Knowledge Management in QbD environment

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Vice President / International Business Leader

Rotkreuz (CH) / Penzberg (GER)

Göttingen, 17. February 2014
Introduction Roche Custom Biotech

QbD and Knowledge Management

ISPE Datamanagement: Assessment Tool

Case Study: DAMAS at Roche Penzberg

Conclusion
The Roche Custom Biotech
Providing service and high quality products to Pharma & Biotech companies

worldwide Pharmaceutical and Biotech industry
Roche Custom Biotech Team
Global Reach

Roche Custom Biotech local headquarters
Indianapolis Laval Mannheim Singapore Tokyo

Roche Custom Biotech global headquarter Penzberg

Tuscon Branchburg Mannheim Rotkreuz Penzberg
Roche production facilities
# Diagnostics Global Operations

Manufacturing, Supply Chain and Direct Procurement for all Business Areas

<table>
<thead>
<tr>
<th>Global Operations</th>
<th>Branchburg</th>
<th>Branford</th>
<th>Tucson</th>
<th>Supply Chain</th>
<th>Direct Procurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>~4700 employees</td>
<td>~500 employees</td>
<td>~80 employees</td>
<td>~450 employees</td>
<td>~800 employees</td>
<td>~70 employees</td>
</tr>
<tr>
<td>8 sites</td>
<td>RMD reagents &amp; assays</td>
<td>Sequencing instruments</td>
<td>RTD reagents</td>
<td>2 global hubs: Mannheim, Indy</td>
<td>Represented at all Operations sites</td>
</tr>
<tr>
<td>6400 reagent kits</td>
<td></td>
<td>Sequencing reagents and consumables</td>
<td>RTD instruments</td>
<td>Storage and delivery of 24533 products</td>
<td>Total number of suppliers 3000</td>
</tr>
<tr>
<td>14400 reagent components</td>
<td></td>
<td></td>
<td></td>
<td>Transportation volume per year: 73000 tons/year</td>
<td></td>
</tr>
<tr>
<td>140 instruments</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Purchase volume 2.5 billion CHF</td>
</tr>
<tr>
<td>2060 accessories &amp; consumables</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

- **Mannheim**
  - ~1300 employees
  - RPD assays & reagents
  - RPD instruments assembly, calibration & testing
  - Labeling, packaging for all products produced in Mannheim and Penzberg

- **Rotkreuz**
  - ~450 employees
  - Instruments assembly RPD, RAS, RMD
  - RMD reagents

- **Penzberg**
  - ~850 employees
  - DOZ is the Center of Excellence for Raw Material and supplies all BAs with active diagnostics ingredients through specialized finished goods (approx. 7000 articles incl. custom biotech products)
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A-mAb: a case study in bioprocess development, CMC Biotech Working Group, 2009, Version 2.1
Quality Attributes: Continuum of Criticality

- Potential Impact to Safety Efficacy & Quality?
  - YES
    - Severity
  - LOW
  - HIGH

- Continual Improvement Iteration

Severity = Impact x Uncertainty

IPSE PQLI Team, 2010, 2010
A-mAb Case Study

**IMPACT Risk Assessment Approach**

<table>
<thead>
<tr>
<th>Biol. Activity + Efficacy</th>
<th>PK/PD</th>
<th>Immunogenicity</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very High (20)</td>
<td>Very significant change</td>
<td>Significant change on PK</td>
<td>ATA detected and confers limits on safety</td>
</tr>
<tr>
<td>High (16)</td>
<td>Significant change</td>
<td>Moderate change/impact on PD</td>
<td>ATA detected, confers limits on efficacy</td>
</tr>
<tr>
<td>Moderate (12)</td>
<td>Moderate change</td>
<td>Moderate change, no impact on PD</td>
<td>ATA detected, in vivo effect, can be managed</td>
</tr>
<tr>
<td>Low (4)</td>
<td>Acceptable change</td>
<td>Moderate change, acceptable impact on PD</td>
<td>ATA detected with minimal in vivo effect</td>
</tr>
<tr>
<td>None (2)</td>
<td>No change</td>
<td>No change with impact on PK</td>
<td>ATA not detected or ATA detected, no in vivo effect</td>
</tr>
</tbody>
</table>

AE= Adverse event, ATA= Anti-therapeutic Antibody

A-mAb: a case study in bioprocess development, CMC Biotech Working Group, 2009, Version 2.1
**A-mAb Case Study**

