TOXALIM QUALITY MANUAL V1

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TOULOUSE, ON OCTOBER 28, 2013

TOXALIM – Research Centre In Food Toxicology
UMR 1331 – INRA/ INP (ENVT-EIP)/ UPS
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Research Center of Toulouse
Animal Health Division & Human Nutrition Division

Foreword

This quality manual includes provisions implemented within the UMR 1331 Toxalim to ensure the quality of its research, according to the quality standard of INRA version 2.

The objective of this manual is to enable our staff and our partners to have a complete view of the organization engaged in Toxalim.

This manual refers to processes, procedures, instructions and records that constitute the bulk of the documentation of our Quality System.

Management commitment

Towards a quality, safety and environment conscious management

UMR 1331 TOXALIM (Research Centre in Food Toxicology) is a INRA joint research unit (with ENVT & EI-Purpan, under contract with the University Toulouse 3). Its activities include the study of the effects of chemical contaminants and food components, alone or in combination. The consequences of chronic exposure to low doses, are more particularly addressed within a goal of preventing human or animal health. Toxalim's ambition is to become a reference in toxicology and food safety research.

Since TOXALIM inauguration in January 2011, the Management board pointed out Quality as a priority project to be implemented as an integrated component of the scientific approach. The approach was structured by harmonizing the existing procedures in the founding units to build a unique quality system, both innovative and progressive, respecting the activities of the research teams, technology platforms and animal facilities.

Our goals:

- To provide reliable analytical and publishable results as well as quality services in the field of project management and coordination, expertise, training, customer service,,
- To preserve knowledge and expertise and foster communication and transmission of knowledge,,
- To meet regulatory requirements, and legal standards regarding:
  - health and safety,
  - the use of radionuclides,
  - animal experiments.
- To continuously improve our performance in terms of quality, safety and environmental impact, with the commitment of alll.
- To align our ongoing system quality management with the changing needs of our partners.

Our objectives:

- Meeting the requirements of the 2012 version of the INRA quality repository, regarding the activities of research teams, support research services and animal facilities, to ensure traceability of work and the reliability of results and, in a process of continuous improvement..
- Achieving ISO 9001: 2008 for our three technological platforms which are connected to IBiSA platforms.

Régine Pradera is appointed as quality officer. As a representative of the Management, its mission is to develop, implement, maintain, improve and verify the processes of the quality system, staff awareness of quality requirements of the INRA, develop and lead the quality system of the unit and report its operation.

The entire staff is involved in the quality process to ensure the success of the adopted policy.

The Management is committed to give its support, as well as the human and material resources necessary for implementation of this policy and push TOXALIM up to a system of continuous improvement of quality in research to ensure the excellence of the work done at all levels Unit for all our stakeholders.

Bernard Salles
Toulouse le, 24 Août 2012
original signed

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PART A : Presentation of TOXALIM research unit

1. Missions

UMR 1331 Toxalim is a joint research unit INRA-ENVT-EI-Purpan under contract with Toulouse 3 University, under the supervision of INRA's Human Food (ALIMH) and Animal Health (SA) Divisions, under the scientific direction "Alimentation" and "Agriculture"). Toxalim was created in January 2011 as a merger of 4 pre-existing research unitis.

TOXALIM contributes to the development of knowledge on the long-term effects on human and animal health, of food contaminants such as toxic agricultural inputs, pesticides, mycotoxins, packaging migrants and other chemicals present in foods. Projects specifically cover chronic exposure to low doses of contaminants, generally in mixtures and in critical development (neonatal or perinatal) phases.

TOXALIM skills cover various crosscutting areas ranging from digestive physiology to gene expression perturbations involved in the development of metabolic diseases and cancer.

TOXALIM is heavily involved in vocational education and agro-veterinary toxicology at master and doctoral level as well as in technology transfer and partnership with leading food and veterinary medicine companies.

2. Organization

1.1. Staff

TOXALIM includes more than 220 people, including 150 permanent, currently in 11 research teams, 4 technical facilities and research support services.

1.2. Premises

UMR 1331 Toxalim is located on two sites: the site of Saint Martin du Touch (nine teams) and the campus of the National Veterinary School of Toulouse which houses two teams.

Toxalim premises cover 7000 m2 including 3,500 m² of laboratories and experimental rooms, 1000 m² of offices, 380 m² of storage and 180 m² of meeting rooms.

