Joint BWP / QWP workshop with stakeholders in relation to
prior knowledge and its use in regulatory applications

How to Use Prior Knowledge in Defining the Control Strategy

EMA, London; 23 November 2017

efpia
European Federation of Pharmaceutical Industries and Associations

ebe
european biopharmaceutical enterprises

Vaccines Europe
An industry for healthy lives

medicines for europe
better access. better health.

EMA Prior Knowledge Workshop

Case Study: Use of Prior Knowledge in the Control Strategy for Biotechnology Products

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&

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Key Steps in Implementation of QbD and Use of Prior Knowledge for the Control Strategy of a Biotechnology Product (ICH Q8 (R2))

Quality Target Product Profile (QTPP) – forms basis of design for the development of the product

- Prior knowledge within and across modalities are used in establishing targets for early development
- Balancing achievement for highest potential of the drug candidate while at same time allowing manufacturing flexibility to accommodate process and product changes

Product Quality Attribute Assessment – primarily based upon severity of potential harm and does not change as a result of risk

- Understanding of criticality of attributes and their impact on safety, efficacy and immunogenicity across multiple products, modalities and therapies helps provide knowledge and their potential impact to patients
- The attribute acceptable level will vary based on the CQA's risk to product quality determined by prior knowledge, biological impact of the product attribute, and clinical experience with the product
- CQAs may have justified thresholds below which there is no expected impact on safety/efficacy
- Similar molecules and peer-reviewed literature along with studies using in vitro and in vivo models

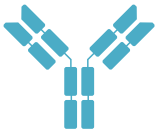
Product Quality Risk Assessment(s) – links product attributes and process parameters to CQAs

Control Strategy – designed to ensure that a product of required quality will be consistently produced

Lifecycle management – importance of continuous improvement

Amgen is Applying Prior Knowledge in Many Areas of Process and Product Development

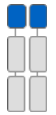
PLATFORMED MODALITIES AND ASSOCIATED ATTRIBUTES:



Mabs: IgG1s and IgG2s

Canonical BiTE®

Half-life Extension BiTE®

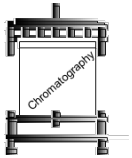


Fc fusion Proteins

PROCESS DEFINITION AND MANUFACTURING TECHNOLOGIES:

Batch, Perfusion, Continuous, Disposable technologies

Harvest, VI and Filtration



Affinity, CEX, HIC and Mixed Mode

UF/DF

ANALYTICS, ADVANCEMENT OF PAT:

Category	Analytical Technique	Lot Release	Category	Analytical Technique	Lot Release
Primary Structure	Intact mass		Product Related Substances and Impurities	Size Exclusion HPLC	√
	Reduced deglycosylated mass			CEX HPLC / cIEF	√
	Peptide map(s)	√*		Reduced SDS-PAGE or CE-SDS	√
	Glycan map	√*		Non-reduced SDS-PAGE or CE-SDS	√*
	AAA (extinction coefficient)			RP-HPLC	
	cIEF (pI determination)		Particles and Aggregates	HIAC	√
	Identity ELISA	√		MFI	
Higher Order Structure	FTIR			DLS	
	Near UV CD			FFF	
	DSC			AUC-SV	
Biological Activity	Potency bioassay	√		SEC-LS	
	FcRn		General Properties	Protein Concentration	√
	Fcγ Receptor binding	√*		Osmolality	√
	ADCC	√*		pH	√
	CDC	√*		Color /Clarity	√

√* Based on Specific Product and/or Regional Requirements

ANALYTICAL METHODS

PAT and MAM Advancement

Quality Attributes where Prior Knowledge Applied to Mabs Can be Useful

- Methionine oxidation in Fc region
- High molecular weight species
- Heavy Chain C-terminal modification
  - C-terminal lysine
  - C-terminal proline amidation
- Glycan structure in N-linked Fc region
  - Mannosylation
  - Galactosylation
  - Fucosylation
- Deamidation in Fc region
- Tri-sulfides
- Glycation in non-CDR regions

