The National Academies of
SCIENCES · ENGINEERING · MEDICINE

Board on Chemical Sciences and Technology

VIRTUAL WORKSHOP ON TECHNICAL AND REGULATORY BARRIERS TO INNOVATIONS IN PHARMACEUTICAL MANUFACTURING

INNOVATIVE STRATEGIES TO CONTROL PRODUCT QUALITY ATTRIBUTES AND REDUCE COMMERCIALIZATION TIMELINES

PATRICK SWANN
VICE PRESIDENT, QUALITY

AMGEN 40 YEARS

OUTLINE & SUMMARY

1. **Attribute-based Control Strategy**

   A focus on product quality attributes and ranges allows for optimal process and testing controls.

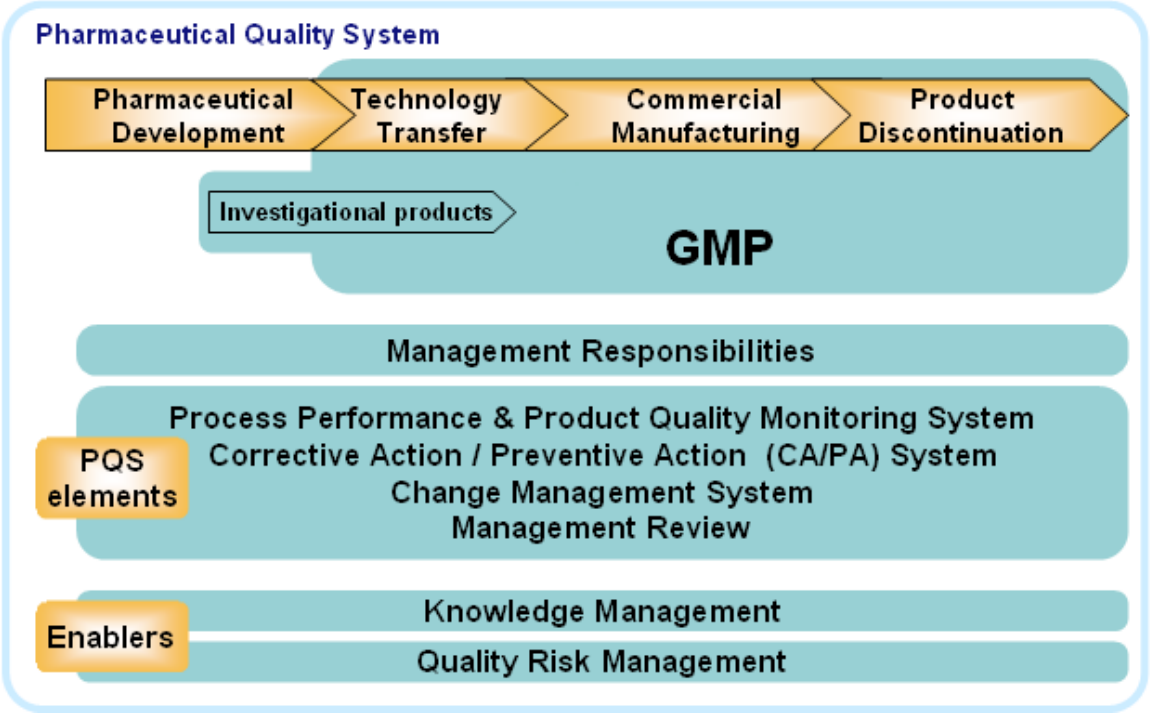
2. **Analytical Method Modernization**

   Methods that allow specific measure of attributes of concern enable this approach.

3. **Prior Knowledge and Modeling**

   Predictive stability and method models (built on above framework) can accelerate CMC development.

Pharmaceutical Quality System - Q10

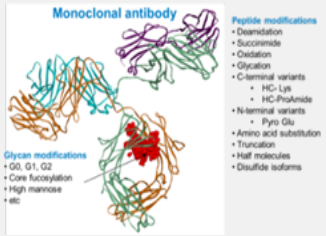


ATTRIBUTE-BASED CONTROL STRATEGY

Patient Centric Process Development

Target Product Profile → **Product Quality Attribute Assessments** → **Quality Target Product Profile**

