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PILOT PLANTS UNIT: INTEGRATED QUALITY AND ENVIRONMENT MANAGEMENT SYSTEM

AfriQ´units. Alicante, 11 December 2008

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1.INTRODUCTION TO ISO RULES

What is ISO? International Organisation for Standardisation

- **Federation of national standardisation organisations**
- **Headquarters:** **Geneva, Switzerland**
- **Missión:** **Development and promotion of common standards at an international level**
- **Members:** **more than 140 countries**

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1.INTRODUCTION TO ISO STANDARDS ISO 9001:2000 E ISO 14001:2004

1.1. ISO 9001:2000

- **QUALITY MANAGEMENT SYSTEM. REQUIREMENTS**

1.2. ISO 14001:2004

- **ENVIRONMENT MANAGEMENT SYSTEM. SPECIFICATIONS AND ESPECIFICACIONES Y DIRECTIVES FOR ITS USE**

  - **- Common requirements**
  - **- Specific requirements for quality**
  - **- Specific requirements for environment**
  - **- Same philosophy:**

  - **"THE IMPROVEMENT CONTINUES"**

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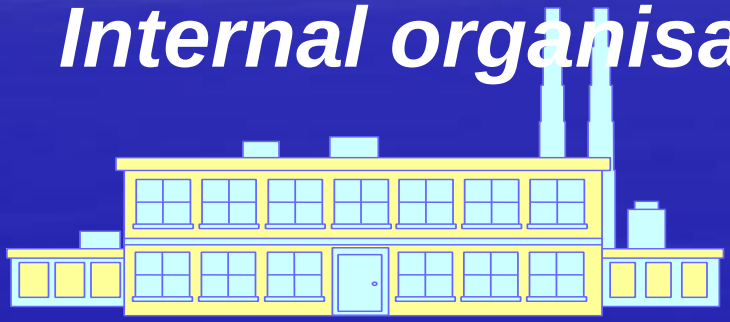
1.1. ISO 9001:2000
Quality management

THREE REASONS TO DISCUSS QUALITY

Internal organisation



The user and the Admin

Competency

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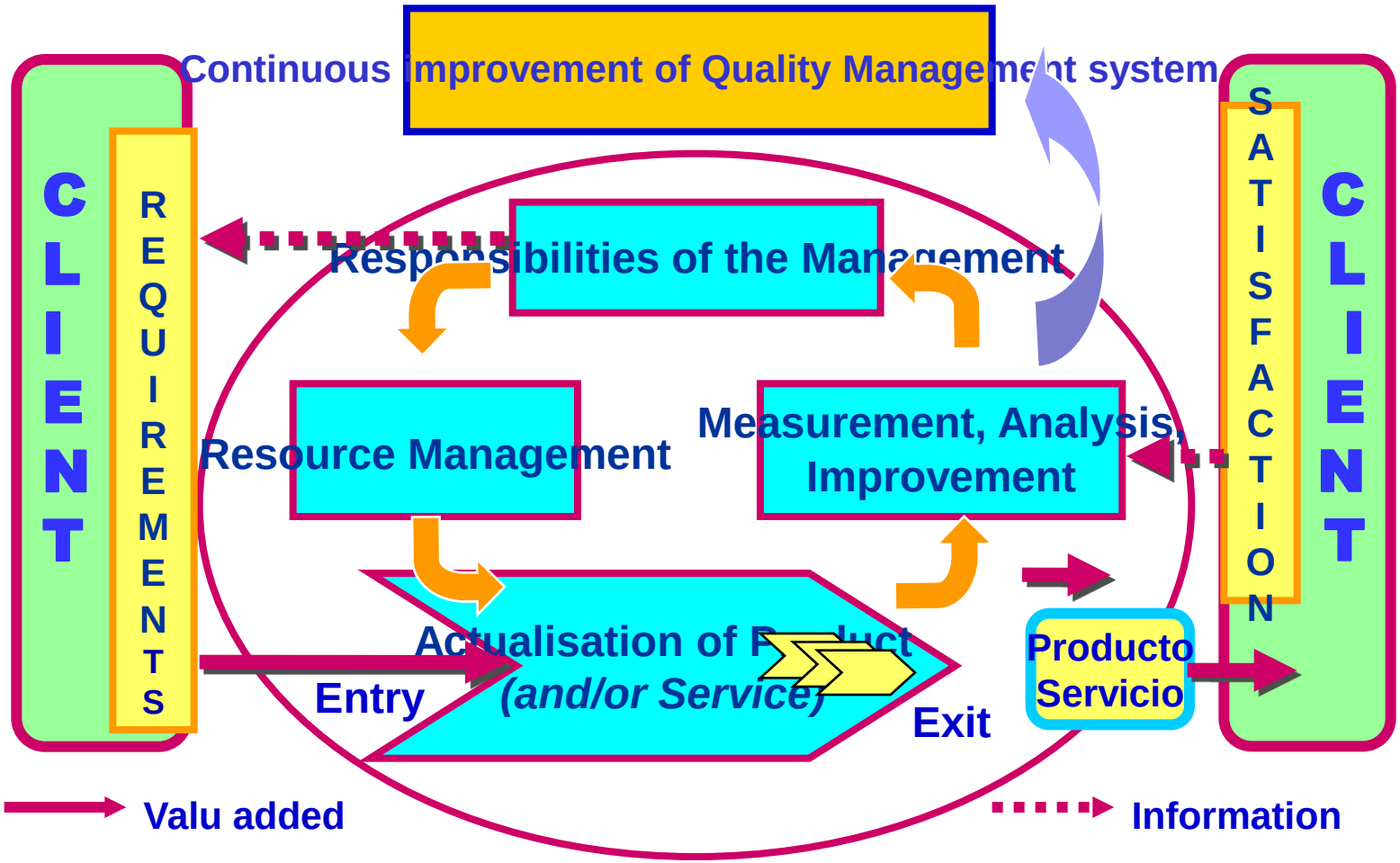
1.1.ISO9001:2000

