Success in Highly Potent API Manufacturing

Conrad Roten, Tobias Merz, Rainer Jossen/ Lonza Ltd/ 21 April 2011
Success in Highly Potent API Manufacturing

- Introduction - Lonza offering for highly potent APIs at Lonza
- Key factors for successful HPAPI manufacturing
- Case studies on
  - PAT in HPAPI projects
  - Realization of a HPAPI in a manufacturing asset
- Conclusion
Lonza Offers a Full Range of Manufacturing Services – also for HPAPI Products

Discovery
- basic research
- disease discovery
- drug discovery

Development
- drug development

Manufacture
- clinical trials
- production

Distribution
- packaging
- marketing sales distribution

R&D (multiple labs)
Kg labs (4 - 20L glass vessels)

Small-scale plants
- 8 reactors
  (160 to 250L)

Launch plant
- multi-use trains
  (630 – 3 000L)

Large scale HPAPI plant (10 m³)
Lonza’s Offering for HPAPI:
5 Different Technologies / Product Areas

HPAPI capabilities available for 5 different technologies:

- Advanced Chemical Synthesis
- Antibody Drug Conjugates (ADC)
- Fermentation
- Peptides
- Continuous Flow Technology

Other specifics

- Specialized assets
- Dedicated teams
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# Highly Potent APIs Have Different Requirements

**Safety - EHS aspects**  
- occupational health

<table>
<thead>
<tr>
<th>Product</th>
<th>Risk-based exposure control</th>
</tr>
</thead>
<tbody>
<tr>
<td>API</td>
<td>OEL ≥10 µg/m³</td>
</tr>
<tr>
<td><strong>Highly Potent API (HPAPI)</strong></td>
<td>OEL ≤ 10 µg/m³</td>
</tr>
</tbody>
</table>

**cGMP compliance**  
- cross contamination

- steroids
- cytotoxics
- hormones
- ß-lactams

- 'highly potent compounds'

**Protect employees and environment**

**Protect patients**
Key Factor Regulatory Strategy
Highly Potent APIs: What Does Lonza Handle?

- Industry agrees - segregated equipment/plant necessary, for:
  - Beta-Lactams
  - Products containing live microorganism and ectoparasiticides

Lonza does not currently have dedicated equipment for those categories.*

- Equipment requirements for Cytotoxics, Cytostatics not as clear

 Lonza: conservative approach

*figures 2009; Lonza internal data evaluation
Key Factor Toxicology and Occupational Health Expertise: OEBs

Lonza Categories 1-6 and OEL (mg, μg & ng /m³)

10 mg 1 mg 100 μg 10 μg 1 μg 100 ng 1 ng

- **Manufacturing**
  - Standard trains

- **R&D and QC Labs**
  - Standard hoods/ labs
  - Specialty hoods/ labs
  - HPAPI trains
  - PCP
  - Isolators

Safebridge Categories

1 2 3 4
Key factor - Risk Assessment and Containment strategy

- Collect basic information
  - Physical properties of substances
  - Hazardous properties of substances
  - Processing steps and conditions / operational steps
  - OEL-evaluation
- Primary Containment
  - Exposure Potential
  - Primary Containment Strategy
- Secondary Containment
  - Displacement Potential
  - Secondary Containment Strategy
- PPE is only safety net

*figures 2009; Lonza internal data evaluation
Key Factor Lab and Manufacturing Assets: Setup and Containment for HPAPI

- **Location**
  - Lonza Visp plant is the Lonza HPAPI Centre of Excellence
  - Centrally located in Europe

- **Track record**
  - Since 1897
  - Specialist in hazardous chemistry
  - Swiss quality and maintenance

- **Key facts**
  - From kg to 10’s of tons
  - Broad technology base incl. support plants and logistics
  - Compliance track record
  - Specialized HPAPI labs and plants
Key Factor People – Know-how, Experience, Training, Performance

- **Experts and experience**
  - Technical and regulatory expertise in all necessary areas
  - Experience with HPAPI projects since years

- **Working culture of people – know where the substance is!**
  - HPAPI assets working team – specialists in the labs and operations
  - Training
  - Verification control of system, people and process performance

- **Passionate and loyal workforce**
Analytical Labs – Containment

- **Dedicated lab teams**
  - Analytical development
  - Handling of AHSK 4/5 compounds

- **Containment features**
  - Access via pressure controlled locks
  - Exhaust air via HEPA-filters
  - Skan workstations
  - a1-Safetech weighing hood (stainless steel)
  - Workbench Berner FlowSafe
Verification of Containment by Occupational Health Monitoring