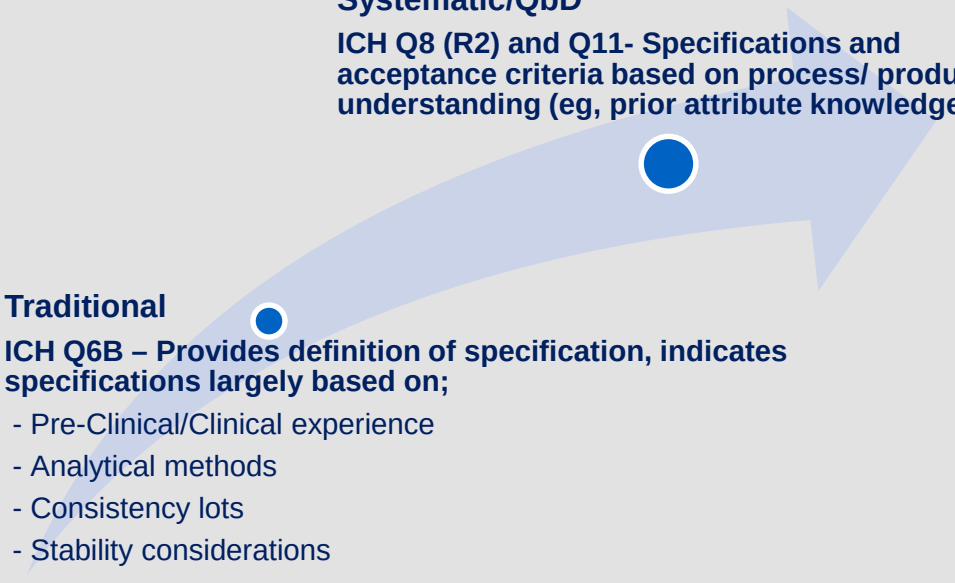
- Indication & use
- Dosage & administration
- Tolerability
- Dosage forms & strength
- Efficacy
- Safety/side effects
- Value & access



- CQA identification
- Scoring for potential impact to safety/efficacy

- Critical quality attribute selection
- Attribute range determination
- Designing quality into product during PD

A SYSTEMATIC/QbD DEVELOPMENT APPROACH ALLOWS THE USE OF PRIOR KNOWLEDGE



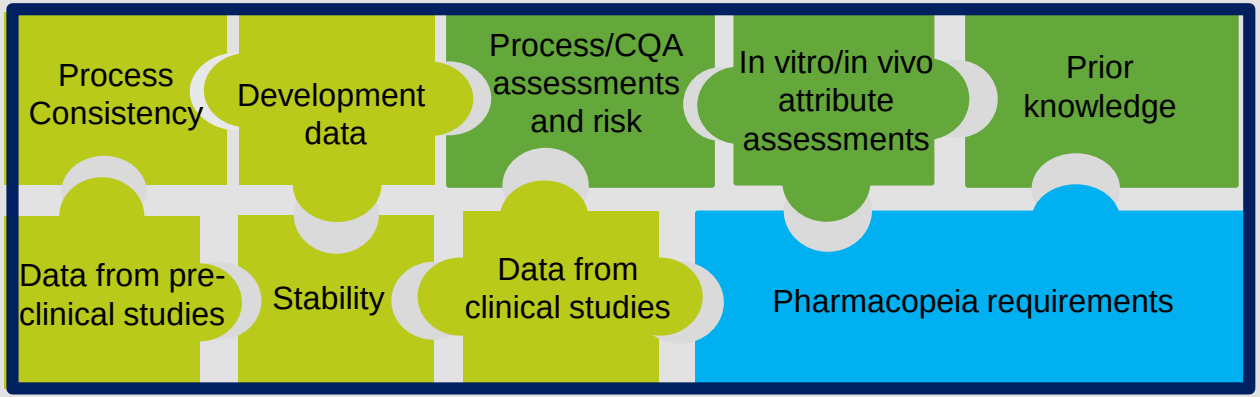
- ICH Q8 – Q11
- A greater understanding of the product and its manufacturing process can create a basis for more flexible regulatory approaches
- The degree of regulatory flexibility is predicated on the level of relevant scientific knowledge provided in the registration application
- Adoption of the principles in this guideline can support the justification of alternative approaches to the setting of specification attributes and acceptance criteria as described in Q6A and Q6B

Based on ICH guidance and the QbD development paradigm, it is appropriate to use risk and science based strategies, which include the use of in vitro and in vivo attribute assessments, to establish specifications that ensure patient safety and product efficacy if appropriately supported

FACTORS IN ESTABLISHMENT OF COMMERCIAL SPECIFICATIONS

- ICH Q6B identified key data sources used to establish and justify specification acceptance criteria
- ICH Q8, Q9, Q10 and Q11 provide additional information on definition of an overall control strategy and establishment of specifications that supports Quality by Design approaches. Allows for regulatory flexibility based on depth of knowledge and QMS
- Pharmacopeia requirements

The Commercial Specification Puzzle



Based on Juliana Kretsinger, 2019 CASSS Strategy Forum presentation '*IQ Consortium Biologics Working Group on Specification Setting Strategies*'

STEPS IN ESTABLISHMENT OF A PATIENT CENTRIC CONTROL STRATEGY AND QUALITY STANDARD

Assess:

