

TECHNIP LIFE SCIENCES

30th of October, 2014, DCVMN Meeting in New Delhi, INDIA

FACILITY UPGRADE AND WHO PREQUALIFICATION

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AGENDA

TECHNIP LIFE SCIENCES

FACILITY UPGRADE AND WHO PREQUALIFICATION

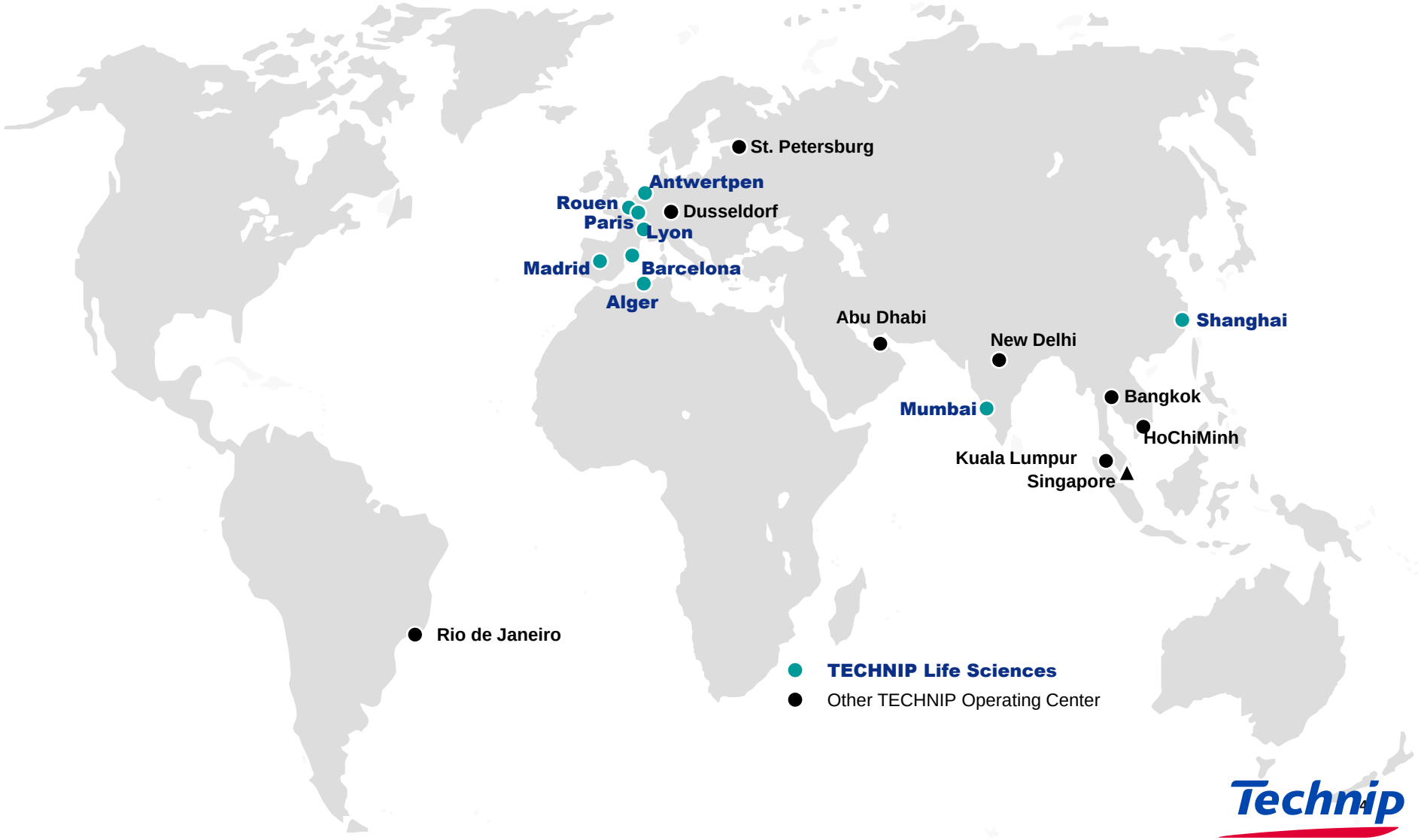
- **AUDIT**
- **GMP COMPLIANCE PROGRAM**
- **REVAMPING EXECUTION WORK**
- **QUALIFICATION WORK**

