ESTABLISHMENT OF PATIENT CENTRIC QUALITY STANDARDS: MONOCLONAL ANTIBODY CASE STUDIES

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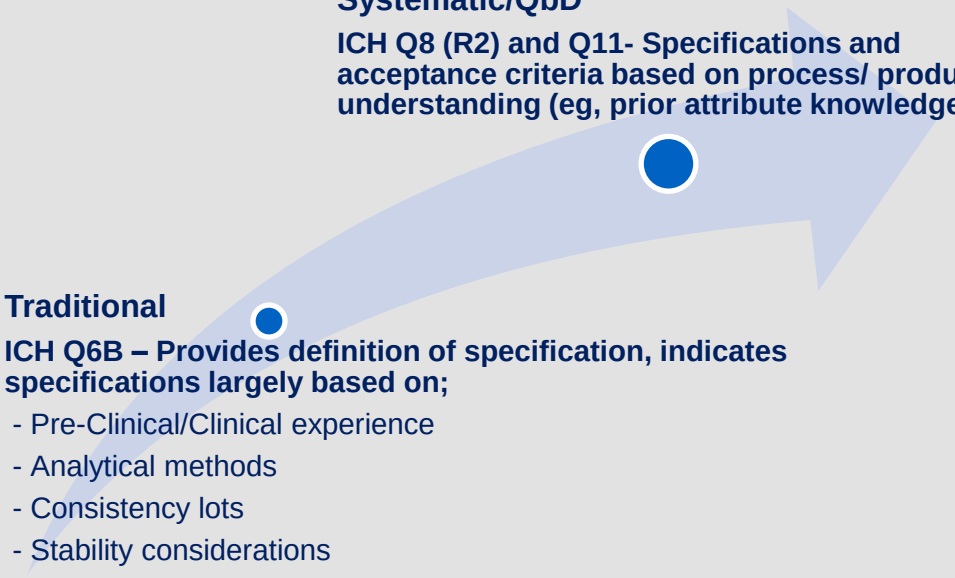
PRESENTATION CONTENT

- Introduction of the Quality by Design develop paradigm
- Steps in the development of a patient centric control strategy and quality standard
- Case studies

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



- 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

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

Assess:

1a. Attribute criticality and whether attribute testing is required

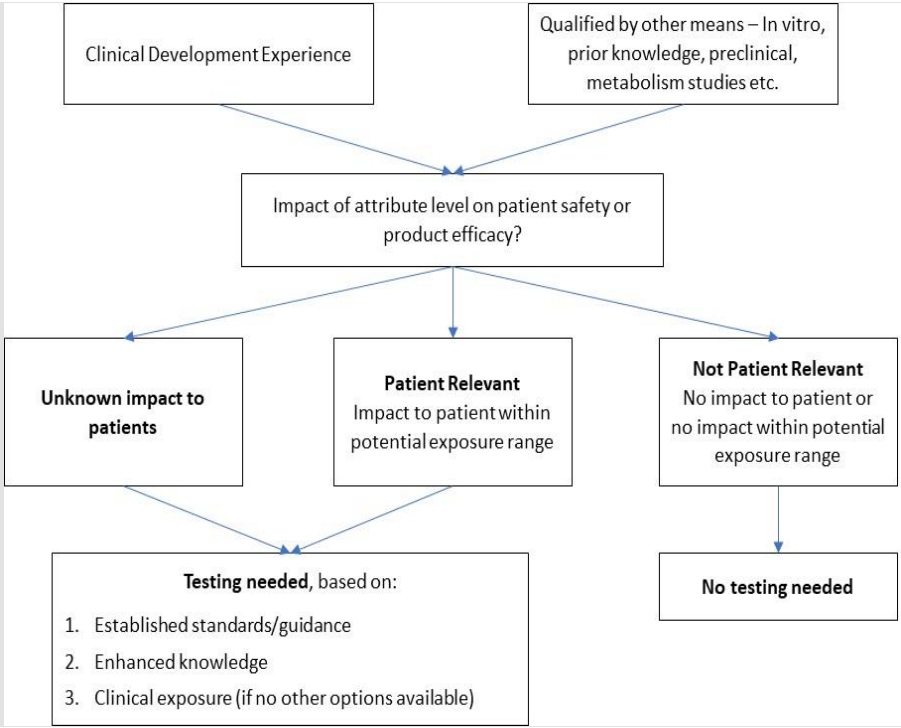
Product Quality Attribute Assessment (PQAA) : Assesses attribute criticality and ranks the potential risk of an attribute having a clinical impact