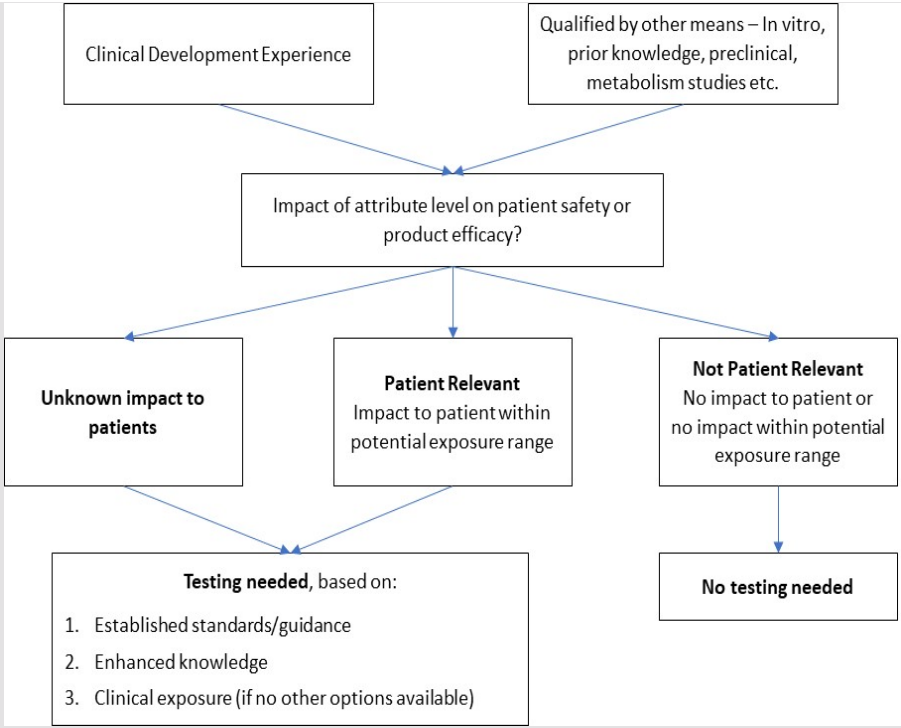
1a. Attribute criticality and whether attribute testing is required

Product Quality Attribute Assessment (PQAA) : Assesses attribute criticality and ranks the potential risk of an attribute having a clinical impact

Product Quality Risk Assessment (s) (PQRA) links material attributes and process parameters to CQAs

1b. Attribute test method – ID most appropriate method+parameter for attribute

2. **Testing point (s) –** ID optimum testing point
3. **Attribute range –** ID range that maintains safety and efficacy



PATIENT CENTRIC CONTROL STRATEGY (PCCS)
1 - ATTRIBUTE FOCUSED CONTROL

Traditional:
- Limited process/product knowledge
- Method/Specification Focused

- ✓ Appearance
- ✓ SE-HPLC
- ✓ rCE-HPLC
- ✓ CEX-HPLC
- ✓ Potency
- ✓ pH
- ✓ Osmolality
- ✓ Protein concentration
- ✓ Etc

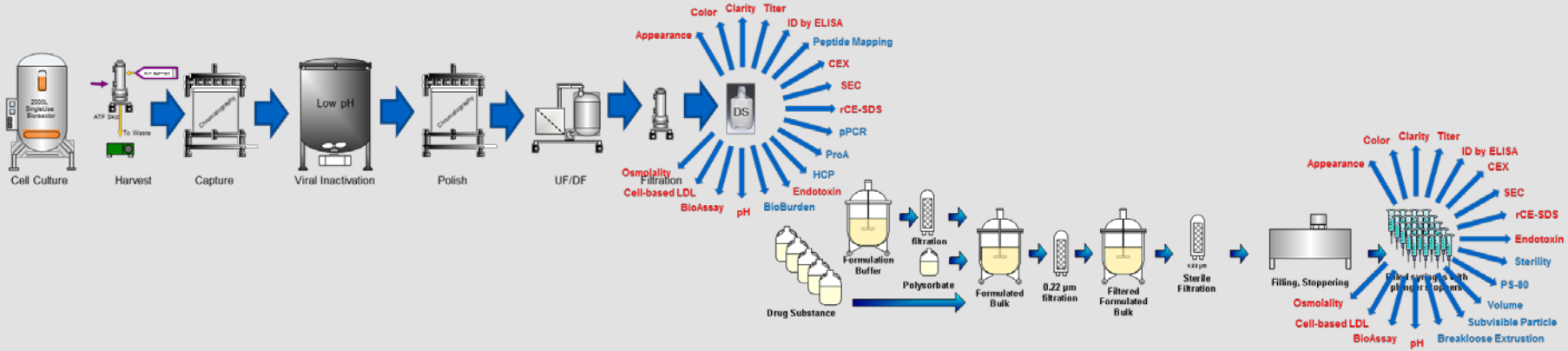
PCCS
- Focus on critical attributes (PQAA)
- Product ‘purity’ ensured through control over impurity CQAs such as HMW, fragmentation
- Select most sensitive method/parameter for monitoring/detection