Questions / Answers

TECHNIP LIFE SCIENCES

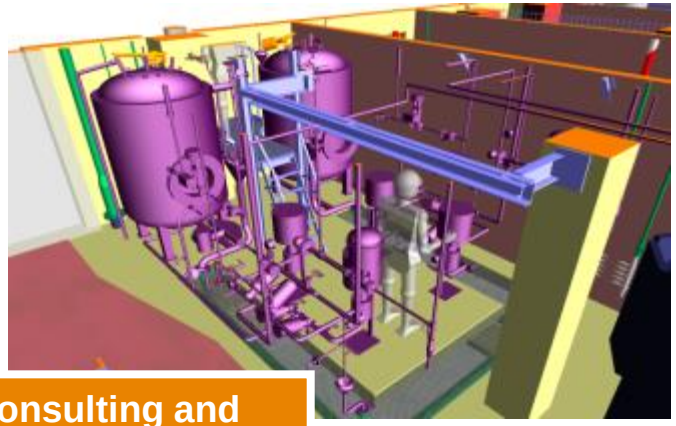
TECHNIP LIFE SCIENCES MAP

Technip is present throughout different centers in the word in order to support as close as possible our clients development



SERVICES PROVIDED BY TECHNIP LIFE SCIENCES

Audits, Concept, Basic, Detailed Design



Consulting and Expertise, Mock Inspections

Procurement & Sub-contracting

Construction & Project Management

Commissioning & Qualification

Permitting

Technip is a full-service provider of integrated solutions from design to qualification

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Vaccine references

Minhai - China

Sanofi Pasteur V16 – France

Merial – France

Chengdu Institute of Biological Product, Chengdu, China

Innovax – China

GPO- MBP – Thailand

OUR CLIENTS


SERVIER
Guerbet
sanofi pasteur
La division vaccins du Groupe sanofi-aven
IPSEN
Innovation for patient care
GALDERMA
SANOFI
MERCK
MERIAL
赛诺菲巴斯德
LEO
GUERLAIN
PARIS
Merck Serono
Living science, transforming lives
LFB
L'ENGAGEMENT ÉTHIQUE
Guerbet
Vétoquinol
genopole
genzyme
Made in
Chimex
procédés réfléchis
L'ORÉAL
CEVA
SANTE ANIMALE
novo nordisk
TORNIER
GALDERMA
Intervet
Schering-Plough Animal Health
septodont
Pfizer
BAYER
SHISEIDO

