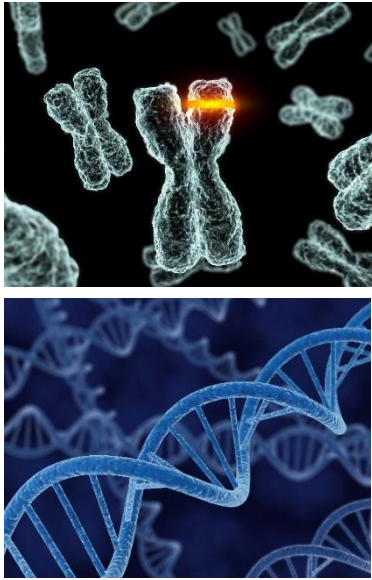# LEVERAGING KNOWLEDGE OF MATERIAL ATTRIBUTES AND DATA ANALYTICS AS KEY ELEMENTS OF A RAW MATERIAL CONTROL STRATEGY

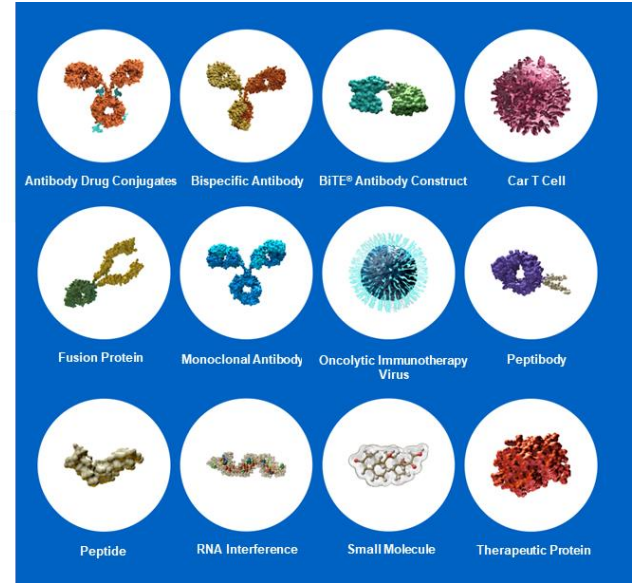**SUSAN BURKE, PHD**
**DIRECTOR, PROCESS DEVELOPMENT**

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# AMGEN COMBINES BIOLOGY-FIRST THINKING WITH ADVANCED TECHNOLOGIES TO DELIVER INNOVATIVE MEDICINES



**Next-generation manufacturing technologies**

Antibody Drug Conjugates   Bispecific Antibody   BiTE® Antibody Construct   Car T Cell

Fusion Protein   Monoclonal Antibody   Oncolytic Immunotherapy Virus   Peptibody

Peptide   RNA Interference   Small Molecule   Therapeutic Protein
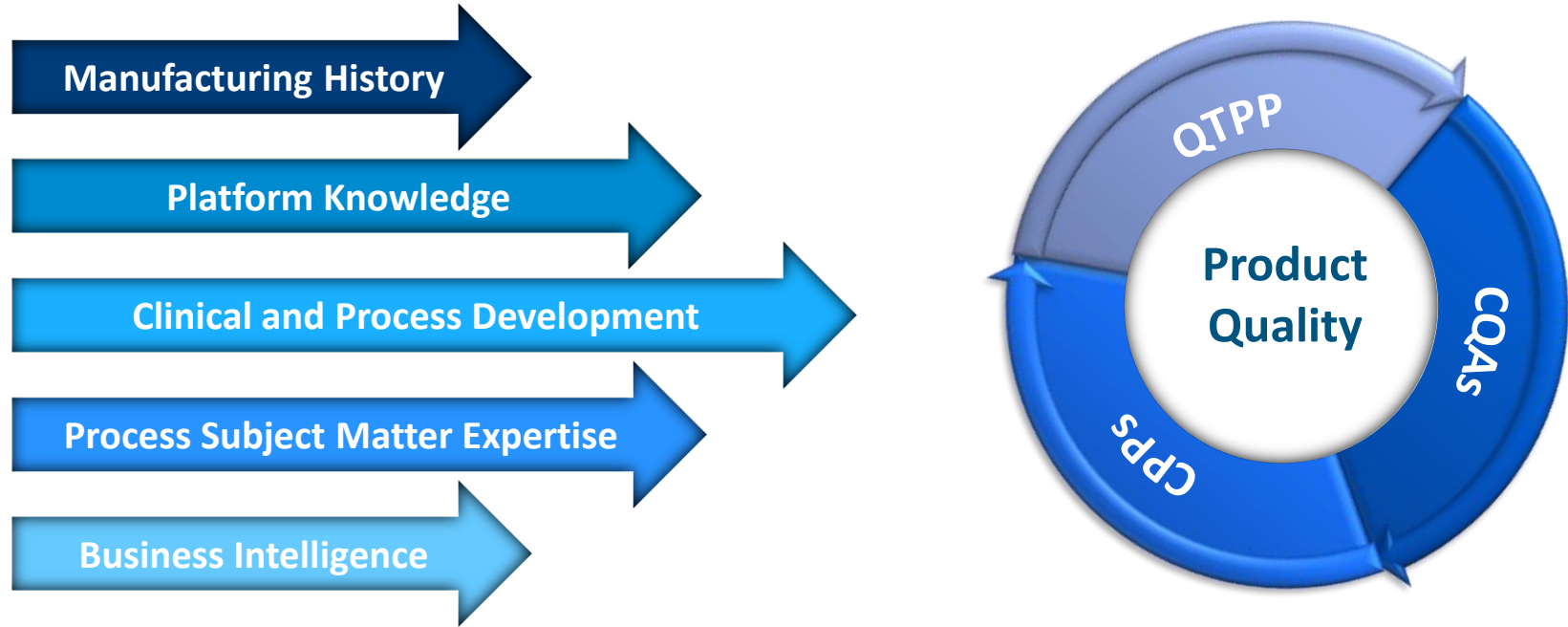
# Therapeutic diversity facilitates patient-centric outcomes