SGC - ISO 9001:2000 model



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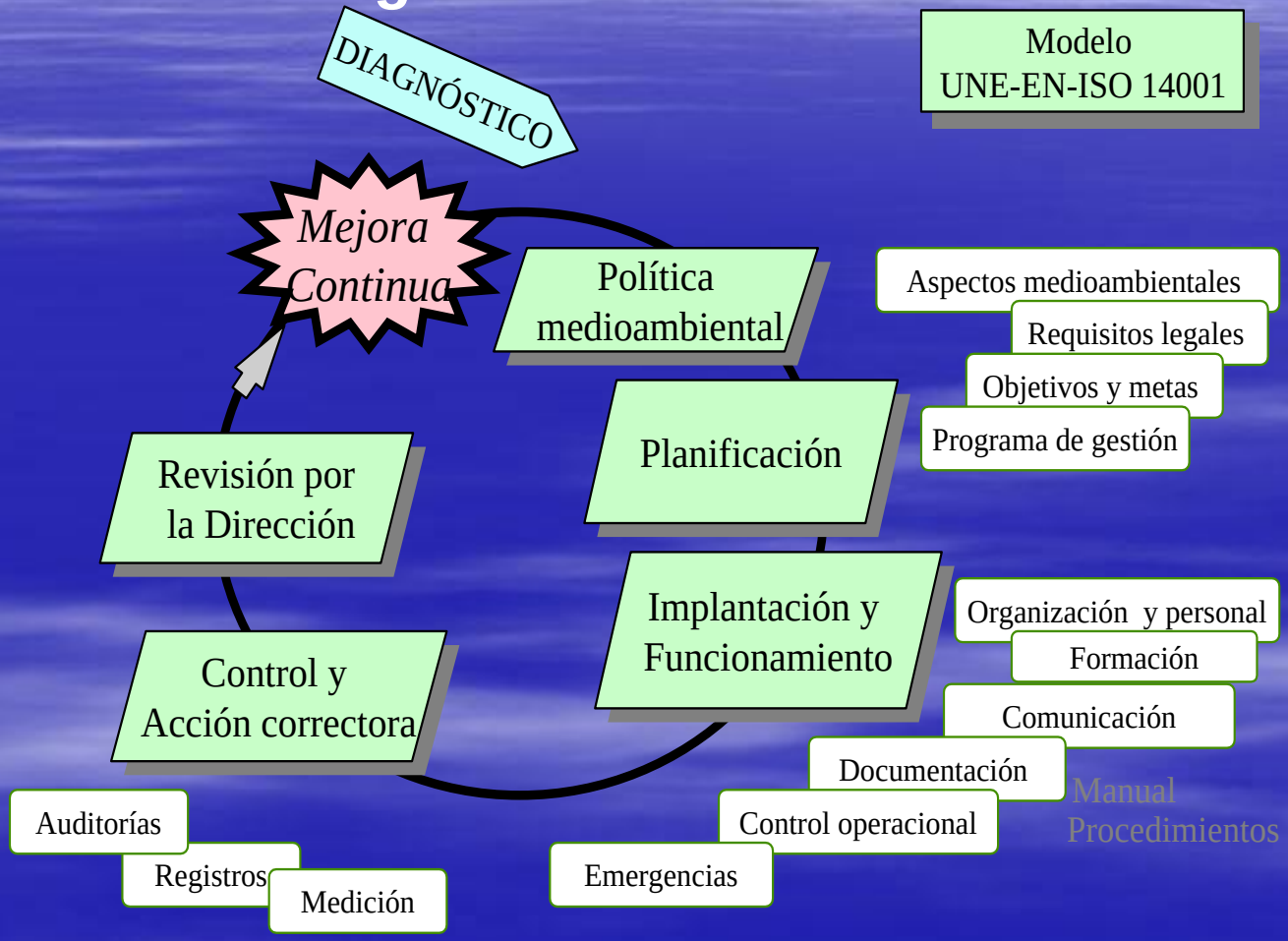
1.2 ISO 14001:2004
Environmental management