**Risk Assessment Approach**

VH or H considered CQA

Decrease score during Life Cycle through prior knowledge

Include CQA into Control Strategy

Assessment of CQA criticality + process ability to control the QA

<table>
<thead>
<tr>
<th>Product Quality Attribute</th>
<th>Impact</th>
<th>Uncertainty</th>
<th>Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggregation*</td>
<td>12</td>
<td>5</td>
<td>60 (H)</td>
</tr>
<tr>
<td>C-terminal lysine</td>
<td>2</td>
<td>2</td>
<td>4 (VL)</td>
</tr>
<tr>
<td>Deamidated isoforms</td>
<td>2</td>
<td>2</td>
<td>4 (VL)</td>
</tr>
<tr>
<td>Galactose Content*</td>
<td>16</td>
<td>3</td>
<td>48 (H)</td>
</tr>
<tr>
<td>Afucosylation*</td>
<td>20</td>
<td>3</td>
<td>60 (H)</td>
</tr>
<tr>
<td>Sialic Acid Content*</td>
<td>12</td>
<td>5</td>
<td>60 (H)</td>
</tr>
<tr>
<td>High Mannose Content*</td>
<td>16</td>
<td>5</td>
<td>80 (VH)</td>
</tr>
<tr>
<td>Non-Glycosylated Heavy Chain*</td>
<td>16</td>
<td>5</td>
<td>80 (VH)</td>
</tr>
<tr>
<td>Oxidation</td>
<td>4</td>
<td>3</td>
<td>12 (L)</td>
</tr>
<tr>
<td>DNA</td>
<td>2</td>
<td>3</td>
<td>6 (VL)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>16</td>
<td>1</td>
<td>16 (L)</td>
</tr>
<tr>
<td>HCP*</td>
<td>12</td>
<td>3</td>
<td>36 (M-H)</td>
</tr>
<tr>
<td>Protein A</td>
<td>16</td>
<td>1</td>
<td>16 (L)</td>
</tr>
</tbody>
</table>

A-mAb: a case study in bioprocess development, CMC Biotech Working Group, 2009, Version 2.1
Some Key Lessons

2. Quantitative risk ranking definitions should be used wherever possible.

3. The justifications for the cut-off ranges used for the various risk ranking and filtering tools (RRF) tools should be included in the appropriate sections of the submission or accessible via links. It would be extremely helpful to the reviewer to reference and link to the sections where the RRF tool descriptions and individual reports are located when a particular tool is mentioned for a CQA.

<table>
<thead>
<tr>
<th>Impact and Rating</th>
<th>Biological Activity or Efficacy</th>
<th>PK/PD</th>
<th>Immunogenicity</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (18)</td>
<td>80-100% change</td>
<td>&gt; 40% change</td>
<td>ATA detected and confirm limit on efficacy</td>
<td>Reversible AEs</td>
</tr>
<tr>
<td>Moderate (12)</td>
<td>20-80% change</td>
<td>20-40% PD change</td>
<td>ATA detected with in vivo effect that can be managed</td>
<td>Manageable AEs</td>
</tr>
<tr>
<td>Low (4)</td>
<td>&lt; 20% change</td>
<td>&lt; 20% change</td>
<td>ATA detected with minimal in vivo effect</td>
<td>Minor, transient AEs</td>
</tr>
<tr>
<td>None (2)</td>
<td>No change</td>
<td>No impact on PK or PD</td>
<td>ATA not detected or ATA detected with no relevant in vivo effect</td>
<td>No AEs</td>
</tr>
</tbody>
</table>

AE = adverse event; ATA = anti-therapeutic antibody

Barbara Rellahan, Team Leader DMA/QBP/CDER, Bioproduction Berlin, 10-2011
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Conclusion
ISPE PAT Community of Practice
The global Data Management Task Team

CO-Chair:
– Andreas Schneider  Roche Diagnostics International Ltd, Switzerland
– Michael Voss  Consultant, Germany,

Core Team Members:
– Marcel de Grutter,  Abbvie, The Netherlands
– Vishal Rosha,  Novartis Pharma, Switzerland
– Christoph Herwig,  Vienna University of Technology, Austria
– Jose Cardoso de Menezes,  Technical University of Lisbon, Portugal
– Falk Schneider,  DASGIP, Germany
– Martin Dittmer,  Rockwell Automation, Germany

Mission: To help process developers, manufacturers, suppliers, organizations and authorities to determine how data from processes can be efficiently managed so that all QbD/PAT-relevant and critical parameters are available for knowledge management and continuous improvement.
To act as a team, for consulting and advising on the application of existing standards and the development of new standards.
A-mAb Case Study Mapping

Source: ISPE PAT CoP global Data Management Task Team
# A-mAb Case Study Mapping

## Drug Discovery Process Development Manufacturing

<table>
<thead>
<tr>
<th>Design of molecule (from research)</th>
<th>Product Quality Attributes</th>
<th>QTPP (Quality Target Product Profile)</th>
<th>QTPP (Quality Target Profile) (from business)</th>
<th>Animal testing</th>
<th>COA/KPI</th>
<th>Operational Setup Information &amp; Operational Setup Information &amp; Raw Materials</th>
<th>Process Understanding/Batch History/Platform Process Knowledge</th>
<th>Risk Assessment/Scale-up/down Models</th>
<th>Design space, Control strategy</th>
<th>Master Recipe</th>
<th>BR (Batch Record)</th>
<th>Process monitoring data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manufacturing</strong></td>
<td>Design space, Control strategy</td>
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<td></td>
<td>Master Recipe</td>
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</table>