# DELIVERING HIGH QUALITY MEDICINES REQUIRES KNOWLEDGE OF IMPORTANT PROCESS AND PRODUCT ATTRIBUTES
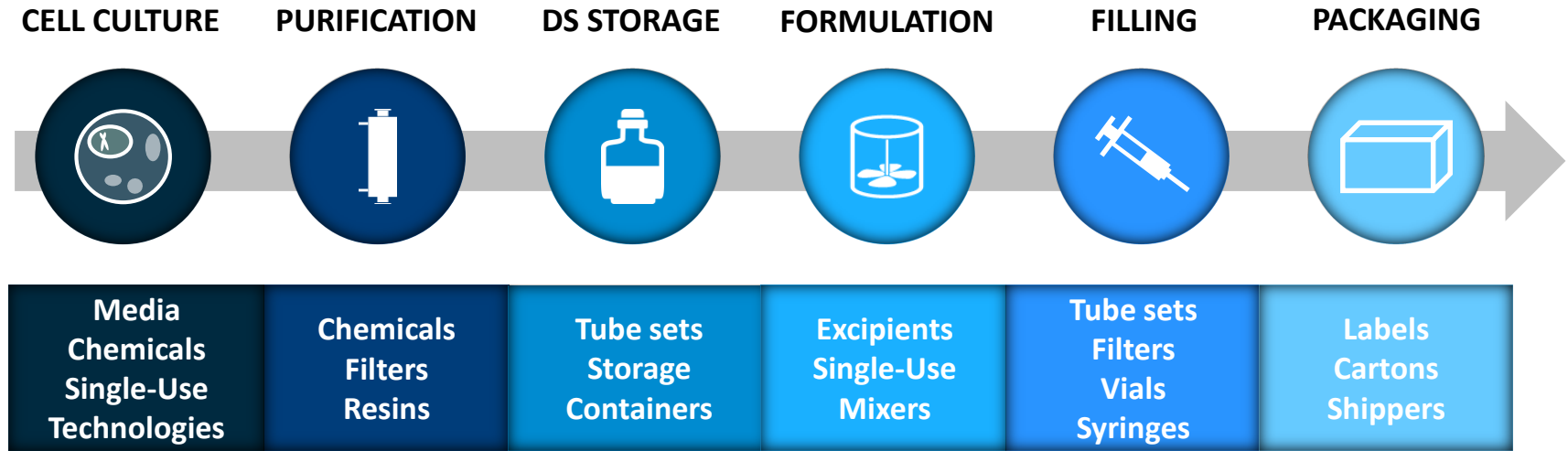
**Manufacturing History**

**Platform Knowledge**

**Clinical and Process Development**

**Process Subject Matter Expertise**

**Business Intelligence**

QTPP

CQAs

CPPs

**Product Quality**

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# THERAPEUTIC DIVERSITY AND MULTIPLE MANUFACTURING PLATFORMS CAN INTRODUCE ADDITIONAL COMPLEXITY