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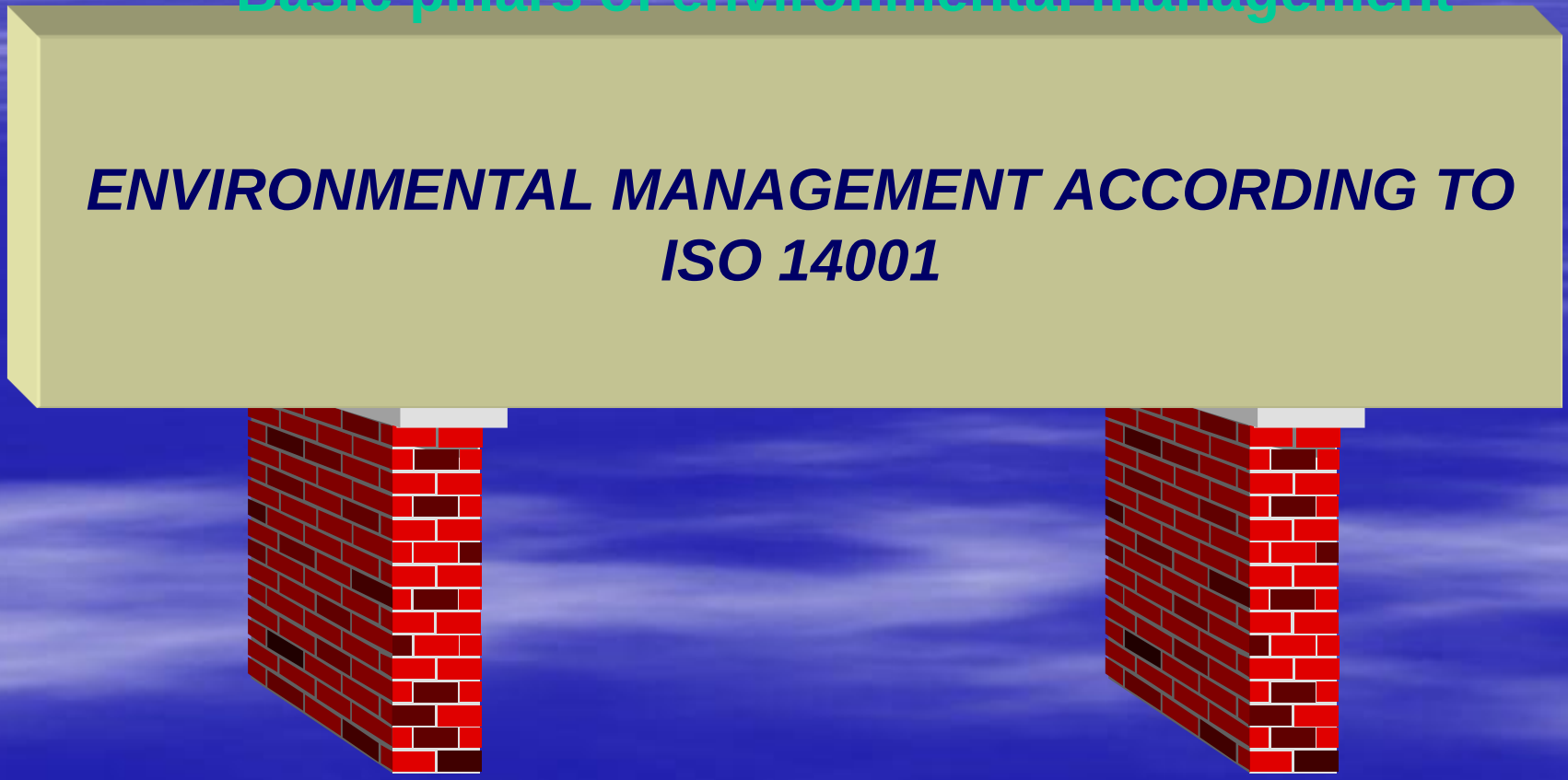
1.2 ISO 14001:2004
Environmental management

Basic pillars of environmental management



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2. BRIEF ANALYSIS OF THE INTEGRATED SYSTEM

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2. Brief analysis of the system.