FACILITY UPGRADE AND WHO PREQUALIFICATION

INTRODUCTION

All facilities manufacturing drug products for human use are required to be

DESIGNED

CONSTRUCTED

OPERATED

MAINTAINED

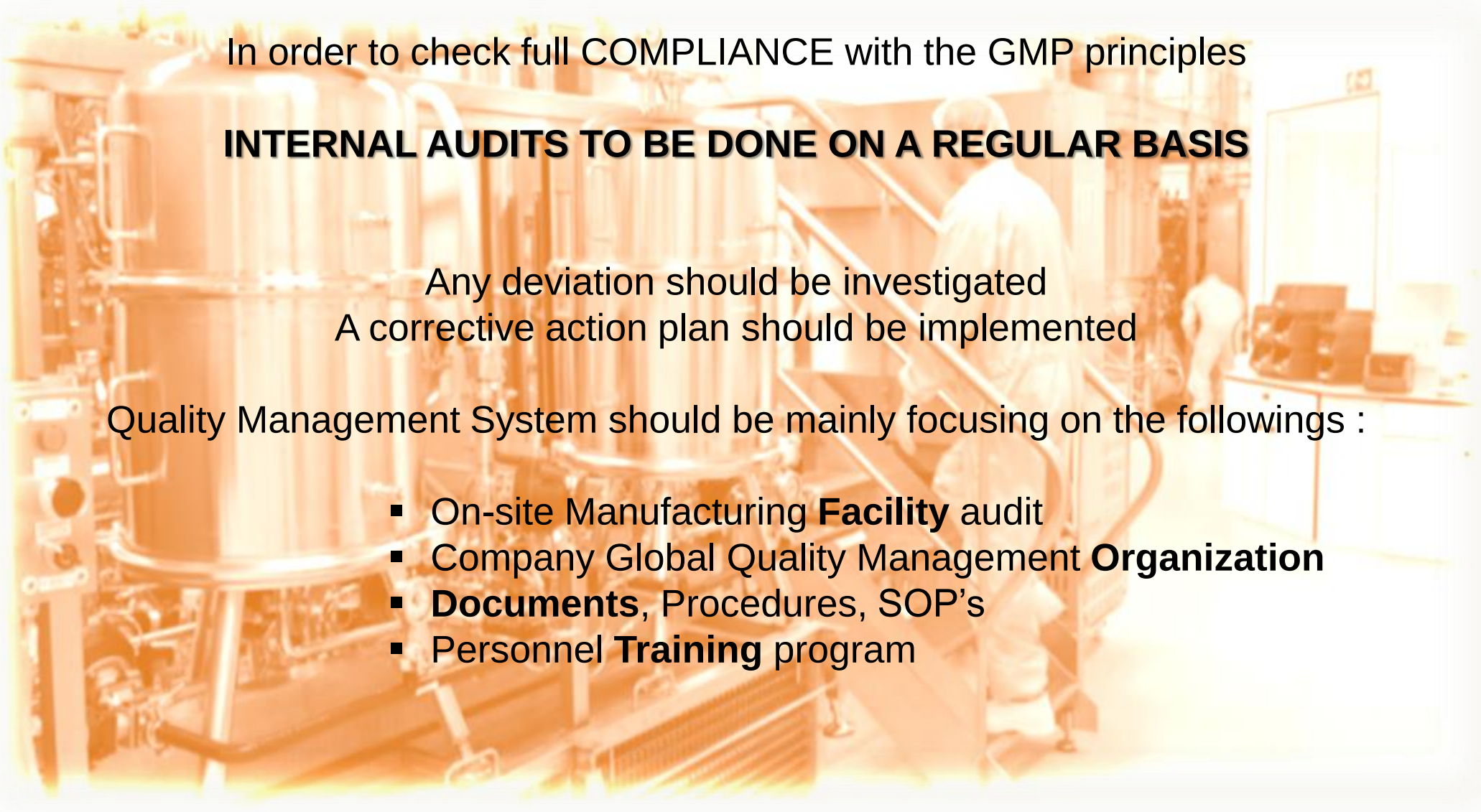
in a way which is in compliance with the

Current Good Manufacturing Practices regulations cGMP

- Regulations evolves and advances : « current »
- Facilities have to follow them !

What about your's?

QUALITY MANAGEMENT & GMP's COMPLIANCE



In order to check full COMPLIANCE with the GMP principles

INTERNAL AUDITS TO BE DONE ON A REGULAR BASIS

Any deviation should be investigated
A corrective action plan should be implemented

Quality Management System should be mainly focusing on the followings :

- On-site Manufacturing **Facility** audit
- Company Global Quality Management **Organization**
- **Documents**, Procedures, SOP's
- Personnel **Training** program

METHODOLOGY

1 / Audit

2 / GMP Compliance Program

3 / Revamping Works Execution

4 / Qualification / Validation

Training Program

QUALITY MANAGEMENT SYSTEM

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1. GMP AUDITS

Purpose

- The objective is to organize an audit of your existing Facility and check whether it complies with GMP requirements
- It is mandatory to execute GMP audit on a regular basis. They will be run following GMP and Quality Risk Management approach for your existing facilities, API suppliers and / or subcontractors.

In-Depth GMP facility audit

- Pharmaceutical industry must audit their suppliers on a regular basis
  - Some of raw materials used in Production comes from other countries and need to be monitored.
  - With his location worldwide TECHNIP can provide assistance to carry out such in-depth audit
  - Utilization of TECHNIP local resources (chemist, pharmacist, process engineer, QC) assisted by Consultants will make cost effective audit with a high level of knowledge
  - TECHNIP local staffs will ease audit and data collection by local language practice and translation review