1.3. Teams and their main activities

Each team develops its own research programme in relation to priority areas of INRA's **Animal Health** and **Human Nutrition** divisions.

Fields covered by the research teams include:

- Determination of the impact of xenobiotics (drugs, mycotoxins, food contaminants, endocrine disruptors) on organisms by functional, genomic and analytic approaches (Team 1: TIM)
- Metabolism of Xenobiotics (Team 2: MeX)
- Endocrine Disruptor Pesticides (Team 3: PEP)
- Neuro-Gastroenterology & Nutrition (Team 4: NGN)
- Characterization of the toxicity of mycotoxins produced by certain fungi, natural contaminants of animal of human foods on the immune system (Team 5: immuno-myco-toxicology ; IMT)
- Study of the ABC transporters involved in the resistance to xenobiotics, among them veterinary drugs and their expression in parasites or insects (Team 6: Membrane transporters and resistance ; TMR)
- Models and Methods for the evaluation of resistance to antibiotics (Team 7: Pharmacokinetics, Pharmacodynamics & Modelisation ; PPM)

- Genotoxicity & signaling (Team 8: GS)
- Understand why cured and red meat can cause colon cancer, and seek how to prevent this toxicity (Team 9: Prevention and Promotion of Carcinogenesis by Food ; PPCA)
- Molecular & Cellular Toxicology of Xenobiotics (Team 10: TCMX)
- Intestinal development and immuno-toxicological effects of xenobiotics (endocrine disruptors, nanoparticles ...), with focus on the perinatal period as a crucial exposure window (Team E11: DIXIT)

1.4. Funding

The unit budget for operation and equipment (small and medium-sized) come from different sources, from both public and private origin :

- Public grant given by the INRA Human Nutrition and Animal Health divisions (which represents 20% of our overall budget ;
- Contractual resources, from either public or private origin, represent the major part of our funding : e.g. research projects funded by ANR (National Research Agency), european FP projects, industrial projects,.... ; Regional research contracts or State-Region grants (CPER), specific financing for Experimental Units … etc…
- ...

PART B : Quality Management System (QMS)

1. Management principles

1.1. The Quality Project: a management priority

The 4 founding units of UMR 1331 Toxalim were all engaged in a quality approach for several years, yet at different maturity levels. In this context, it was necessary to define and implement a unique quality TOXALIM Project taking into account specificities of the different teams and objectives of the Direction.

The Direction placed the Quality approach at a top-priority rank integrated with the scientific project. The implementation of the quality process of the future UMR 1331 began as early as 2010. From 2011, at the start of TOXALIM, a quality manager was appointed. The approach was structured by harmonizing the existing in the founding units to build a single innovative and scalable quality system, taking into account the specificities of teams, platforms and experimental rooms.

1.2. Quality Policy and its objectives

The management is committed to establish and maintain a system of quality management. The conduct of such a system is based on the concept of PDCA. The principle is based on the establishment of four successive steps in monitoring actions: Plan, Do, Check, Act.

Management regularly reviews the Quality Policy. It recalls the context determines goals and provides means (see page 3).