Attribute	Method
Size variants – HMW	SE-HPLC
Size variants – Fragmentation	rCE-SDS
Charge Variants	CEX-HPLC
Glycans	Glycan Map
Identity	Immunoassay

PATIENT CENTRIC SPECIFICATIONS
2 – OPTIMIZE TESTING SCOPE AND CONTROL POINT

- Is routine testing required?
  - Remove redundant tests that control the same attribute and/or are performed at multiple points in the process
  - Removal of tests for impurities with well understood mechanisms for removal and proven process capability (eg. HCP, DNA, Protein A)
  - Remove tests for quality attributes that are well controlled during manufacturing and where adequate detections are in place to identify issues. Monitor only after changes made for comparability
- IPC vs Specification/RTRT
  - Non CQAs used as process consistency measures have action limits not rejection limits
- Stability
  - Removal of stability tests for attributes that are not stability indicating or are indirectly monitored by other, more sensitive tests (eg. use of purity assays to monitor potency)
  - Right size stability testing of DS when stored frozen and no changes observed

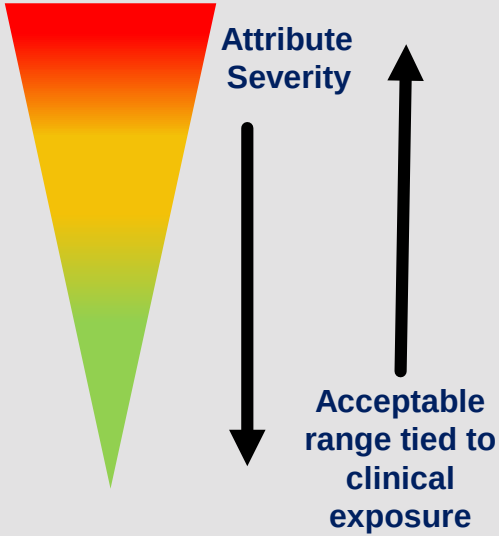
CURRENT ANALYTICAL TESTING STRATEGY *BIOLOGICS*