2.1. DOCUMENTATION OF THE MANAGEMENT SYSTEM

- **Quality and Environment policies**
- **Integrated management manual**
- **Procedures:**
  - **integrated**
  - **quality**
  - **environmental**
- **Instructions**
- **Required records**

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2. Brief analysis of the system.

2.2. RELATED PROCESSES WITH THE INTEGRATED SYSTEM

- MANAGEMENT OF PROPOSALS AND CONTRACTS WITH THE CLIENT
- PLANNING OF RESEARCH PROJECTS
- SALES (actualisation, realización, suppliers' control, receipt of merchandise and verification)
- PROCESS OF RESEARCH (from contracting to delivery)
- MAINTENANCE AND EQUIPMENT CONTROL DE EQUIPOS
- STORAGE

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2. Brief analysis of the system.
2.2. RELATED PROCESSES WITH THE INTEGRATED SYSTEM (continuation)

- CLIENT SATISFACTION
- INTERNAL & EXTERNAL COMMUNICATION
- TRAINING
- CONTROL DE DOCUMENTACIÓN
- IDENTIFICATION & EVALUATION OF ENVIRONMENTAL ASPECTS
- ENVIRONMENTAL LEGAL REQUIREMENTS
- ACTIONS BEFORE EMERGENCY SITUATIONS

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2. Brief analysis of the system.
2.2. RELATED PROCESSES WITH THE INTEGRATED SYSTEM (continuation 2)

- CONTROL OPERACIONAL (Management of residues, spills, emissions, legionella, etc.)
- Management tools (improvement actions, audits, reviews for Management, etc.)

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2. Brief analysis of the system.
2.3 Departments involved in the System

- SIC
- Maintenance department.
- Prevention department.
- Technical Office.
- Directorate of departments. Teaching/Dean

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3. METHODOLOGY FOR IMPLANTATION

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3. Methodology for implantation.

3.1. IMPLANTATION STEPS

1. Diagnostic
2. Training
3. Documentation
4. Implantation
5. Pre-audit
6. Certification audit

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4. PROCEDURES & INSTRUCTIONS

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4. PROCEDURES AND INSTRUCTIONS

4.1. DEFINITION

- PROCEDURES: **General organisational document which describes, with the level of detail necessary for each case, how a particular role is developed and which interdepartmental relationship is established that purpose**

- INSTRUCTION: **Document that serves to describe in a more detailed form some of the operations mentioned in the procedures**

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4. PROCEDURES & INSTRUCTIONS

4.2. Contents of a work manual

Objetive: Define the purpose of the manual
Scope: Describe the limits of the application of the manual
Definitions: Describe those difficult terminologies or abbreviations that are used
Instruction: In paragraphs or subparagraphs (as needed), explain the development of the process to take in order to adequately perform the activity to which it relates, indicating the method of implementation, the necessary resources, responsibilities, documents or forms used or generated, etc.
Records: Describe those records that are derived from the application of the research, the file manager and the duration of file.
Annex: Includes as much formats as is deemed necessary to facilitate understanding and implementation of the manual

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4. PROCEDURES & RESEARCH

4.2. Control of the instructions

- The technical instructions are elaborated corresponding to its contents

- Once elaborated, they are referred to the Head of Project, to the Directorate of the SIC or to the Head of the corresponding department to be reviewed.

- The revised instructions are approved by the Head of System of each pilot plant or by the Directorate of the STTYC.

- Once the approval is given, they are published on the UA web page, which will signify its approved status. Only the instructions and procedures on the web are to be considered as "approved".

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5.BENEFITS FOR THE ORGANISATION

- Personal motivation
- Improvement of management system
- Improvement of operating systems
- Decrease in quality cost
- Improvement of customer-client relation
- Increase in competitiveness
- Increase in profit

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- *(d) Stores/Warehouse facilities:*
- The Pilot Plant has a completely independent storage facility for raw material handling which has been divided into sections for the proper handling of materials under cGMP conditions.

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- *(e) General facilities:*
- Scrubber system in borosilicate glass of 300 L capacity.

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- In 2004, the staff of our pilot plant took the decision of improving our quality standards because of our customers' demands.
- Also, the evolution of the projects showed us the necessity of GMP´s implementation. We have presented our first EDMF to UK authorities. We are now waiting for its approval.

