Manuel Qualité / Quality Manual

	Name	Position	Date
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SUMMARY

POLYPLUS-TRANSFECTION®, PRESENTATION OF AN INNOVATIVE BIOTECH

Polyplus-transfection® is specialized in developing innovative solutions for the **transfection of exogenous nucleic acids into mammalian cells**.

The transfection agents marketed by Polyplus-transfection® are divided into **four product lines**:

- Life sciences research products,
- Non-viral in vivo transfection,
- Production of proteins and antibodies,
- Production of viral vectors for gene and cell therapy.

Since 2001, the company has been marketing its transfection agents worldwide through **a large distribution network**. The company reinvests part of its revenues in research and development. Its mission is to **support scientists with its products and tailored scientific and regulatory support**.

Transfection is a genes or interfering RNA transfer technique that allows the introduction of experimental or therapeutic biomolecules into the heart of cells. A video presenting our different transfection techniques is available on our YouTube channel.

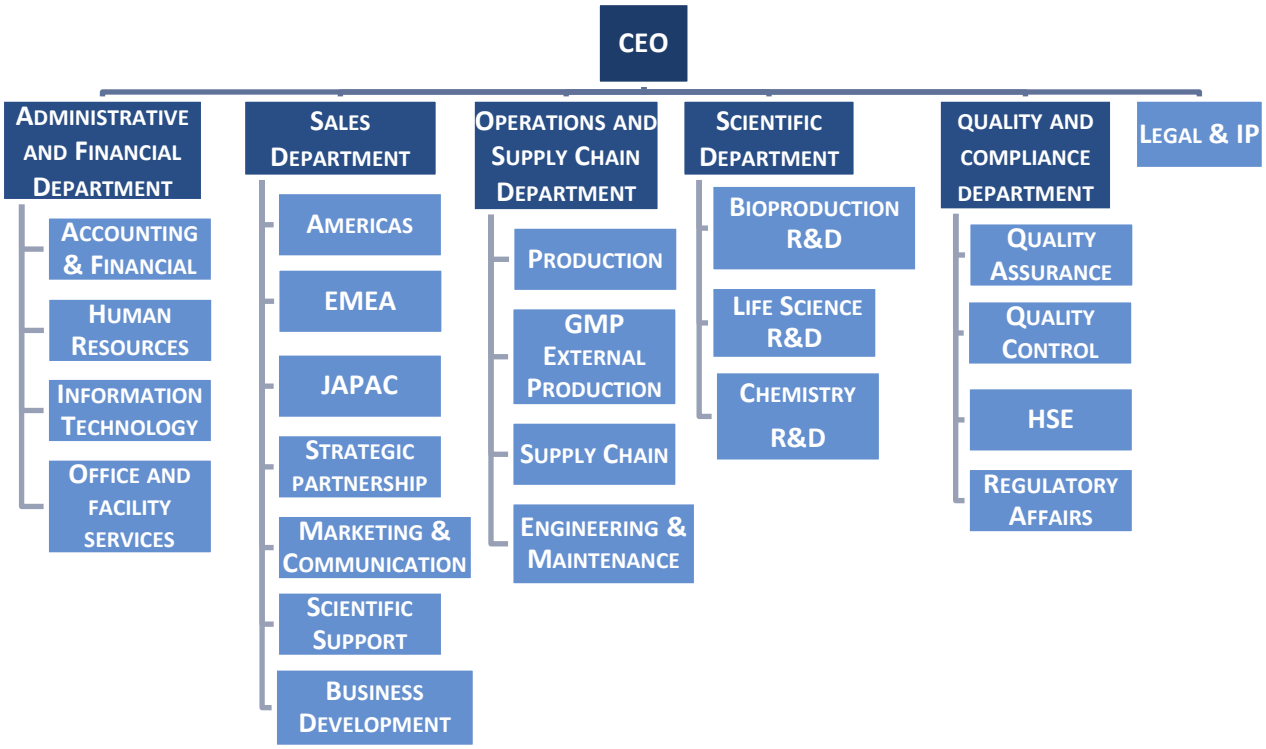
With its expertise in nucleic acid delivery, the Polyplus-transfection® R&D department is dedicated to the development of innovative chemical compounds adapted to the new challenges of biomolecules transfer. This dynamism places the company as **one of the technological leaders in the transfection market**. Polyplus-transfection® holds exclusive licenses of the French National Center for Scientific Research (French: Centre National de la Recherche Scientifique, CNRS) and filed numerous patents.