**Source:** ISPE PAT CoP global Data Management Task Team
# A-mAb Case Study Mapping

<table>
<thead>
<tr>
<th>Information-Management</th>
<th>Knowledge-Management</th>
<th>Interfaces</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collect data</td>
<td>Investigate</td>
<td>Interfaces of unit operations (site-transfer, phase-to-phase)</td>
</tr>
<tr>
<td>Store data</td>
<td>Modeling/(Re-)Design</td>
<td>Technical Interfaces</td>
</tr>
<tr>
<td>Organize data</td>
<td>Monitoring for continuous improvement</td>
<td></td>
</tr>
<tr>
<td>Structure data</td>
<td>Product- and process-design</td>
<td></td>
</tr>
<tr>
<td>Convert data to information</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Missing tools, interfaces, knowledge**
- **Today available**
- **Not fully covered**

Source: ISPE PAT CoP global Data Management Task Team
A-mAb Case Study Mapping

DRUG DISCOVERY

Description

- Design of molecule (from research)
- Product Quality Attributes
- QTPP (Quality Target Product Profile)
- QTPP (Quality Target Product Profile) (from business)
- Animal testing

Information-Management
- Collect data
- Store data
- Organize data
- Structure data
- Convert data to information

Knowledge-Management
- Investigate
- Modeling/Re-Design
- Monitoring for continuous improvement
- Product- and process-design

Interfaces
- Interfaces of unit operations (site-transfer, phase-to-phase)
- Technical interfaces

Source: ISPE PAT CoP global Data Management Task Team
Finding Drug Discovery

**Gaps**
- Unstructured
- QTPP business
- Data complexity
- Implementation of innovative technology

**Benefits**
- Predictive design of molecule
- Predict platform technology
- Support filing records

**Suggestion**
- Structure data
- Interface discovery and process development

**Design of molecule**
- CQAs
- QTPP (business)
- Animal Testing Clinical trials

Source: ISPE PAT CoP global Data Management Task Team
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Conclusion
Where was the data in the past? – Distributed over different media, departments and regions

- Lab Journals
- Excel-Tables, Word documents
- Isolated Databases
Technical Process Development

- Development to market scale in compliance with regulatory guidelines and authorisations
- Protein product manufacturing for preclinical & clinical studies
DAMAS – Data Acquisition, Management and Analysis System

an integrated Electronic Lab Notebook

- Analytical data
- Online process data
- Raw material & media data
- Specifications & instruction
- Documentation
- Reporting
- Analysis
DAMAS - Transfer of Analytical Data

Overview of devices connected to the system

Appr. 200 devices connected

Appr. 700,000 samples p.a.

Analytical Device Types

Photometer
Goebel Uvikon XL/XS
Varian Cary 50

HPLC
Dionex Series

FPLC
GE Äkta Series

pH/LF-Meter
WTW 3310, 340i, 197i, InoLab2

Osmometer
Gonotec Osmomat 030, auto

MTP-Reader
Molecular Devices Versa Max

Bloodgas
cobas b 221 1)

Metabolite
CedexBio, CedexBio HT 1)

Cellcounter
Cedex Standard/HiRes 1)

Immuno-Assay
cobas® 411 1)

1) COBAS, COBAS B, COBAS C, CEDEX and COBAS INTEGRA are trademarks of Roche
DAMAS – How it was achieved

- Extend analysis of existing software solutions in the market was performed.
- No single, monolithically solution was able to cover the whole *end to end process* in a sufficient way.
DAMAS - Transfer of Analytical Data

Smart Data Cockpit (SDC) Middleware

Data integration with SDC

LIMS/MES/ERP/ELN

one single interface

Smartline Data Cockpit®
21 CFR Part 11 compliance

validated
validated
validated
validated
planned
planned
possible

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Conclusion
Fermentation in the 21st Century
in the perspective of the pharmaceutical industry

Good process = Control of product quality and yield during i.e. fermentation

QbD has strong IT component: Assess the impact of QbD strategy to your IT environment. Establish seamless transfer of data and information from R&D to manufacturing.

Identify interface gaps and fix them.

Data Quality matters: Bioprocess modeling is just as good as the quality of data. Don’t underestimate the impact of signal quality to your process and models.

Reliability of sensors/analytical instruments is critical.

Involve all stakeholder: Knowledge management is nothing you can establish only on PPT slides. There is a business case behind Knowledge Management and QbD implementation.
Acknowledgement

The global ISPE Data Management Task Team (PAT CoP)

**CO-Chair:**
Michael Voss, Consultant, Germany,

**Core Team Members:**
Marcel de Grutter, Abbvie, The Netherlands, Vishal Rosha, Novartis Pharma, Switzerland
Christoph Herwig, Vienna University of Technology, Austria
Jose Cardoso de Menezes, Technical University of Lisbon, Portugal
Falk Schneider, DASGIP, Germany, Martin Dittmer, Rockwell Automation, Germany

**Roche Teams Penzberg:**
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Tim Noetzel, Doerthe Druhmann, Holger Opitz, Herman Tebbe, Josef Burg, Berthold Szperalski, Josef Gabelsberger,
Andreas Jux, Mark Dietrich,
Roche Diagnostics, Penzberg & Rotkreuz
Peter Hloch, Jurgen Leser, Christina Krause, Christian Weilke,
AGU: Harry Voges, Harald Bruch
Doing now what patients need next