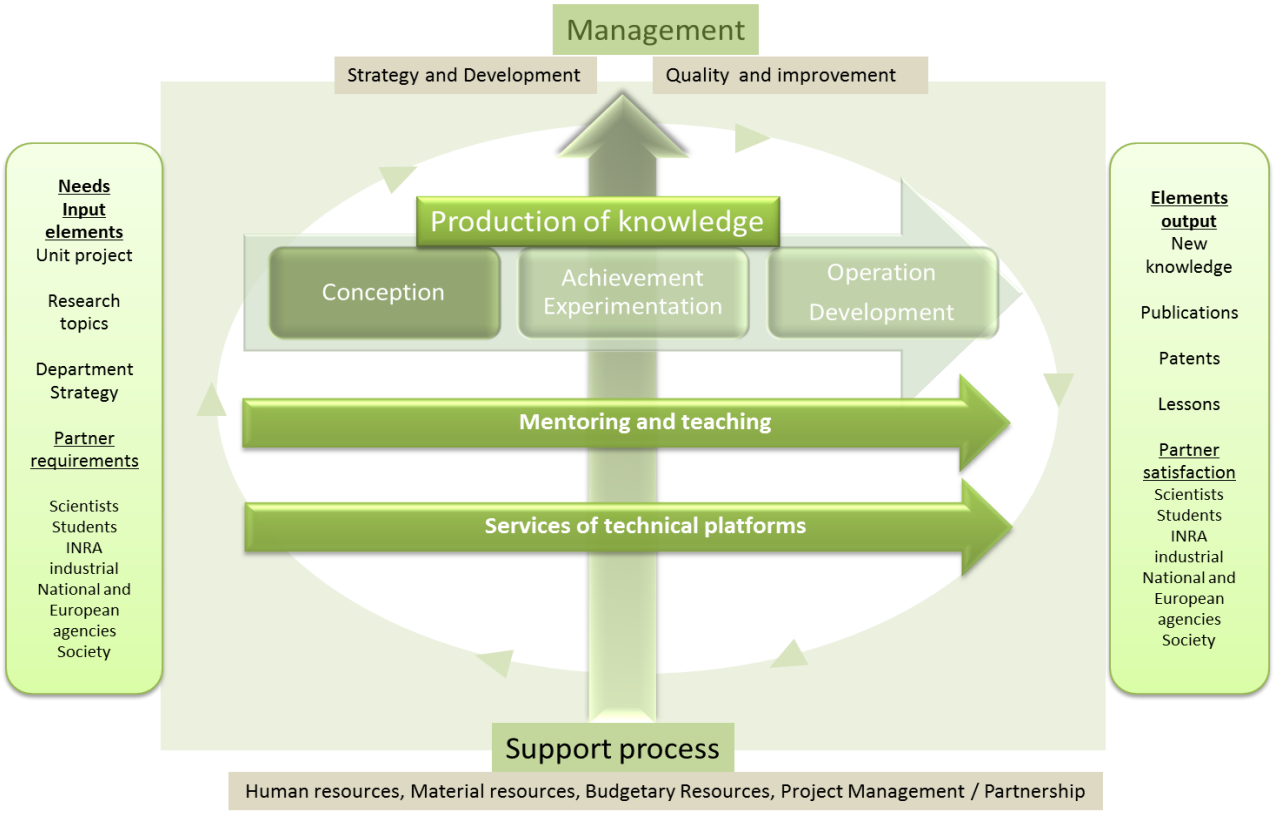
Management is committed to lend its support as well as human and material resources to this policy and TOXALIM up in a system of continuous improvement of quality to ensure the excellence of the third work done at all levels Unit.

2. Quality management System: QMS

2.1. Mapping and process

Key unit processes were identified. The representation of these processes allows structuring activities, identify key points quality and implement continuous improvement on the basis of appropriate documentation. Our priorities in modeling our processes have brought:

- **1** process control
- **2** support processes
- **3** the sub-process "Making / Testing" of "knowledge production" process



Mapping process Toxalim

1 process control: they describe the actions necessary for quality management and help steering of Toxalim by the Direction.

3 business processes: they correspond to the main activities of Toxalim, that is to say, his heart business.

4 support processes: They correspond to activities in support of business processes by providing the necessary resources to participate in their smooth progress:

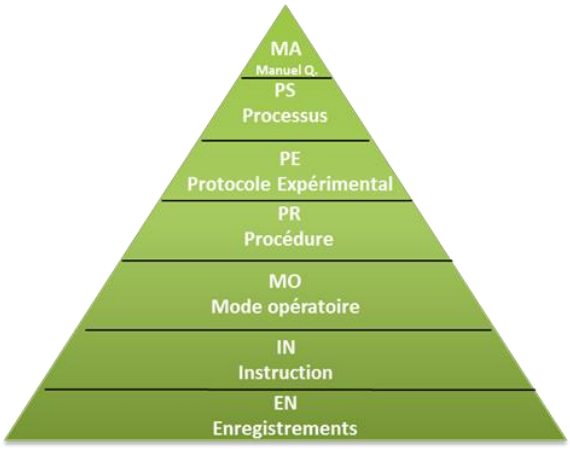
- Human resource management provided by the unit's managers in connection with the SDAR *;
- Management of budgetary resources provided by the director, the account manager of Toxalim and SDAR * services;
- Management of material resources provided by Toxalim;
- Administrative Assistance in project management.

* At the INRA Toulouse research centre, the SDAR (research support services) provide the following: human resources management and continuing education, public procurement, fluids, construction and part of facilities maintenance.