Severity Score	Immunogenicity (IG): Use decision tree if not listed below:	Safety Potential for:
9 Severe	• PQA may enhance IG AND • Clinical experience: High IG and hypersensitivity or loss of endogenous protein function observed	• Death • Serious patient injury • Microbiologically related infections
7 Major	• PQA may enhance IG AND • Clinical experience: High IG w/ change in therapeutic function or unknown IG in patients with increased immune activity	• Hospitalization • Toxicity known to be associated with PQA • Undesirable change in PQA after pivotal trials
5 Moderate	• PQA may enhance IG AND • Clinical experience: High IG w/ no observed impact, low IG with change in therapeutic function or unknown IG in pts w/ normal or low immune activity	• Treatment required without hospitalization • Impact to patient • Undesirable change in PQA after P2 trials • Moderate to high concentration of PQA (greater than level qualified in Tox studies)
3 Minor	• PQA may enhance IG AND • Clinical experience: Low IG with no observed impact	• Adverse event not requiring treatment • Customer annoyance • Chronic treatment or disease • Cell-based therapeutic target
1 Insignificant	• PQA not expected to enhance IG	• No known safety issues • Acute treatment only • Serious disease with no alternative treatments

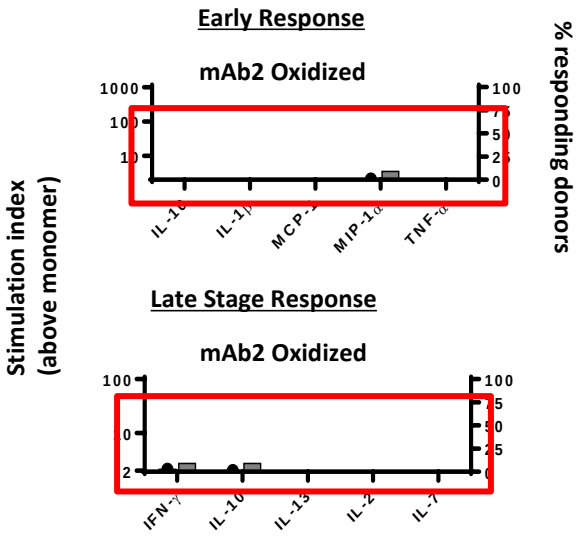
Severity Score	PK Potential for:	Potency Potential for:
9 Severe	• Progression of disease due to change in PK	• Progression of disease due to change in potency or effector function
7 Major	• Major change in PK	• Major change in potency or effector function
5 Moderate	• Moderate change in PK	• Moderate change in potency or effector function
3 Minor	• Minor change in PK	• Minor change in potency or effector function
1 Insignificant	• No expected change in PK	• No expected change in potency or effector function