BVQi

Certification

Awarded to

UNIVERSIDAD DE ALICANTE
PLANTA PILOTO: QUÍMICA ORGÁNICA

ALICANTE

CAMPUS DE SAN VICENTE DEL RASPEIG, 03080, ALICANTE

BVQI España certify that the Management System of the above organisation has been audited and found to be in accordance with the requirements of the management system standards detailed below

STANDARD

ISO 9001:2000

SCOPE OF SUPPLY

RESEARCH, DEVELOPMENT AND SYNTHESIS OF RAW MATERIALS, SYNTHETIC INTERMEDIATES AND FINAL PRODUCTS IN FINE CHEMISTRY INDUSTRY

Original Approval Date : 17 June 2005

Subject to the continued satisfactory operation of the organisation's Management System, this certificate is valid until :

20 January 2008

To check the validity of this certificate please call (91 270 22 00)
Further clarification regarding the scope of this certificate and the applicability of the management system requirements may be obtained by consulting the organisation

Certificate Number 5000401 Date: 17 June 2005

Managing office: BVQI ESPAÑA, S.AU.
Issuing office: BVQI ESPAÑA, S.AU.
Francisca Delgado, 11.
Parque Empresarial Arroyo de la Vega.
28108 Alcobendas Madrid

UKAS QUALITY MANAGEMENT

008

PILOT PLANTS UNIT

- To obtain ISO certificate we had to improve in several aspects: responsability definition, vendor appraisal, training programmes, equipment legalisation, waste program, refuse collection, warehouse organisation, etc.
- It represented an important economical and personal effort, that we could tackle them because of client list and with the support of the University of Alicante, mainly because of the Vicerrectorado de Investigación .

BUREAU VERITAS Certification

Certification

Awarded to

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ALICANTE
CAMPUS DE SAN VICENTE DEL RASPEIG, 03080, ALICANTE

Bureau Veritas España certify that the Management System of the above organisation has been audited and found to be in accordance with the requirements of the management system standards detailed below

STANDARD

ISO 14001:2004

SCOPE OF SUPPLY

RESEARCH, DEVELOPMENT AND SYNTHESIS OF RAW MATERIALS, SYNTHETIC INTERMEDIATES AND FINAL PRODUCTS IN FINE CHEMISTRY INDUSTRY

Original Approval Date : 15 July 2005

Subject to the continued satisfactory operation of the organisation's Management System, this certificate is valid until :
20 January 2008

To check the validity of this certificate please call (91 270 22 00)
Further clarification regarding the scope of this certificate and the applicability of the management system requirements may be obtained by consulting the organisation

Certificate Number 5000631 Date: 20 April 2007

UKAS ENVIRONMENTAL MANAGEMENT

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- Consequences of the GMP´s implementation:
- Equipment and facilities qualification.
- Process validation, which ensures the quality of the obtained products. These products could be used directly in clinical trials.

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- Instruments under quality control:

- Karl-Fischer titrator
- Potentiometric titrator
- Gas Chromatographs
- GC/MS
- FT-IR spectrophotometer
- HPLC chromatographs
- Climatic chambers

GMP IMPLEMENTATION

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Background

- Plant Start-up year 2001
- Quality integrated system: Quality and Environment certificate (ISO-9001:2000 and ISO-14001:2004) since 2005
- Expertise in Fine Chemical Development
- Expertise in API projects (lab, pilot and industrial scale)
- GMP implementation in 2007

- *Reference Guideline: ICH-Q7*

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Organisation

- Validation Team (task force for GMP implementation).
- Clear definition of responsibilities.
- Organisation chart is available
  - Quality is independent of Production
  - Quality cover QA and QC
  - Quality is involved in all quality-related issues
  - Production is responsible for operations
  - Quality and Production report independently to high management