- Where: labs, production, QC
- Procedure – design / review / act
- Surrogate monitoring (naproxen, lactose) or actual compound

- Air monitoring
  - Personnel
  - Equipment
  - Background

- Wipe tests
  - Equipment
  - Environment
### Results – Surrogate Monitoring QC Lab

- Weighing 20 mg of surrogate (naproxen)
- Target: Air concentration < 40 ng/m³

<table>
<thead>
<tr>
<th>Sampling results in ng/m³</th>
<th>1st Run</th>
<th>2nd Run</th>
<th>3rd Run</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Safetech weighing hood</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operator</td>
<td>&lt; 7.4</td>
<td>&lt; 6.1</td>
<td>&lt; 14</td>
</tr>
<tr>
<td>Front, left</td>
<td>&lt; 7.4</td>
<td>&lt; 6.1</td>
<td>&lt; 15</td>
</tr>
<tr>
<td>Inside</td>
<td>42</td>
<td>103</td>
<td>685</td>
</tr>
<tr>
<td><strong>Berner FlowSafe</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operator</td>
<td>&lt; 12</td>
<td>&lt; 8.4</td>
<td>&lt; 8.7</td>
</tr>
<tr>
<td>Front, center</td>
<td>&lt; 12</td>
<td>&lt; 8.5</td>
<td>&lt; 8.7</td>
</tr>
<tr>
<td>Inside</td>
<td>&lt; 12</td>
<td>&lt; 8.5</td>
<td>-</td>
</tr>
</tbody>
</table>
HAPI R&D Lab 6 Lab Suites – 1 kg lab, 20 Liter Scale

Floor and pressure zoning plan of HAPI lab E38

Above: Safetech hoods
Below: Hallway HAPI lab E38
LCRDH HAPI Lab E38 – Labs Containment, Characteristics

- Containment adaptable to process, combination of
  - Glove boxes
  - Safetech hoods
  - Laminar flow standard lab work benches
  - flexible, staggered approach
### Results – Air-monitoring

**Isolator vs Safetech**

<table>
<thead>
<tr>
<th>Location</th>
<th>Safety hood</th>
<th>Isolator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operator</td>
<td>&lt;2.36</td>
<td>&lt;2.51</td>
</tr>
<tr>
<td>Front outside</td>
<td>&lt;2.72</td>
<td>&lt;2.62</td>
</tr>
<tr>
<td>Inside</td>
<td>7012</td>
<td></td>
</tr>
<tr>
<td>Under door of lock</td>
<td>&lt;0.536</td>
<td>&lt;2.60</td>
</tr>
<tr>
<td>Background lab</td>
<td>&lt;0.516</td>
<td>&lt;1.70</td>
</tr>
<tr>
<td>Personnel lock</td>
<td>&lt;0.516</td>
<td>&lt;1.74</td>
</tr>
</tbody>
</table>

Above: Isolator  
Below: Safetech hood
## Difference Between Different Operators

<table>
<thead>
<tr>
<th>Operator</th>
<th>Sampling results in ng/m³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operator</td>
<td>&lt; 6.24</td>
</tr>
<tr>
<td>Front outside</td>
<td>&lt; 6.19</td>
</tr>
<tr>
<td>Inside</td>
<td>14392</td>
</tr>
<tr>
<td>Work opening</td>
<td>62</td>
</tr>
<tr>
<td>Background lab</td>
<td>&lt; 4.97</td>
</tr>
</tbody>
</table>

- **Air sampling setup**
- **Bench chemist operating in safetech hood**
Manufacturing Assets – Small Molecules

- HAPI lab 1080 / 20 lt
- SSP plant / 160-2500 lt
- Launch plant / 630 - 2500 lt
- HAPI plant / 10 m3
Key Factor Development Process – Tailored to Meet Customer and Product Needs

Familiarization → Development → Qualification → Validation / Production

Team Work
Expertise
Innovation and Creativity

Voice of Customer – Customer Expectations

Target Product Profile
Critical Quality Attributes
Risk Assessment
Design Space
Control Strategy
Continuous Improvement

Pre-Clinical Phase → Phase I → Phase II → Phase III → Launch/Production
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Analytical PAT Solutions for HAPI Manufacturing