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



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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

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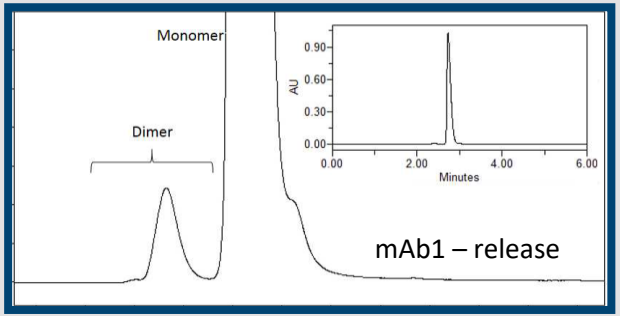
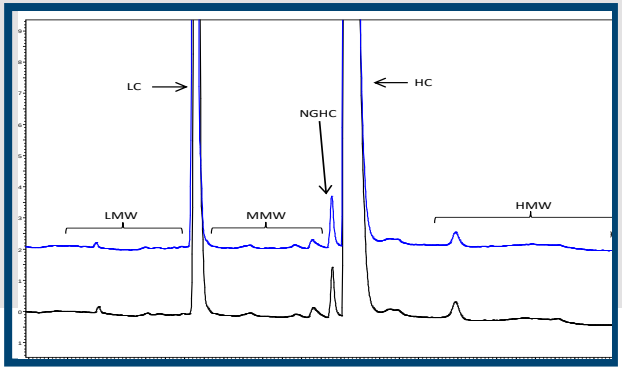
PCQS - ATTRIBUTE FOCUSED CONTROL
HMW SPECIES BY SE-HPLC/FRAGMENTATION BY RCE-SDS

- SE-HPLC is a sensitive, robust method for measuring HMW species
- SE-HPLC main peak often contains both intact and fragmented species and is not an accurate assessment of ‘product purity’. SE-HPLC is therefore only used to measure HMW species.
- rCE-SDS used to monitor fragmentation
- Strategy has been accepted globally in multiple MAs
- It is now a platform approach

HMW by SE-HPLC



Fragmentation by rCE-SDS



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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 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

PCQS - OPTIMIZE TESTING SCOPE AND CONTROL POINT PARTIALLY REDUCED SPECIES BY NRCE-SDS

- ✓ Partially reduced species can occur when the disulfide bond in the mAb is broken due to a redox process
- ✓ Some mAbs sensitive to partial reduction at harvest but it can be well controlled and is typically not a pathway of degradation during storage. Susceptibility IgG1>IgG2
- ✓ May be assessed as a CQA or non-CQA depending on the amount of information available
- ✓ Control via IPC as a process consistency measure if testing is warranted

Taken from MBL

Efficacy/safety risk is low

- Reduced antibodies remain intact and maintain their biological activity[1, 2]
- mAbs re-oxidize after administration[1]

Approved Control Strategies

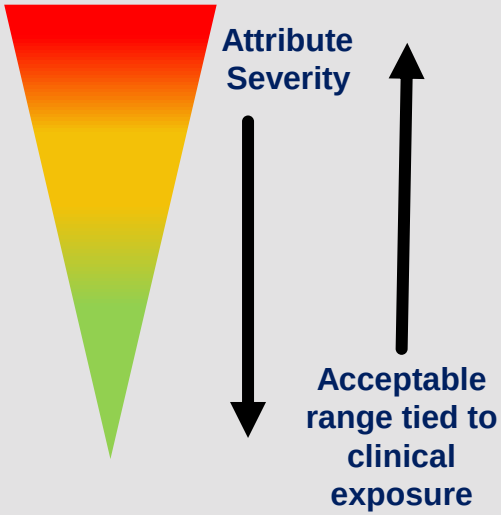
- 2 IgG1s with IPC reject limit (low risk CQAs)
- 1 IgG1 with IPC action limit (low risk CQA + additional process knowledge)
- 1 IgG1 with no IPC (non-CQA)
- 2 IgG2s with no IPC (non-CQA based on product specific knowledge)