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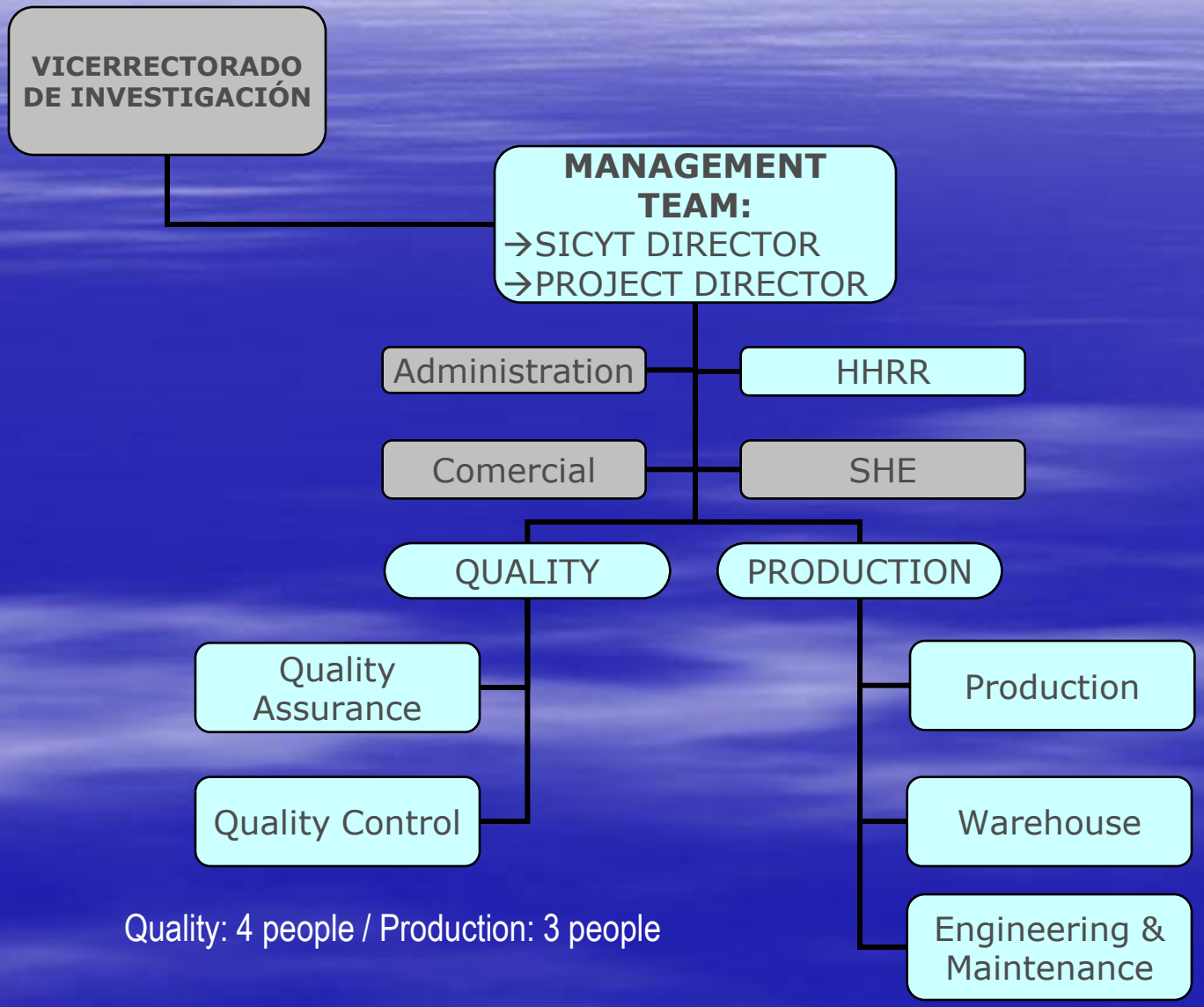
Organization Chart



Quality: 4 people / Production: 3 people

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Validation Master Plan

- Validation Team has written and approved (March/07) a Validation Master Plan (VMP) that establishes policies related to GMP's.
- This VMP has the following sections:
  - Introduction
  - Plant Description
  - Validation Activities
  - Qualification Master Plan
  - Process Validation
  - Analytical Method Validation
  - Cleaning Validation
  - Personnel
  - Change Control
  - Summary


