform their duties efficiently.

BIOSIDUS has a maintenance area responsible for periodically reviewing and arranging for the different stages of maintenance of its production equipment and plant services facilities. Maintenance is scheduled taking into account the needs and availability of the production lines.

When maintenance tasks cannot be carried out by the company's own staff, services are contracted, which are qualified according to their track record and suitability to perform the tasks entrusted to them.

BIOSIDUS has organized procedures for the proper maintenance of its facilities, equipment and critical services in order to ensure that the processes performed therein are carried out properly and guarantee satisfactory results.

To this end, there is documented information describing the mechanism for organizing and carrying out equipment maintenance according to the frequency defined in each case. Likewise, for some critical equipment, there are specific procedures that describe the different maintenance required, the frequency and the specific tasks for each of them.

Similarly, there is documented information describing the program defined to ensure that the facilities are kept adequate for the tasks.

Associated documentation

»CIZZ-004/** Preventive Maintenance of Plant Equipment
»CIOZ-115/** Building Maintenance

Work environment

The Management of **BIOSIDUS** is particularly aware of the need to create an appropriate work environment to achieve a harmonious performance between the various actors of the processes that integrate its IMS.

To this end, it is committed to the continuous improvement of communication and the creation of participation and consultation channels.

The Management, through its Health and Safety area, defines and manages the environmental working conditions necessary to achieve safe and reliable operations and to comply with the legal framework and commitments acquired that apply to its performance.

Actions related to the maintenance and improvement of the work environment are promoted, such as the maintenance of order and cleanliness, the separation of waste, the care of the transition areas in the plant processes, the adequate conditioning of the cafeteria area and the changing rooms.

Associated documentation

»CHWZ-013/** Operational Controls, Hazards, Risks, Aspects, and Environmental Impacts

Monitoring and measurement resources

BIOSIDUS provides all the means to carry out monitoring and measurement activities, having a file of management indicators whose data are fed by the computer resources available to our organization.

The company also considers as monitoring and measuring devices the computer applications that manage resources, times or deadlines for the execution of tasks supported by such applications. The programs are permanently maintained by specialized staff and the necessary updates are made according to new requirements for the optimization of the service or due to changes in the regulations in force.

All the manufacturing processes of our products are subject to both process and product controls that ensure compliance with the quality and efficiency requirements of each production line.

In order to ensure that the results of these processes are satisfactory, **BIOSIDUS** has defined a series of process controls that are carried out either routinely to ensure the suitability of the facilities and services where the processes are carried out, or during the processes, on some critical parameters that require evaluation and, if necessary, adjustment to ensure compliance with the respective specifications.

These controls extend to the instrumentation necessary to ensure the proper operation of the plant's auxiliary services.

For these controls, measuring and monitoring equipment is available, which is verified and, if necessary, calibrated based on recognized national and international standards reference.

The checks and measurements carried out on these production processes, as well as on the plant services, are periodically verified by the regulatory authorities.

Associated documentation

»ACMZ-029/** Sampling and Microbiological Analysis of Purified Water
»BCTZ-392/** Physico-chemical Analysis of Purified Water
»BCIZ-379/** Water for Injection (WFI) Sampling
»BCMZ-382/** Microbiological Analysis of Water for Injection (WFI) and Pure Steam

»BCTZ-383/** Physico-chemical Analysis of Water for Injection (WFI) and Pure Steam
»CCMZ-078/** Microbiological Control of Air and Surfaces in Classified Areas and Staff
»BPZZ-561/** Process Line Control
»CHWZ-013/** Operational Controls, Hazards, Risks, Aspects, and Environmental Impacts
»Indicator board

Organizational knowledge

BIOSIDUS has the necessary knowledge to efficiently manage the processes of manufacturing, storing and shipping its products under conditions that comply with national and international pharmaceutical industry requirements.

This knowledge is based on:

- The solid academic background of our professionals.
- The personal and collective experience of the people who make up our company.
- The technical support of our associated companies around the world.
- Historical operational information stored in our archives and management systems.
- External and internal training.

BIOSIDUS pays special attention to safeguarding the practical knowledge acquired in the operation of its processes and seeks to promote the training of its staff as a relevant asset for its performance.

8. Operational Control

Operational planning and control

BIOSIDUS plans and develops the processes necessary for the manufacture of its products in accordance with the approved specifications and the applicable legal requirements, taking into account its strategic objectives and the requirements of its Integrated Management System.

The planning is carried out taking into account the commitments made with the customers, the definition of the processes and the documented information related to their control, as well as the conditions of acceptance of the partial and final results of the realization of each process, under safe conditions and ensuring the avoidance of contamination and the protection of the environment.