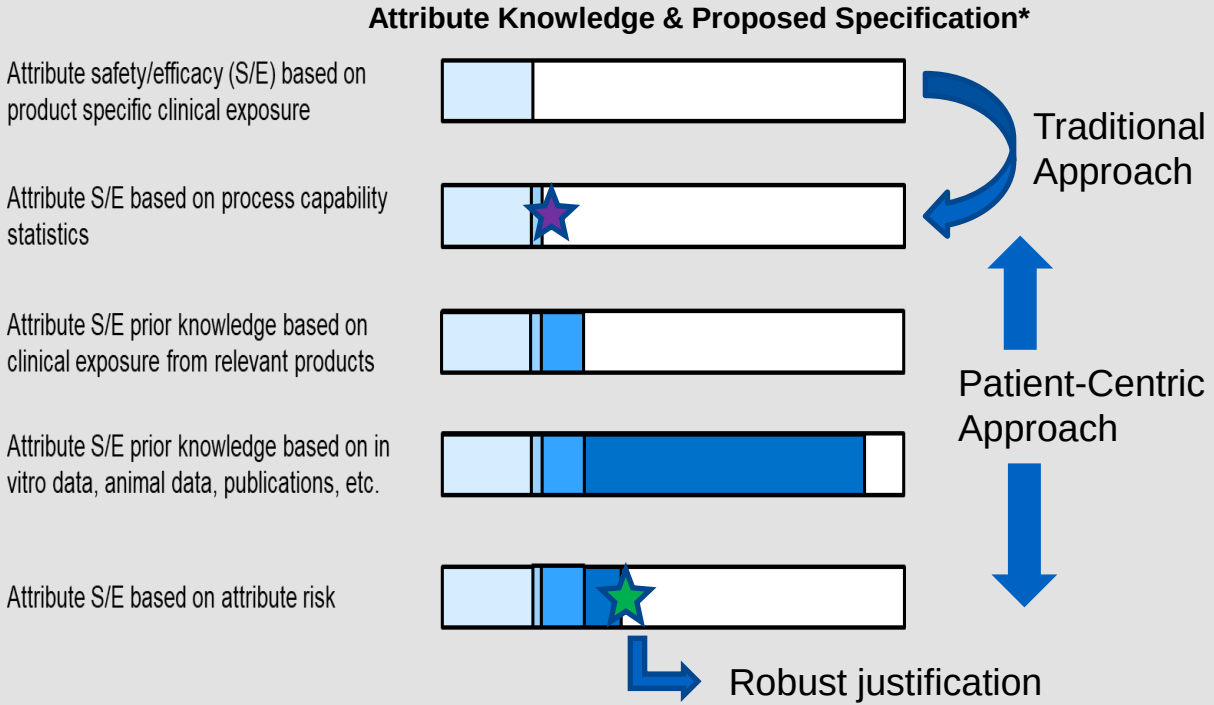
[1] Wang, T. etal, 2015. J Pharm Biomed Anal 102:519-28. DOI: 10.1016/j.jpba.2014.10.023
[2] Internal Amgen information

PATIENT CENTRIC SPECIFICATIONS
3 - ESTABLISHING AN ACCEPTABLE ATTRIBUTE RANGE

- The safety (including immunogenicity) and efficacy of products is established in the clinical trials
- Attribute knowledge can be used to evaluate the potential risk that a change in an attribute level will impact the established safety/efficacy profile