**SPEED TO PATIENT**

**COMPLEX & NEW RAW MATERIALS**

AGILITY – MODALITY INDEPENDENT

NEW SOURCES OF VARIABILITY

LOWER OPERATING COST

EMERGING TECHNOLOGIES

LESS PRIOR KNOWLEDGE

Equipment

Materials

Process Consistency & Product Quality
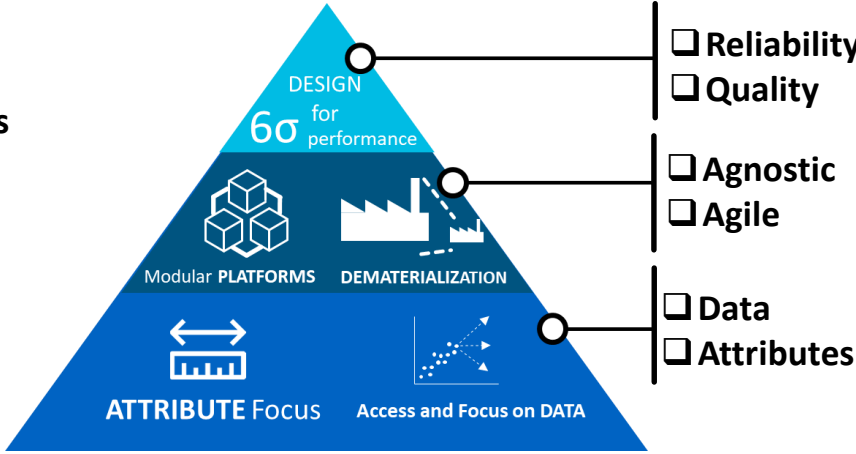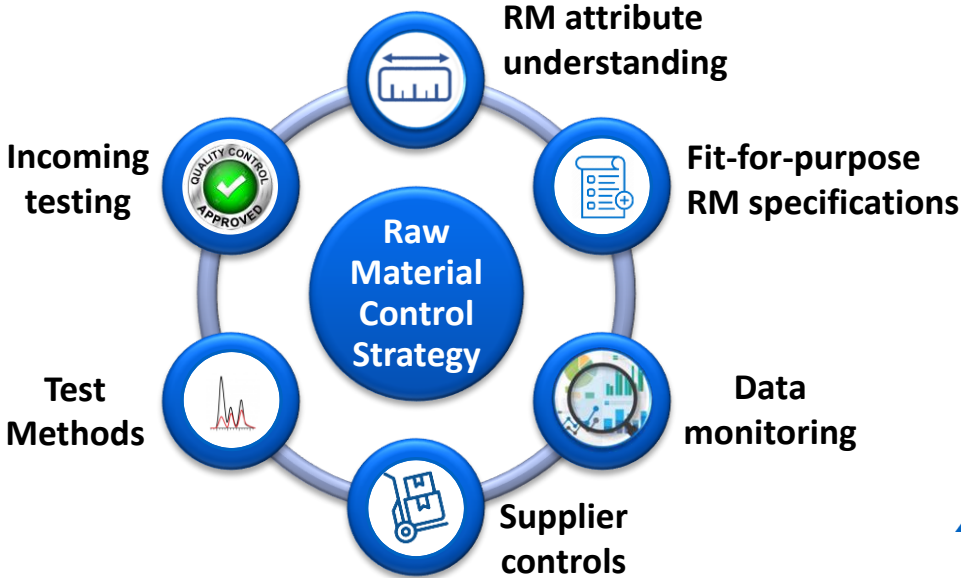
Process

Methods

**An understanding of ALL potential sources of variation is needed to develop robust control strategies**

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# MANUFACTURING OPERATIONS REQUIRE A WIDE VARIETY OF RAW MATERIAL TO ENSURE SUPPLY FOR PATIENTS



**CELL CULTURE** — **PURIFICATION** — **DS STORAGE** — **FORMULATION** — **FILLING** — **PACKAGING**

| Media Chemicals Single-Use Technologies | Chemicals Filters Resins | Tube sets Storage Containers | Excipients Single-Use Mixers | Tube sets Filters Vials Syringes | Labels Cartons Shippers |
|---|---|---|---|---|---|

## Raw materials can be a challenging source of variation

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# MANY ELEMENTS ARE NEEDED FOR A MATERIAL CONTROL STRATEGY



RM attribute understanding

Fit-for-purpose RM specifications

Incoming testing

Raw Material Control Strategy

Data monitoring

Test Methods

Supplier controls

**Informed by Raw Material Risk Analysis**

DESIGN for performance
6σ

Modular PLATFORMS

DEMATERIALIZATION

ATTRIBUTE Focus

Access and Focus on DATA

☐ Reliability
☐ Quality

☐ Agnostic
☐ Agile

☐ Data
☐ Attributes

## Well understood and controlled raw materials are fundamental for optimal process performance and ensuring the QTPP is met

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# 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**

LOD? purity? density? pH? bioburden? trace elements?

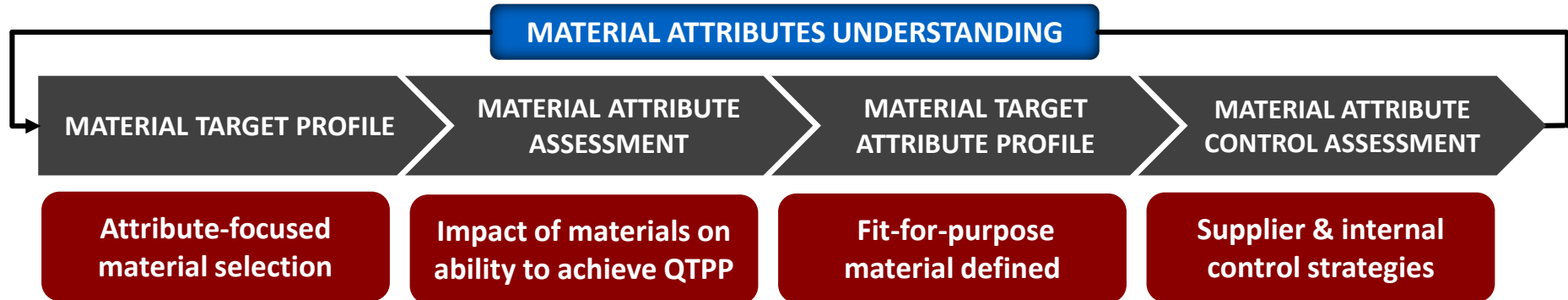**Establish controls to minimize material variability**