1. GMP Audits

GMP Non-Compliances identification

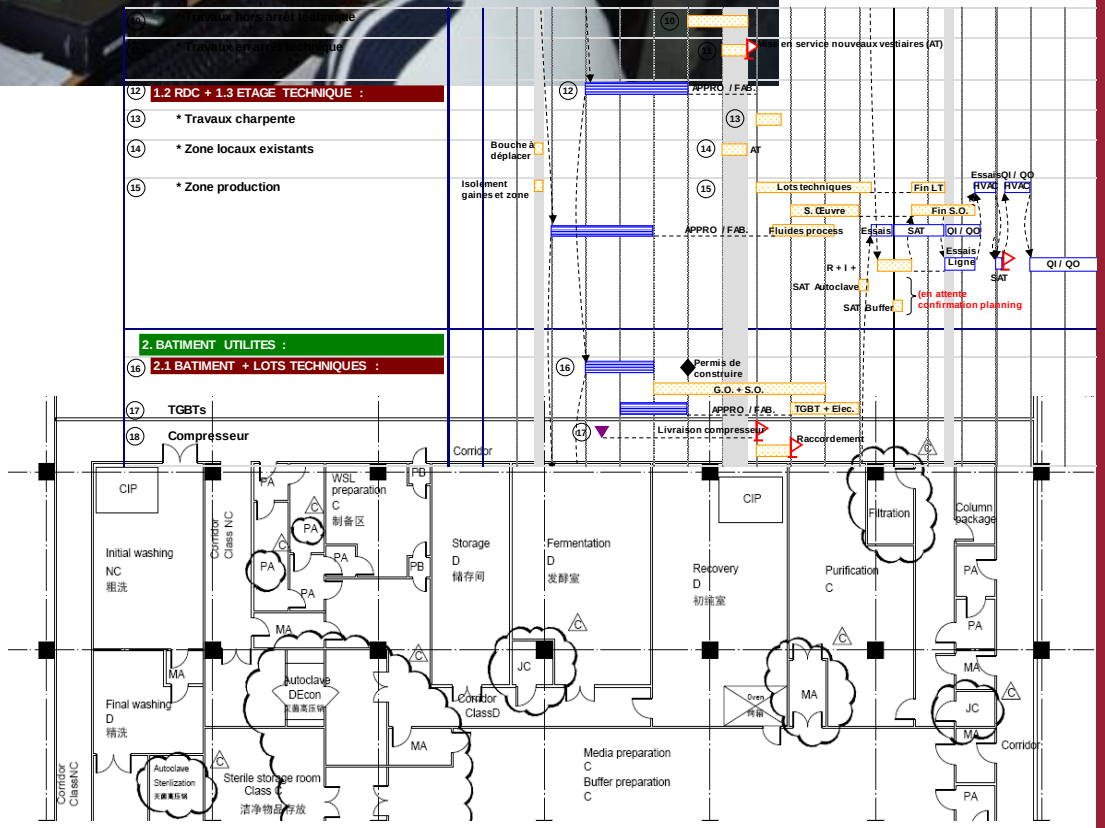
- External Consultants have the knowledge of national/international GMP requirements and, thanks to their knowledge of the regulators focusing way, are able to execute a Mock inspection before regulatory authorities inspection .
- External Auditors will have an external eye and will bring improvement.
- They will issue an outstanding working list and actions plan proposal for your facility as well as for your QA / QC organization

WHO Regulators Inspections

- Regulatory authorities inspections require right answers and the ability to implement and follow action plans
- Through their Production and QC experience, external auditors can provide assistance to deliver such action plan and get authorities approval to resume.
- Training prior audits will bring confidence to the teams and decrease the stress level.

2. GMP Compliance Program

Execution Plan



Any GMP deviations identified with the internal or external Audit requires correctives actions. The GMP Compliance could be split in specific programs:

- **Manufacturing facilities revamping**

  Premises and process equipment modification works should be designed, planned, executed and qualified in a way that will no impact the actual production.

- **Qualification / Validation Update**

  To ensure a documented evidence that equipment, facilities, processes and procedures used in the production and control of drugs are adequate for compliance with the GMP- Validation requirements.

- **Quality Management System**

  Consultants will provide your staff assistance in writing and preparing SOPs compliant with Quality Management System and GMP

- **Training program**

  To deliver training courses on technical subjects:

  - GMP linked to construction projects
  - Facilities conception to comply with Risk Management and GMP's
  - Facilities conception to comply with LEAN Organization and GMP's

3. Revamping Works Execution

Revamping Challenges

We have identified some of the challenges for the management of a revamping project and a good know-how in the vaccine specific domain of biotechnology will allow the team to focus immediately on the key issues gathering information and limit the time consumption of the project.

