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Analytical Strategies for Defining Biotech Product Quality

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Practical Applications of Mass Spectrometry in the Biotechnology Industry, Chicago, 18-September-2019

Outline

- CQA Assessment
- Specifications
  - Clinical
  - Commercial
- Post-approval and clinical comparability
- MAM
- Regulatory perspective

1. What to measure

2. Reliable methods

3. Suitable results

1. What to measure ⟸ *Challenging issues*

2. Reliable methods

3. Suitable results ⟸ *Industry / conference focus*

What to Measure (Specifications, Comparability)

Obligatory: content, composition, strength, safety

- Protein Content
- Osmolality, pH
- Appearance (Color, Opalescence, Clarity)
- Buffer, Excipient, Surfactant Content
- Endotoxin, bioburden, particles
- Potency

Product variants

- Size: SEC, CE-SDS,
- Charge: IEC, icIEF
- Glycosylation
- Degradative: oxidation, deamidation, cleavage, Asp isomerization
- Structural variants: cysteine-related, terminal heterogeneity, internal cleavage
- Sequence variants: unique at one site, or one replacement at multiple sites

Process-related impurities

- Host cell proteins, DNA, leached Protein A

CQA assessment

Based on ICH Q6B: ***SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR BIOTECHNOLOGICAL / BIOLOGICAL PRODUCTS***

Critical Quality Attributes: Practical Challenges

- **Critical Quality Attribute:**

  "A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality." [ICH Q8 R2]

- Initial efforts to use FMEA (severity, occurrence, detectability) for CQAs foundered
  - occurrence complication

- CQA assignments should be based on patient impacts
  - setting limits is a second step
  - clinical product quality history is relevant
  - process capability is not relevant

- How to translate this into a rigorous system?

“Depend upon it, sir, when a man knows he is to be hanged in a fortnight, it concentrates his mind wonderfully.”

– Samuel Johnson (1709-1784)

Earlier Q&A: No Charge-Based Method on a mAb Control System

FDA:

Comprehensive assessment of [mAb] charge variants (e.g., by capillary IEF or ion exchange chromatography) is not routinely performed. You state that charge variants are not monitored because identified variants do not have reduced potency and are considered unimportant.

We do not agree that all such variants can be classified as unimportant based on a lack of altered activity in the potency assay. Charge variants could theoretically affect pharmacokinetics and/or immunogenicity and should be monitored.

With regard to stability, the lack of an assay to measure all charge variants is not compliant with ICH Q5C...

Please incorporate an assay that can comprehensively measure [mAb] charge variants for the establishment of new reference material, lot release, and stability studies...

CQA Assessment Tool: Impact Scales

Impact & Risk Score	Biological Activity	PK / PD	Incremental Immunogenicity Risk	Safety
Very High (20)	>100% change	>40% change on PK	ADAs detected that may be life threatening	Irreversible AEs
High (16)	40% - 100% change	20% - 40% change with impact on PD	ADAs detected that may be associated with non-life-threatening loss of efficacy	Reversible AEs
Moderate (12)	20% - 40% change	20% - 40% change with no impact on PD	ADA detected with effect that can be managed by clinical treatment (i.e., dose titration, medication)	Manageable AEs
Low (4)	<20% change	<20% change with no impact on PD	ADAs detected with effect on PK or PD, but no effect on safety or efficacy	Minor, transient AEs
None (2)	No change	No impact on PK or PD	ADAs not detected or ADAs detected with no effect on PK, PD, safety, or efficacy	No Adverse Events

- Developed in 2008 by Harris, Motchnik and Taticek
  - Incorporated into the "Amab Case Study", v2.1 Oct 2009 (CASSS website)

Alt et al., Determination of critical quality attributes for monoclonal antibodies using quality by design principles, Biologicals (2016), http://dx.doi.org/10.1016/j.biologicals.2016.06.005

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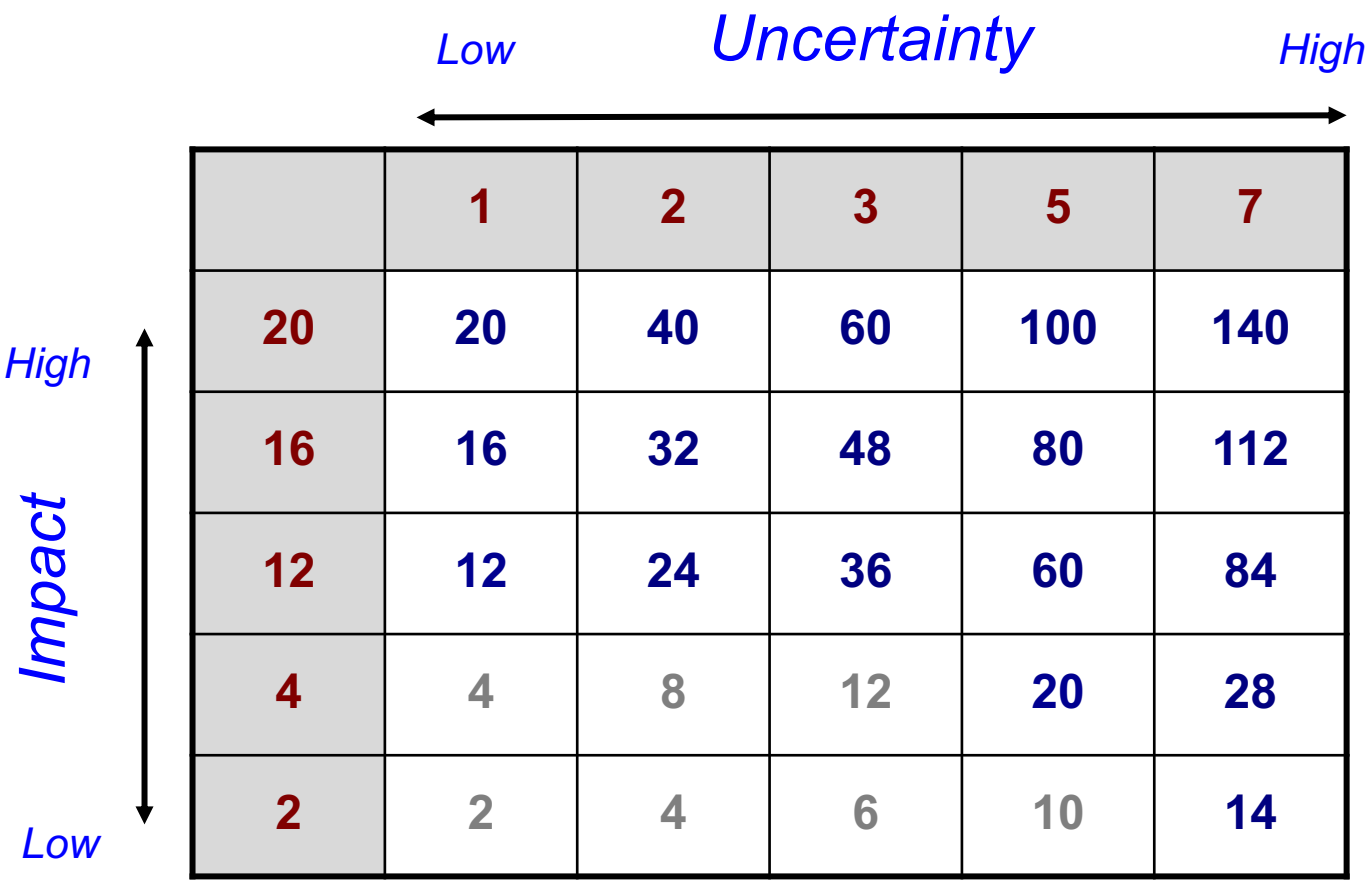
Uncertainty Scale: Akin to ”Prior Knowledge”

Rank	Uncertainty	Product Variants & Process-Related Impurities
7	Very High	No information (new variant or attribute)
5	High	External literature for variant or attribute in a related molecule
3	Moderate	Non-clinical or *in vitro* data with this molecule. Non-clinical, *in vitro* or clinical data from a similar class of molecule
2	Low *	Variant has been present in clinical trial materials
1	Very Low	Impact of specific variant established in clinical studies

*** Low (2) uncertainty is aligned with ICH Q6B (specifications) guidance:**

“If a consistent pattern of product heterogeneity is demonstrated, an evaluation of the activity, efficacy and safety (including immunogenicity) of individual forms may not be necessary.”