PATIENT CENTRIC SPECIFICATIONS
3 - ESTABLISHING AN ACCEPTABLE ATTRIBUTE RANGE





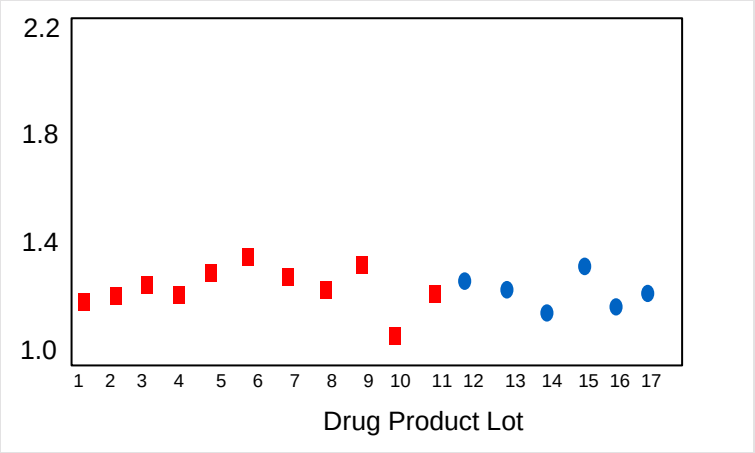
*See EMA/CHMP/BWP/812924/2018

CASE STUDY: HMW SPECIES BY SE-HPLC DRUG PRODUCT SPECIFICATION

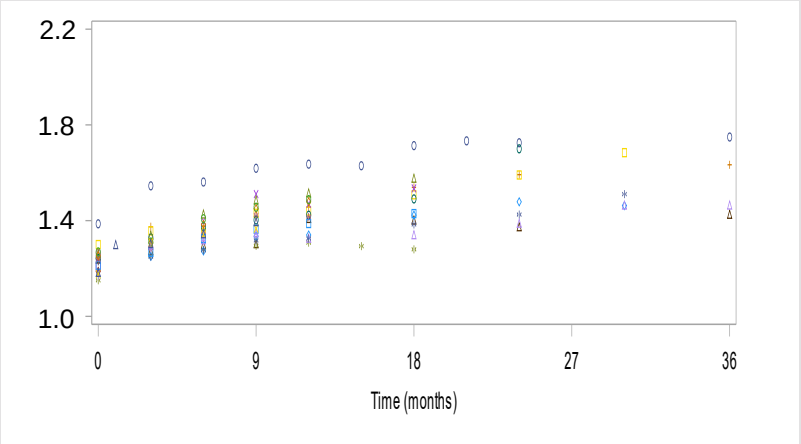
HYPOTHETICAL CASE STUDY: HMW SPECIES BY SE-HPLC DRUG PRODUCT SPECIFICATION

Product is a human IgG1 with Fc-effector function. Used for treatment of oncology and autoimmune indications

Drug product release trend chart (clinical (red) and commercial (blue))



% HMW increase during DP storage



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PCQS - ESTABLISHING AN ACCEPTABLE ATTRIBUTE RANGE

PROPOSED SPECIFICATIONS

Tolerance Interval for Drug Product: SE-HPLC (% HMW)

Parameter	LTL (start)	UTL (start)	LTL (end 36 mo)	UTL (end 36 mo)
HMW	0.881	1.431	1.015	1.648

Proposed Specifications for Drug Product: SE-HPLC (% HMW)

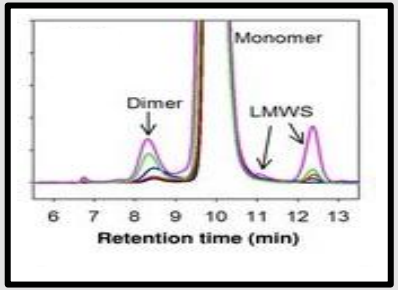
Process Stage	% HMW
Drug Product, release	≤ 1.7
Drug Product, stability	≤ 2.5

- Relatively limited manufacturing experience (17 DP lots from 5 campaigns derived from 8 DS lots from 3 campaigns, and two drug product manufacturing sites).
- Proposed drug product specification range is outside statistically derived limit to provide flexibility for future process and product improvement/changes
- Product knowledge indicates no impact to safety or efficacy within proposed range
- While specification limits are outside historical experience, QMS will monitor release/stability results and investigate OOT results as appropriate