Phase I, II and III clinical trials for cancer therapies using Polyplus-transfection® reagents produced according to Good Manufacturing Practice (GMP) standards and processes are currently ongoing in Europe and in the United States. In the world of gene and cell therapy, our products are also used as raw materials for the **manufacturing of Advanced Therapy Medicinal Products** (ATMP).

OUR ORGANIZATION

Polyplus-transfection® has more than 80 employees and the research and production site is located at the Innovation Park in Illkirch-Graffenstaden, in the suburbs of Strasbourg (France).

The company is structured according to the following simplified organizational chart:



OUR QUALITY COMMITMENTS

Polyplus-Transfection® has been actively engaged in Quality since 2001 and implemented management of its Health, Safety and Environment (HSE) aspects as well. As a proof of its involvement, the company is committed to define and enforce its internal requirements through its policies and engagements.

The Quality Policy (POL-2019-000001, available on the next page and online) evolved in 2019 to integrate new aspects related to its business growth. The commitments are grouped into three main pillars:

- Customer Focus
- Resources Management
- Continuous Improvement

These quality commitments are deployed in all the company functions through more than twenty processes as presented in this Manual, section "Our Management System Quality". Indeed, **each process exists and defines its objectives through commitments to our Quality Policy**. To ensure and formalize this deployment, a quality and process matrix of commitments was defined (POL-2019-000003). This is analyzed and adjusted during process reviews and management review to continuously reflect the contribution of processes to the implementation of the Quality Policy.

1) Quality Policy

QUALITY POLICY

Polyplus-transfection®'s Quality Management System has structured the organization of the company since its foundation. Hence, the Quality Policy is adapted to the company's framework and supports the global strategy. The Quality Policy is built on three pillars: Product and service development, Resources Management and Continuous improvement. Each pillar gathers specific engagements that provide the necessary framework for each process to attain their objectives.

Our **Product and service development** strategy is defined by the following engagements:

- Respond to customer needs, notably by continuous product innovation
- Satisfy customers to secure their loyalty
- Take into account the needs, expectations and impact of relevant stakeholders
- Consolidate the company's image and its products in terms of quality and reliability

Our **Resources management** is framed by the below engagements:

- Preserve the whole value chain of the company by effective monitoring of all stakeholders (distributors, suppliers, subcontractors, transporters, etc.)
- Organise and secure our equipment and premises for our employees and external providers
- Guarantee an efficient knowledge and skill development management
- Ensure the profitability and durability of the company

Our Quality management system is in **continuous improvement** particularly via the following engagements:

- Control the quality of manufactured products and provided services
- Improve continuously the organization by mastering deviations, changes, risks and opportunities
- Continuously ensure the process management and the achievement of its objectives

With this Policy, Polyplus-transfection® is committed to satisfy applicable legal and regulatory requirements and employees' awareness. In order to enforce our Policy and quality engagements, they are communicated to all employees and to the company's stakeholders.

Illkirch, January 5th 2021

Chief Executive Officer
Mario PHILIPS

Director of Quality & Compliance
Claire WARTEL

2) HSE Policy

HSE POLICY

Our Health, Safety and Environment Policy aims to continuously improve the working conditions in order to ensure a safer and healthier workplace while reducing the environmental footprint of our activities. Through the HSE service, Polyplus-transfection® commits to implement the necessary actions for safety of people and goods and to fulfill the required commitments related to the following three pillars :

Compliance with **hygiene** rules:

- Make aware our employees of the health rules to follow
- Ensure medical check-ups for our employees
- Carry-out audits to ensure compliance to health and safety rules
- Define performance indicators for the monitoring of HSE actions
- Ensure pest control

Safety of goods, individuals and installations:

- Ensure individual safety by improving working conditions to prevent accidents and incidents
- Identify risks, especially chemical and psychosocial, and implement actions intent to reduce and control them
- Ensure that actions are respected by the unique document for professional risks evaluation

Control of **environmental** footprint :

- Control consumption energy resources (water, gas, electricity)
- Recycle packaging and waste (paper, carton, wood, polystyrene boxes, ink cartridge, old equipment)
- Ensure proper management of hazardous products (streamlining of solvent stocks, removal and disposal of waste from laboratory waste)
- Limit consumption of paper (reduce the number of papers send to customers) and access to the document via the website of the company
- Set up an action plan to prevent pollution risk and ensure environmental compliance

A regular monitoring of the above commitments, in particular via HSE audit, ensure the assessment of the actions' effectiveness. Polyplus-transfection® agrees not only to satisfy applicable legal and regulatory requirements, employees' awareness and training. Our HSE policy is communicated to all employees, customers, investors and others relevant stakeholders.