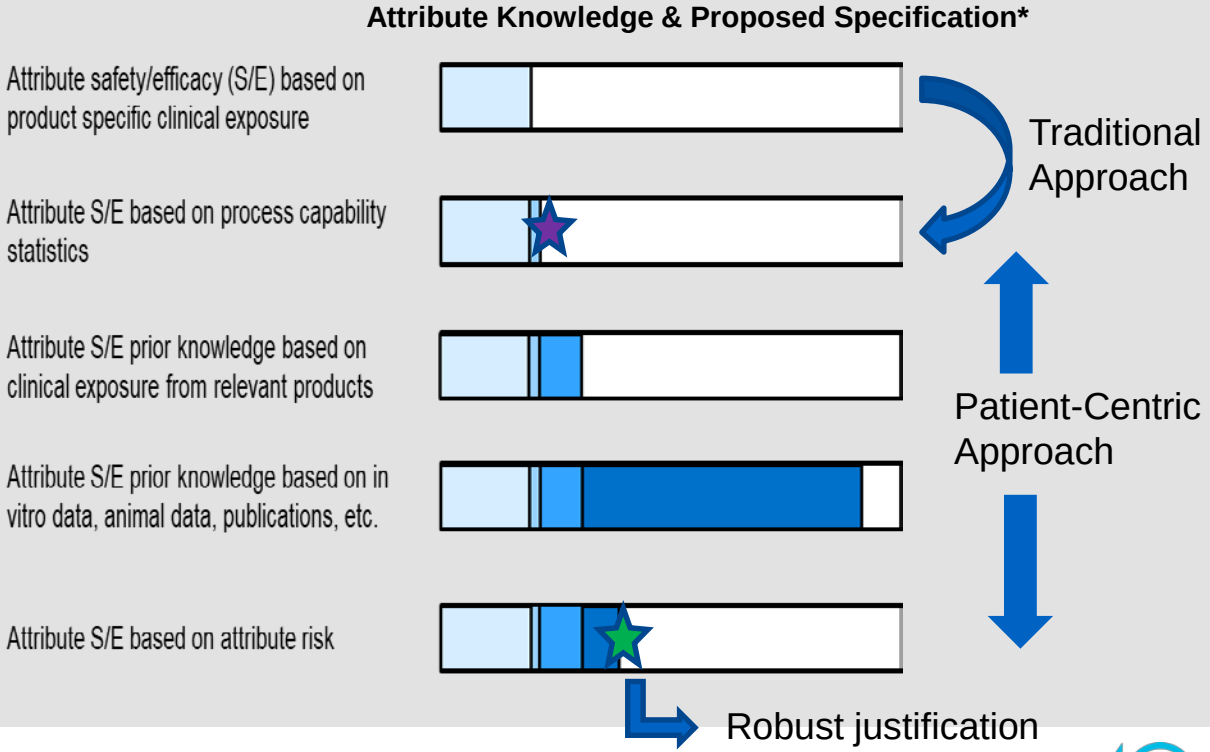


- Total of 30+ assays (some redundant over DS & DP)
- End point manual testing
- Complex and resource intensive

Courtesy of Jette Wypych

PATIENT CENTRIC SPECIFICATIONS
3 - ESTABLISHING AN ACCEPTABLE ATTRIBUTE RANGE

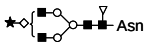
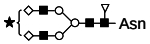
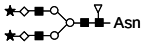


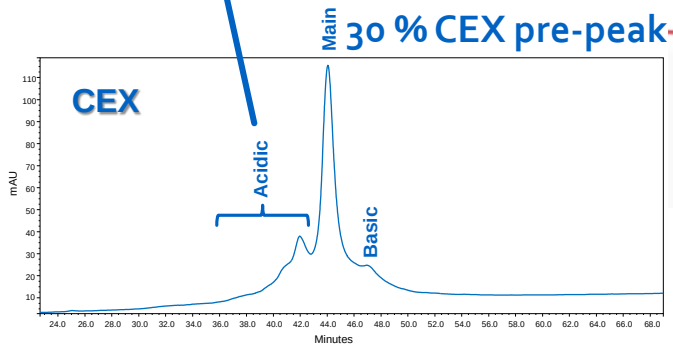


*See EMA/CHMP/BWP/812924/2018

ANALYTICAL METHOD MODERNIZATION

PROFILE-BASED ASSAYS ARE NOT ATTRIBUTE SPECIFIC

Modifications	% Modification in CEX main peak	% Modification in CEX pre peak	% Difference	Net Charge Change
HC: K74 Glycation	2.0%	5.3%	3.3%	-1
	0.1%	0.8%	0.7%	-1
	0.3%	4.8%	4.5%	-1
	0.0%	2.0%	2.0%	-2
HC: N386 to D386	0%	5.4%	5.4%	-1
HC: N61 to D61	0.2%	0.8%	0.6%	-1



Disconnection Between Profiled-based Assays & QbD: QTPP → CQA → Control Strategy

Attributes	Criticality Score	Target Range	Current Obtained Range
Oxidation 1	7	< 3%	1.5-2.5%
Isomerization 2	7	< 2%	< 2%
Glycosylation 3	8	< 0.5%	< 0.5%
.....	.....	.....	.....

Elucidation of degradants in acidic peak of CEX in an IgG1 monoclonal antibody formed on long-term storage in a liquid formulation. Gandhi S, Ren D, Xiao G, Bondarenko P, Sloey C, Ricci MS, Krishnan S. *Pharm Res.* 2012; 29(1):209-24.

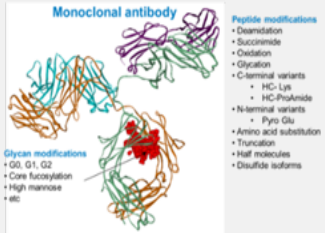
MULTI-ATTRIBUTE MONITORING (MAM) CAN DIRECTLY IDENTIFY AND QUANTIFY PQAS AT AMINO ACID LEVEL

Patient Centric Process Development

Target Product Profile

- Indication & use
- Dosage & administration
- Tolerability
- Dosage forms & strength
- Efficacy
- Safety/side effects
- Value & access

Product Quality Attribute Assessments



- CQA identification
- Scoring for potential impact to safety/efficacy

Quality Target Product Profile

- Critical quality attribute selection
- Attribute range determination
- Designing quality into product during PD