2.2. Documentation

Documentation system Architecture

The quality management system is based on a retrieval system having a pyramidal structure consisting of 6 levels:



Documentary pyramid of Toxalim

Management of quality documentation

All documentation of the quality system follows the rules for the creation, updating and dissemination that are defined in the procedure PR- DOC- GEST- 001: Creating and managing quality documents. This procedure ensures the timeliness of content and explains the dissemination of documents in order to avoid the use of obsolete documents. Documents are developed mainly by the staff involved in the specific activity, using their expertise and experience, and following regulatory requirements. Procedures editorial guidelines, protocols, procedures , instructions and records are mentioned in this procedure

All applicable documents and records are listed in AQRoDOC (unit's documentation management database) and the lists of documents in force ***EN- DOC- GEST- 002*** : List of quality materials of UMR 1331 Toxalim by domain and ***EN -DOC -GEST -003*** : List of quality documents by subdomains.

3. Management's Responsibility

3.1. Management commitment

To define its quality policy, the management of UMR 1331 Toxalim incorporates INRA guidelines, the regulatory requirements applicable to the unit, its own policies and priorities. At quality meetings, quality policy can be redefined according to new requirements.
The direction of the unit ensures the quality management of the unit by regularly participating in the analysis of data collected during quality meetings. It ensures that regulations are enforced.

3.2. Quality policy

The quality policy unit was initiated by the first statement of commitment in May 2010. The current quality policy has been explained in paragraph 1.2: Quality policy and objectives.

3.3. Planning

Planning consists in organizing preventive activities or projects by defining responsibilities, deadlines and actions to be undertaken. Planning of Toxalim quality actions is formalized in the action plans.
At cruising speed, the various outstanding actions in management quality system can be defined in the following meetings: management board, management / team and technical platform leaders meetings, quality meetings or specific work group meetingss (eg metrology, General Assembly …)

3.4. Responsibility, authority and communication

3.4.1. Responsibility and authority

The unit manager has authority over the UMR 1331 Toxalim (see organisation chart).

3.4.2. Management Representative

The operational management of the unit is assigned to different team and technical platform leaders. They participate and work with (the) the person in charge of quality within their team to implment the quality policy and objectives.

The management of the quality system is under the responsibility of the unit's quality manager. His/her function allows direct access to the highest management level of the unit. He/She has a functional role in the unit's and his/her main tasks are:

- to facilitate, implement, maintain and develop the quality system, especially through the process approach, and to ensure compliance with the quality standards applicable to the unit;
- coordinate the actions of different actors in the quality control process;
- promote the image of Toxalim's quality towards our authorities, partners, customers, and participate in various national quality groups;
- organise the planning of internal audits and ensure their implementation;
- organize the analysis of audit results and improvement sheets;
- be accountable to the Direction of the progress of quality management and of any need for improvement

3.4.3. Quality cell

The Quality Cell consists of:

- The Director of UMR TOXALIM
- The quality manager of the UMR
- Team quality correspondents appointed by their team leader and validated by the unit director
- Persons invited on specific topics

The role of the Quality Cell is to ensure the organization and animation of the Quality system of UMR 1331 Toxalim. Its mission is to make every effort to meet the requirements of INRA Quality regulations, and for some research activities, to comply with the ISO-9001 specifications. For this purpose, it offers relevant solutions for the advancement of the quality approach.