CQAs Are Assigned Based on Their Severity Score



	1	2	3	5	7
20	20	40	60	100	140
16	16	32	48	80	112
12	12	24	36	60	84
4	4	8	12	20	28
2	2	4	6	10	14

Critical Quality Attribute

Not a CQA

CQA Identification: Does it Work?

System has been in use for about a decade, part of several license applications

- ✓ Impacts to bioactivity, PK, immunogenicity, safety
  - Safety: immunogenicity, safety
  - Efficacy: bioactivity, PK
- ✓ Accepted as a suitable CQA interpretation
- ✓ Immune tolerance is assumed for familiar modifications
- – Approach led to specifications with reported values only for variants and impurities (e.g., no “main peak”)
- – Pharmacodynamic consideration is rarely applicable
- – How to differentiate immunogenicity of the intended form vs. variants and impurities

> “A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.”

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Critical Quality Attributes and Control Systems

- Start with structural characterization and process-related impurity measurements
- Presumptive (pCQA) assessment for early clinical control strategy
  - Look for gaps in platform test packages
- Complete CQA assessment for to-be-commercial control strategy
  - What's the mechanism of action (or, mechanisms...)?

Ex Vivo Studies to Establish MoA: Darzalex

Janssen's Darzalex (xCD38; daratumumab), approved by EMA for R&R MM

"The results from these forced degradation studies, along with the analysis of structural models, release and stability data, and clinical serum samples were used to identify critical quality attributes (CQAs) for daratumumab and develop the appropriate process and analytical control strategy."

"In studies using the Daudi cell line, daratumumab induced ADCC with an average EC_{50} of 20.9 ng/mL, compared to HuMab-CD38 (52.5 ng/mL) and rituximab (55.3 ng/mL). Similar results were seen in assays using MM-derived cell lines."

"The binding of daratumumab to CD38 on the surface of tumour cells and engagement/ligation of the Fc domains of bound antibodies leads to multiple biologic effects, including CDC, ADCC, ADCP, tumour cell apoptosis, and modulation of CD38 enzymatic activity in patient derived cells and cell lines expressing human CD38."

"Daratumumab-dependent phagocytosis by human monocyte-derived macrophages was demonstrated *ex vivo* in 11 out of 12 patient-derived MM cells tested, even at low CD38 expression…"

Assessment report EMA/278085/2016

Overdijk et al. (Genmab). Antibody-mediated phagocytosis contributes to the anti-tumor activity of the therapeutic antibody daratumumab in lymphoma and multiple myeloma. mAbs 7: 311–320 (2015)

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1. What to measure

2. Reliable methods

3. Suitable results

- Release acceptance criteria
  - Phase I/II
  - To-be-commercial
- Comparability exercises

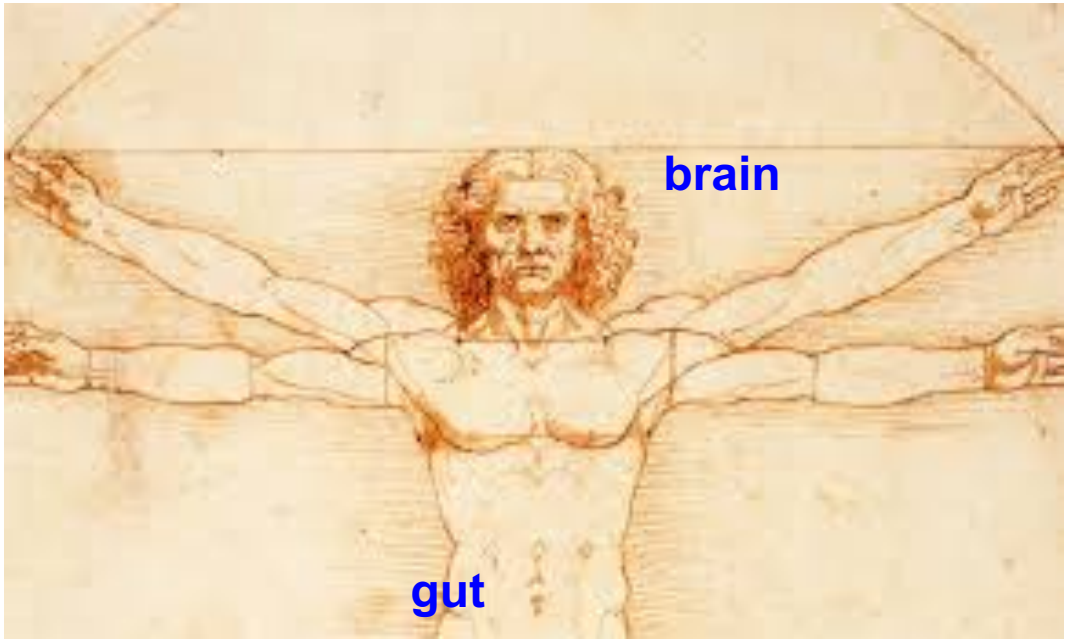
Product Quality Ranges or Limits are Not Always Empirical

Brain:

- Science-based
- USP, EP, WHO standards

Gut

- "I know it when I see it"
- Precedent
- Unfamiliar/familiar risks



Specifications for Early Stage Clinical Products

- Formerly: we used “report value” acceptance criteria for early clinical programs
  - In practice, we rejected or short-dated lots when we obtained unexpected QC results
  - Health authorities wanted to see limits, even if wide
  - What’s the basis for those limits?

FDA Guidance for Industry: CGMP for Phase 1 Investigational Drugs (July 2008).

The manufacturer should establish acceptance criteria for specified attributes on each material. For some materials, all relevant attributes or acceptance criteria may not be known at the phase 1 stage of product development. However, attributes and acceptance criteria selected for assessment should be **based on scientific knowledge** and **experience for use** in the specific phase 1 investigational drug. The material attributes and acceptance criteria will be reviewed in the IND application...

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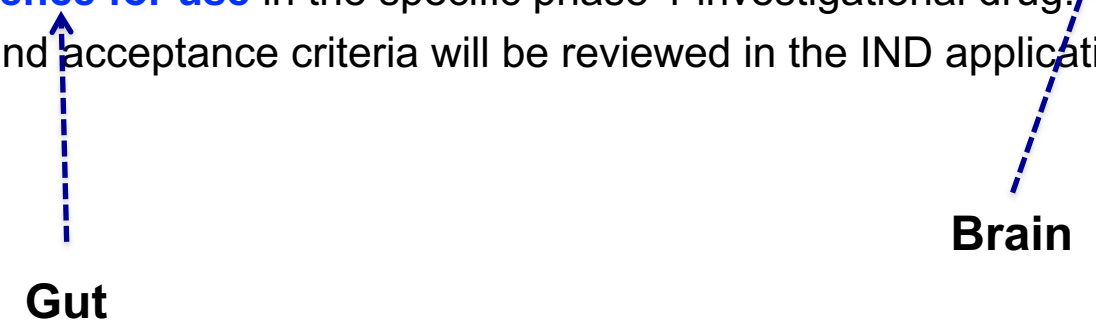


IQ Biologics Consortium: FIH Specifications Publication

Non-Numerical Acceptance Criteria During Early-Stage Specification Setting

Initial feedback within the IQ working group discussions revealed that numerical as well as non-numerical acceptance criteria such as “report result/to be monitored” or “compares to reference/standard” were used by different IQ member companies. However, growing concerns from regulators about the use of “report results” acceptance criteria were also reported by several IQ working group members.