**Define the role of the material in the process**

**ATTRIBUTES**

**Track material performance to ensure consistency**

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# APPLY QTPP APPROACH TO RAW MATERIALS FOR ENHANCED UNDERSTANDING AND CONTROL

**PRODUCT ATTRIBUTES UNDERSTANDING**

| TARGET PRODUCT PROFILE | PRODUCT QUALITY ATTRIBUTE ASSESSMENT | QUALITY TARGET PRODUCT PROFILE (QTPP) |
|---|---|---|
| **Attribute-focused process development** | **Drive reliability through process understanding** | **Process designed to achieve QTPP** |

**MATERIAL ATTRIBUTES UNDERSTANDING**

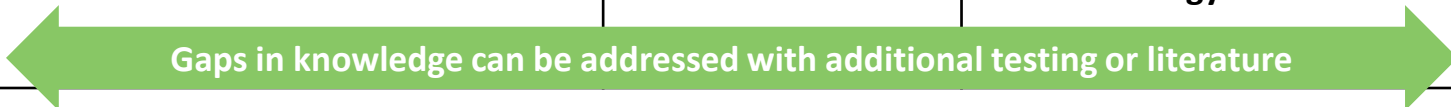| MATERIAL TARGET PROFILE | MATERIAL ATTRIBUTE ASSESSMENT | MATERIAL TARGET ATTRIBUTE PROFILE | MATERIAL ATTRIBUTE CONTROL ASSESSMENT |
|---|---|---|---|
| **Attribute-focused material selection** | **Impact of materials on ability to achieve QTPP** | **Fit-for-purpose material defined** | **Supplier & internal control strategies** |

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# FRAMEWORK FOR IDENTIFYING IMPORTANT MATERIAL ATTRIBUTES

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

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

**Gaps in knowledge can be addressed with additional testing or literature**

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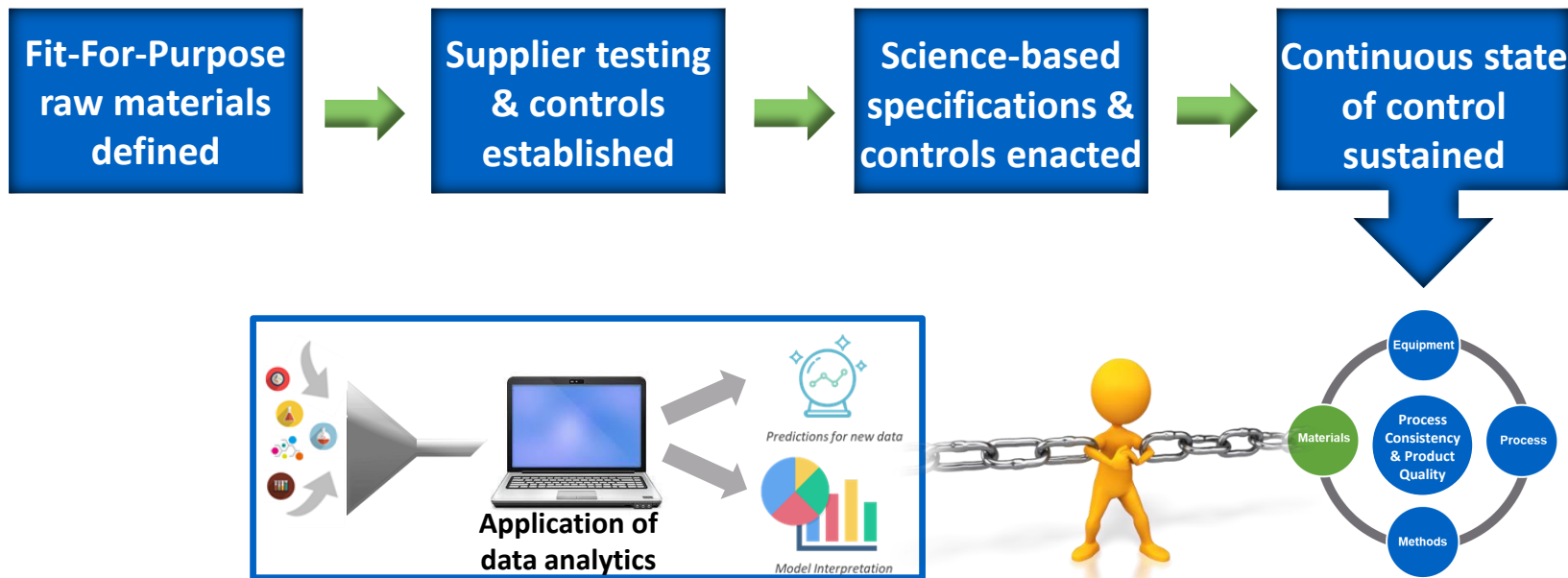# FIT-FOR-PURPOSE RAW MATERIALS ARE DEFINED WHEN ALL IMPORTANT ATTRIBUTES ARE UNDERSTOOD

