Applikon Biotechnology

Turn-key solutions for vaccines biosafety and production
Applikon Biotechnology

- Largest privately owned bioreactor company in the world
- Started in 1974 by Jan van Burg
- Keywords:
  - Reliable
  - New technologies
  - Long term customer relation
  - Micro scale to production scale systems
  - Local experts for sales, service and support
  - Bioreactor systems only
- Daughter companies in UK, USA, China

Jan van Burg
1983

Now: the most used and most copied laboratory bioreactor in the world
World Distribution

Local support in over 37 countries
Experience in large scale systems

- Vaccine & Mab-market
- Global supply
  - Project communication
  - Installation
  - Validation
  - Field support
- Separate skids and integrated skids
- Automation: Standardized Allen Bradley & Siemens PLC
- Turnkey delivery & Integration (Storage & Supply tanks CIP, Utilities, Centrifuges, SCADA ...)

applikon
tm
BIO TECHNOLOGY
Individual skid or super skid
Some Applikon Customers

- Sanofi Pasteur
- Biocon
- NVI (Nederlands Vaccin Instituut)
- Abbott
- Amgen
- MedImmune
- Pfizer
- Merial
- Siemens Healthcare Diagnostics
- Schering-Plough
- Genentech
- Bayer
- Lonza
- MSD
- GlaxoSmithKline
- Roche
- CMC Biologics
## Vaccines projects experience

<table>
<thead>
<tr>
<th>Europe &amp; Americas</th>
<th>Asia</th>
<th>Rest of World</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilthoven Biologicals/SII</td>
<td>China National Biotech Group (SIBP, Lanzhou institute, Kunming institute)</td>
<td>Vacsera, Egypt</td>
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<tr>
<td>Intravacc</td>
<td>Beijing Minhai</td>
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<tr>
<td>Chemocomplex, Hungary</td>
<td>Walvax</td>
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<tr>
<td>Merial, USA &amp; France (veterinary)</td>
<td>Bravovax</td>
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<tr>
<td>GSK, USA, UK &amp; France (veterinary)</td>
<td>Biofarma</td>
<td></td>
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<tr>
<td>Sanofi, USA &amp; France</td>
<td>Serum institute India</td>
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<td>Pasteur Institutes Kasauli and Conoor, India</td>
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Role of bioreactor supplier in Biosafety

• Essential collective efforts to ensure biological safety for a clean and safe environment
• Containment principle and monitoring aspects of bioreactors
  – Sealing arrangement
  – Pressure relief systems
  – Sampling systems
• Measuring and monitoring containment:
  – Number of tests prior to the operation (i.e. pressure hold test)
  – Planned Maintenance and Training

Leaver, G. Interpretation of regulatory requirements to large scale biosafety — the role of the Industrial Biosafety Project. 1994. Biosafety in Industrial Biotechnology, 213-239
Case Study: Manufacturing a cGMP vaccine production plant

- Fully integrated production upscale facility
- Full cGMP
- Scalable systems and transfer lines
- Integration of 3rd party systems
- Fully automated operation
Human vaccine producing company

- Buffer preparation vessels
- Inoculation fermenters
- Scale-up fermenters (up to 1500L)
- Addition tanks (Glucose feed & buffers)
- Continuous centrifuge
- Harvesting vessel
- Collection vessels
- Kill tanks
- Transfer lines
- CIP/SIP fully automated
- Total 14 vessels and transfer lines
cGMP case study Human Vaccine

1. User Requirement Specifications (URS) + questionnaire
2. Quotation
3. Order
4. Design specifications
5. Risk Analysis
6. Detail design specifications
7. Engineering
8. DQ
9. Production
10. IQ
11. OQ
12. FAT
13. SAT
14. PQ

Customer Requirements

Validated System

validation

verification

verification

verification
# User Requirement Specifications

## URS FERMENTOR 1000 L
(GENERAL REQUIREMENTS)

<table>
<thead>
<tr>
<th>No.</th>
<th>Item</th>
<th>URS</th>
</tr>
</thead>
</table>
| 1   | Type          | - Double jacketed  
- Integrated : fermentor 1000 L, continuous centrifuge, harvest tank.  
- CIP, SIP |
| 2   | Capacity      | Working volume : 1000 Liter  
Total volume : 1500 Liter |
| 3   | Design/Feature| - cGMP  
- Agitation : Stirrer  
- Air inlet 1 : - Overlay, air  
- Air inlet 2 : - Sparger, air + O2  
- Air outlet : - Housing filter with heating element  
- Mechanical foam breaker : 200 L/min, From MBR  
- Addition line 1 :  
  - Included housing filter for medium (housing filter compatible with filter cartridge Pall B1NF7PH4). |
From specifications to operational product