Example Quality Attributes with Prior Knowledge for Mabs

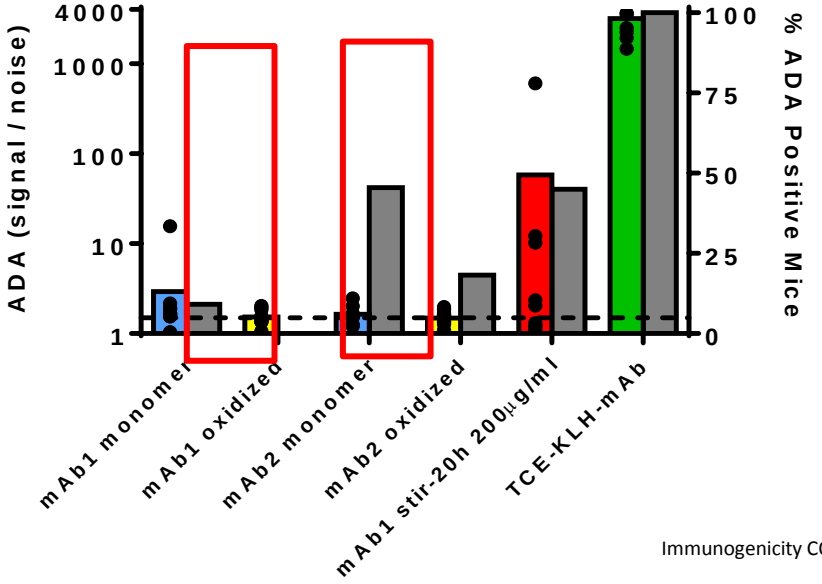
Attribute	Immune Safety	Non-Immune Safety	Efficacy: PK	Efficacy: Potency	
Fc Methionine Oxidation	1	NA	3	NA	Based on general understanding of attribute impact, not specific molecule information Gao et al., JOURNAL OF PHARMACEUTICAL SCIENCES 104:368–377, 2015 Stracke et al. mAbs 6, 1229-1242, 2015 Bi et al. JOURNAL OF PHARMACEUTICAL SCIENCES 102, 3545-55, 2013
Aggregates	7	7	5	7	Includes aggregates that form subvisible and visible aggregates Carpenter et al. JOURNAL OF PHARMACEUTICAL SCIENCES 98, 1201 – 1205, 2009 Singh et al. JOURNAL OF PHARMACEUTICAL SCIENCES 99, 3302 - 3321, 2010
Dimer	5	NA	5	7	For most Mabs immune safety is evaluated as part of clinical studies. For many Mabs, dimers have reduced potency.
Heavy Chain C-terminal Lysine	1	NA	1	1	Based on general understanding of attribute impact, not specific molecule information. Cai et al., BIOTECH BIOENG 108, 404 – 412 2011 104:368–377, 2015 Antes et al. J Chromatography B 852 250-6, 2007 Van den Bremer et al. mAbs 7, 672-680, 2015
Heavy Chain C-terminal Proline Amidation	1	NA	1	1	Based on general understanding of attribute impact, not specific molecule information Johnson et al. Anal. Biochem. 360, 75 – 83 (2007). Kaschak et al. mAbs 3, 577 – 583 (2011). Tsubaki et al. International Journal of Biological Macromolecules 52, 139-147 (2013).