In each case, the following are determined:

- Documented information to be kept.
- Controls to be performed on the process and its results.
- Competencies of the staff involved.
- Equipment and personal protection elements to be used.
- Contingency plans.

When it is necessary to use the services of third parties to carry out a process or part of it, the controls to be implemented are defined to ensure that the external supply does not affect the quality of the products and that the environmental, health and safety requirements are met.

Customer communication

BIOSIDUS communicates with its customers in order to provide them with adequate information regarding their expectations and to obtain from them their perception of the company's response to their expectations.

This communication ensures that customers are provided with all the information they need about the products and their correct use.

This communication is carried out through telephone contacts, e-mail, web site and direct contacts by our staff.

A mechanism is available to receive customer complaints and claims, through any of the aforementioned channels.

All complaints and grievances will be addressed and responded to within the timeframes established in our internal procedures.

Associated documentation

»Internal and External Communication Policy
»CHWZ-011/** Management of Non-conformities and Opportunities for Improvement

Research and development

The research and development process is one of the pillars that distinguishes **BIOSIDUS** and is an essential part of its growth and expansion process.

In addition to other specific technical aspects related to this process, in which the technical capacity and solid training of the professionals in charge of research and development, who strictly follow the rules of the art and good manufacturing practices, are maintained in all cases and at all stages, an approach oriented to the life cycle of the products and production processes resulting from their development, taking into account their impact on the environment, as well as the safety aspects, both for consumers and for the workers in the production plants.

Control of products and services provided externally

BIOSIDUS ensures effective control over the products and materials purchased, as well as the services it decides to delegate to third parties, so that in all cases the requirements established for its own Integrated Management System are met, where applicable.

To this end, it has documented internal procedures that define the conditions under which purchases and contracts must be formalized, as well as the conditions that suppliers must meet to be qualified and approved in order to be considered in the event of need.

Suppliers are periodically evaluated on their overall performance and records of these evaluations are maintained.

Purchases are made from approved suppliers who are selected and evaluated based on their ability to provide products and services of the required quality and quantity according to specifications.

Formal communications with suppliers ensure

that they have been informed of the methods and criteria by which BIOSIDUS will define the acceptance of products and the provision of services, since these conditions include not only compliance with quality specifications, but also, where applicable, environmental and health and safety aspects.

Associated documentation

»CACZ-030/** "Planned purchases of coded indirect materials and under stock"
CACZ-031/** "Purchases of inputs, spare parts, capital goods, general services, coded or uncoded as indirect"
»CGGZ-241/** Selection and Qualification of Suppliers
»CGGZ-244/** Supplier Audit
»CGGZ-369/** Third party audit (fason)
»CIZZ-012/** Contractor Management
»CGGZ-241/** Supplier Selection and Qualification
»CGGZ-376/** Auditor Qualification

Production

BIOSIDUS' production processes are divided into two groups. The first group corresponds to the production of Active Pharmaceutical Ingredients (API) of biotechnological origin, specifically recombinant proteins. The second group corresponds to the production of biotechnological pharmaceutical products containing recombinant proteins as active ingredients.

Both processes require specific knowledge, technologies, equipment and facilities, which is why **BIOSIDUS** has dedicated its facilities in Almagro to the production of biotechnological APIs and its facilities in Bernal to the production of biotechnological pharmaceutical products using APIs obtained in the Almagro plant.

BIOSIDUS considers, evaluates and controls the environmental aspects of the production processes according to the Aspects and Impacts Matrix. Likewise, the risks associated with these processes have been taken into account in order to minimize the occupational health and safety risks, taking into account what is established in the Hazards and Risks Matrix.

To ensure the operational planning of these processes, we follow the Operational Control of Hazards, Risks and Environmental Aspects SOP.

»API production

The **BIOSIDUS** portfolio includes both proteins from Mammalian Cell Culture (MCC) and Bacterial Fermentation (BF).
In view of the different starting points, the different processes required and the by-products to be purified, BIOSIDUS has separate facilities at its Almagro plant dedicated entirely to the cultivation and purification of proteins by cell culture and other similar facilities also dedicated entirely to the production of proteins by bacterial fermentation.

In both cases, the starting point is a set of cells or bacteria from the Master Banks (MCB) and Working Banks (WCB) made up of transfected cell lines each containing the genetic information for the production of a specific human protein.

Starting from each of these cell banks, a process of expansion of the number of cells or bacteria called "upstream" is carried out, during which the producing organism (cells or bacteria) produces a particular human protein together with a large set of other chemical substances as a consequence of its metabolism.

