LEVERAGING KNOWLEDGE OF MATERIAL ATTRIBUTES AND DATA ANALYTICS AS KEY ELEMENTS OF A RAW MATERIAL CONTROL STRATEGY

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Therapeutic diversity facilitates patient-centric outcomes
DELIVERING HIGH QUALITY MEDICINES REQUIRES KNOWLEDGE OF IMPORTANT PROCESS AND PRODUCT ATTRIBUTES

Manufacturing History
Platform Knowledge
Clinical and Process Development
Process Subject Matter Expertise
Business Intelligence

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An understanding of ALL potential sources of variation is needed to develop robust control strategies.
MANUFACTURING OPERATIONS REQUIRE A WIDE VARIETY OF RAW MATERIAL TO ENSURE SUPPLY FOR PATIENTS

Raw materials can be a challenging source of variation

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Well understood and controlled raw materials are fundamental for optimal process performance and ensuring the QTPP is met.
A ROBUST RAW MATERIAL CONTROL STRATEGY CAN BE ACHIEVED WITH AN ATTRIBUTE FOCUS

Evaluate supplier’s ability to test and control material attributes

Understand material attributes impacting the process and product

Define the role of the material in the process

Establish controls to minimize material variability

Track material performance to ensure consistency

ATTRIBUTES

APPLY QTPP APPROACH TO RAW MATERIALS FOR ENHANCED UNDERSTANDING AND CONTROL

PRODUCT ATTRIBUTES UNDERSTANDING

TARGET PRODUCT PROFILE
Attribute-focused process development

PRODUCT QUALITY ATTRIBUTE ASSESSMENT
Drive reliability through process understanding

QUALITY TARGET PRODUCT PROFILE (QTPP)
Process designed to achieve QTPP

MATERIAL ATTRIBUTES UNDERSTANDING

MATERIAL TARGET PROFILE
Attribute-focused material selection

MATERIAL ATTRIBUTE ASSESSMENT
Impact of materials on ability to achieve QTPP

MATERIAL TARGET ATTRIBUTE PROFILE
Fit-for-purpose material defined

MATERIAL ATTRIBUTE CONTROL ASSESSMENT
Supplier & internal control strategies
**FRAMEWORK FOR IDENTIFYING IMPORTANT MATERIAL ATTRIBUTES**

### Material Target Attribute Profile (MTAP) for a chemical raw material

<table>
<thead>
<tr>
<th>MATERIAL TARGET PROFILE</th>
<th>MATERIAL ATTRIBUTE ASSESSMENT</th>
<th>MATERIAL TARGET ATTRIBUTE PROFILE (MTAP)</th>
<th>MATERIAL ATTRIBUTE CONTROL ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intended use: buffering agent</td>
<td>Purity: Process can tolerate conc. at target ± 10% Process can dispense at target +/- 2%</td>
<td>Purity &gt; 92% 97%</td>
<td>Supplier spec: purity &gt;98% Get info on supplier controls / testing / release strategy</td>
</tr>
<tr>
<td>Material Compatibility: no unacceptable impurities/levels</td>
<td>Impurities: Known impurities pose no process or product risk</td>
<td>Supplier able to meet requirements established by Amgen</td>
<td>Impurity info and control strategy from supplier</td>
</tr>
<tr>
<td>Process Compatibility: ensure material can be accurately dispensed</td>
<td>Water content (material is hygroscopic) Clumping observed at water &gt; 4 % Dispensing performed in air</td>
<td>Water content &lt; 3%</td>
<td>Supplier spec: water &lt; 2% Control / testing / handling / release strategy?!!</td>
</tr>
</tbody>
</table>

Gaps in knowledge can be addressed with additional testing or literature
FIT-FOR-PURPOSE RAW MATERIALS ARE DEFINED WHEN ALL IMPORTANT ATTRIBUTES ARE UNDERSTOOD

Cross-functional review of new materials or new uses of existing materials starts early

The MTAP framework facilitates the development of science-based raw material specifications and phase-appropriate decisions across the lifecycle of that material.

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ONCE FIT-FOR-PURPOSE MATERIALS ARE ESTABLISHED, HOW DO WE ENSURE WE MAINTAIN CONTROL?

- **Fit-For-Purpose raw materials defined**
- **Supplier testing & controls established**
- **Science-based specifications & controls enacted**
- **Continuous state of control sustained**

Data can be leveraged to monitor raw material performance enabling the control of variability through predictive assessment
AMGEN HAS INVESTED IN A DATA INFRASTRUCTURE FOR ENHANCED PROCESS AND PRODUCT INSIGHTS

- Highly Scalable Technologies
- Hybrid Cloud Infrastructure
- Embedded Data Analytics and Reporting Tools
- Data access by default
THE INFRASTRUCTURE PROVIDES THE ABILITY TO INTEGRATE MILLIONS OF PROCESS DATA POINTS

Incorporating raw material data can provide additional insights about the relationship between raw material attributes and product quality attributes.

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ADDITIONAL DATA SOURCES ENHANCE OUR UNDERSTANDING OF RAW MATERIAL VARIATION

Partnering with suppliers to share data, gain insights, reduce variability, and improve raw material performance

TRENDING REPORT WITH INTEGRATED DATA

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SYSTEMATIC REVIEW AND RESPONSE PROCESS

CROSS-FUNCTIONAL TEAM REVIEW

- Recurring data review meeting
- Action tracker to monitor progress

PREDICT & PREVENT FRAMEWORK

1. Review Raw Material Prioritization
2. Signal observed
   - Do we need to respond? (Yes/No)
   - Is the risk known & accepted? (Yes/No)
3.ятия
   - Product impact prediction and proactive mitigation strategy
   - Keep Calm and Let It Go
   - Ensure decision has been documented w/ justification

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PREDICT & PREVENT CAPABILITY REALIZED

PROBLEM STATEMENT: large variation in assay value for raw material with some lots close to specification limit

TEAM REVIEW

INVESTIGATION:
Variation attributed to method and handling

RISK MITIGATION:
- Supplier & Amgen Engagement
  - Minimize method variability by strict titrant control
  - Amgen aligned to supplier best practices for material handling

Ppk predicted to increase to > 1.0 with implementation of additional controls
APPLYING MACHINE LEARNING MODELS CAN AID OUR PREDICTIVE CAPABILITIES

PROBLEM STATEMENT: impurity in drug substance formed in-process

Evaluate the impact of raw materials using machine learning models that can be trained to achieve predictability

Evaluate the impact of raw materials using machine learning models that can be trained to achieve predictability

Model 1: no raw material data included
Model 2: with all raw material data included
Model 3: with only attribute data for RM 1

Correlation between product quality attribute and raw material (RM 1) attribute – follow-up verification of weak signal required

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CONCLUDING REMARKS

Therapeutic diversity facilitated by multiple manufacturing platforms enable patient-centric outcomes, but adds complexity.

All potential sources of variation must be understood and controlled or accounted for during process design, this includes raw materials.

A robust, attribute-focused raw material control strategy is needed to ensure process performance and to achieve a consistent product profile.

Data analytics can provide additional insights about the impact of raw material variability offering predict & prevent capability.

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QUESTIONS?

THANK YOU!

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