**EARLY ENGAGEMENT**

**MTAP FRAMEWORK**

**FIT-FOR-PURPOSE RAW MATERIAL**
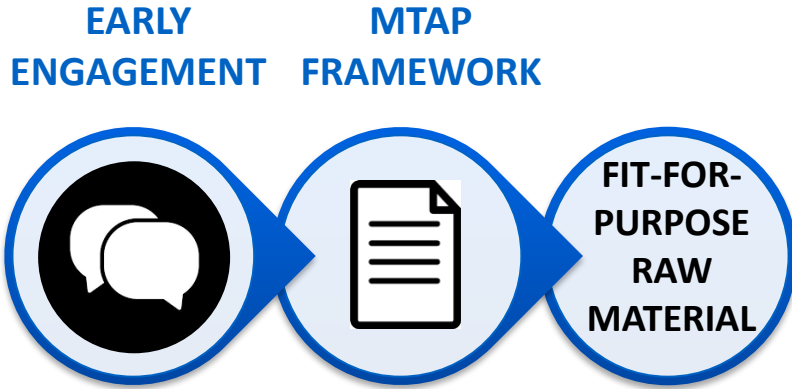
**Cross-functional review of new materials or new uses of existing materials starts early**



Early Development

Late Development

Spec Creation

PC Studies (Design & Results)