Illkirch, le 28/04/2021

Chief Executive Officer	*HSE Manager*	*Director of Quality & Compliance*
Mario PHILIPS	**Valérie TOUSSAINT**	**Claire WARTEL**
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OUR CERTIFICATIONS

Since 2002, Polyplus-transfection® is ISO 9001 certified by AFNOR **for all its processes**. This allowed the company to build and develop its management system on a solid quality basis.

Over time, the company retained and refined the control of its processes through a continuous improvement strategy. The ISO 9001:2015 certification (certificate below and online) obtained during a surveillance audit carried out in October 2016 confirms the company commitment.

This achievement certifies that the customer needs are taken into account and that the organization responds to the requirements consistently by considering its environment, controlling its processes and fulfilling its commitments. This guarantees **products and services quality** and ensures **customer satisfaction**.

The requirements of ISO 9001 and the certification process of the organization enable company to maintain and develop its Quality Management System described below.

20 years of engagement and appreciation

CERTIFICATION

AFAQ

N° QUAL/2002/19379

POLYPLUS TRANSFECTION

DEVELOPPEMENT, FABRICATION, COMMERCIALISATION DE PRODUITS DANS LE DOMAINE BIOTECHNOLOGIQUE ET LE GENOME HUMAIN.

DEVELOPMENT, MANUFACTURING, MARKETING AND SALES OF PRODUCTS IN BIOTECHNOLOGICAL AND HUMAN GENOME FIELDS.

BP 21 F-67401 ILLKIRCH

AFAQ certifie que pour les activités et les sites référencés ci-dessus toutes les dispositions mises en œuvre pour répondre aux exigences requises par la norme internationale :
AFAQ certifies that all the arrangements covering the above mentioned activities and locations are established to meet the requirements of the international standard :

ISO 9001 : 2000

ont été examinées et jugées conformes.
have been examined and found conform.

2002-12-17

(année/mois/jour) Il est valable jusqu'au / *It is valid until* 2005-12-16 (year/month/day)

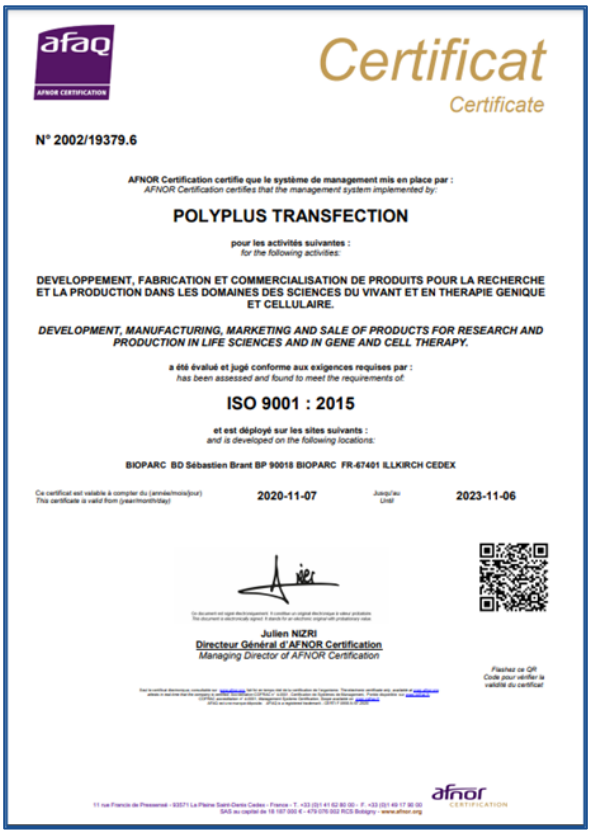
Le Président du Comité de Certification / *The President of the Certification Committee* — G. AUBERT

Le Directeur Général d'AFAQ / *The Managing Director of AFAQ* — O. PEYRAT

Le Représentant de l'Entreprise / *On Behalf of the Firm* — J. BLOCH

AFAQ - 116, AVENUE ARISTIDE BRIAND - BP 60 / F-92224 BAGNEUX CEDEX FRANCE

First certification of Polyplus-Transfection: 17/DEC/2002.



afaq — AFNOR CERTIFICATION

Certificat
Certificate

N° 2002/19379.6

AFNOR Certification certifie que le système de management mis en place par :
AFNOR Certification certifies that the management system implemented by:

POLYPLUS TRANSFECTION

pour les activités suivantes :
for the following activities:

DEVELOPPEMENT, FABRICATION ET COMMERCIALISATION DE PRODUITS POUR LA RECHERCHE ET LA PRODUCTION DANS LES DOMAINES DES SCIENCES DU VIVANT ET EN THERAPIE GENIQUE ET CELLULAIRE.