Attribute Measurements

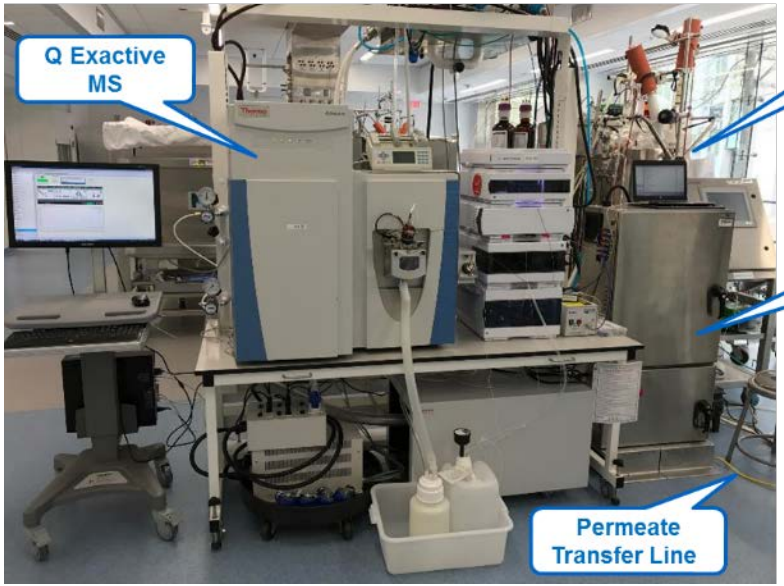
- MAM provides specific attribute measurement
- Allows Amgen to control the levels of individual molecular CQAs

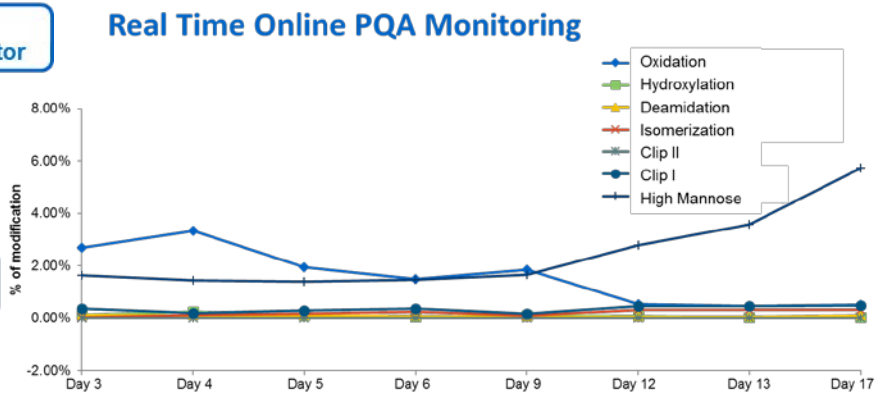
ATTRIBUTE UNDERSTANDING: RATIONALE FOR MAM TO REPLACE MULTIPLE CONVENTIONAL METHODS

Conventional Assays	Purpose	Rationale for Replacement by MAM
CEX HPLC	Charge variants, deamidation, glycosylation, etc	Charge variants are detected at peptide level by monitoring deamidation, glycation etc.
rCE-SDS	Clips	Clips are detected at peptide level with cleavage site information
Glycan Map	Glycosylation	Glycosylation can be quantified at peptide level
Immunoassay	Identity	Unique CDR peptides are used for identity confirmation

Courtesy of Jette Wypych

BRING MAM ONLINE: REAL TIME PQA MONITORING





- **Evaluate product attributes in real time**
- **Correlate process parameters with product quality attributes**

ANALYTICAL METHOD MODERNIZATION IS IMPERATIVE

WHY?

- **Advance "modern technologies and innovative approaches to achieve HIGHER QUALITY through continual improvement"[1]**
- **Implement attribute based test methods to achieve product understanding (Multi-Attribute Method, MAM)**
- **Enable next evolution of manufacturing involving process intensification and analytical integration (PAT across modalities)**

[1] US FDA (2018) Facts About the Current Good Manufacturing Practices (CGMPs), available at https://www.fda.gov/drugs/pharmaceutical-quality-resources/facts-about-current-good-manufacturing-practices-cgmps

LEVERAGING PRIOR KNOWLEDGE TO EXPEDITE DEVELOPMENT

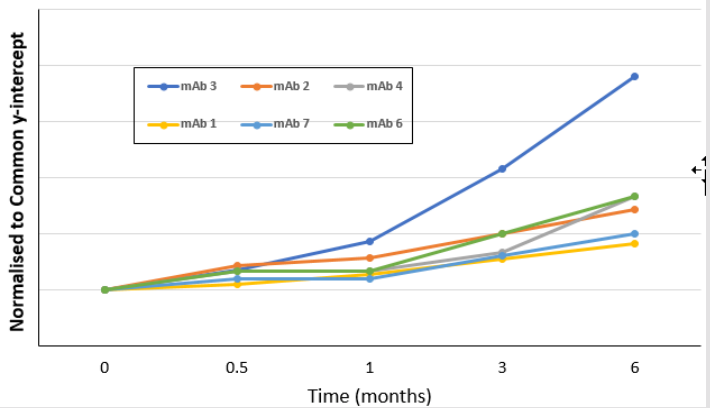
APPLYING PRIOR KNOWLEDGE STABILITY DATA TO DETERMINE SHELF-LIFE FOR A FAMILY OF RELATED BIOLOGIC PRODUCTS