- Engineering (Applikon)
- Qualification (Applikon)
- Production (Applikon)
- Qualification (Applikon)
- FAT & Training (Applikon)
- Packing & Shipping (Applikon)
- Unpacking & Installation (Applikon)
- SAT & Training (Applikon)
- Performance Qualification (Customer)
- Validation (Customer)
- After sales support (Applikon)
PFD made according URS
P&ID made according URS
Project Management Center

4. Software

- 4) SCADA (Planned (not active)) [Piet den Hartog]
  - 4.1 Release SCADA Configuration Specification (Planned (not active)) [Piet den Hartog]
  - 4.2 Release Configuration Software SCADA (Planned (not active)) [Piet den Hartog]

5. Qualification

- 5) Qualification (Planned (not active)) [Piet den Hartog]
  - 5.1 Installation Qualification (IQ) (Planned (not active)) [Piet den Hartog]
    - 5.1.1 Release IQ Protocol (Planned (not active)) [Piet den Hartog]
    - 5.1.2 Perform IQ (Planned (not active)) [Piet den Hartog]
  - 5.2 Operation Qualification (OQ) (Planned (not active)) [Piet den Hartog]
    - 5.2.1 Release OQ Protocol (Planned (not active)) [Piet den Hartog]
    - 5.2.2 Perform OQ (Planned (not active)) [Piet den Hartog]
  - 5.3 Factory Acceptance Test (FAT) (Planned (not active)) [Piet den Hartog]
    - 5.3.1 Release FAT-protocol (Planned (not active)) [Piet den Hartog]
    - 5.3.2 Perform FAT (Planned (not active)) [Piet den Hartog]

6. Transport

- 6) Transport (Planned (not active)) [Piet den Hartog]
  - 6.1 Transport (Planned (not active)) [Piet den Hartog]

7. Installation / Commissioning

- 7) Installation / Commissioning (Planned (not active)) [Piet den Hartog]
  - 7.1 Installation / Commissioning (Planned (not active)) [Piet den Hartog]
  - 7.2 Site Acceptance Test (Planned (not active)) [Piet den Hartog]
    - 7.2.1 Release SAT Protocol (Planned (not active)) [Piet den Hartog]
    - 7.2.2 Perform SAT (Planned (not active)) [Piet den Hartog]

8. Training

- 8) Training (Planned (not active)) [Piet den Hartog]
  - 8.1 Training (Planned (not active)) [Piet den Hartog]
3D CAD design
1 User Requirement Specifications (URS) + questionnaire
2 Quotation
3 Order
4 Design specifications
5 Risk Analysis
6 Detail design specifications
7 Engineering
8 DQ
9 Production
10 IQ
11 OQ
12 FAT
13 SAT
14 PQ
Factory Acceptance Test
Site Acceptance Test
Turn Key Solution

Analyzing
- Specifications
- Critical aspects
- Time
- Cost effectiveness

Designing
- System configuration
- Process related
- Optimum design

Engineering
- Coherence of design and process
- Confirmation of all parts on the system

Commissioning
- Start up, training
- Compliance to URS, EHS

TIME & Expectations
Case Study 2- Lesson to be learned

Vaccine manufacturer
- cGMP production
- No input from supplier at the initial stage

RESULTS
- Overqualified system
- Cost does not fit to the projected budget

2 YEARS LATER:
- New specifications
- Final calculation
- Final documentations
- Moving on to next step

Analyzing
- Over priced system
- Recalculation
- Revision of all documentations

Supplier
- Depending on manufacturer specifications
- No input on the specifications
Turn Key Solution – System Supplier perspective

- Take part on the bioreactor specifications with vaccine manufacturer
- Involve in detail design of bioreactor
- Containment principle – Engineering that prioritize safety!
- Continuous monitoring by training, preventive maintenance on the bioreactor system
Turn Key Solution – Broader perspective

Analyzing

Designing

Engineering

Commissioning
Value Proposition of the Netherlands Vaccine Initiative (NVI)
Why this Vaccine Initiative?