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutical Biotechnology

Expectations for Phase-Appropriate Drug Substance and Drug Product Specifications for Early-Stage Protein Therapeutics

Juliana Kretsinger [1,*], Neha Frantz [2], Scott A. Hart [3], Wayne P. Kelley [4], Bob Kitchen [5], Shawn Novick [6], Barbara Rellahan [7], Daniela Stranges [8], Corné J.M. Stroop [9], Ping Yin [10], Martin H. Gastens [11,*]

Specification Acceptance Criteria: Quantitative

- IND-enabling toxicology studies help establish safety for new products
  - The clinical lots should resemble the Tox material
  - Tox lot is the first reference material, and assigned 100% potency

- Platform validated ("platform") assays for many familiar attributes
  - Charge, size, content, glycans, HCPs, DNA, color, excipients etc.
  - Perform a potential CQA assessment to identify control system gaps

- Some Phase I mAb specifications have default acceptance criteria
  - SEC ≥ 95% main peak, seems to be an industry standard
  - CE-SDS ≥ 85% main peak, based on a threshold for detection of mAb reduction
  - Host cell proteins, endotoxin, strength, osmolality etc. have standard ranges or limits

- Tox material profile is the basis for some product-specific Phase I criteria
  - 60%–140% potency at Phase I (with < 75% and > 125% alert limits)
  - IEC/IEF: % main peak for Tox lot ±10%–20%, sometimes with intermediate alert limits

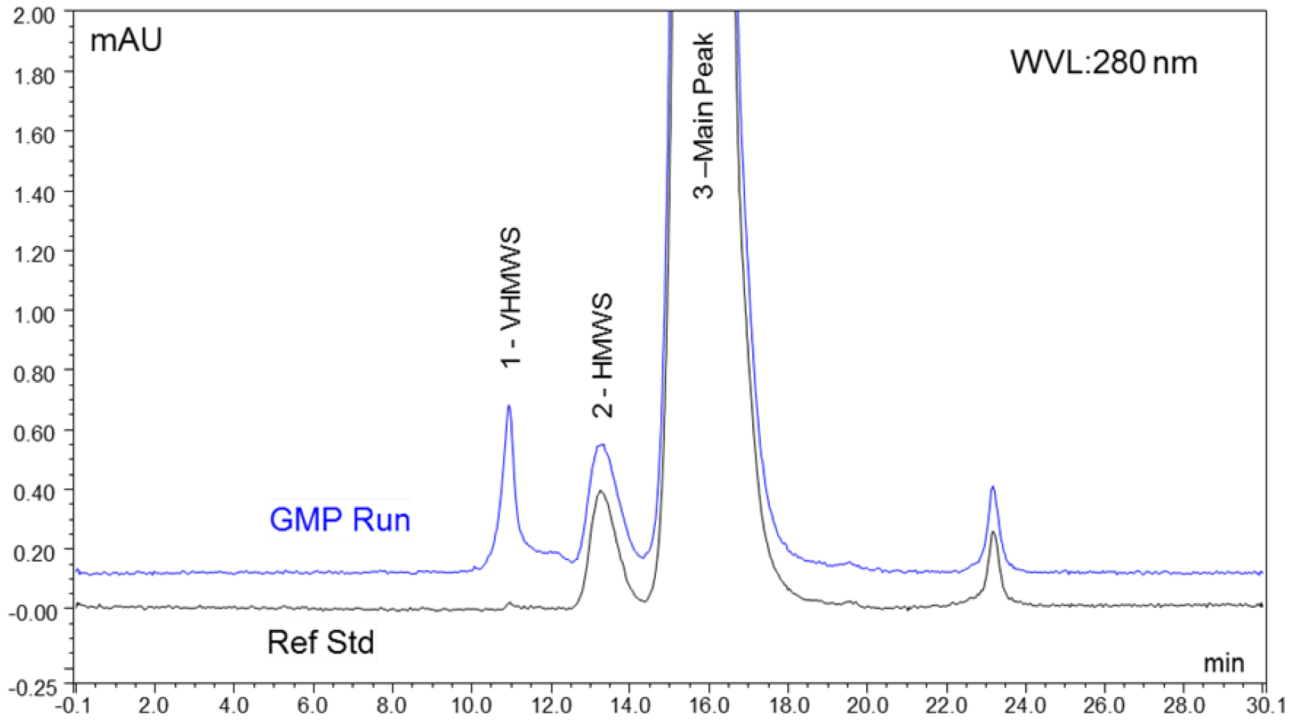
  – *What's the value of **wide** quantitative acceptance criteria?*
    - *Use profile review to complement AC*

Specification Acceptance Criteria: Profile Reviews

- Supplement quantitative criteria with careful QC analyst review of chromatographic or CE profiles

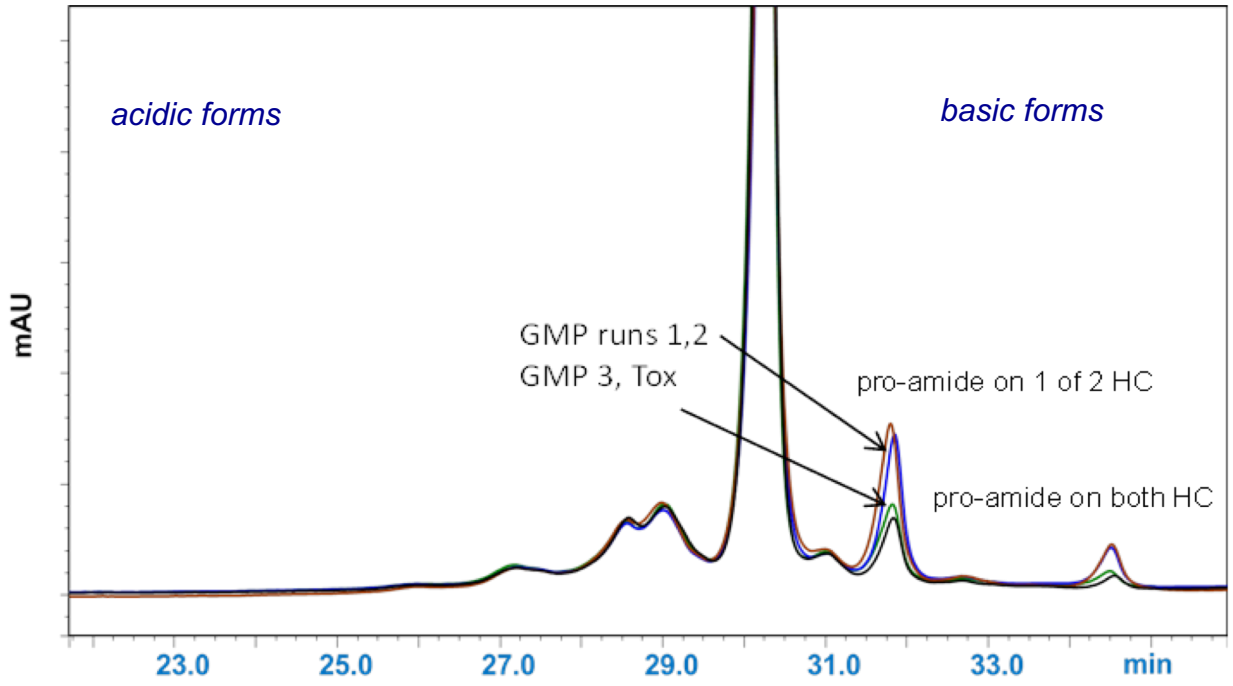
1. Flag new peaks or unexpected peak shapes
2. Understand nature of variation
3. Assess potential safety/efficacy impacts

Phase 1: Unexpected SEC Profile



- Quantitative results met the ≥95% main peak criterion
  - Profile assessment showed unexpected 0.1% level of a very high MW species (peak 1)
  - Batch was not processed forward to drug product

Phase 1 IEC Profiles for Accepted Lots:
three Phase I lots vs. Reference



- Quantitative results met the main peak criterion
  - Profile assessment showed higher levels of basic forms for two lots
  - Variability due to the inconsistent proline amidation at heavy chain C-termini
  - Pro amidation variability unlikely to affect patients; batches were accepted
  - Cell culture studies determined that the origin of this variability was copper addition (Kaschak et al., mAbs 3, 577-583, 2011)

Commercial Acceptance Criteria Proposals: Start with Strategy

1. Decide on the approach or strategy:
   - what's the claim you're making about future batch quality?
2. Relevant test results e.g., Phase III materials

- *Avoid starting with the numbers you want and then working backward…*

Rationale and Issues for Commercial Spec Acceptance Criteria Proposals

	Future Batches are…	Range Proposal	Regulatory Acceptance
A	• Not different from pivotal clinical study lots	• Minimum to maximum Phase III range	• Lowest risk
B	• Not statistically different from pivotal clinical lots	• Phase III batches • mean ± k*SD	• Reflects pivotal clinical experience • Depends on normality of data.
C	• Not statistically different from process capability • Low OOS risk • Classical approach	• Phase III **and PPQ** batches • mean ± k*SD	• Process capability basis (not exactly patient-based) • May be challenged if the PPQ batches do not match Phase III • May require updating with additional mfg experience
D	• Same safety and efficacy as pivotal clinical lots • Risk-based (“QbD”) approach	• Outside minimum to maximum Phase III ranges • Determine cumulative bioactivity and PK impacts	• Depends on acceptance of estimated patient risk • Better acceptance with CQAs due to bioactivity or PK impacts • Does not apply to CQAs due to immunogenicity or safety impacts

k: may use 3 as default, or calculate using tolerance interval

May also consider using earlier clinical batch data if safety and efficacy are same as Phase III