Criteria are required to justify the transferable stability data of related molecule prior knowledge (PrK):

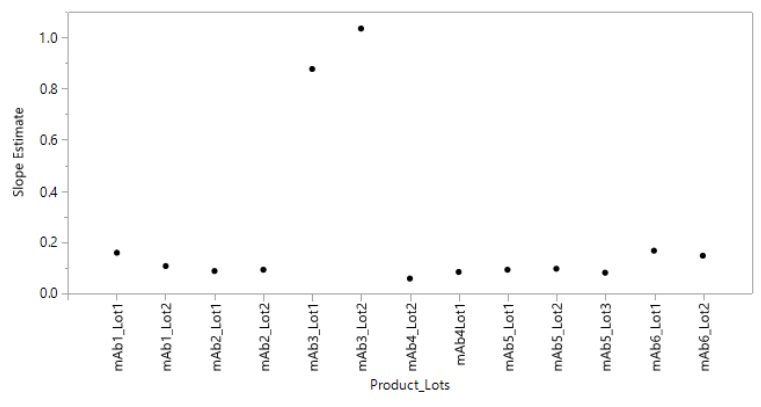
- **Structural Modality**
- **Characterisation of Degradation Pathways**
- **Cell Substrate, Manufacturing Process & Control Strategy**
- **Pharmaceutical Form & Storage Conditions**
- **Formulation & Protein Concentration**
- **Container Closure Type, Dimensions & Composition**
- **Stability-indicating Assays**

ACCELERATED DATA TO SUPPORT THE MODEL AND IDENTIFY NON-FIT MOLECULES

Trend Plot for High Molecular Weight Species Formed in IgG Drug Product at 25°C



Kinetics of High Molecular Mass Species Formation in Individual IgG Lots

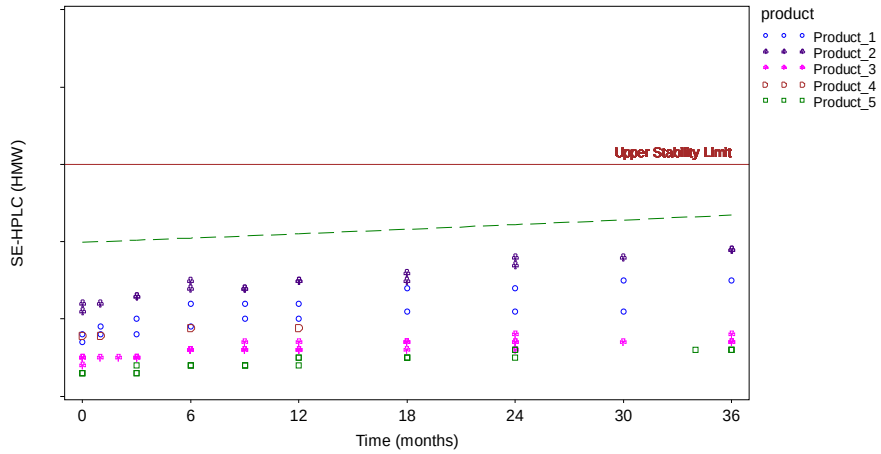


Accelerated stability data confirms the molecules included in the model and identifies molecules that should be excluded from the model - mAb3

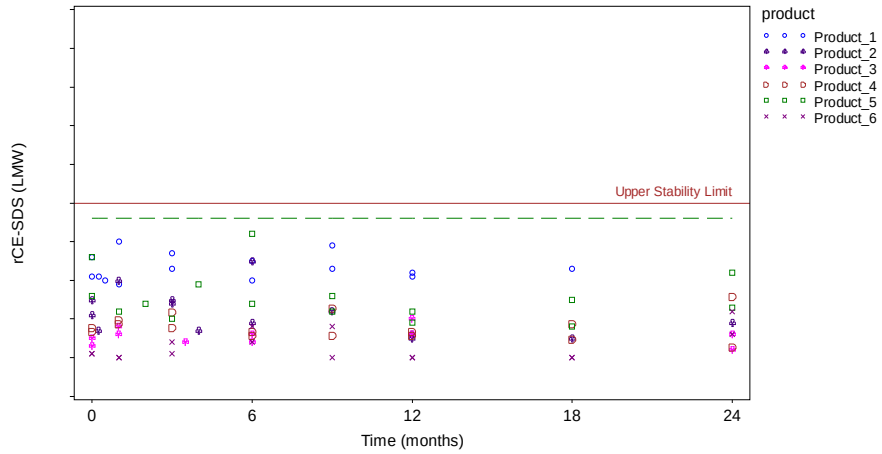
CASE STUDY FOR HMW & LMW SPECIES FOR DRUG PRODUCT IN 2 MODALITIES

- The rates of change for HMW and LMW Species were not significantly different across molecules.
- Only HMW Species had a significant trend, where the 95% TI meets specification at 8.75 years.
- A 36 & 24 months shelf-life may be assigned for molecules of the IgG and HLE-BiTE® modalities, respectively.

