QbD Implementation in Commercial Manufacturing and PALM: A GAZYVA® Case Study

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Outline

• Introduction to Obinutuzumab
• QbD Elements and their Implementation
  – Critical Process Parameters (CPPs)
  – Design Space
  – Control Strategy
  – Post Approval Lifecycle Management (PALM)
• Real Life, Lessons Learned and Outlook
Obinutuzumab (INN)

Glyco-engineered therapeutic Mab targeting CD20

DS – Development and Manufacturing in Penzberg

DS – 12,000 L Fermentation Scale

DP – Development in Basel, Manufacturing in Mannheim

DP – Concentrate for solution for infusion

Quality by Design Approach
QbD Aspects

- Full QbD approach to DS and DP development
- Process-wide Design Space proposal
- Approvals for CLL treatment by
  - FDA 11/13, Health Canada 11/14, tradename GAZYVA®
  - Swissmedic 06/14 and EMA 07/14, tradename GAZYVARO™
  - Including QbD-based control system and design space
  - Approvals/reviews in other jurisdictions
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The Approach to a Process Model

- Use qualified small scale models
- Perform multivariate studies whenever possible
- Perform multiple rounds of experiments if required (e.g. screening and response surface)
CPP Identification

ICH Definition: “A process parameter *whose variability has an impact on a critical quality attribute* and therefore should be monitored or controlled to ensure the process produces the desired quality“

- CPPs are all PPs that have a **meaningful impact** on any CQAs i.e. lead to a
  - > 10% CQA change relative to the allowed range (“low-impact” CPP)
  - > 33% CQA change relative to the allowed range (“high-impact” CPP)

- CPPs are determined based on their impact **within** their allowed limits (i.e. definition is not based on excursions from these limits)

- CPP limits cover all **parameter interactions** and **worst-case linkage** of all process parameters end-to-end (WCB to drug product end of shelf life)
Criticality is relative to the Considered Range

**Specified range (design space)**

**Normal operating range**

**Process Parameter**

**Low Limit**

**High Limit**

**Setpoint**

**High-Impact CPP:** CQA impact > 33%

**Low-Impact CPP:** 10% ≤ CQA impact ≤ 33%

**Non-CPP:** CQA impact < 10%

**CQA Target**

40% of allowed CQA range

‡ high-impact CPP

**Model prediction CI_{95%} of process model prediction**
Allowed Process Parameter Ranges
Consider Worst-Case Linkage (Small scale data)

CQA Limit

Amount CQA 1

Effect of unit operation

Unit operation 1
e.g. production bioreactor

Unit operation 2
e.g. cation-exchange chromatography

Unit operation 3
e.g. galenical operations

Worst-case setpoint
Target setpoint

Result of worst-case linkage
Result of target process
**Link between Process Parameters and CQAs is Clearly Understood**

Simplified example for the production bioreactor

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CQA 1</th>
<th>CQA 2</th>
<th>CQA 3</th>
<th>CQA 4</th>
<th>CQA 5</th>
<th>CQA 6</th>
<th>Summary Designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>pO₂</td>
<td>non-CPP</td>
<td>non-CPP</td>
<td>non-CPP</td>
<td>non-CPP</td>
<td>non-CPP</td>
<td>High</td>
<td>High Impact CPP</td>
</tr>
<tr>
<td>pH</td>
<td>non-CPP</td>
<td>non-CPP</td>
<td>non-CPP</td>
<td>non-CPP</td>
<td>non-CPP</td>
<td>High</td>
<td>High Impact CPP</td>
</tr>
<tr>
<td>Temperature</td>
<td>non-CPP</td>
<td>non-CPP</td>
<td>non-CPP</td>
<td>High</td>
<td>non-CPP</td>
<td>High</td>
<td>High Impact CPP</td>
</tr>
<tr>
<td>Glucose concentration</td>
<td>non-CPP</td>
<td>non-CPP</td>
<td>non-CPP</td>
<td>non-CPP</td>
<td>non-CPP</td>
<td>High</td>
<td>High Impact CPP</td>
</tr>
<tr>
<td>Seeding density</td>
<td>non-CPP</td>
<td>non-CPP</td>
<td>non-CPP</td>
<td>non-CPP</td>
<td>non-CPP</td>
<td>Non-CPP</td>
<td>Non-CPP</td>
</tr>
</tbody>
</table>

*Note: Summary designation considers worst case designation*
The Drug Substance and Drug Product Design Space includes:
- All unit operations and their sequence
- All process parameters describing the operation of each of the unit operations (described in Section S.2.2 and P.3.3)
- All raw materials

The Design Space is limited by the multivariate acceptable ranges (MARs) for all relevant process parameters:
- CPPs
- Non-CPPs

Working within Design Space is not considered as a regulatory relevant change (however, internal change control applies)
Implementing the Design Space

- Acceptable region for CPPs and non-CPPs (= MAR limits i.e. the Design Space) is described by **action limits** in manufacturing instructions.
- Design Space is derived from small scale models and is wider than commercial scale experience - it must be **verified** in commercial scale.
The Overall Control Strategy is a Risk Management Strategy

Using the QbD approach, lot release & stability testing is risk-based and addresses critical attributes or those impacted by the process.

- How critical is the attribute?
- How well does the process control it?