Cumulative Bioactivity Impact Table

- Assess the bioactivity impact of variation between the acceptance criteria range extremes and the reference material

	CQA-AC	Reference Standard Amount	Relative Bioactivity Factor	Negative Delta % Bioactivity	Positive Delta % Bioactivity
CQA – 1	≤31.9%	16.0%	26% lower	– 4.2%	+ 4.2%
CQA – 2	≤2.1%	0.5%	53% lower	– 0.8%	+ 0.3%

(partial list)

Potency Impact for mAbs if Using Peptide LC/MS Approach

- 10% CDR modification by peptide-LC/MS
- Modification causes a potency loss

	90% unmodified	10% modified
90% unmodified	81%	9%
10% modified	9%	1%

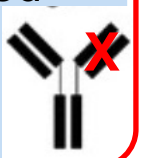
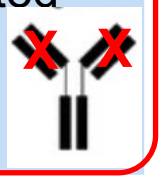
Potency Impact for mAbs: Monovalent Example

- 10% CDR modification by peptide-LC/MS
- Modification causes a potency loss

	90% unmodified	10% modified
90% unmodified	81% unaffected	9% unaffected
10% modified	9% unaffected	1% affected

Potency Impact for mAbs: Bivalent Binding Needed

- 10% CDR modification by peptide-LC/MS
- Modification causes a potency loss

	90% unmodified	10% modified
90% unmodified	81% unaffected	9% affected 
10% modified	9% affected 	1% affected 

Biotransformation: Impacts to Specification Acceptance Criteria

- Fast *in vivo* modification = lower concern about initial (release) values

Fast (per H. Liu et al., 2019)

CDR Asn deamidation

Fc region (PENNY peptide) deamidation

Thiol exchange, trisulfide conversion

OligoMan processing (to Man5)

C-terminal Lys processing

Slow

Gln/Glu conversion to pGlu

Asp isomerization, succinimide formation

Glycation

Met oxidation

H. Liu (Alexion) Modifications of recombinant monoclonal antibodies in vivo. Biologicals 59: 1–5 (2019).

Y. Li (Biogen). Quantitation and pharmacokinetic modeling.. mAbs 8:6, 1079-1087 (2016)

Bults (U. Groningen). LC-MS/MS-Based Monitoring of *In Vivo* Protein Biotransformation... Anal Chem, 88, 1871−1877 (2016).

Schmid (Roche). Assessment of susceptible chemical modification sites... Nat Commun Biol, DOI: 10.1038/s42003-018-0032-8|

Specifications Summary

- What to measure, reliable methods, suitable results
- CQA assessment:
  - Bioactivity, PK, immunogencity, safety
  - Uncertainty (prior knowledge)
- Suitable results are based on science and familiar risks
- Clinical development:
  - Wide platform acceptance criteria plus alert limits and profile assessments
- Commercial specification acceptance criteria: what's your claim?
- Ability to widen beyond clinical range depends on MoA credibility
- Rapid biotransformation can help justify relaxed release limits

Outline

- CQA Assessment
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  - Clinical
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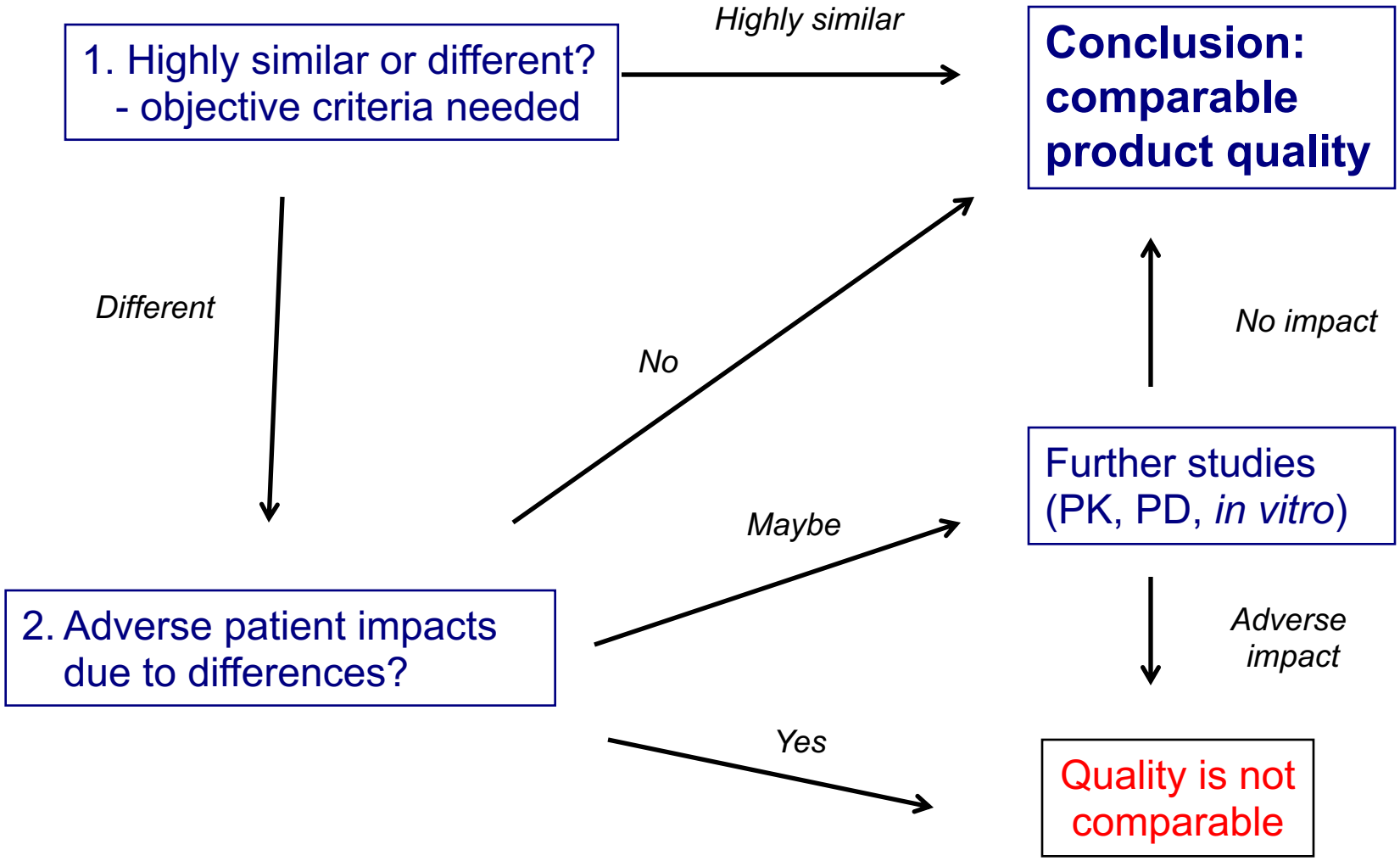
- Post-approval and clinical comparability
- MAM
- Regulatory perspective

Comparability: Interpretation of ICH Q5E

Bridge between pre- and post-change materials:

- "*The goal of the comparability exercise is to ascertain that pre- and post-change drug product is comparable in terms of quality, safety, and efficacy.*"
- "*The demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change product are identical, but that they are highly similar and that the existing knowledge is sufficiently predictive to* ***ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product****.*"
- *"In consideration of this evaluation,* ***appropriate criteria*** *to define highly similar post-change product can be established…"*
- *"The comparison of the results to the* ***predefined criteria*** *should allow an objective assessment of whether or not the pre- and post-change product are comparable."*

Comparability: Two Questions



What is “Highly Similar” for a Commercial Product?