RM Risk Assessments

Program Reviews

Material Screening / Selection

Mfg Data

RFI / RFP

**MATERIAL TARGET ATTRIBUTE PROFILE**

Spec Revision

Technical Visits & Audits

Change Control Notification

CC Evaluations

2nd Sourcing Decisions

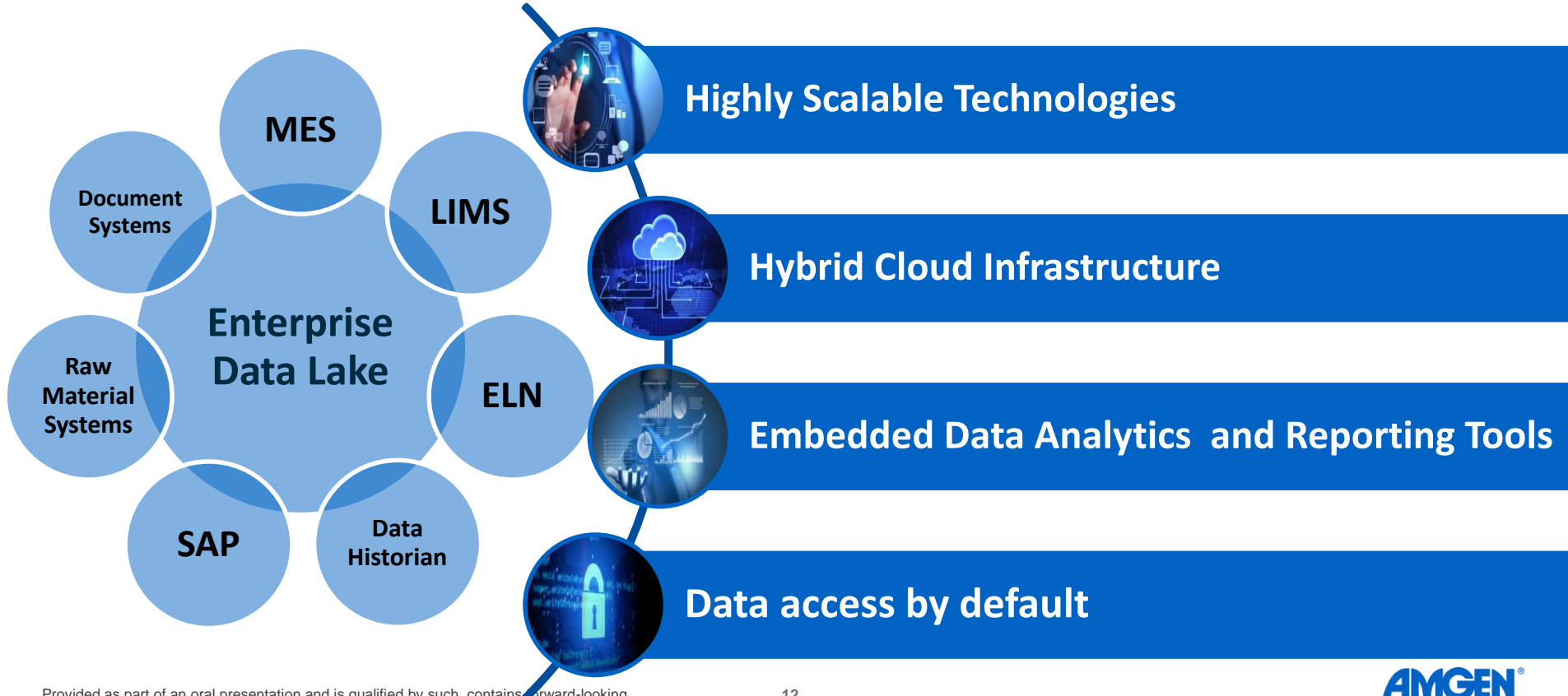Supplier Interactions

Production and LCM

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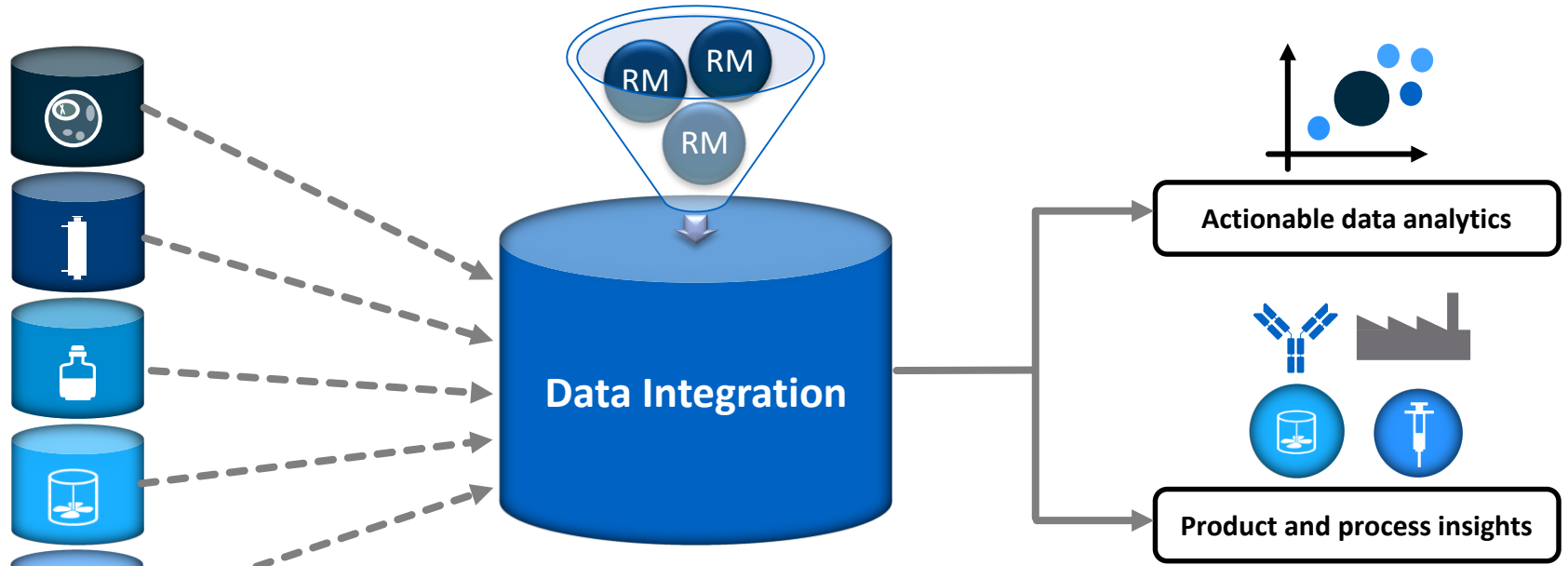# ONCE FIT-FOR-PURPOSE MATERIALS ARE ESTABLISHED, HOW DO WE ENSURE WE MAINTAIN CONTROL?

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



**Application of data analytics**

Predictions for new data

Model Interpretation

Equipment

Materials

Process Consistency & Product Quality

Process

Methods

**Data can be leveraged to monitor raw material performance enabling the control of variability through predictive assessment**

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# AMGEN HAS INVESTED IN A DATA INFRASTRUCTURE FOR ENHANCED PROCESS AND PRODUCT INSIGHTS

## Enterprise Data Lake

- MES
- LIMS
- ELN
- Data Historian
- SAP
- Raw Material Systems
- Document Systems

**Highly Scalable Technologies**

**Hybrid Cloud Infrastructure**

**Embedded Data Analytics and Reporting Tools**

**Data access by default**

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# 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**