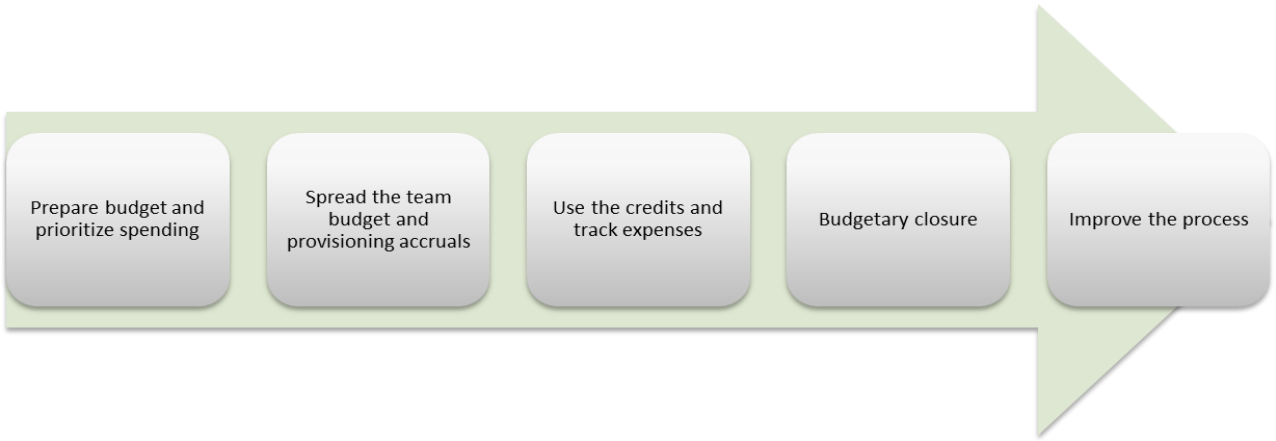
3.4.4. Internal communication

Considering the size of Toxalim and the existence of several teams in different buildings and two sites, a particular effort has been made in information and communication by the use or creation of media: creating an intranet site, dissemination of information by mail and mailing-list, quality points at meetings between management and team leaders, at unit boards, general assembly, dissemination of meetings minutes, access to quality documents using the AQRoDOC database...

4. Resource Management

4.1. Management funding ressources

Annually, in addition to the payroll, a budget is allocated to the UMR 1331 Toxalim. It is composed of credits awarded by INRA Human Nutrition and Animal Health divisions and external contractual resources. A small share of this budget is specifically earmarked for investments necessary to improve the quality management system



Process management of budgetary resources Toxalim

4.2. Management of human resources and skills development

To ensure a match between the skills of staff, needs and objectives of the unit, personnel management is carried out within the unit in agreement with the general rules of public staff management.
The team leaders are responsible for mastering their team's human resources in terms of skills and development.

Process management of human resources and skills development at Toxalim

4.2.1. Home

Welcome of a new employee is made according to the points of the document ***PR-ORG-001-PERS***: Newcomer Reception.
A welcome booklet is given to each newcomer.
The document ***FR-ORG-PERS-002:*** *Newcomer follow-up fiche* must be completed. A feedback questionnaire is aimed to be completed by students at the end of their period ***(EN-ORG-PERS-003)***

4.2.2. Skills and formations

The quality of our services requires a high level of staff expertise in relation to the development of technical, scientific and regulatory work. Management of training is provided by 2 unit training correspondents in connection with the continuing education service of the INRA Toulouse centre.

The identification of new skills to be acquired through training or recruitment is formalized, among others, at team leader meetings and management board meetings.
Follow-up of acquired skills is recorded in the individual « Activity report » file. Following discussions concerning the permanent and contractual staff, the annual training plan is drafted and submitted to the local training commission (FPL).
The external training that have an impact on the activity are evaluated for effectiveness of training to determine whether the training has met the expectations and objectives jointly by the agent and the supervisor ***EN-ORG-PERS-010***.
Finally, new skills can also be acquired through mentoring by agents or more experienced practitioners: these skills can be recorded in a tutoring certification fiche ***EN-ORG-PERS-004.***