- **Patients will always get the same product quality**
  - Independent of change type
  - Different from a QRM approach: change type, impact of change, test selection

- **Lot release test data: licensed vs. new process or facility**

  - use 95/99 tolerance intervals for quantitative test results (historical data set)
  - cannot exceed specification limits
  - all release test results must meet these acceptance criteria

- **Extended characterization studies**

  - may include testing of every 4th or 5th lot
  - post-change test results must meet these acceptance criteria

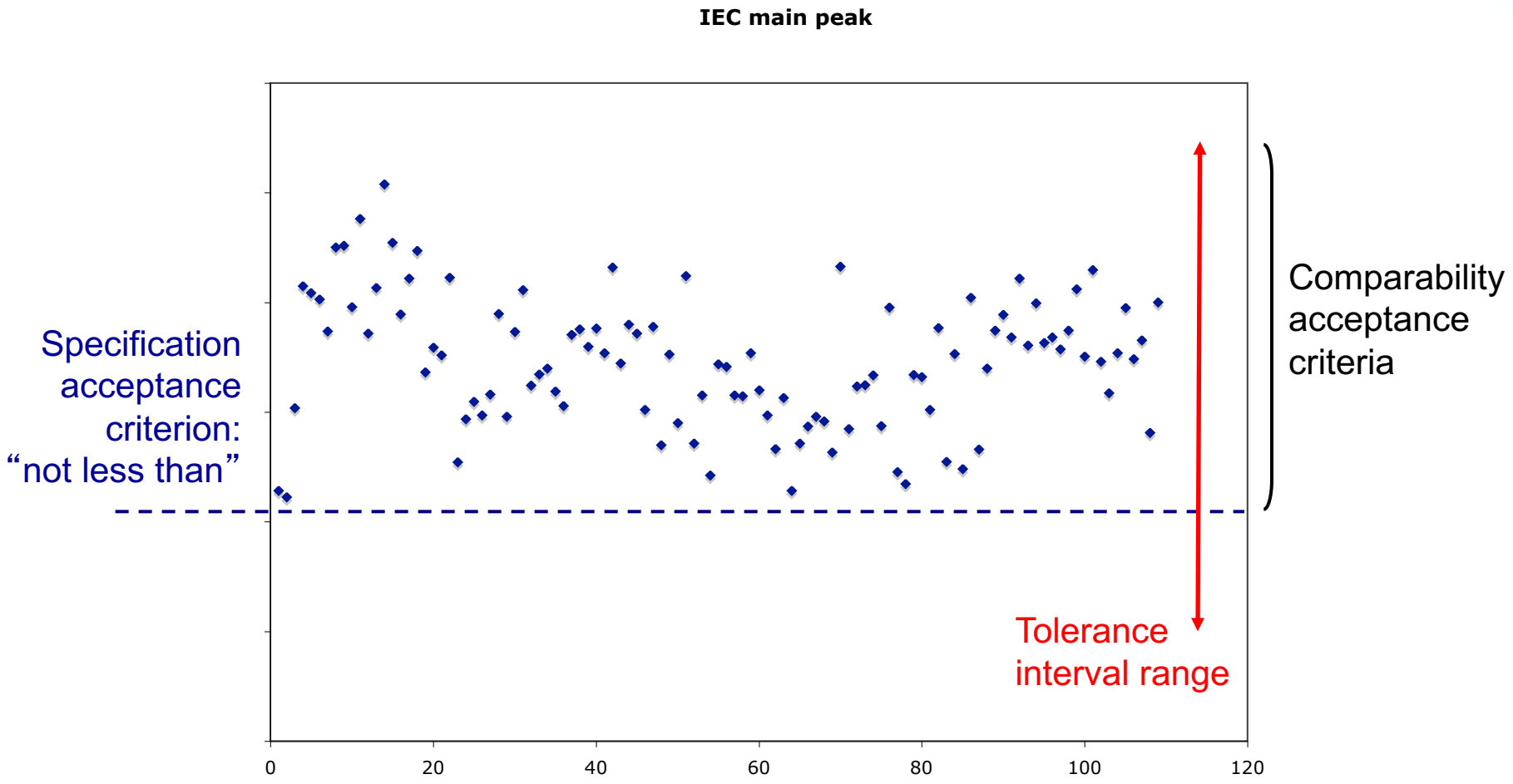
- **Accelerated degradation (30° – 40° C)**

  - temperature and duration depend on known rates and routes of degradation
  - quantitative tests: degradation slope ratio assessment

- **Profile comparisons**

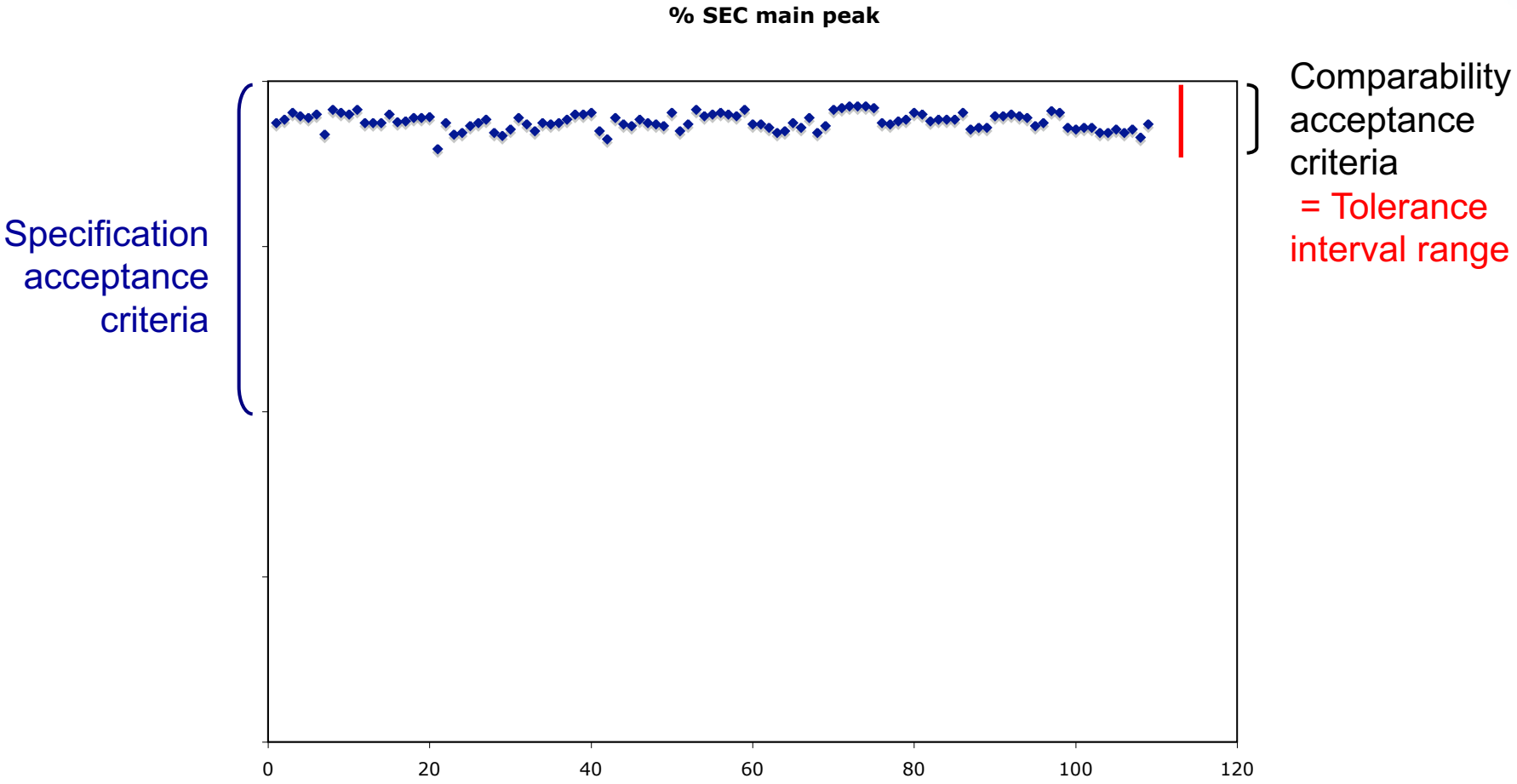
  - e.g., IEC, SEC, peptide maps, CE, glycans