# ADDITIONAL DATA SOURCES ENHANCE OUR UNDERSTANDING OF RAW MATERIAL VARIATION
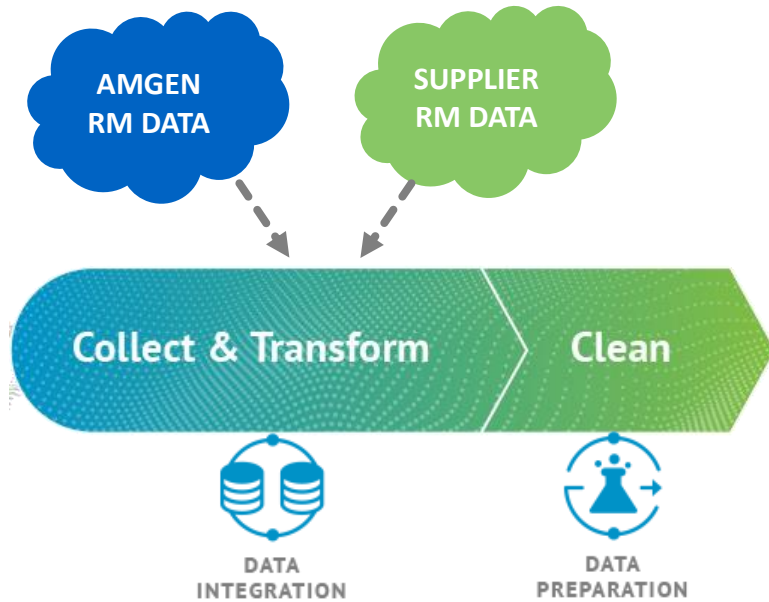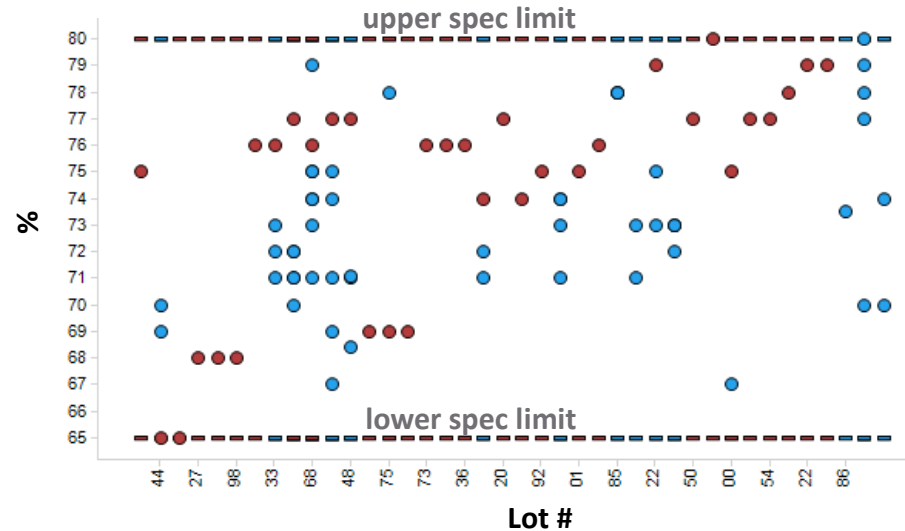


**Partnering with suppliers to share data, gain insights, reduce variability, and improve raw material performance**
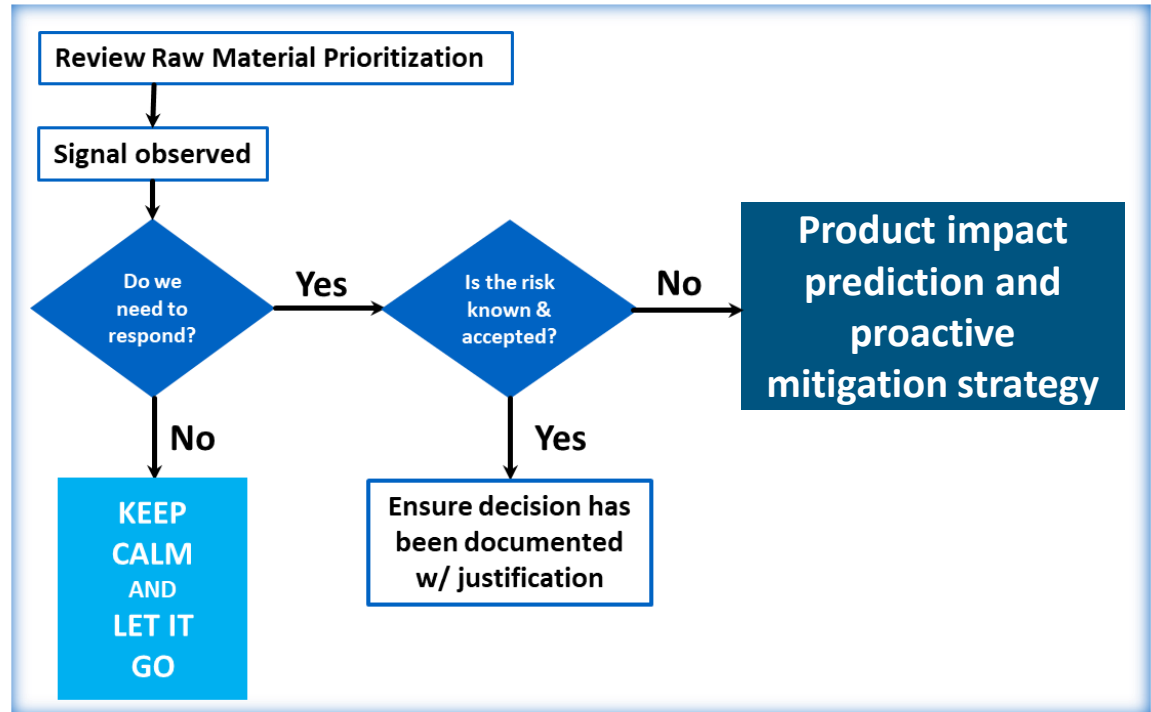
# SYSTEMATIC REVIEW AND RESPONSE PROCESS