This is followed by a stage of elimination of all the substances different from the protein of interest, called "downstream", using a wide range of purification strategies and methods, to finally obtain a protein with a high degree of purity that meets the specifications and criteria described in the relevant monographs of the European Pharmacopoeia.

»Pharmaceutical products manufacturing

The Bernal plant is entirely dedicated to the production of liquid and lyophilized injectable pharmaceutical products in the form of vials, prefilled syringes, cartridges and ampoules.

For the production of each of these products, precisely weighed quantities of the active ingredient and its excipients are brought into contact according to specifically defined procedures, which end with a final sterilization by filtration through 0.22 microns, obtaining bulk formulated solutions.

After carrying out certain process controls, if necessary, the bulk formulated solutions are aseptically fractionated in their respective primary packaging, using dedicated areas and fractionation lines for each different dosage form.

The final stage corresponds to secondary packaging using labeling, blistering and cartoning lines according to each customer's requirements.

The batches of product obtained are stored in the warehouse from where they are shipped to customers in our country or abroad.

Documented information

In order to carry out the production processes of APIs and pharmaceutical products, BIOSIDUS has specific documents called Master Batch Records (MBR) for each case or process step, of which specific and controlled copies are issued for the production of each particular batch.

Each of these MBRs is linked to and supported by a large number of specific Standard Operating Procedures (SOPs) and process records.

The set of documents created for each specific batch of each product provides the evidence that the process was performed correctly, following the defined sequence of steps and achieving compliance with the appropriate specifications.

»CHWZ-012/** Environmental Aspects and Impacts
»CHWZ-003 /** Hazards and Risks
»CHWZ-013/** Operational Control of Hazards, Risks and Environmental Aspects
»Environmental Aspects and Impacts Matrix
» Hazards and Risks Matrix

Identification and traceability

Identification is a fundamental requirement of Good Manufacturing Practices that applies to all stages of the product manufacturing process, including inputs, products, equipment, areas, services, etc.

Correct labeling, indicating not only the product/input concerned and its batch number, but also other aspects or characteristics required for proper handling and preservation, is one of the mechanisms necessary to minimize the risk of cross-contamination.

The labeling/identification system shall include concepts that allow adequate traceability throughout the process or shelf life of each item.

The traceability system applies to all inputs and finished products. The system is based on two main concepts.

On the one hand, it assigns each material a unique and unequivocal identification, consisting of a **description** and a **code**.

On the other hand, it assigns to each new input entry or to each new process an **identification batch number**, which is associated with a series of characteristics such as quantity, number of packages, expiration date, etc. This batch number allows each component to be identified throughout its useful life in **BIOSIDUS**, until it is consumed or expires.

In addition to these two identification concepts (code and batch number), there is a third traceability component, namely **its status** (approved, quarantined or rejected), which allows not only the correct identification of each input or batch of a given product, but also to decide whether its use is possible or not.

Another fundamental aspect of the traceability system is the use of **production orders**, where the batches of each input assigned and used are listed. In this way, through the production orders, it is possible to identify in which different products and processes each batch of each input has been used, thus achieving a complete traceability that covers all production stages.

BIOSIDUS has a computerized support where all these issues are parameterized to achieve the adequate traceability necessary to comply with the requirements of the control authority and the international organizations that require it.

Likewise, there are records that allow the traceability of the actions and operational controls related to the environmental management and with those controls that have been defined for the safety of the operations and the protection of the workers.

9. Performance evaluation

Monitoring, measurement and analysis

BIOSIDUS plans and implements the necessary monitoring, measurement, analysis and improvement processes to demonstrate the conformity of its services, to ensure the continuity of the Integrated Management System and to continuously improve its effectiveness.

Customer satisfaction evaluation

BIOSIDUS carries out monitoring to find out how its customers perceive its response to their needs and expectations.

This information is essential both for the continuous improvement of processes and for the identification of opportunities to offer the customer extensions or variations of the service.

This monitoring is constantly and regularly carried out by commercial and technical contacts, for which we have formal and informal channels.

In addition, a customer satisfaction survey is sent out annually to supplement the information obtained from personal contacts. These surveys may be conducted by mail, e-mail, social networks, or telephone.

The results of the surveys are analyzed in continuous improvement and/or management review meetings.