mAb IEC: % Main Peak



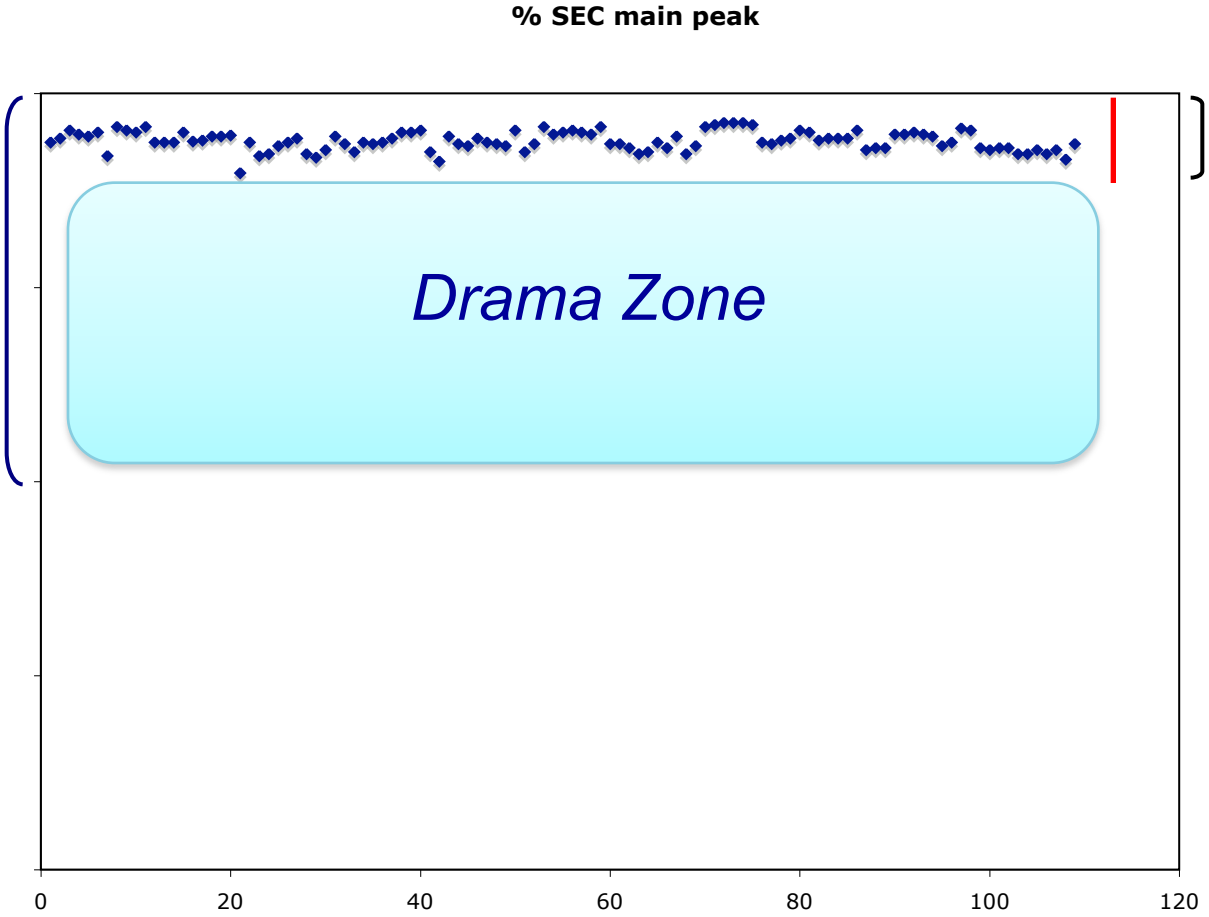
- Comparability acceptance criteria are constrained by specification limits

mAb SEC: % Main Peak



- Comparability acceptance criteria are more restrictive than specification limits

mAb SEC: % Main Peak



Specification acceptance criteria

Comparability acceptance criteria = Tolerance interval range

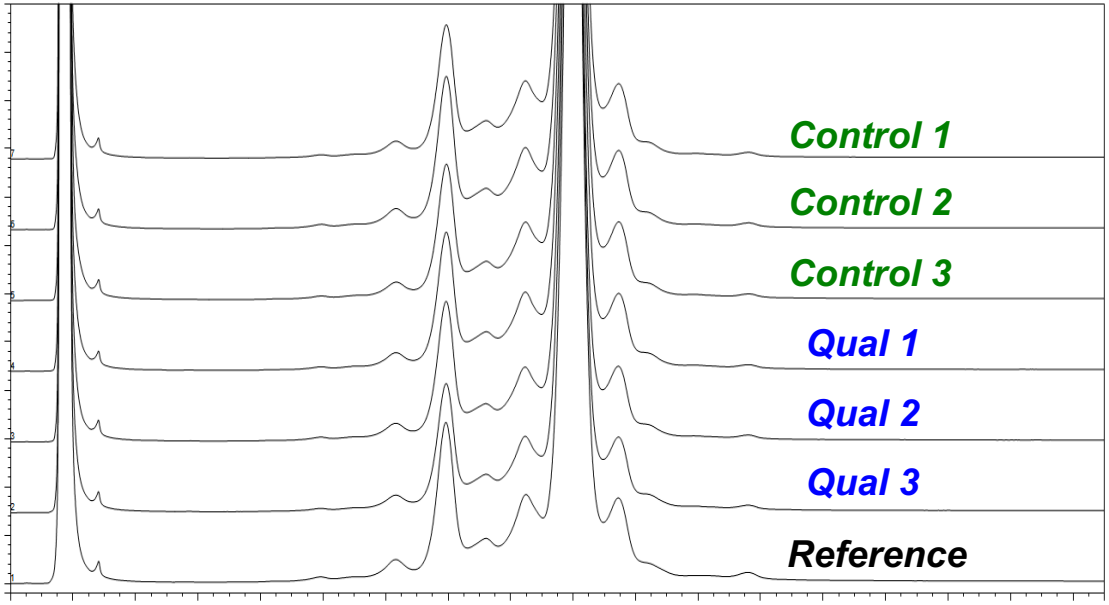
- Comparability acceptance criteria are more restrictive than specification limits

Comparability and Specifications are Different

- **Comparability** exercises ask:
  - is the new material similar or different?
  - what are the patient impacts of any differences?

- **Specifications** define tests and ranges that ensure suitable quality
  - is the quality good enough?

Profile Comparison Acceptance Criteria



- Acceptance criteria for profile comparisons:
  - "no new peaks" in the full-scale profiles for post-change lots
  - "same general peak shape" in the expanded-view profiles for post-change lots
  - alternate: "rank order of forms is maintained"

- Objective acceptance criteria are pre-defined
  - avoid "no significant new peaks"

- Should be possible to make this less subjective, using software

Comparability During Clinical Development

This is harder to assess:

- We **expect to see differences** as we change processes and dosage forms
- Insufficient production lots to use statistics

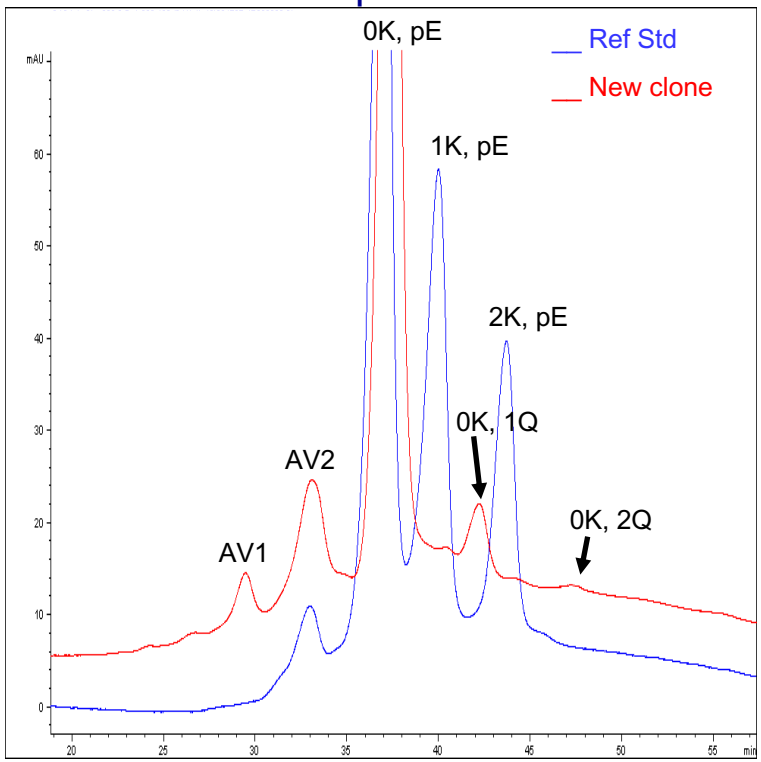
We're making a commitment to patients that we understand the risks and potential benefits of a certain therapy

- Based on Tox studies for new molecular entities and/or new administration routes
- Based on earlier clinical studies