PLAN MAESTRO DE VALIDACIÓN

VALIDATION MASTER PLAN

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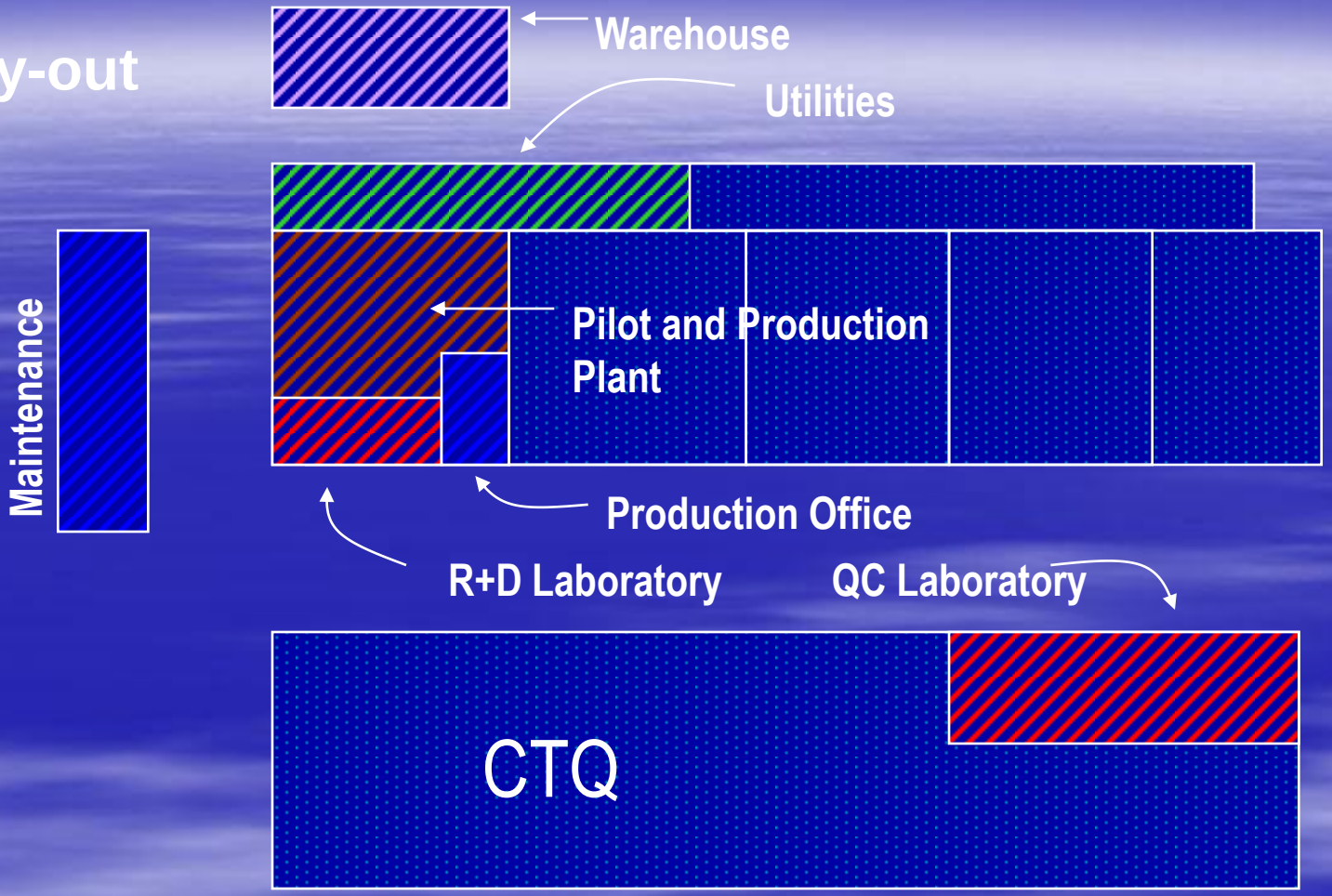
Sant Vicent del Raspeig (Alacant)

Marzo-2007

Versión V01.00

Plant Lay-out



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Qualification

- Quality Policy follows the well known scheme:

  DQ: Design Qualification.

  IQ: Installation Qualification

  OQ: Operational Qualification

  PQ: Performance Qualification

  - Risk assessment and analysis is applied in the qualification process.
  - UA is now finishing the Qualification of Equipment and Utilities.

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Activities related to Qualification are also under improvement:

- Preventive Maintenance Plan: New system to specify and record preventive maintenance operations.
- Calibration Plan: Inventory of critical instruments, calibration instructions, frequency of calibration and documentation.
- Pest Control Plan: Formal program developed together with a contract specialised company.

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Water System

- Water is used for cleaning and process. Different water qualities have been considered. Finally, drinking water is used.
- Quality of water is checked at the use point (microbiological and chemical controls have been established at regular intervals).
- If higher quality water was needed, the system would be subject to qualification process.

HVAC

- In areas where product is exposed to the environment, filtered air (HEPA) is supplied and positive pressure is maintained during operation.
- Areas are under qualification.

Computerized Systems

- UA-Pilot Plant is inventorying their computerized systems and determining the compliance of CFR-21 part 11

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Documentation

- UA-Pilot Plant has an in-place procedure that controls and standardises all documentation generated:
  - Instructions and Standard Operating Procedures.
  - Master production records and labels.
  - Production and Analytical procedures.
- Documentation allows full traceability of materials used, operations, people involved in production and quality control.
- This system is already implemented

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Materials Management

- Materials are managed according to written procedures
- Lot numbering system is in place
- Packaging material is also qualified
- Label system with colour code is in place
- Quarantine and Released areas are established in warehouse
- Rejected material is segregated
- Quality Dept. is responsible for sampling, testing and releasing materials

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Laboratory Controls

- Quality Control Laboratory is organised according to ICH
- Results are recorded manually
- Double check is a routine in all operations
- QC lab is fully equipped with chromatographic equipment together with the classical analytical equipment
- Equipment is qualified and calibrated when needed.
- Samples are retained for future investigations
- Stability programme has been recently established.
- Samples for stability programmes are stored in recently purchased climatic chambers and qualified previously to use
- Validation of analytical procedures follows ICH guidelines

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Validation

A formal Validation Protocol is established for every process with validation requirements.