Associated documentation

Analysis and evaluation

BIOSIDUS analyzes and evaluates the data and information obtained from its continuous monitoring in relation to the evolution of its processes. This information includes, for example:

- The level of customer satisfaction
- The level of conformity achieved by the products
- Environmental performance
- Health and safety performance
- Occupational health performance
- The extent to which actions to address risks and opportunities are effective
- The results of participation and consultation
- The level of supplier performance
- The need to implement improvements

This data is evaluated in management meetings, work team meetings, and performance reviews conducted by management.

Where appropriate and applicable, simple statistical techniques are used to evaluate trends and draw conclusions about a process.

Associated documentation
» IMS Performance Review Report

Internal audits

BIOSIDUS periodically conducts internal audits to verify compliance with IMS requirements and implemented standards, according to the corresponding documented procedure.

Internal audits of the Integrated Management System are scheduled considering the importance of the activities, the results of previous audits, data analysis, process status and the results of the management review.

Non-compliance situations identified during system audits are reported to the areas involved, which handle them appropriately according to their documented procedure for dealing with deviations.

The audits are carried out by qualified staff specially trained in the company and/or designated by the head of the company. The requirements for the qualification of the auditors are described in the aforementioned procedure.

Records are kept of the audit program, of the reports with the results and of the actions taken on the basis of the information reported.

Associated documentation
»CHWZ-010/** Internal IMS Audits
»Internal Audit Program
»Internal Audit Reports
»CHWZ-011/** Management of Non-conformities and Opportunities for Improvement
»IMS Performance Review Report

Management review of IMS performance

At least once a year, the Management of **BIOSIDUS** reviews all processes of the Integrated Management System to ensure their consistency, adequacy, effectiveness and continuous improvement.

The review is carried out during the managers' meetings or during special meetings for this purpose. It anticipates the need for changes to the Integrated Management System, including the Management Policy, related objectives and targets. The main topics covered are:

- Review of the Integrated Policy.
- Review of the annual objectives.
- Results of audits.
- Customer feedback from complaints or satisfaction surveys.
- Process performance and service compliance.
- Incident and accident statistics/Environmental incidents.
- Environmental and health and safety performance results.
- Occupational health performance results.
- Internal and external communication effectiveness.
- Participation and consultation results.
- Status of corrective and preventive actions.
- Monitoring actions from previous management reviews.
- Planned changes that may affect the Quality Management System.
- Recommendations for improvement.

As a result and output of this IMS performance review process, decisions and actions usually arise associated with:

- Actions related to achieving unmet objectives.
- Actions related to improving business results.
- Actions to improve the performance of the Integrated Management System.
- Improvement of building infrastructure, facilities and equipment.
- Improvement of the work environment.
- Resource needs.
- Planning of new objectives.

Associated documentation
» IMS Performance Review Report

Continuous improvement

Continuous process improvement is part of the approach **BIOSIDUS** uses to constantly analyze the information generated by its IMS in order to identify and implement improvements wherever possible.

Associated documentation

»SWOT
»Objectives
»Management Plan
»IMS Performance Review Report

10. Improvement

BIOSIDUS HAS FORMAL AND SYSTEMATIC MECHANISMS IN PLACE TO IDENTIFY AND EVALUATE OPPORTUNITIES FOR IMPROVEMENT AND, WHERE POSSIBLE, DEFINE ACTIONS TO IMPLEMENT THEM.

These improvements are aimed at:

- Correcting and/or preventing deviations from practices or expected results with undesired effects.
- Service improvements.
- Improvements in staff skills.
- Reduction of accidents.
- Reduced consumption of non-renewable resources.
- Improvements in overall IMS performance.

These include, where appropriate, the possibility of innovation and eventually reorganization of processes.

Associated documentation

»SOP XX-Corrective Actions and Improvements
»IMS Performance Review Report

Non - conformity and Corrective Actions

Whenever a non-conformity with one of the requirements of the IMS is detected, either as a claim or a customer complaint, **BIOSIDUS** implements a systematic mechanism for recording and handling in order to minimize the impact of the non-conformity, analyze its cause(s) and take action to prevent its recurrence.

To this end, there is a documented procedure that describes the steps to be followed and ensures that records are kept of all stages of the treatment process.

- Description of non-compliance / deviation.
- Immediate action.
- Root cause analysis.
- Proposed correction.
- Monitoring of implementation.
- Evaluation of effectiveness.

Associated documentation

»CHWZ-011/** Management of Non-conformities and Opportunities for Improvement

Continuous improvement

Continuous process improvement is part of the approach **BIOSIDUS** uses to constantly analyze the information generated by its IMS in order to identify and implement improvements wherever possible.

Associated documentation
»SWOT
»Objectives
»Management Plan
»CHWZ-011/** Corrective Actions and Improvements
»IMS Performance Review Report

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