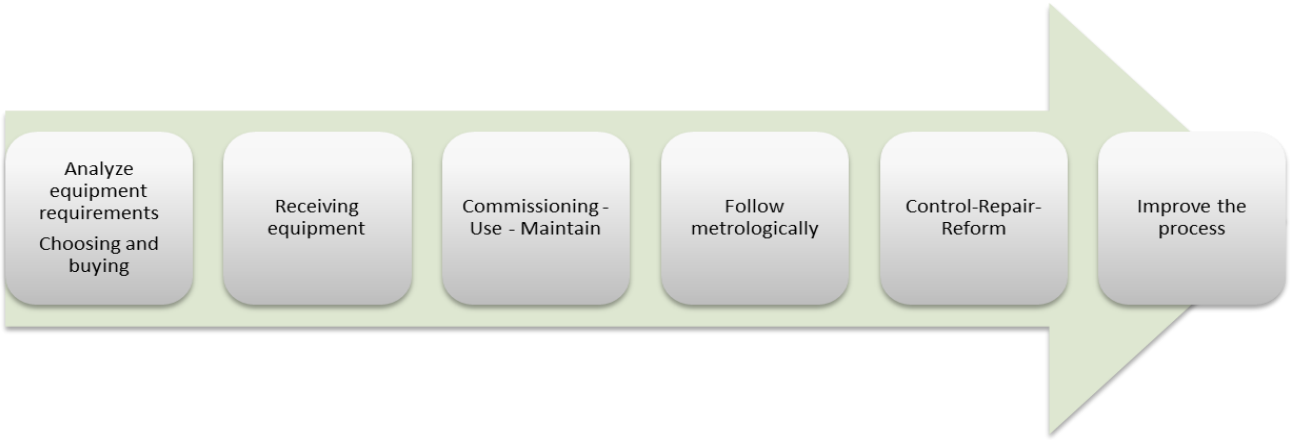
4.3. Infrastructure and equipment

4.3.1. Management of local

Toxalim facilities were built, and some renovated between 1965 and 2013. Work requests or heavy interventions are made with the SDAR. Programming and resources are defined annually in the property scheme of the centre units. Following the opinion of the Centre Management Coucil the President of Centre endorses the work to be carried out.

4.3.2. Management of scientific and technical equipment

UMR 1331 Toxalim must have, at any time, means or material resources to ensure the proper conduct of its activities.
Equipments are listed in the "Computer Aided Management Technique" (GTAO) software deployed in the unit and are subject to a management procedure described in ***PR-MAT-GEST-001***: Management of equipment.
The material resources management process aims to ensure control of the equipment park and ensure the reliability of the equipment used.
The full analysis of this process is detailed in the document ***PS-MAT-GEST-001:*** Process management of material resources.



Material resources management process of Toxalim

4.3.3.Management of monitoring and measurment devices

The metrology cell, consisting of metrologists all trained in principles of general metrology implements ways to monitor and track all materials having an impact on the results. All these means of surveillance and monitoring are the subject of procedures.
Temperature sensors in breeding cells and sample storage units are under constant alarm. In case of failure, a staff on duty intervenes on site.

4.3.4.Health - Safety – Environment

The INRA Toulouse supports controls and regulations related to the safety of people and property such as electrical audits, fire safety, the upgrading of facilities.
The unit ensures that regulations are enforced in terms of health and safety, and agreements. Various written documents specify business rules on the safety of personnel, access to facilities (entry and exit of personnel, animals, equipment), waste treatment. The work environment must avoid the risk of contamination of the milieu and personnel. To this aim, all procedures have a health and safety part.

To liaise on safety aspects on the ground, there is a working group that includes the prevention officers (ACP) of the unit.
This group's mission is to:

- Identify the risks to animals, equipment, biological agents and chemical risks;
- Reflect on organisation improvement of entry and exit of staff and visitors;
- Signpost potential risks from the ground and classify them according to their severity;
- Welcome newcomers to raise awareness of potential hazards and precautions to be taken.

The Experimental ZOotechnic Platform t(EZOP) complies with the regulations currently in force. Different points notified in the Decree 2013-118 and orders arising were implemented by the platform's 4 approved user establishments (UE) that compose it.
To comply with these regulations, Toxalim's EZOP has set-up:
- A common Animal well-being structure, to the 4 EU, to audit the EU projects, and perform on a regular basis any other activities related to animal wellfare.
- A skills monitoring process, to monitor the qualifications of staff, ethical and well-being for any experimental project carried out in one of the EUs.
Moreover, as a spin-off of Toxalim, the Animal care ansd Use (ethics) committee of Pharmacology - Toxicology of Toulouse - Midi-Pyrénées was created in 2012 and officially awarded by the Ministry of Research (CNREEA N°86) as an independent committee, working partly with staff from outside Toxalim and able to accommodate additional external public or private user establishments.

In addition to facility agreements, these structures report to the Departmental Directorate for the Protection of Populations (DDPP31) and the Ministry of Higher Education and Research (MESR) on the quality of work performed within the unit on animals used for scientific purposes.

The elimination of produced waste complies with the regulations and instructions of waste sorting according to the procedure **PR-HSR-DECH-002:** Management and disposal of waste on the site of Saint Martin du Touch and instruction **IN-HSR-DECH-003:** Sorting and disposal of biohazards waste on Saint Martin du Touch Toxalim site.
After each experiment, premises and equipments are decontaminated using the most appropriate methods (chemical disinfection by soaking, autoclaving, oven ...). These activities are recorded.

The logistics service of Toxalim, in connection with the prevention service of INRA Toulouse centre and SDAR, performs periodic regulatory controls : electrical (equipment and buildings), steam pressure appliances (autoclaves, ...) ...