- Anticipate all potential constraints related with the existing building which should impact the budget and/or planning.
- Good scheduling is required to stay within the facility stops schedule
- Prevent cross contaminations in accordance with GMP's
- Minimize the cost of goods and the construction cost
- As the revamping area could be closed of the operation facility, the interferences with current production shall be as limited as much as possible with no impact on production
- Consider all related safety issues
- In order to anticipate potential issues and to develop a realistic schedule, a constructability review is required with all involved engineering disciplines.

4. Qualification / Validation

Integrated Engineering, Commissioning & Qualification Approach

Integration of qualification activities with engineering and construction activities according to the ISO 9001 quality system, to provide certified documentation required for validation thus minimizing schedule and cost.

Commissioning & Qualification activities

- Validation Master Plan
- Science and Risk-Based Approach
- Design Qualification
- Installation & Operational Qualification
- Performance & Process Qualification
- Cleaning Validation
- 21 CFR part 11 compliance
- GAMP application
- Building Monitoring System

Training Program

A tool to reach your target

- Training partner have developed training modules and offer to deliver training courses on various technical subjects
  - GMP rules linked to your products and general rules.
  - GMP linked to construction projects
  - Facilities conception to comply with Risk Management and GMP's
  - HVAC
    - Conception to avoid cross contamination
    - Conception to comply with energy saving
    - Conception to comply with various Pharma air cleanness
  - Clean Utilities
    - Sizing production and Storage following Production schedule
    - Design to comply with GMP's
    - Construction monitoring to consider to have a qualified system
  - Qualification
    - Methodology to comply with GMP-Qualification and process validation implementation
    - How to use engineering company commissioning tools to match with Qualification expectations

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QUESTIONS / ANSWERS

Doing the right thing
Trusting the team
Encouraging a fair return for all
Building the future

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THANK YOU

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MINHAI - Vaccine Industrialization Project – Beijing

- Client: Beijing Minhai Biotechnology
- Production: 2 vaccine production workshops and two filling workshops
- Value: ~ 25 M€
- Scope: Concept and basic design
- Implementation: 2012

Implementation of complex processes : one based on viral cell culture and the other on different bacterial strain fermentation

Scale-up from pilot to large production plant

Integration in restricted areas in compliance with new Chinese GMP's, segregation and containment requirements

SANOFI PASTEUR - V16 – France

- Client: Sanofi Pasteur
- Production: Multiproduct bulk vaccine
- Value: 70 M€
- Scope: Basic Design + EPCm
- Implementation: 2010

3250 sqm foot-print fermentation based manufacturing plant to produce multiple vaccines and expand existing downstream processing capacity

- Media prep, fermentation suite, downstream processing suite and facilities (lockers, washing areas) with biosafety levels 2 through 3 areas
- HVAC and utilities
- CIP systems
- Cold rooms
- Alcool-phenol-formol suites, detox and decontamination suites

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SANOFI PASTEUR - B44 – France

- Client: Sanofi Pasteur
- Production: New bulk plant for 30 vaccines
- Value: 50 M€
- Scope: Basic Design + EPCm
- Implementation: 2009

10 000 m² new building to accommodate for the formulation of 30 vaccines and an existing production capacity increase

- Formulation area including 7 booths fitted with fixed tanks
- Formulation area for intermediates
- Powders weighing booth
- Manufacturing area of products concentrate under class A
- Washing area (autoclaves, washing machines) ）
- CIP/SIP stations

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MERIAL – France

- Client: Merial
- Production: New Bulk Animal health Vaccine plan
- Value: 35M€
- Scope: Basic Design + EPCm
- Implementation: 2009

Building : ground floor area = 3 300 m² footprint (3 levels)

- **2.500 sqm clean rooms up to grade B**
- **Laboratories**
- **Cleaning**
- **Offices**

Media preparation, buffer need / Cell culture based on production bioreactors up to 4.000 liters / Viral production / Inactivation / Recovery

SANOFI PASTEUR - V15 – France

- Client: Sanofi Pasteur
- Production: V15 bulk inactivated Polio vaccines plant
- Value: 60 M€
- Scope: Basic Design + EPCm
- Implementation: 2005

3-storey brown roots building, 3.300sqm footprint
3.700 m class C clean rooms
1.700 sqm P3 containment areas
- Upstream Production
- Downstream purification
- Additional production (Media preparation vessels, Filling & Storage, Sterilization & Washing)
- HVAC and utilities

