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

- Basic research
- Disease discovery
- Drug discovery
- Drug development
- Clinical trials
- Production
- 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)

**Slide 3**

28-Oct-11
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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- Introduction - Lonza offering for highly potent APIs at Lonza
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- Case studies on
  - PAT in HPAPI projects
  - Realization of a HPAPI in a manufacturing asset
- Conclusion
Highly Potent APIs Have Different Requirements

Safety - EHS aspects
- occupational health

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

cGMP compliance
- cross contamination

Protect employees and environment

Protect patients

- 'highly potent compounds'
- steroids
- cytotoxics
- hormones
- β-lactams
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
Lonz 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)**

<table>
<thead>
<tr>
<th>Category</th>
<th>OEL (mg, μg &amp; ng/m³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 mg</td>
</tr>
<tr>
<td>2</td>
<td>1 mg</td>
</tr>
<tr>
<td>3</td>
<td>100 μg</td>
</tr>
<tr>
<td>4</td>
<td>10 μg</td>
</tr>
<tr>
<td>5</td>
<td>1 μg</td>
</tr>
<tr>
<td>6</td>
<td>100 ng</td>
</tr>
</tbody>
</table>

**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
Key Factor Lab and Manufacturing Assets: Setup and Containment for HPAPI

■ Location
  ■ Lonza Visp plant ist 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

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  - Background
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  - Environment
Weighing 20 mg of surrogate (naproxen)

Target: Air concentration < 40 ng/m³

<table>
<thead>
<tr>
<th>Safetech weighing hood</th>
<th>1st Run</th>
<th>2nd Run</th>
<th>3rd Run</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Berner FlowSafe</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<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
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></th>
<th>Sampling results in ng/m³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Safety hood</td>
</tr>
<tr>
<td>Operator</td>
<td>&lt;2.36</td>
</tr>
<tr>
<td>Front outside</td>
<td>&lt;2.72</td>
</tr>
<tr>
<td>Inside</td>
<td>7012</td>
</tr>
<tr>
<td>Under door of lock</td>
<td></td>
</tr>
<tr>
<td>Background lab</td>
<td>&lt;0.536</td>
</tr>
<tr>
<td>Personnel lock</td>
<td>&lt;0.516</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Operator</th>
<th>Sampling results in ng/m$^3$</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>

- **Operator**: < 6.24, < 6.60
- **Front outside**: < 6.19, < 6.60
- **Inside**: 14392, 23583
- **Work opening**: 62, 38
- **Background lab**: < 4.97, < 2.58

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
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
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- Conclusion
Analytical PAT Solutions for HAPI Manufacturing
Strategy

Phase 1
- Feasibility study
- Know how collection

Phase 2
- Scale-up
- Process monitoring

Phase 3
- Process control

Analytical afford
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>Feature</th>
<th>UV/VIS</th>
<th>NIR</th>
<th>MIR</th>
<th>Raman</th>
<th>FBRM</th>
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</thead>
<tbody>
<tr>
<td>Selectivity</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Sampling</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Aqueous solution</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+++</td>
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</tr>
<tr>
<td>Applicability</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Process capable</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Light guide/glas</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
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<tr>
<td>Signal</td>
<td>Absorption</td>
<td>Absorption</td>
<td>Absorption</td>
<td>Intensity</td>
<td>Chord length</td>
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<tr>
<td>Samples</td>
<td>solid, liquid, gaseous</td>
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<td>solid, liquid, gaseous</td>
<td>solid, liquid, gaseous</td>
<td>liquid</td>
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<td>Techniques</td>
<td>Transmission Reflexion ATR</td>
<td>Transmission Reflexion ATR</td>
<td>ATR Transmission Reflexion</td>
<td>Reflexion</td>
<td></td>
</tr>
<tr>
<td>rel. costs</td>
<td>1</td>
<td>3-5</td>
<td>6-10</td>
<td>8-12</td>
<td>8-10</td>
</tr>
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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
Raman Spectroscopic Tools

Quantification of a HAPI through glass vials

Calibration

Predicted Y

Measured Y

Regression parameters:
- Elements: 5
- Slope: 0.999145
- Offset: 0.264494
- Correlation: 0.999103
- R-Square: 0.999007
- RMSEP: 1.126180
- SEP: 1.240786
- Bias: -0.191421

Samples:
- BSA10gL_10x20se
- BSA20gL_10x20se
- BSA40gL_10x20se
- BSA60gL_10x20se
- BSA80gL_10x20se

Prediction

Measured Y

Samples:
- Antikeeper_10x
- BSA10gL_10x20se
- BSA20gL_10x20se
- BSA40gL_10x20se
- BSA60gL_10x20se
- BSA80gL_10x20se

28-Oct-11
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

seeding
Raman Spectroscopic Tools

Polymorph investigation with multi-curve resolution (MCR)

Original

Calculated
Raman Spectroscopic Tools

Prediction in production

- Seeding form I
- Seeding with form II
- Raman Trends Batch 196

Graph showing peak ratio over time with labels for Monohydrat, Trihydrate, andZIP. Lsg.
Implementation of a HPAPI Product in Production

R. Jossen / Lonza Ltd/ 21 April 2011
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

Train 102

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>
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<th>Result</th>
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<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

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<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