DEVELOPMENT, MANUFACTURING, MARKETING AND SALE OF PRODUCTS FOR RESEARCH AND PRODUCTION IN LIFE SCIENCES AND IN GENE AND CELL THERAPY.

a été évalué et jugé conforme aux exigences requises par :
has been assessed and found to meet the requirements of:

ISO 9001 : 2015

et est déployé sur les sites suivants :
and is developed on the following locations:

BIOPARC BD Sébastien Brant BP 90018 BIOPARC FR-67401 ILLKIRCH CEDEX

Ce certificat est valable à compter du (année/mois/jour) / *This certificate is valid from (year/month/day)* 2020-11-07 — Jusqu'au / *Until* 2023-11-06

Julien NIZRI
Directeur Général d'AFNOR Certification
Managing Director of AFNOR Certification

Flashez ce QR Code pour vérifier la validité du certificat

afnor CERTIFICATION

Applicable certification of Polyplus-Transfection: 07/NOV/2020

OUR QUALITY MANAGEMENT SYSTEM

1) Transversal management

a) Process approach

Process approach allows the company to manage its activities efficiently to achieve the objectives set while controlling the interactions and interdependencies between the processes.
Polyplus-transfection® choose to use this approach in the development, implementation and improvement of its Quality Management System. Regular updates take place to adapt the quality system to the company evolution (example: creation of a new process, merging of processes).

The company's **process map** includes 3 types of processes:

The Strategic process:

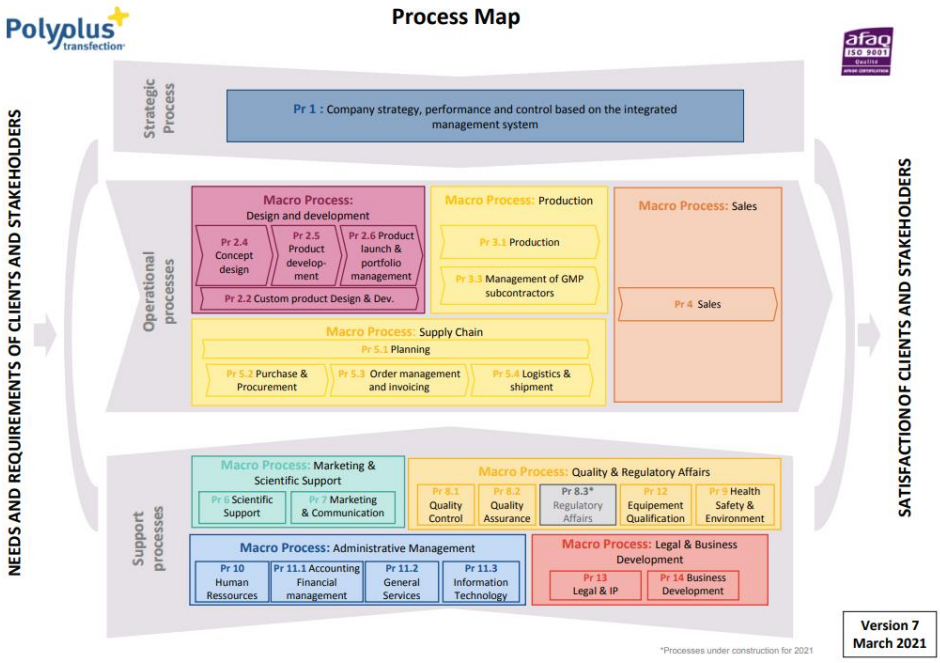
It sets the strategy, defines the commitments, the areas for improvement and allocates the necessary resources for other processes.

The Operational processes:

They follow each other to implement the products and services.

The Support processes:

They work transversally in order to develop and/or maintain the resources needed for the Operational processes.



Process Map, CP-2018-000001 version 5.