Key Experiments Were Performed to Assess the Impact of MET Oxidation on Safety

In Vitro Comparative Immunogenicity Assessment (IVCIA) Assay



Xeno-het Mouse



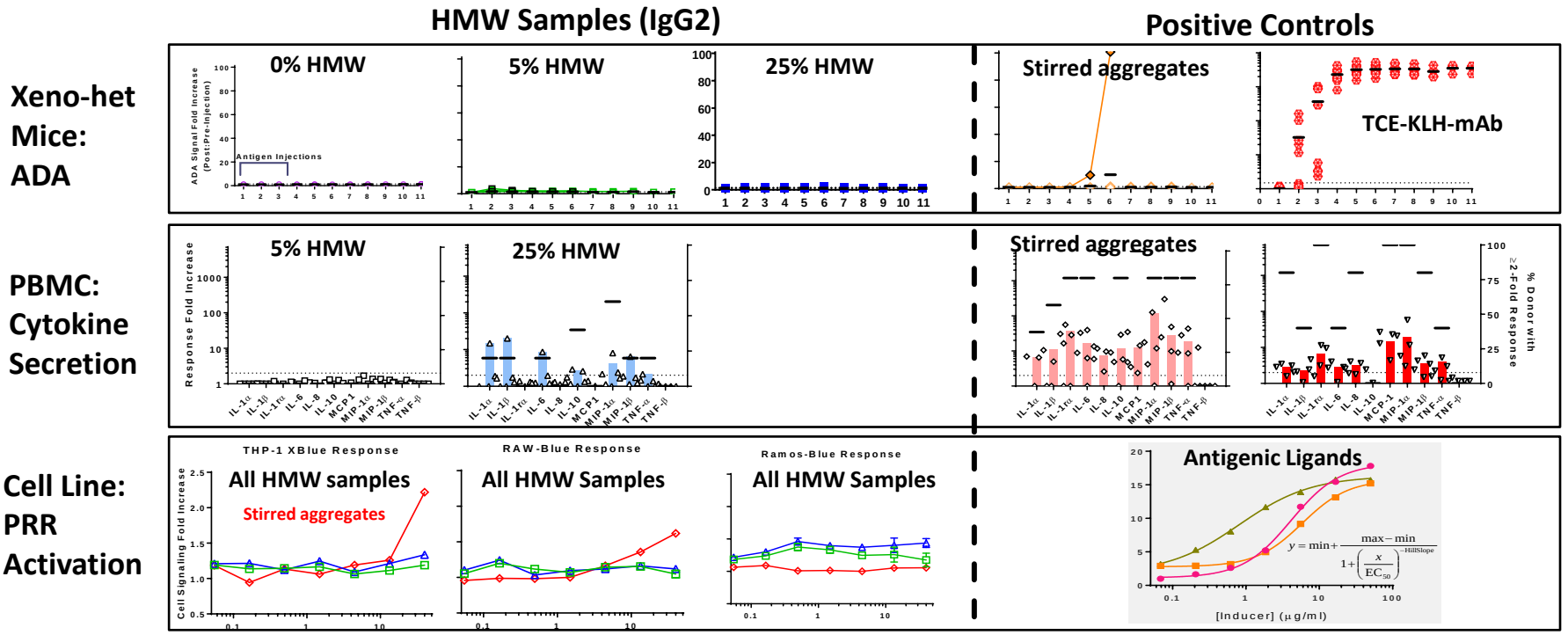
Immunogenicity CQA team

Conclusions:

- **Safety:** Met oxidation does not appear to increase immunogenicity risk as shown by the in vitro cell-based assays and the in vivo Xeno-het mouse model
- **Clearance:** Oxidation at the conserved Fc met 252 and 428 under reasonable conditions has negligible impact on FcRn binding and subsequent PK clearance (Stracke et al., mAbs, 2015 6:5, 1229-1242)

These results strongly suggest that oxidation of Met residues in Amgen antibody products does not pose an increased risk of immunogenicity or impact on PK

Product-related HMW Species Did Not Induce a Significant Immune Response in Any Model System



- Process-related IgG1 did not induce ADA in the mini-repertoire mouse model (Bessa et al, Pharm Res, 2015 32(7); 2344-59)

High levels of HMW species, well above that observed in products, do not pose an increased risk of immunogenicity

C-terminal Lysine, the Most Common C terminal Variant, Has Minimal Impact on Safety and Efficacy

Minimal safety risk due to natural occurrence in humans and short exposure in circulation

- Naturally occurring, endogenous human antibodies are expressed with a C-terminal K
- Rapidly cleaved by endogenous serum carboxypeptidase B (CpB) in vivo after intravenous injection with half-life of about an hour

Minimal impact on efficacy due to spatial distance from CDR, FcRn, and Fc gamma receptor binding regions; and short exposure in circulation

- The C-terminus of the HC is not within the known binding sites of CDR, FcRn or Fc gamma receptors
- Most C-terminal Lys is clipped shortly after patient administration

C-terminal lysine is naturally occurring and not near any known binding sites making it unlikely to impact safety or efficacy

C-terminal Proline Amidation : No Known Impact on Safety or Efficacy

Minimal safety risk due to natural occurrence in humans

After HC C-terminal Lysine is processed by carboxypeptidase to yield Glycine at the terminus, enzymatic activities of peptidylglycine-α-hydroxylating monooxygenase (PHM) and Peptidyl- α-hydroxyglycine α-midating lyase (PAL) can generate the proline amidated C-terminus.

(Johnson et al. Anal. Biochem. 360, 75 – 83 (2007). Tsubaki et al. International Journal of Biological Macromolecules 52, 139-147 (2013), Kaschak et al. mAbs 3, 577 – 583 (2011).)