Metrologists keep track of periodic regulatory controls of centrifuges, biological safety cabinets and fume hoods.

The data present on the servers at INRA Toulouse centre and at Toxalim are routinely backed up every night on a backup robot. The data storage system restores all data in case of failure of one of the hard disks.

4.3.5.Maintenance management

The care and maintenance of utilities, small equipment and buildings are done by the unit's logistics service. However, the maintenance of certain equipments are entrusted either to SDAR (eg generators, air conditioning ...) or external providers as part of a maintenance and / or regulatory obligation maintenance contract / (eg autoclaves).

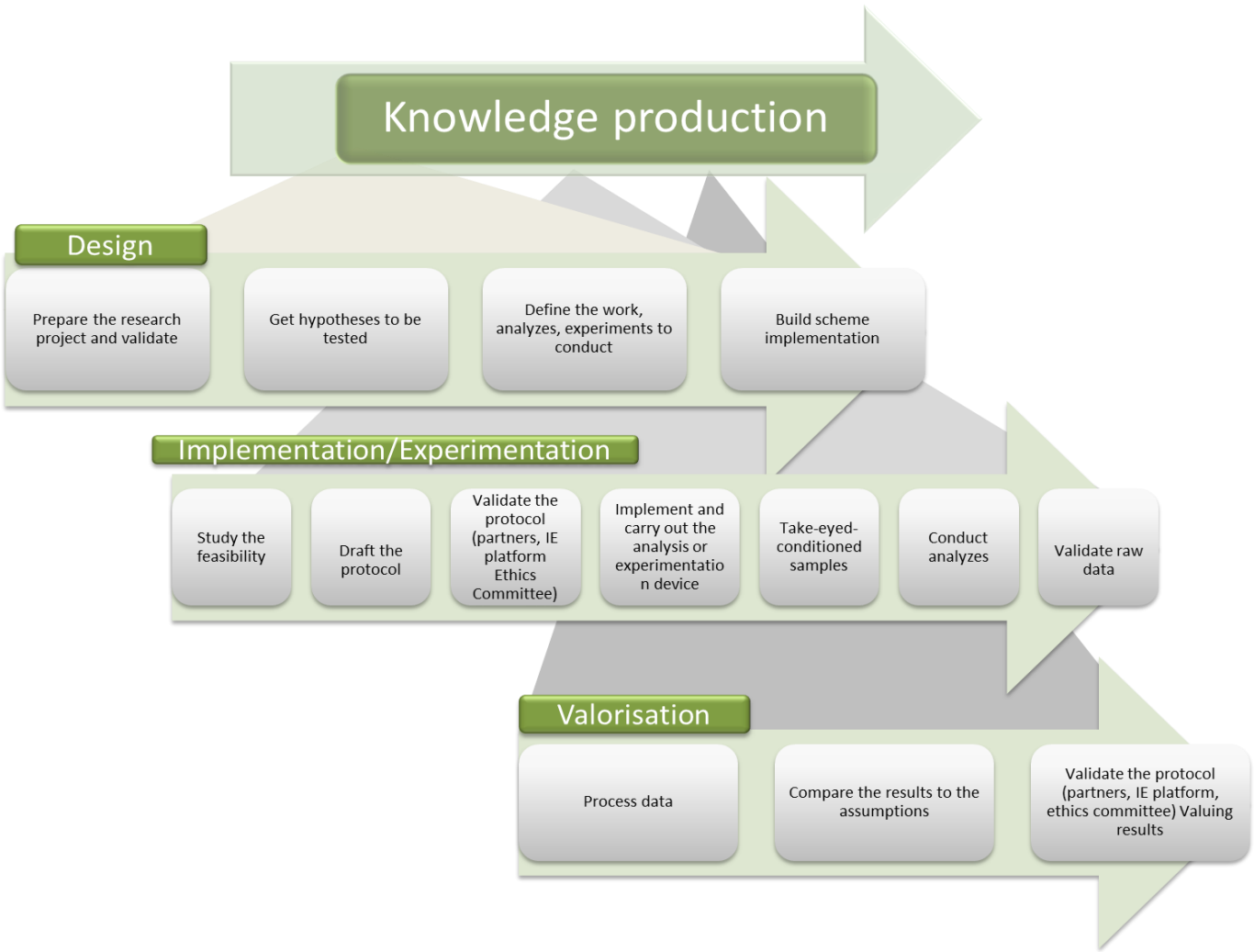
4.3.6.Fluids management

Fluids necessary for the operation of Toxalim are distributed by differentiated networks. These networks: heating, potable water, hot water, demineralized water, softened water, wastewater, stormwater, electricity distribution (HV, LV), compressed air, laboratory gas, air conditioning.
Their management is under the responsibility of SDAR.