In addition to this "Process Map", the company also deploys **"Process Sheets".**

Each process sheet synthetizes:

- The link with the Quality Policy, the objectives and the process indicators,
- The process pilot and the actors
- The activities carried out and the relative records
- The links between the processes (links with the suppliers (internal/external) using SIPOC)

In order to ensure the consistency of these sheets, they are annually reviewed during the Process reviews (PRO-2018-000049).

b) Staff commitment and training

The Quality System of Polyplus-Transfection® is carried by its employees. Our quality approach has been implemented since the foundation of the company, when the company counted less than 10 employees, and that contributed to create a **"quality culture"**.
Each employee is as an actor of one or several processes and contributes to it/them not only by completing his/her activities but also by documenting his/her process (ex: redaction of instruction or procedure), recording adverse events and carrying out actions aimed at improving his/her process/processes.

The commitment of all the employees is stimulated thanks to the following:

- Training on the Quality Management System is given to new employees at their arrival in the company (PRES-2019-000001),
- Trainings on our quality management software are given by the Quality Department (PRES-2019-000002 and PRES-2019-000004),
- The inclusion in the annual evaluation interview of criteria taking into account the contribution to the quality system (PRO-2019-000010),
- The participation to process reviews and internal, external and customer audits
- Several awareness initiatives organized throughout the year (ex: reminders of good practices, presentation of new methodologies regarding risk analysis).

The skills and knowledge of the employees are developed and monitored by the managers and the quality and human resources departments. Our quality system ensures the complementarity of these three types of actors and the methods they use. A procedure (PRO-2018-000046) formalizes this activity.

2) Surveillance system

The control and continuous improvement of the Quality Management System is ensured by several surveillance elements as defined in the next two paragraphs. These elements come from the analysis of the **relevant internal and external issues and interested parties**.

a) Internal monitoring and measurement

Polyplus-Transfection® defines its methods for the internal monitoring and measurement based on the requirements and recommendations of ISO9001:2015 standard.

AFNOR CERTIFICATION | External audit

Carried out by a certification body, it is an annual systematic, independent and documented review to get evidences of our QMS and assess them in an objective way, in compliance with ISO 9001 requirements.

Ref: PRO-2018-00036

| Internal audit

Annual review using an approach similar to an external audit. This review is carried out for all the company processes by an internal auditor.

Ref: PRO-2018-00036

| Adverse events

They are detected by the employees and recorded. An investigation of the root causes of these adverse events is then completed to identify appropriates corrective and/or preventive to avoid recurrence.

Ref: PRO-2018-000037

| Indicators

Established for each process, they are defined according to the objectives linked to our quality commitments. They are updated and monitored during the processes review, management review. They reflect the company's state and encourage improvement.

Ref: PRO-2018-000049

| Process & Needs review

Managed beginning of the year by process pilots, they include a performance overview, the follow-up of the planned actions & the identification of needs for improvement or documentary resources. Process reviews are supplemented by a needs review (human, material, financial) carried out at the end of the third quarter.

Ref: IN-2021-000001 & PRO-2018-000049

| Management review

Carried out twice a year after the Process Reviews and after Needs Reviews, the Management Review is held in the presence of the directors and all the process pilots. The performance and needs are identified and evaluated during these meetings.

Ref: IN-2021-000001 & PRO-2018-000049

| Change management

We analyze the internal and external changes impacting our Quality Management System, our products, our processes and our customers. A change is conducted such as a full-fledged project and may need to be notified to customers.

Ref: PRO-2018-000039

| HR Management

Employees are relevant stakeholders, their contribution and their development are ensured by annual evaluation and professional interviews.

Ref: FP-2019-000018

b) External monitoring and measurement

According to the update of its Policy, Polyplus-Transfection® highlights the monitoring and measurement methods used to control and/or satisfy its external partners.

| Supplier evaluation

Suppliers of incoming materials used in the manufacturing of our products and services are evaluated annually on their ability to satisfy our requirements. The actors of the Purchase Process are attentive to many criteria defined in our assessment form.

Ref: IN-2018-000029

| Qualification by our customers

Our products and services are becoming critical for more and more customers. According to their Risk management, customers send us qualification questionnaires, they request an audit planning and/or the implementation of a Quality Agreement.

Ref: n/a

| Qualification of our subcontractors

The qualification of subcontractors is an activity implemented by the Quality Assurance process and the process "Production: Management of GMP subcontractor". Depending on the critical level of the product or service provided, a subcontractor may be qualified on the basis of a questionnaire, or after conducting an on-site audit.