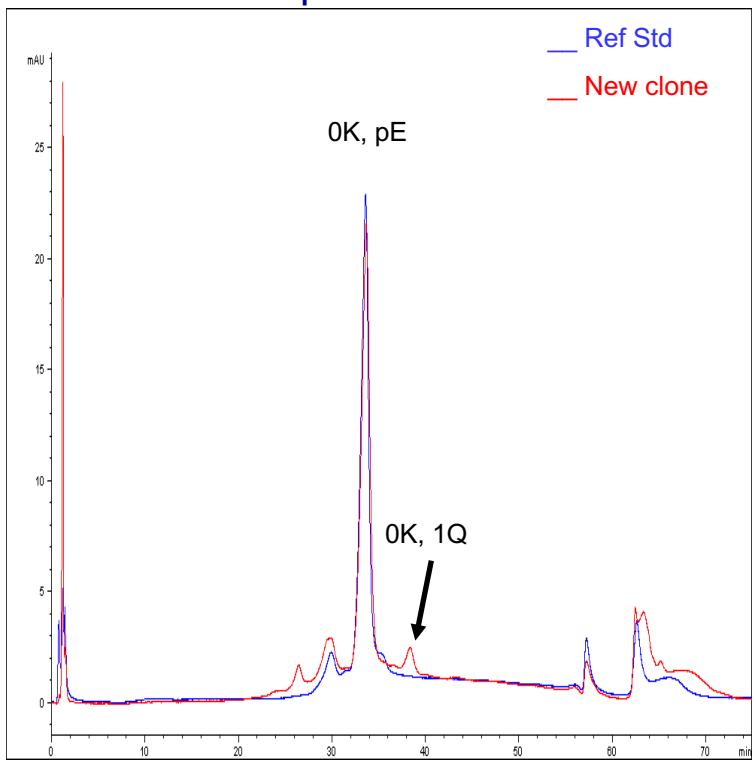
"Do the differences undermine earlier Tox or clinical safety & efficacy conclusions?"

mAb Cation Exchange Chromatography

Without CpB Treatment



With CpB Treatment



- Acidic variant differences can be eliminated with neuraminidase treatment
  - AV1 and AV2 contain some sialylated forms

- Two types of basic variants are observed:
  - due to HC C-term Lys
  - partially cyclized HC N-term Gln to pyroGlu

Jennifer Wang

mAb Phase IIb / III Process Differences

	Phase I / IIa	***Phase IIb / III***
Cell line	NS0	CHO
Sialic acid	0.05 mol/mol NGNA	0.13 mol/mol NANA
C-terminal Lys	~40%	trace levels
Gln / pyroGlu on heavy chain	0% / 100%	~5% / ~95%

- Consider individual and **cumulative impacts**

- Conducted a rat PK comparability bridging study
  - 20/group, subcutaneous administration
  - AUC and Cmax were within 80%–125% ratio between groups

- Conclusion: material is different, but with ***comparable product quality***; *can switch to new material with confidence*

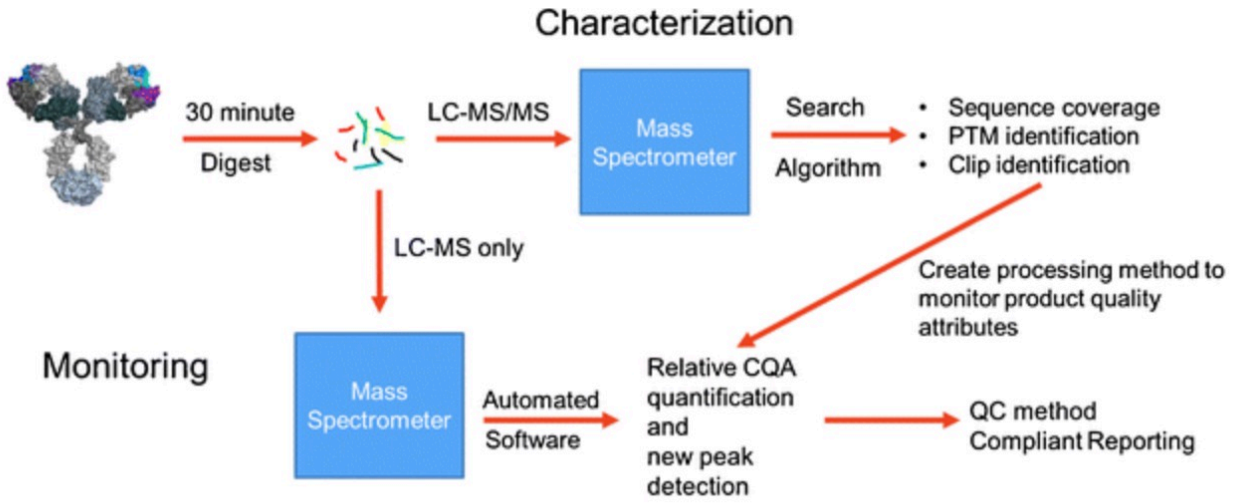
Srikanth Chary et al.

Explain Your Approach

- Sample selection
- Test selection
- Results
- Assessment system
- Conclusions

Don’t submit only the results, and then expect the reviewer or assessor to figure it out...

MAM Applications



✓Direct attribute testing, each site
✓Multiple attributes
✓Detect unexpected variants

– Distribution information
– Peptide recovery
– Disulfide information lost

The AAPS Journal (2018) 20: 7
DOI: 10.1208/s12248-017-0168-3

CrossMark

Commentary

A View on the Importance of "Multi-Attribute Method" for Measuring Purity of Biopharmaceuticals and Improving Overall Control Strategy

Richard S. Rogers,[1,8] Michael Abernathy,[2] Douglas D. Richardson,[3] Jason C. Rouse,[4] Justin B. Sperry,[5] Patrick Swann,[6] Jette Wypych,[2] Christopher Yu,[7] Li Zang,[6] and Rohini Deshpande[2]

FDA U.S. FOOD & DRUG ADMINISTRATION

Multi-Attribute Method (MAM) Evaluation and Regulatory Considerations for Implementation

CASSS MS 2018
Sarah Rogstad
FDA/CDER/OPQ/OTR
September 12, 2018

MAM for QC Release and Stability Testing

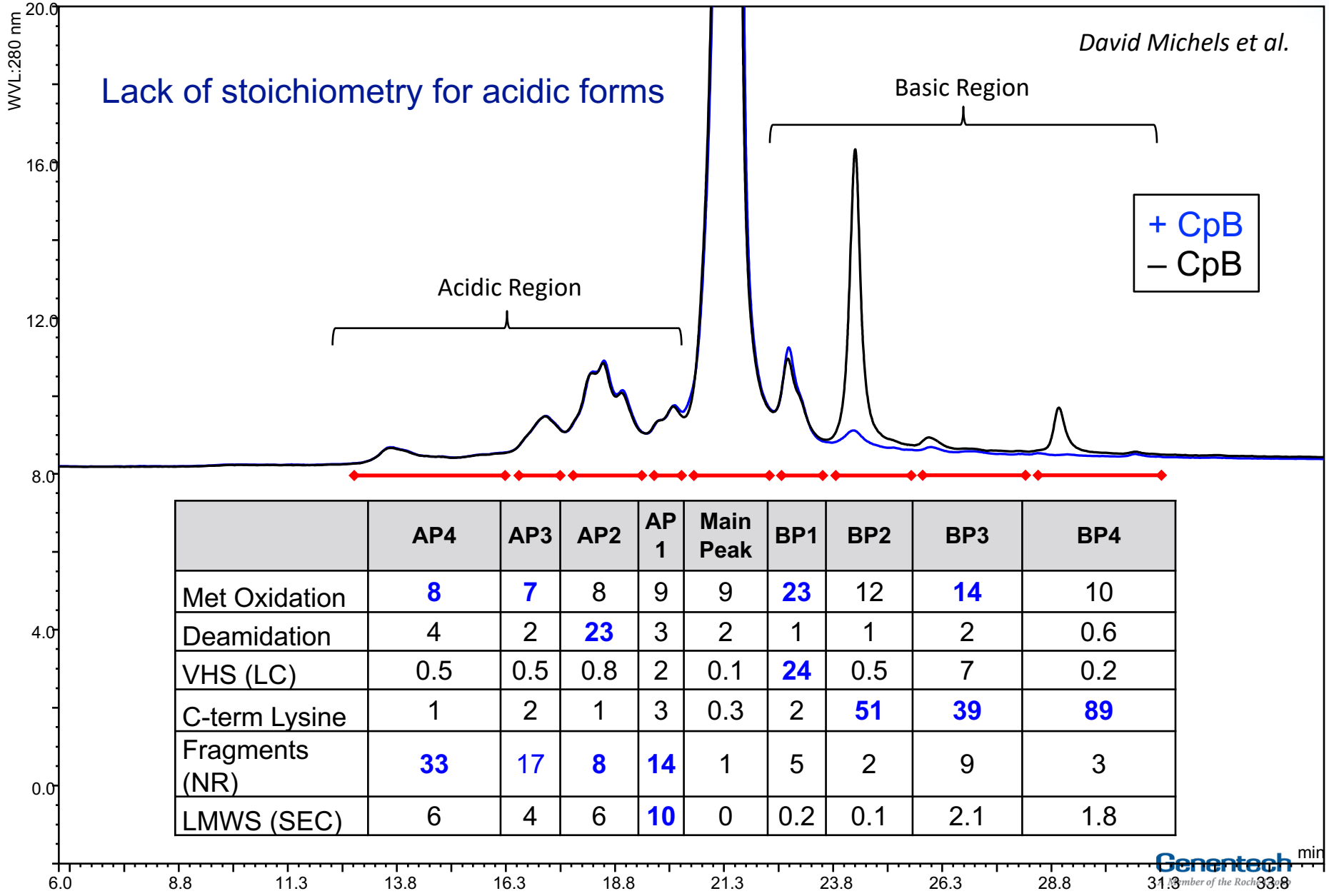
- **Reasons for rejection or quarantine of clinical DS or DP batches**