The Validation Protocol has the following sections:

-Introduction

-Objectives *Quality Specifications, Chemical Yield, Signatures.*

-Plan *Type of Validation, Batch size, Planning, Evaluation of resources, Sampling, Critical Parameters*

-Equipment Qualification *Process needs vs Qualifications*

-Cleaning *Cleaning Plan*

-Procedure of manufacture *Master Batch*

-Production of validation batches *Copy of Batch Records*

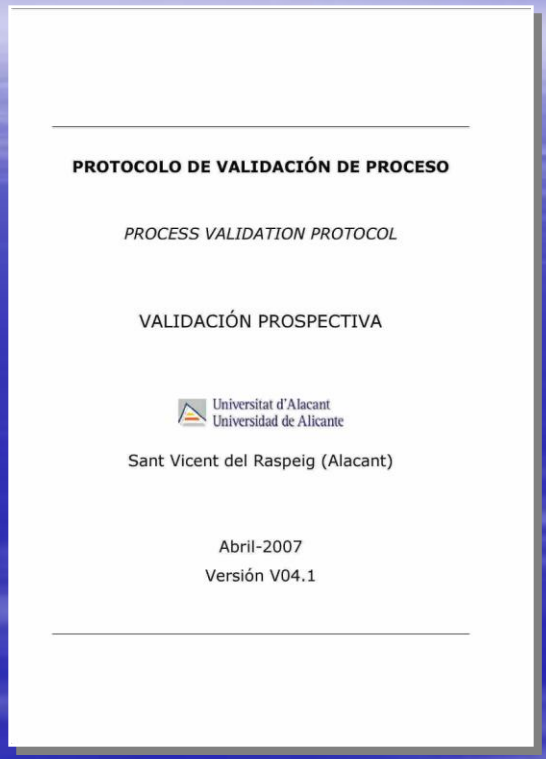
-Raw Material Controls *Specifications*

-Finished Product *Specifications and Stability*

-Results *Tables of Process parameters) and Quality (especially Critical Parameters)*

-Conclusions *The process is/is not validated, Signatures*

-Follow-up


PROTOCOLO DE VALIDACIÓN DE PROCESO

PROCESS VALIDATION PROTOCOL

VALIDACIÓN PROSPECTIVA

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Sant Vicent del Raspeig (Alacant)

Abril-2007
Versión V04.1

UA is working now in its second Process Validation Protocol

High management (together with Quality) approves initial objectives and final conclusions.

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Cleaning Validation

- As the Plant is multipurpose, Cleaning Validation is a priority in order to avoid cross contamination.
- Cleaning validation is based on:

  Classification of products into families according to: solubility, potency, therapeutic dose, difficulty of cleaning, …
- Worst cases are chosen in order to validate the operation.
- Sampling procedures are established:
  - Rinse samples (additional reflux) for reactors.
  - Swab samples for dryers, centrifuges, …
- Textile material is exclusively dedicated to one product
- Cleaning Validation Program has been recently approved

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Quality Assurance Procedures

UA-Pilot Plant QA is working in the following areas, some of the procedures are in place and other are news:

- Approval of procedures and validation plans
- Batch release based on QC compliance and batch record review
- Vendor Appraisal
- Change Control
- CAPA: Corrective and Preventive Actions
- Investigation of deviations and OOS (out-of-specification results)
- Customer Complaint Procedure
- Recall Procedure
- Internal audit programme
- Annual Product Review

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- **Kilo-Lab operations under GMP**
- Operations follow ISO-9001:2000 and standard GMP-procedures (ICH-Q7 especially chapter 19:API for clinical trials)

- Full Traceability:
  - Materials
  - Equipment
  - Operations

- **GMP-Risk Analysis following ICH-Q9 approach:**
- (No high potent drugs are manufactured, only one project per fume cupboard).
- 3 main areas of concern:
  - Environment: Area restricted, drying in a "clean environment"
  - Equipment traceability: identification of pieces of equipment
  - Cleaning-Options:
    - Dedicated glassware equipment → high cost
    - Cleaning procedure + rinse analysis + some dedicated parts
    - Idem + thermal treatment of glassware

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Personnel and Training

- Job descriptions are established for all positions
- Most of the staff has PhD degree in Chemistry.
- UA-Pilot Plant has a training programme that assures the competence of its people.
- Specific training about GMP's is included in the annual programme.
- Training is registered in the employee personal record