20/20 Vision: the future of ICH Q12 in practice

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Predicting the future:

Opportunities:
- Be proactive (anticipate potential change) and build robustness/antifragility

Challenges:
- Predicted harms can also have unanticipated benefits
- Failing to account for exponential change
- Black swan events

You cannot predict the future.

— Stephen Hawking —
Future manufacturing processes will utilize:

- Enhanced process controls - much greater level of process understanding and control
- Scientific models and process signatures will support product quality prediction
- Adaptive control will be a critical element of process consistency

What does this mean for ICH Q12 and Established Conditions?
Established Conditions for Enhanced Process Control Manufacturing

Reduced CCPs; critical outputs are the only proposed ECs for many steps

More knowledge/Less Uncertainty/Fewer ECs

- Robust Risk Assessments/Criticality
- Knowledge Space
- Adaptive Process Control/Robust Predictive Models
Futuremab

- Disease modifying therapy for unmet medical need
- Patient population size in the millions
- Unprecedented manufacturing capacity needs
- Enhanced manufacturing process controls and analytics
- Patient centered drug development

<table>
<thead>
<tr>
<th>Post-approval change to be introduced</th>
<th>Q12 Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>New drug substance/ drug product manufacturing sites</td>
<td>PACMP/ECP</td>
</tr>
<tr>
<td>Application of advanced technologies as alternate for traditional analytical technology</td>
<td>If non-EC, PQS If EC, PACMP or eCP</td>
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<tr>
<td>Replacement of traditional/parameter based EC with enhanced ECs (including advanced process controls)</td>
<td>PACM/eCP</td>
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<tr>
<td>Addition of analytical method with an equivalent method</td>
<td>Frequent changes and EC</td>
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<tr>
<td>Change to primary or secondary packaging</td>
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Futuremab: Enhanced Process Controls
Goal: Eliminate batch failures due to RM & process variability

Multivariate analysis for process monitoring and disposition decisions, Predictive model for RTRT or FF control

Foundations:
- Extensive RM, process, product characterization and understanding
- Right technologies at right places – value added, reasonable cost
- A fully-integrated, implementable, reliable and sustainable control system
## Raw Material Established Conditions

<table>
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<tr>
<th>Traditional ECs</th>
<th>Enhanced ECs</th>
<th>Enablers</th>
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| Specifications/vendors for all non-compendial raw material attributes | Specifications for only **critical** raw material attributes. Feedforward controls to account for variability in critical raw material attributes | Requires:  
  • an established raw material understanding rooted in criticality and risk assessment and predictive models.  
  • an understanding of the functional relationship between critical raw material attributes and critical product quality attributes  
    • Example: heavy metals that may impact glycosylation |
# Cell Culture
## Established Conditions

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| Critical input parameters:  
• Online pH, temp, DO  
• Culture duration  
• Nutrient feed daily amounts | Fewer critical input parameters, outputs - multivariate process signature (linked to CQA), and feedback control loop. | Requires an established knowledge space of input parameter impact to titer and culture viability  
• Inter-relationship between pH, temp, DO and cell growth |
| Critical output controls/tests:  
• Micro and viral contamination  
• Culture viability  
• Titer | | |
| Noncritical descriptions | | |

**Enablers**

- Requires an established knowledge space of input parameter impact to titer and culture viability
  - Inter-relationship between pH, temp, DO and cell growth
Purification Example

Impurity control = established condition

Bioreactor Harvest

Purification

Capture
Intermedi
Polish

Column load ratio

DS

On-line sampling

Multi-attribute method

At Line Rapidly Measure % Impurity in Column Load

≤2.5%
2.6-3.4%
≥3.5%

Established Condition Impurity controlled to ≤ 2.5%

No FF Load ≤ [x] (n cycles)
FF Load ≤ [x – y] (n + 1 cycles)
FF Load ≤ [x – 2y] (n + 2 cycles)
Analytical Methods Established Conditions

• “Do and Tell’ provided the general type of analytical technique remains unchanged (chromatographic, or spectroscopic, or electrophoretic etc) AND the validation results are in accordance with the agreed validation criteria.’

• PQS documents continuous verification of method performance and risk assessments.

• Established conditions= only performance characteristics for control strategy methods

• Validation would include variables that affect the performance characteristics.

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<th>Example</th>
<th>ECs</th>
<th>Non-ECs</th>
<th>Change Example</th>
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<tr>
<td>Size Exclusion Chromatography</td>
<td>• Basis of separation and detection</td>
<td>• Column used</td>
<td>Change from HPLC to UPLC would not need to be reported.</td>
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<td>• System suitability criteria (theoretical plates, resolution, tailing factor)</td>
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<td>• Assay and sample acceptance criteria</td>
<td>• Quantities used</td>
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Example ECs and Non-ECs for Size Exclusion Chromatography:

- **ECs**
  - Basis of separation and detection
  - System suitability criteria (theoretical plates, resolution, tailing factor)
  - Assay and sample acceptance criteria

- **Non-ECs**
  - Column used
  - Solutions used
  - Quantities used

Change Example: Change from HPLC to UPLC would not need to be reported.
**Development**
Least robust
(1 DS/DP site, few batches, single sourced vendors, limited data sets)

**Submission**
LCM Flexibility built in
(Dual sourcing, LCM Plan (comparability protocols, use of PQS, and Established Conditions)

**Post-approval**
Increasing robustness (resilient to disorder)
Reliant on PQS & expanded knowledge space, utilization of LCM flexibility.

Flexible and harmonized life cycle management (ICH Q12) is a commitment to increasing product supply robustness.

Lack of harmonization and flexibility for LCM is impedes robustness and increases supply risk.
LCM Plan: Pulling it all together

Operating in a state of control

- PQS (and justification for EC)
  - Example: high level description of how automation controls are qualified and maintained
- Process monitoring/trends
  - Example: description of how predictive models are maintained and kept current with increasing product quality knowledge
- Continuous Process Verification
- Excursion/deviation monitoring
- Post-market surveillance

Change Control

- Risk Assessments/Quality risk management
- Outline for “do and tell” changes
  - Example: Notification or “tell and do” categories for changing potency assay from a manual process to an automated process
- PACMP/eCP link
  - Examples: new facility, increased scale, change in potency assay that impacts performance characteristics
- Reporting categories for Established Conditions
What can we do to improve the lives of patients now and in the future?
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I predict that I will give the first VR presentation to a CASSS audience.