Either high criticality or high process impact drive testing.
# CQA Testing Program

<table>
<thead>
<tr>
<th>CQA</th>
<th>Scope</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control system attributes</td>
<td>Within one batch</td>
<td>Before release</td>
</tr>
<tr>
<td></td>
<td>Between several batches</td>
<td>Before release</td>
</tr>
<tr>
<td>Additional monitoring attributes  - Continual  - Periodic</td>
<td>Within one batch/between several batches</td>
<td>Retrospectively</td>
</tr>
</tbody>
</table>

- **CoA attributes**
  - Assess unexpected values/trends before release

- **CQA attributes**
  - CQAs well controlled by process
  - Traditional approach would have „validated off“ these CQAs

- **Additional notes**
  - Category results from QbD approach
  - Provides additional assurance about tools and process models
  - Detects long term trends
  - Testing frequency (continual/periodic) may be adapted during lifecycle
The Post Approval Lifecycle Management (PALM) plan links development and commercial phase of a product.
Elements of the PALM Plan

The PALM Plan is a regulatory agreement between the Sponsor and the Health Authorities that specifies how the Sponsor will

- **Monitor** the manufacturing process and product quality attributes to ensure that both remain within a controlled state post-approval
- **Manage changes** to process parameters within the design space
- **Update the control system** as necessary based on further process and product knowledge

The PALM plan is implemented in the respective quality documents e.g. specifications, process descriptions and monitoring protocols.
Process Parameter Change Management within Design Space

Manufacturing Instructions:
- Process Parameter Target Ranges

Design Space

CPP 1

CPP 2
European Medicines Agency and US Food and Drug Administration release further guidance on quality-by-design approach.

The European Medicines Agency (EMA) and the United States Food and Drug Administration (US FDA) have published a second joint and-answer document that provides guidance on the quality-by-design concept.

1. Why would a design space be verified during the product lifecycle?

In both Agencies’ experience, the design space verification at commercial scale is not necessarily complete at the time of submission of the application but should occur over the lifecycle of the product and process. Initial design space verification often occurs solely at or near the target operating ranges. However, movements from one area to another area within the design space (e.g., re-establishing the Normal Operating Ranges (NOR)) within the approved design space in an unverified area) may pose higher or unknown risks due to potential scale-up effects and/or model assumptions. It is important that these risks are understood and evaluated utilizing an appropriate control strategy, including but

4. How can a design space be verified at commercial scale?

It is not necessary to repeat at commercial scale the experiments initially conducted to define a design space at lab or pilot scale. Furthermore, it is not necessary to verify entire areas of design space nor to identify the edge of failure. In principle, more than one area of a design space may be verified at the time of submission but the design space can, as appropriate, also be further verified over the product lifecycle.
**Design Space Verification**

- PALM plan specifies assessments required for parameter target changes within design space
- Extent of change assessment depends on risk level

<table>
<thead>
<tr>
<th>Risk</th>
<th>Examples for Process Change Assessment Requirements</th>
</tr>
</thead>
</table>
| **Low** (e.g., change of non-CPPs or one Low-Impact CPP) | Control system testing done at manufacturing scale.  
No influence on testing frequency of monitoring attributes. |
| **Medium** (e.g., change of multiple Low-Impact CPPs or one High-Impact CPP) | Testing of control system and appropriate monitoring attributes done at manufacturing scale **under validation protocol** to verify model prediction (minimum of one batch).  
No influence on testing frequency of monitoring attributes. |
| **High** (e.g., change of multiple High-Impact CPPs) | Testing of control system and appropriate monitoring attributes done at manufacturing scale **under validation protocol** to verify model prediction (minimum of three batches).  
Increased testing frequency of relevant monitoring attributes, as appropriate. |
Change Assessments

- Verify CQA impact that process models predict for a CPP set point change within design space
- Expectation is that CQA lies within historical range, e.g. (preliminary) trend limits, modified by the predicted effect

![Graph showing change assessments with trend limits and predicted effect](image)
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Design Space Verification: Real Life Example

- Change in pO₂ target for all fermentation steps
- Motivation: Move pO₂ target to design space center
- pO₂ is a high impact CPP, so according to PALM plan a validation protocol was written and 1 batch was required to confirm small scale model prediction

- Acceptance criteria:
  - CQAs for which no change is predicted are within trend limits
  - CQAs for which change is predicted (Glycosylation CQAs) are within preliminary trend limits modified by process model prediction from scaled estimate
Design Space Verification: Lessons learned

- Short manufacturing history leads to wide preliminary trend limits for some CQAs; In comparison predicted effect is small (~ 5% of trend limit range)
- Within validation approach, predicted effect cannot be statistically “proven” (1 batch by far not sufficient), but long term effects would be seen in process monitoring
- Regulatory status for change is crystal clear (i.e. covered by license), even though release-relevant CQAs are affected by the change
- QbD offers systematic approach to assess parameter changes and to learn from the results
- Process understanding is a high value for the commercial organization
Outlook

- Refinement of QbD tools ongoing
- Proposal not to require linkage of worst case process parameter settings for process-wide design space claim
  - Process-wide design space can be sufficiently supported by process characterization/validation (PC/PV) studies of unit operations
  - Combining worst cases of all unit operations at the same time is unrealistic and the resulting knowledge of little practical value
  - PALM plan may be adapted accordingly
Potential PALM Plan Adaptations

- If small scale data don’t support a planned commercial change (e.g. simultaneous changes in several unit operations), additional PC/PV data may be required to verify acceptable product quality – in addition to commercial scale verification.

- Consider the direction into which - based on model data - a CQA will move when determining the change assessment criteria (“lower risk region” = movement away from CQA acceptance criteria).
Acknowledgements

- Obinutuzumab development teams led by Rolf Schäfer and Jacques Bourquin
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- QbD Team led by Lynne Krummen

- Ron Tatischek
- …and many more
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