We help you to realize vaccine manufacturing capabilities, in time and performing as intended, by providing

- Technology transfer and training
- Translation of process design into a flexible facility
- Validation of the process and facility
- Meet the international regulatory guidelines
The unique offering of the Netherlands Vaccine Initiative

To create state of the art vaccine manufacturing capabilities based on established & transferable platform vaccine technologies

By means of an integrated multidisciplinary approach ensuring:
• Cost effectiveness, by doing it first time right
• Fast track delivery leading to early return on investment
• Access to global vaccine markets
• Thorough understanding of your critical business & technology processes
The Netherlands Vaccine Initiative offers you (1)

- Vaccine process and analytical technology
  → Proven technology, low risk
- GMP process and facility engineering
  → Support and execution for successful validation
  → Acceptance by international and national regulatory authorities
  → Facilitate smooth licencing process for export
- Sustainability engineering
  → State of the art energy efficient, reliable and flexible process and facility concepts
  → Responsible to society and environment
The Netherlands Vaccine Initiative consists of four companies. Per company they bring the following value to the Initiative:

**Intravacc**
- The Institute for Translational Vaccinology, is an experienced, not-for-profit R&D organization. We optimize vaccines, vaccine processes and vaccine technologies.
- Developing and improving vaccine design, production processes, analytics and technologies
- **Share and transfer our knowledge** and technologies to public and private partners worldwide and work on collaborative R&D.

**Applikon**
- Privately owned world leader in developing and **supplying advanced bioreactor systems** with a focus on (human) healthcare.
- A global network of well-trained local distributors to guarantee good and fast local support for our customers.
Xendo

- XENDO focusses on **product and process quality and regulatory aspects**.
- Process engineering and validation capabilities, enable the translation from laboratory scale concepts to a full-fledged manufacturing facility.
- Qualification, validation, QA system implementation and regulatory support services ensure GMP and regulatory compliance of the product and the process.

Deerns

- Deerns is an international, independent technical consultancy and engineering firm, that creates a **sustainable, comfortable and safe built environment**.
- Providing feasible solutions, based on innovative designs. Deerns delivers solutions for facilities in which contamination control is paramount.
- **Decades of expertise and experience in developing, designing and putting into operation cleanrooms and laboratories.**
Our Project Execution Vision provides:

• An integrated project approach
• A joint approach to achieve regulatory compliance and licensing
• Up front specification before realisation
• Continuous communication on the project status
• Effective project control measures
Vaccine Development

Discovery
Preclinical
Phase 1
Phase 2
Phase 3
Product Licensure
Phase 4

Research
Process & Assay Development, Scale-up
Animal models

Clinical & Regulatory
Pilot manufacturing, QC & QA
Techtransfer

Facility development (See next detail slide)
Pharmacovigilance
QA / QP oversight including CMO’s CRO’s
CMC Project management
Deliverables Vaccine Development

- Fast-track new vaccine concepts development based on proven technologies
- Process and analytical development up to GMP-grade pilot-scale based on bacterial and viral vaccine development platforms
- Technology Transfer package and hands-on training modules, and active support for vaccine production and quality control
Facility Development

Phase 3
- Tech transfer
- Plant design & engineering
- Project management, Project QA and compliance management
- Procurement
- Facility Construction
- Equipment Delivery
- Quality Systems development
- Completion and commissioning
- Recruitment & training
- Qualification
- Tech transfer and validation
- Factory Licensing

Phase 4
- Product Licensure
- Commercial Manufacturing, QC & QA
Deliverables Facility Development

• Complete functional process and facility design
• Project management, Monthly progress reports on progress, costs and quality
• Procurement packages for contractors defining performance, scope, timing and warranties
• Managed construction site of equipment and facility
• Facility construction and delivery management, installation and commissioning protocols
• Qualification Plan, Qualification Protocols, Execution and reports
• Validation (Master) Plan, Protocols, Execution, Reports
• Quality System
• Support to Registration Dossier
Your solution: The Netherlands Vaccine Initiative

Thorough understanding of your critical business & technology processes

Integrated multidisciplinary approach ensuring:

- Cost effectiveness, by doing it first time right
- Fast track delivery leading to early return on investment
- Access to the global vaccine market
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