5. Operational processes

5.1. Process "Knowledge Generation"

The process of knowledge production is divided into three sub-processes: "Design" , " Implementation / experimentation" and "Valorisation". Currently, only one is modelised : "Implementation / experimentation" . The establishment of the research issue, and the exploitation and utilization of the results are not included in the quality management system of Toxalim.Toxalim.

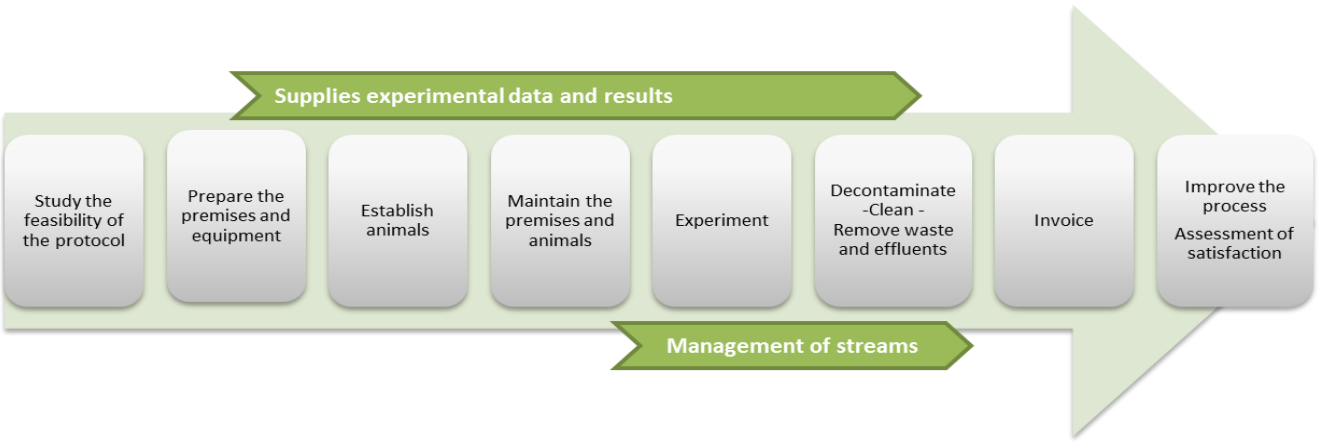


Knowledge production process of Toxalim

To ensure traceability of research and the reliability of results, the unit's Quality Cell has developed a process that covers primarily the domain of activities ranging from the feasibility study of the experimentation to the delivery of validated raw data. Specifically, to meet these goals, specific activities documentation (procedures, operating guidelines, instructions, ...) has been drafted and records have been set up to ensure traceability (laboratory notebooks, records ...). The reliability of measurement results is ensured by provisions made in paragraph 4.3.3. : Management of Monitoring and measurement devices.

5.1.1.Process "EXPERIMENT": Realization of experimental protocols

The objective of this process is the realization of experimental protocols on laboratory animals, on farm animals, free of specific health hazards or conventional pathogens, in confined A2 buildings or conventional buildings.



Animal experimentation process of Toxalim

6. Measures, analysis and improvement

6.1. Annual report quality

The Direction, after considering the level of achievement of quality objectives previously set, analyzes any gaps and sets new goals, decides on the effectiveness of the quality management and decides on actions to improve it.

6.2. Internal audit

All activities covered by the QMS is audited every 4 years. Auditors are internal INRA staff.
Internal audits are followed by an analysis of discrepancies to identify actions for improvement.

Conclusion

The quality manual presented in a synthetic way the quality management system of UMR 1331 Toxalim. This document is a communication vector of the quality process drawn to the attention of :

- **Public and private partners**
- **External evaluators missioned under different certifications of the institute**
- **Internal staff, especially for training of newcomers**

All organizational and technical provisions are defined and detailed in the quality documentation.
Beyond the description of the objectives, authorities and tools, it is the will of the Direction and the contribution of each one on a daily basis that allow the maintenance and development of quality certification.