What happened	How detected	MAM detection?
Reduced forms (reduced interchain S-S)	NR-CE-SDS	+ / –
Colored impurities	COC	–
Sequence variants	UV peptide map	+
Higher MW aggregates	SE-HPLC	–
Unexpected potency loss	bioassay (stability)	–
Low osmolality	Osmolality release test	–

MAM detection is not universal

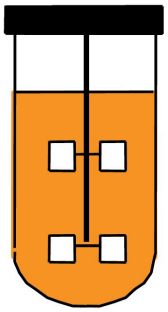
- Will this be additive to existing QC tests?

mAb Charge Variants (IE-HPLC)



	AP4	AP3	AP2	AP 1	Main Peak	BP1	BP2	BP3	BP4
Met Oxidation	**8**	**7**	8	9	9	**23**	12	**14**	10
Deamidation	4	2	**23**	3	2	1	1	2	0.6
VHS (LC)	0.5	0.5	0.8	2	0.1	**24**	0.5	7	0.2
C-term Lysine	1	2	1	3	0.3	2	**51**	**39**	**89**
Fragments (NR)	**33**	17	**8**	**14**	1	5	2	9	3
LMWS (SEC)	6	4	6	**10**	0	0.2	0.1	2.1	1.8

MAM for QC Release Testing



bioreactor

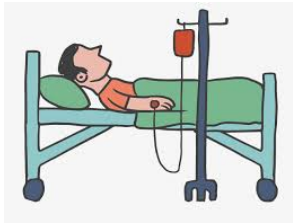
downstream

DS release

DS stability

DP release

DP stability



biotransformation

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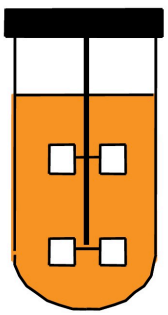
Where Does MAM Belong..?



bioreactor

downstream

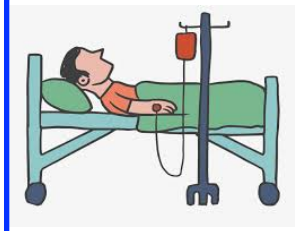
DS release

DS stability

Adaptive process control

DP release

DP stability



biotransformation

MAM offers a way to assess product quality from production to storage to the patient

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Regulatory Perspective

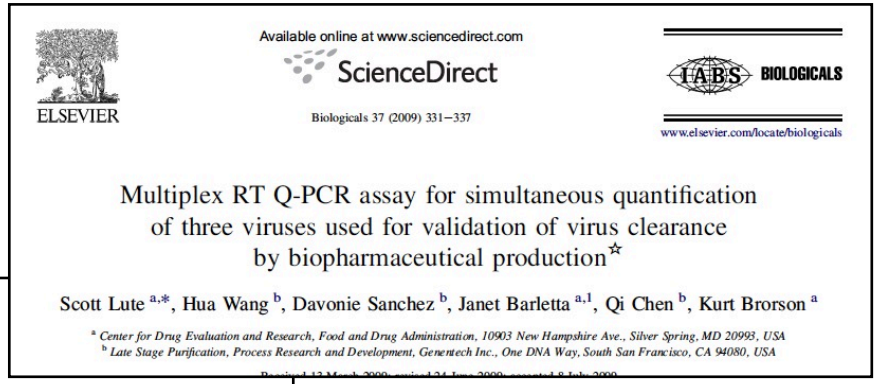
- New approaches, new technologies are encouraged
- Sometimes we get reluctance

Change or Issue	False Negative
From SDS-PAGE to CE-SDS	CE-SDS sensitivity: host cell proteins may be undetected
Using a “risk-based” QbD approach to identify specification tests	Non-model variation (media, equipment, biology, errors)
Clonality	Subset of cells may be producing material with undetected inferior quality
Multi-Attribute Monitoring	Doesn’t inform about variant distribution on intact molecule

- Consistent theme:
  - ➢False negative concerns – adverse quality will be missed

Overcoming Regulatory Reluctance

- **FDA's QbD Pilot, EMA PAT etc.**
- **FDA's Emerging Technology Team**
- **Collaborate with FDA scientists, and publish**
  - Examples:
    - ➢ Q-PCR to replace virus culture-based methods
    - ➢ Viral clearance preserved after AEX re-use



Available online at www.sciencedirect.com
ScienceDirect
Biologicals 37 (2009) 331–337
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www.elsevier.com/locate/biologicals

Multiplex RT Q-PCR assay for simultaneous quantification of three viruses used for validation of virus clearance by biopharmaceutical production☆

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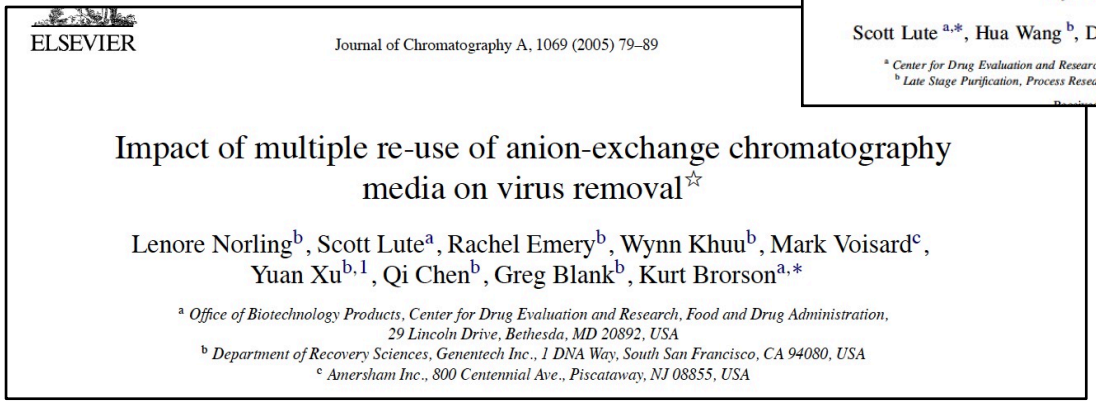

ELSEVIER
Journal of Chromatography A, 1069 (2005) 79–89

Impact of multiple re-use of anion-exchange chromatography media on virus removal☆

Lenore Norling[b], Scott Lute[a], Rachel Emery[b], Wynn Khuu[b], Mark Voisard[c], Yuan Xu[b,1], Qi Chen[b], Greg Blank[b], Kurt Brorson[a,*]

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Wrap Up

- What to measure, reliable methods, suitable results
- CQA assessment:
  - Bioactivity, PK, immunogenicity, safety
  - Uncertainty (prior knowledge)
- Comparability:
  - Highly similar or different, impact of differences
  - Statistics for post-approval changes
  - Judgment for clinical changes
- Consider MAM for adaptive process control, DP stability, and biotransformation
- Regulator's perspective: false negative concerns

Thank You!

"Are you gonna tell us one of your wild stories, Mr. Harris?"

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