Kinetics of IgG Drug Product SE-HPLC HMW Species (%) in Individual IgG Lots



Kinetics of HLE-BiTE® Drug Product Fragmentation (Low Molecular Weight species) by rCE-SDS (%), in Individual Lots



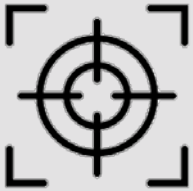
The total data support that a new product stability profile can be mapped against the PrK model

ACCELERATION ENABLERS FOR ATTRIBUTE METHODOLOGIES

1

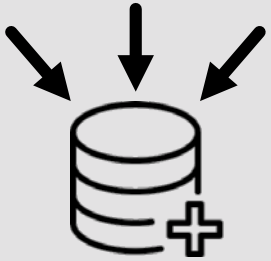
Method Technology Platforms

Analytical Target Profile



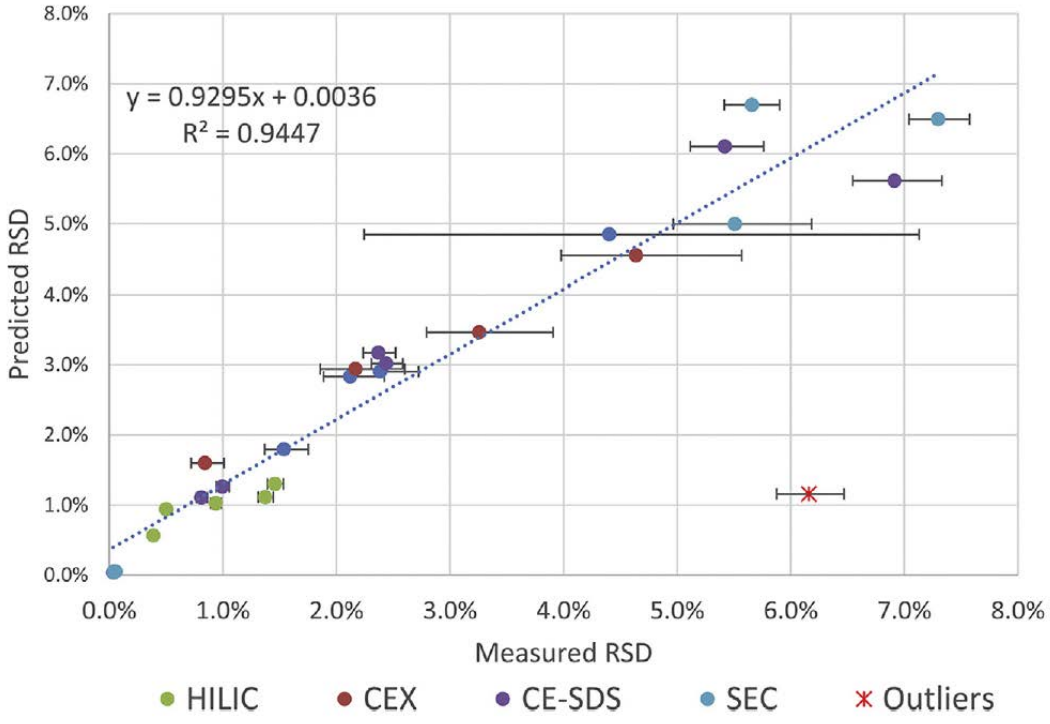
Predictive Analytics Toolbox

Continuous Data Monitoring



Prior Knowledge Data Interface

THE ABILITY TO RAPIDLY ASSESS THE UNCERTAINTY OF MEASUREMENTS UNDER ACTUAL USE CONDITIONS CAN FACILITATE METHOD DEVELOPMENT



Uncertainty based on current information (UCBI) model expresses method performance characteristics as a function of the signal and noise levels, hardware specifications, and software settings.

Prediction of Precision for Purity Methods
Apostol, Izydor et al.
Journal of Pharmaceutical Sciences, Volume 109, Issue 4, 1467 – 1472, 2020

THREE PILLARS OF MODERNIZED CONTROL STRATEGIES FACILITATE ACCELERATION

Clinically relevant specifications

Attribute-focused technologies

Leveraging platform knowledge

Focus on relevant attributes, fit for purpose technologies, and appropriate knowledge management provides speed, quality, and reliability

ACKNOWLEDGEMENTS

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