PCQS - ESTABLISHING AN ACCEPTABLE ATTRIBUTE RANGE

JUSTIFICATION OF SPECIFICATION: HMW SPECIES BY SE-HPLC

- **HMW composition**
  - Primarily composed of non-covalent dimer
  - Formation of higher order aggregates is not a significant degradation pathway
- **Potency risk is low**
  - Sample enriched for HMW at 74.4% had comparable activity to an unfractionated control and to a sample enriched for main peak
- **Immunogenicity risk is low**
  - IgG1/2 dimers occur naturally[1]
  - Low immunogenicity rate in oncology and autoimmune patients
  - HMW composed of non-covalent dimers[2]
- **PK risk is low**
  - Antibody dimer cleared at a rate similar to monomer[3]
  - No meaningful impact at allowable level



Sample	HMW (%)	Relative Potency (%)	Additional Activity 1 (%)
Enriched HMW sample	74.4	109	89
Enriched main peak	0.9	93	99
Unfractionated control	1.3	105	91

[1] Yoo et al. doi.org/10.4049/jimmunol.170.6.3134; Yang et al. doi.org/10.1016/j.molimm.2013.11.011
[2] Bessa et al. DOI 10.1007/s11095- 015-1627-0; Bi, J et al. DOI 10.1002/jps.23663
[3] Piparia et al. DOI: 10.4161/mabs.20099

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PCQS - ESTABLISHING AN ACCEPTABLE ATTRIBUTE RANGE

CASE STUDY: FRAGMENTATION BY RCE-SDS (% HC + LC)[1]

[1] IQ CONSORTIUM PHASE APPROPRIATE SPECIFICATION WHITE PAPER *RUESCH ET AL (2019) J PHARM SCI, SUBMITTED*

- ✓ Product is an IgG1 with effector function
- ✓ Fragmentation was not observed during drug substance or drug product manufacturing, or storage at the recommended storage temperature
- ✓ Proposed specification was approved by major regulator jurisdictions

Method (Parameter)	Historical Range	Lower TI (Stability)	Specification
rCE-SDS (% HC+LC)	96.4 to 97.3	95.921	≥ 95.0

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PCQS - ESTABLISHING AN ACCEPTABLE ATTRIBUTE RANGE
JUSTIFICATION OF SPECIFICATION: FRAGMENTATION BY RCE-SDS

- **Fragment composition is high risk –** The primary site of fragmentation is in the heavy chain Fc-region. Fragmentation has potential to impact effector function
- **Biological activity (potency) – low risk of impact within proposed range**
  - Data from recommended, stressed and forced degradation stability studies demonstrated a similar pathway of degradation by fragmentation
  - Product specific knowledge from forced and stressed degradation studies used to justify no impact within proposed range

Forced Degradation Condition	rCE-SDS HC + LC (%)	Relative Potency (%)	Relative ADCC (%)
Control	96.4	100	107
pH 8.0/25°C	94.8	110	120

Drug Substance Lot	Temperature/ Time Point	rCE-SDS HC + LC (%)	Relative Potency (%) (Potency at T=0)
A	25°C/6 months	87.5	110 (124)
B	25°C/6 months	87.4	117 (87)
C	25°C/6 months	88.4	93 (102)

- **Safety (Immunogenicity/PK) - low risk of impact**
  - No impact to Fab- or Fc-region function within proposed range indicating no meaningful alteration to structure within proposed range.
  - Risk to immunogenicity or FcRn binding is low

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- PhRMA Patient Centric Working Group
- IQ Consortium Phase Appropriate Specification Working Group

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Learn more about IQ

For more information about the IQ Consortium's past work and current activities, we invite you to review the following resources.

IQ Website	https://iqconsortium.org
IQ Annual Report 2019	https://iqconsortium.org/about/annual-reports/ar-2019

To find out how your company can join the IQ Consortium or if your company is already a member and you would like to get involved, please email us at info@iqconsortium.org.

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