- **Levels in therapeutics Mabs: < 1% for Amgen products; 0.3 – 25.9 % in 6 of 10 IgG1 Mabs; 0.8-1.2% in 2 IgG4 Mabs**

Minimal impact on efficacy due to spatial distance from CDR, FcRn, and Fc gamma receptor binding regions

- **The C-terminus of the HC is not within the known binding sites of CDR, FcRn or Fc gamma receptors**
- **Preferential clearance has not been demonstrated**

C-terminal proline amidation is naturally occurring and not near any known binding sites making it unlikely to impact safety or efficacy

Using Prior Knowledge to establish an attribute focused specification

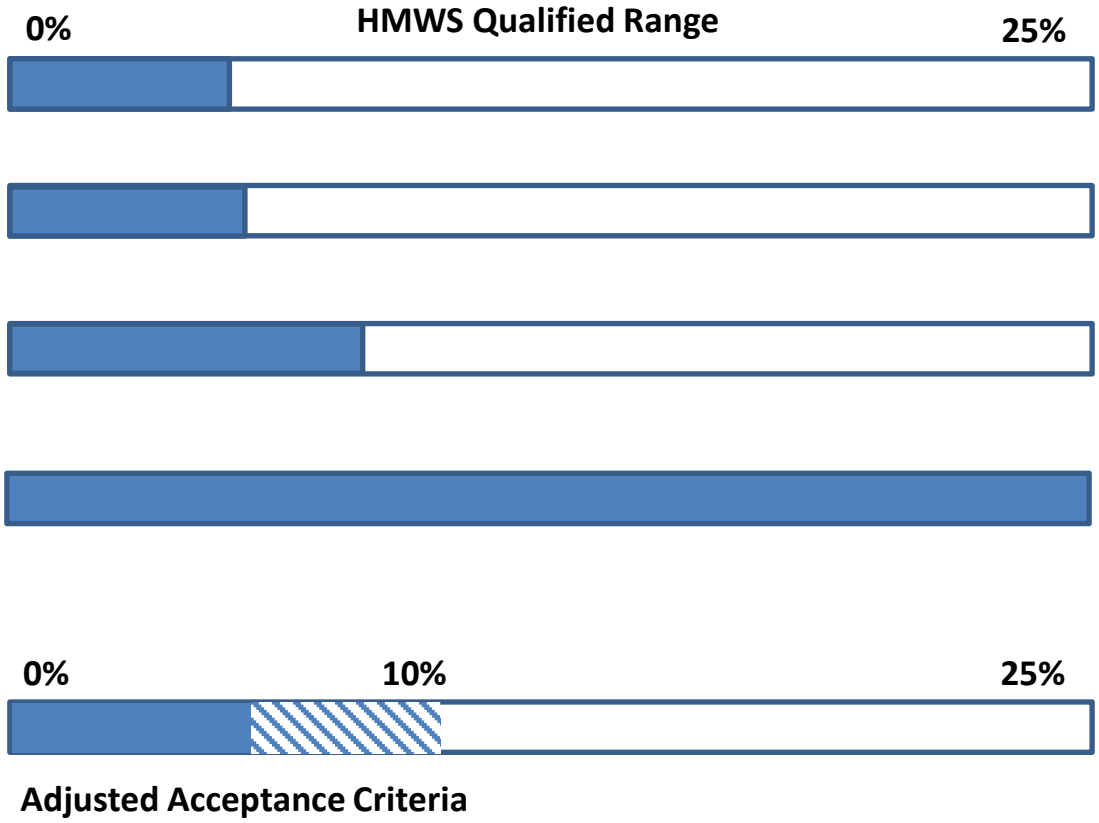
Clinical exposure with highest level of impurity

TI based off of Manufacturing Experience

Prior Knowledge based on clinical exposure of the attribute from relevant products

Prior Knowledge of Product attribute safety threshold from in vitro and animal data

Attribute acceptance criteria = clinical exposure and manufacturing experience + Prior Knowledge (clinical and in vitro)



Prior Knowledge Next Steps

- **Prior knowledge is applicable from molecule design, molecule selection, non-clinical toxicology testing, first in human studies through product lifecycle**
- **Prior knowledge is utilized to develop a risk-based approach for control strategy including specification setting throughout the product lifecycle**
- **Prior knowledge of product attributes and the development of the associated manufacturing process creates a basis for more flexible regulatory approaches**
- **It is important to understand the criticality of attributes and the impact of these attributes across different therapies**