Ref: PRO-2018-00036

| Distributors management

The distributor is an essential partner. It allows customers around the world to access to our products. It is the first contact for the user of the product. Our Business Directors and Business Managers as part of the Sales process work continuously with them to improve the partnership and their practices to finally ensure customer satisfaction.

Ref: PRO-2019-000005

| Customer complaints

Customer complaints are mainly received by the Scientific Support and Supply Chain processes. First, the Scientific Support assists the customer in handling our products while the Supply Chain acts to correct the non-conformities related to the preparation and shipment of the products. Furthermore, these two processes work with the Quality Assurance department to analyze the cause of a customer complaint and to act in a corrective and preventive manner.

Ref: PRO-2018-000023 and PRO-2018-000037

c) Management of risks and opportunities

Polyplus-Transfection® pays attention to its internal and external environment. We have two levels of analysis and control of risks and opportunities.

A company level:

A SWOT analysis is updated annually (LIST-2019-000005, confidential document). During this analysis, we make sure to compensate the risks by developing our strengths and manage threats by taking opportunities. (PRO-2018-000049). Operationally, this is translated into activities and/or actions carried out by the processes.

A process level:

Analyses of risks and/or opportunities can be carried out on several occasions (e.g. change control, treatment of an adverse event, process review). A rating methodology is defined to formalize, detail and provide rationale for decisions concerning risks and opportunities. (PRO-2018-000038)

3) Continuous improvement of the Quality system

Since 2018, the Quality Assurance department has been developing the use of a software dedicated to the quality management. This software includes a module for the electronic document management and a module for the continuous improvement.

a) Formalizing practice and knowledge

To ensure the reproducibility of its activities and ensure compliance with its commitments, our practices are formalised through a broad typology of documents as presented in the "documentary pyramid" (see diagram on the right). All the documents created are integrated into the Electronic Document Management software (EDM) of our Quality software. In order to integrate and optimize our process approach, the Quality Assurance department works for the development of the use of the EDM module. In 2019, the module evolved to host other documents such as HR documents and presentation materials.

Our EDM software allows the security and integrity of information, by assigning different roles in the document validation workflow for example. Procedure PRO-2018-000042 lists the types of knowledge and PRO-2018-000033 defines the rules for the management of all these documents (codification, validity period, validation workflow, etc.).

b) Records related to our activities

Polyplus-transfection® employees and information systems generate a large number of records on a daily basis that constitute the history of the company, of a product or of an activity.
In order to ensure compliance with regulations, control of responsibilities, accurate monitoring of activities and safety of our products, the company defined rules for controlling records and archiving (PRO-2018-000034).

c) Management of corrective and preventive actions

The monitoring system previously described leads to many improvement actions that are conducted throughout the year, or even over several years for the most ambitious projects.
The actions to improve our quality system may originate from one or more events among the various monitoring and measurement methods implemented (e.g.: management review, audit, customer complaint, risk management, etc.).

To ensure the implementation of our improvement actions each action is assigned to a process, one or more actors can be identified, a completion date is set, then a follow-up and an effectiveness review is performed at least during the process review. Since 2019, the follow-up of the actions is carried out through our dedicated software which contributes not only to boost and simplify our quality system but also to secure the follow-up and traceability of our improvement actions.

4) References listed in this manual

Reference	Title
PRO-2018-000023	Product Quality Complaint Management in SFDC
PRO-2018-000033	Management of Quality Documentation
PRO-2018-000034	Control and archive of recordings
PRO-2018-000036	Quality Audits
PRO-2018-000037	Management of adverse events and complaints
PRO-2018-000038	Management of risks and opportunities
PRO-2018-000039	Management of Change Control
PRO-2018-000042	Management of organizational knowledge
PRO-2018-000046	Employee training procedure
PRO-2018-000049	Performance and quality management
PRO-2019-000005	Management of distributors
PRO-2019-000010	Evaluation and professional interviews
POL-2019-000001	Quality Policy
POL-2019-000003	Matrix of quality commitments and processes
FP-2019-000018	Human Resources Process Sheet
IN-2018-000029	Suppliers evaluation (confidential)
LIST-2019-000005	SWOT Analysis (confidential)
PRES-2019-000001	Integration training: Presentation of the QMS
PRES-2019-000002	Training: Document Management Module
PRES-2019-000004	Training: Continuous Improvement Module