T. Merz / Lonza Ltd / 21 April 2011
Strategy

Phase 1
- Feasibility study
- Know how collection

Phase 2
- Scale-up
- Process monitoring

Phase 3
- Process control

Analytical afford

Process understanding
PAT Implementation

- Identification of the **key process parameters**
- Identification of the most appropriate **PAT tools**
  Lab or production scale (analyzer/ sensor/ probe/ software…)
- Automation, sampling, data storage
- Method development in R&D phase
- Process data collection
  - Statistical evaluation
  - Definition of the design space
  - Support process development and validation
- Method transfer in production
  - Statistical evaluation
Why PAT Tools in HAPI Manufacturing

- No sampling necessary  →  no contamination
- Non-destructive analysis  →  no waste
- Real-time information
- In-situ information  →  no sample alterations
- Chemical and physical information
- More information (conc, polymorph)  →  less experimentation

Preferred spectroscopic techniques
# PAT Toolbox – Process Analyzers

<table>
<thead>
<tr>
<th></th>
<th>UV/VIS</th>
<th>NIR</th>
<th>MIR</th>
<th>Raman</th>
<th>FBRM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selectivity</strong></td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Sampling</strong></td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Aqueous solution</strong></td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Applicability</strong></td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Process capable</strong></td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Light guide/ glas</strong></td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Signal</strong></td>
<td>Absorption</td>
<td>Absorption</td>
<td>Absorption</td>
<td>Intensity</td>
<td>Chord length</td>
</tr>
<tr>
<td></td>
<td>solid, liquid, gaseous</td>
<td>solid, liquid, gaseous</td>
<td>solid, liquid, gaseous</td>
<td>solid, liquid, gaseous</td>
<td>liquid</td>
</tr>
<tr>
<td><strong>Samples</strong></td>
<td>Transmission Reflexion ATR</td>
<td>Transmission Reflexion ATR</td>
<td>ATR Transmission</td>
<td>Reflexion</td>
<td>Reflexion</td>
</tr>
<tr>
<td><strong>Techniques</strong></td>
<td>1</td>
<td>3-5</td>
<td>6-10</td>
<td>8-12</td>
<td>8-10</td>
</tr>
<tr>
<td><strong>rel. costs</strong></td>
<td>1</td>
<td>3-5</td>
<td>6-10</td>
<td>8-12</td>
<td>8-10</td>
</tr>
</tbody>
</table>
PAT Tools at Lonza – Important for HPAPI Process Development

- **Spectroscopy**
  - Raman
  - UV/VIS
  - NIR

- **Solid phase**
  - Lasentec
  - Turbidity probes
  - XRD

- **Gas phase**
  - Chemscan
  - Hydrogenation units
  - Online MS

- **Calorimetry**
  - LabMax, Flexylab, Mettler
  - RC, CRC

CRC equipment, in collaboration with Prof. Dr. K. Hungerbühler ETH Zürich

http://www.sust-chem.ethz.ch/research/groups/ReactionCalorimetry
FBRM + PVM

Graph showing data with markers at 1, 2, 3, 4, 5, 6.

- Reactor T [°C]
- Median, No Wt
- counts/sec, No Wt, <10
- counts/sec, No Wt, 10-50

Images 3, 5, 6 show close-up views of the reactor contents.

FBRM-probe
PVM-probe
Raman Spectroscopic Tools

Quantification of a HAPI through glass vials

Calibration

Prediction

Results: 10x20se

Elements: 5
Slope: 0.999145
Offset: 0.264494
Correlation: 0.999102
R-Square: 0.999067
RMSEP: 1.126180
SEP: 1.240766
Bias: -0.191421

Measured Y

0 20 40 60 80

BSA40gl_10x20se

3gl_10x20se

BSA80gl_10x20se

BSA20gl_10x20se

BSA10gl_10x20se

BSA10gl_16x20se

nur BSA konz re.... (Y-var, PC) (Konz.1)

Predicted Y

0 20 40 60 80

Antikörper_10x
BSA10gl_16x20se
BSA20gl_10x20se
BSA40gl_10x20se
BSA80gl_10x20se
BSA80gl_16x20se

Samples

RESULTS: (Y-var, PC) (Konz.1)
Raman Spectroscopic Tools

Crystallization: trend lines of the concentrations (solid and liquid with semi-quantitative modeling)
Raman Spectroscopic Tools

Trending of precipitation in production

Multi curve resolution with 3 components

Educts in Ethanol / Water

Precipitant

Product in Ethanol / Water
Raman Spectroscopic Tools

Polymorph investigation with multi-curve resolution (MCR)

Original

Calculated
Prediction in production

Seeding form I

Seeding with form II

Raman Trends Batch 196

![Graph showing peak ratio over spectra numbers with time indicated as 6:20 h.]