## CROSS-FUNCTIONAL TEAM REVIEW



- ☑ **Recurring data review meeting**
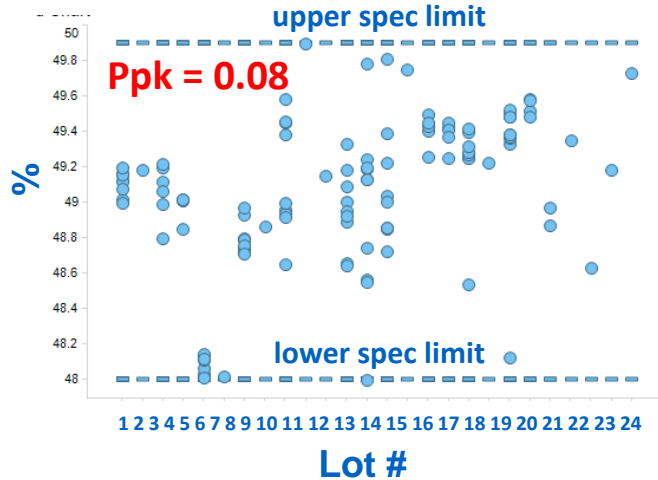- ☑ **Action tracker to monitor progress**

## PREDICT & PREVENT FRAMEWORK



Review Raw Material Prioritization

↓

Signal observed

↓

**Do we need to respond?** — Yes → **Is the risk known & accepted?** — No → **Product impact prediction and proactive mitigation strategy**

No ↓

**KEEP CALM AND LET IT GO**

Yes ↓

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



Ppk = 0.08

**TEAM REVIEW**

**Ppk predicted to increase to > 1.0 with implementation of additional controls**

**INVESTIGATION:**

**Variation attributed to method and handling**
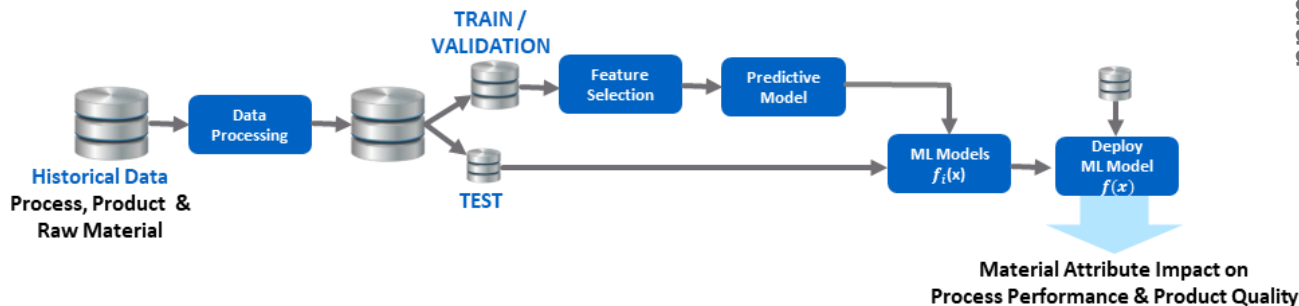
**RISK MITIGATION:**

**Supplier & Amgen Engagement**

- ☑ **Minimize method variability by strict titrant control**
- ☑ **Amgen aligned to supplier best practices for material handling**
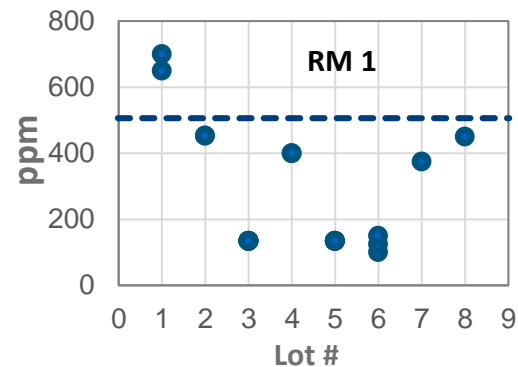
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# APPLYING MACHINE LEARNING MODELS CAN AID OUR PREDICTIVE CAPABILITIES

**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**

**Raw Material Attribute Data**



**TRAIN / VALIDATION**

**Feature Selection**

**Predictive Model**

**Data Processing**

**TEST**

**Historical Data**
Process, Product & Raw Material

**ML Models** $f_i(x)$

**Deploy ML Model** $f(x)$

Material Attribute Impact on Process Performance & Product Quality

| 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**

**Predictive Power of Model**
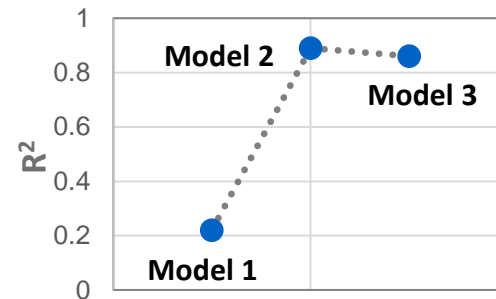
# CONCLUDING REMARKS

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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# THANK YOU!

## ACKNOWLEDGEMENTS

- **Patrick Gammell**
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## QUESTIONS?

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