SANOFI PASTEUR - Marco Polo - Shenzhen

- Client: Sanofi Pasteur
- Grassroots Flu Bulk vaccine production plant
- Value: 70 M€
- Scope: Permitting + Basic Design + EPCM
- Implementation: 2006-2009

60 000 sqm Grassroots including production area, utilities and facilities (canteen, guardhouse, administration)

CDIBP - JEV project - Chengdu

- Client: CDIBP (CNBG)
- Production: 100 million doses per years of vaccine against the Japanese Encephalitis
- Value: more than 20 M€
- Scope: EPCMV
- Implementation: 2006-2009

New vaccine production unit from animal breeding to inspection machine

First Chinese biotech company to receive WHO pre-qualification

Tight schedule: “time to market”

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MERIAL - Nanjing

- Client: Merial
- New animal vaccine production Plant
- Value: Confidential
- Scope: Conceptual + Basic Design + EPCM
- Implementation: 1999-2000

5 500 sqm production area (Bulk & Filling) and utilities

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GPO - Vaccine Packaging Unit – Thailand

- **Client: GPO-MBP**
- **Production: New Human Vaccines Packaging Plant**
- **Value: 14 M€**
- **Scope: Basic Design + EPCm**
- **Implementation: 2002**

- **Production unit**
  - ✓ **Blending**
  - ✓ **Filling and freeze-drying**
  - ✓ **Capping and inspection**
- **Cold rooms**
- **Animal House**
- **QC lab**
- **Administration building**

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INNOVAX - new vaccines production site - China

- Client : INNOVAX
- City, Country: Xiamen, China
- Technologies : VLP's fermentation, purification biotechnologies
- Contrat Type: Lump sum
- Total Investment Cost: Confidential
- Completion Year : 2014

Site Master Plan and Conceptual Design of HEV and HPV vaccines production based on VLP's from r-E. coli.
Upstream and Downstream processes.
Vials and PFS filling.

Expertise & Profiles of Staff

Expert biopharma & biotech

Exceptional projects call for exceptional talent: our international teams of engineers are continually trained to deliver unmatched technical and project management skills. Technip values diversity, and have passion and true belief in each person's contribution. It is the trust and confidence between team members and between teams that take us further.

Our recognized expertise is a strategic asset that drives our competitiveness. Our experts have developed knowledge and skills that are industry benchmarks (disposable, micro and nanotechnology, modular approach, etc.).

Jean-François DULIERE
Pharmaceutical Process Technologist Expert

10 year engineering experience and 20 years production experience in the Pharmaceutical Industry. President of ISPE France Affiliate

Jean-François has conducted many Site Master Plan and Design studies. With his strong knowledge of industrial development and production, he is able to lead Site Master Plan and design phases for revamping or new facilities.

Recent projects:

- CDIBP : Basic and Detailed Design for grass roots facilities for Flu vaccine in China
- GUERBET : Site Master Plan, Basic and Detailed Design for grass roots facilities for sterile products
- GENZYME : Conceptual Design for rabbit serum treatment and Upstream process
- SANOFI AVENTIS : Site Master Plan of Compiègne site facility extension (OSD)

Patrick HIBLE
Pharmaceutical / Biotechnology Senior Process Expert

25 years experience in design of pharmaceutical & biopharmaceutical projects International experience

Patrick has conducted several Master Plan, Feasibility Study, Conceptual Design for pharmaceuticals major groups .

Recent projects:

- GENOPOLE: Site Master Plan for the implementation of a bioproduction unity in Evry, France
- SANOFI PASTEUR: Site Master Plan, Conceptual Design for grass roots facilities for Flu vaccine in China
- LFB: Basic and Detailed Design for blood fractionation unit
- LEO Pharma: Site Master Plan and Basic Design for OSD and Pre-filled syringes production unit
- SANOFI AVENTIS: Site Master Plan of Quetigny site facility extension (OSD and sterile products)

Patrice COUMET
Pharmaceutical Expert

35 years experiences in pharmaceutical production and engineering

Patrice has held management positions in the pharmaceutical industry, primarily in the infusion drugs manufacturing sector. He has a huge experience in management of manufacturing (sterile and non sterile products) and in design, installation maintenance and Quality Assurance of sterile drugs facilities & utilities (workshops, water systems, microbiology labs, HVAC).

Recent projects:

- GSK Biotechnology: many design and QA activities for sterile filling lines
- But also GENZYME, UCB, BOEHRINGER-INGELHEIM…