- Monohydrat
- Trihydrate
- Zip. Lsg
Implementation of a HPAPI Product in Production
Consists of...

- Reactor: chemical reactions
- Reactor: mainly for work up
- Design for volume flexibility
- Isolation equipment (filter dryer)
- No open solid handling, repackaging in glove box
- All 4 operation floors with enclosed working areas and air locks
- Operators in PEDI suits
- Several buffer tanks

Unloading product
Task:
- Production of peptide 100 ng/m³ OEL

Preparation:
- Risk assessment – focus solid or open handling!
- Detailed SOPs for focus activities
- Establishment of the production concept
- Accident containment plan
- Defined interaction with disposal plants, logistics, analytics, production, QA
- Cleaning concept (risk assessment)
Material and personnel flow: Definition and risk assessment

Venting: CIP, filter

Venting line setup for cleaning in place w/o dead volume, safety filters to prevent contamination of vent lines
### Completion of setup – additional risk assessment and test

- Detailed risk assessment at the plant side
- Simulation run utilizing lactose checking for leakage
- Basic spec of test: same conc. as API, process flow same as for API, representative sampling positions (24)

<table>
<thead>
<tr>
<th>Sampling position</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Split butterfly valve 4. St. adding raw materials</td>
<td>17 µg</td>
</tr>
<tr>
<td>Split butterfly valve 4. St. connector</td>
<td>1212 µg</td>
</tr>
<tr>
<td>Flange 1 transfer 102.4.R1/3.R1</td>
<td>0.07 µg</td>
</tr>
<tr>
<td>Transfer to Nutro 102</td>
<td>0.01 µg</td>
</tr>
</tbody>
</table>

Split butterfly valve inside containment clean room; procedure for decontamination established and tested.
Production and cleaning: Verification performance by occupational health

- Air monitoring and swabbing while working
- Results officially published for operators each day
- Overview results supporting working concept
- Dry coupling drum above spec; expected
- Decontamination inside clean room
- Measure working proven by verification samples

<table>
<thead>
<tr>
<th>Sampling position</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manifold RW 102.3.R1</td>
<td>&lt; 2.12 ng/m3</td>
</tr>
<tr>
<td>Next to nutro 102</td>
<td>&lt; 1.45 ng/m3</td>
</tr>
<tr>
<td>Clean room 4.St.</td>
<td>&lt; 1.77 ng/m3</td>
</tr>
<tr>
<td>Utility room 1.St.</td>
<td>&lt; 1.41 ng/m3</td>
</tr>
<tr>
<td>Surface drum</td>
<td>&lt; 0.025 ng/cm²</td>
</tr>
<tr>
<td>Floor next to nutro 102</td>
<td>&lt; 0.025 ng/cm²</td>
</tr>
<tr>
<td>Air lock 1.St.</td>
<td>&lt; 0.025 ng/cm²</td>
</tr>
<tr>
<td>Clean room 1.St.</td>
<td>&lt; 0.025 ng/cm²</td>
</tr>
<tr>
<td>Dry coupling drum (Vaterstück)</td>
<td>534 ng</td>
</tr>
<tr>
<td>Dry coupling drum (Mutterstück)</td>
<td>45000 ng</td>
</tr>
</tbody>
</table>
And There is Disposable Containment – Need for a Centrifuge in a HPAPI Process

Problem:
Filtration $\rightarrow$ high LOD, potential wrong polymorph; OEL 1 µg/m³

Target:
Use of a centrifuge $\rightarrow$ not typical HPAPI equipment

Solution:
Custom made disposable containment

Preparation:
Layout designed by operators, risk assessment, interaction with supplier

Performance verification:
Occupational health monitoring inside containment
All results below LOD of 0.015 µg/m³

Next step:
Optimization of layout based on campaign experience
Summary

Success in HPAPI Manufacturing

**Technology**
- Complex chemistry tool box
- Biotechnology
- Backwards integration of product groups (bio/biochemicals)

**Infrastructure**
- Hazardous waste handling and disposal installations
- Existing infrastructure

**Plant Set-up**
- Multi-purpose / product
- Clean-in-place set-up / decontamination
- Containment / Environment

**Resources / Know-how**
- Handling of toxic substances
- GMP experience
- In-house design and realization capabilities
- High resource pool

PEOPLE
Thank You