OVERVIEW OF PREDICTIVE MODELING METHODOLOGIES FOR STABILITY AND SHELF-LIFE SETTING

CASSS CMC Strategy Forum
24 January 2022

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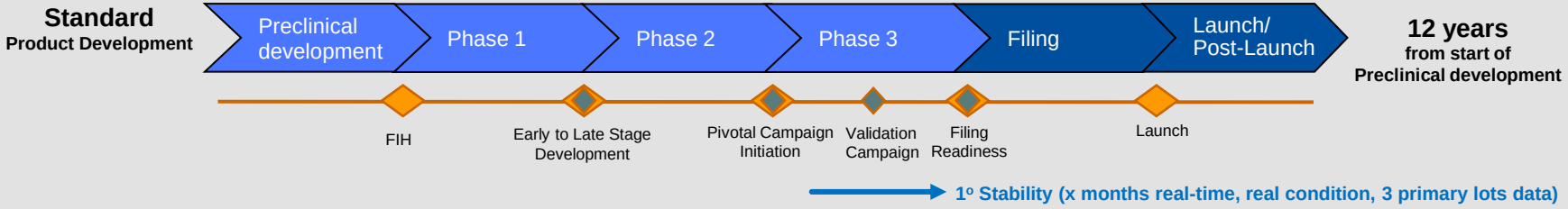
PRESENTATION CONTENT

- Why Science & Risk-based Predictive Stability (SRBPS) is needed
- 2 stability modelling approaches
  - Using Prior Knowledge: classical analysis
  - Kinetic Analysis: Arrhenius-based
- Using Bayesian Statistics to introduce prior knowledge
- Criteria to Justify Prior Knowledge
  - What attributes are important?
- The advent of Artificial Intelligence & Deep Learning
  - Deep learning application to prior knowledge
- The Future with Cloud-based Automation
- Regulatory Landscape
- Post-approval Considerations

STABILITY DATA ARE TYPICALLY RATE LIMITING IN BIOLOGIC PRODUCT DEVELOPMENT



Acceleration of product development	• Facilitate earlier patient access to new medicines
Clinical shelf-life	• Extrapolation from real time, real condition stability data allowed BUT labelling complication in EU
Commercial shelf-life	• Need at least 24m shelf-life at launch to use PPQ lots, lead time, remaining shelf-life

A New Approach to Shelf-life Determination is Needed to Accelerate Product Development

USE OF SCIENCE AND RISK-BASED STABILITY (SRBS) APPROACHES

What is science & risk-based stability?

- **Balances stability data provided at regulatory submission with the product medical need using principles of QbD and risk management**
  - **'new normal', accelerated procedures, pandemic**
- **No relaxation in product quality, risk-based deferral of data provision**
  - **Supported by data using other approaches**
  - **Verified by ongoing, long-term stability studies**
- **Approaches include:**
  - **Stability assay selection from CQAs; focus on key stability-indicating CQAs**
  - **Protocol: attribute testing frequency based on attribute impact on stability**
  - **Using product-specific development stability data, accelerated condition data**
  - **Using prior knowledge from like-molecules to predict stability profile & shelf-life**
  - **Modelling of attribute kinetics for accurate predictions**
- **Requires a fresh look at the current ICH guidelines**

Shelf-life encompasses totality of knowledge

New Approaches Provide a Scientific Basis to Extending Shelf-life Beyond Product-specific Data

SCIENCE & RISK-BASED STABILITY MODELLING APPROACHES

Computational Methods

Data-Driven

- ***Product development data***
- ***Historical data from similar molecules***

Prior-Knowledge

- **Bayesian statistics**
- **AI/Deep Learning**

First Principles

- ***degradation pathways***
- ***kinetics***
- ***temperature dependence***

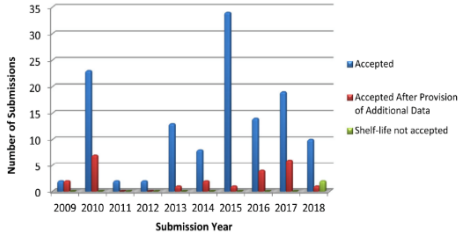
Kinetic Modeling

Hybrid Modeling

Combination of first principles and data-driven models
– totality of stability knowledge

Small Molecules

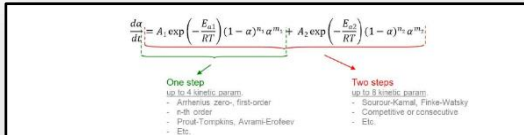
- **ASAP** is broadly used in the industry[1]
  - Based on the Arrhenius equation
  - Currently accepted in development
  - *'Supportive'* for commercial shelf life by regulatory bodies
- Use of **prior knowledge**



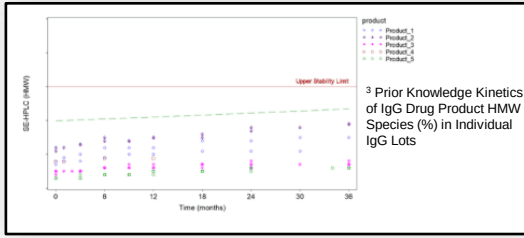
[1] Collective ASAP experience of five companies

Vaccines & Biologics

- **Advanced kinetic modeling[2]**
  - successfully used for vaccines (with conventional stability)
- Use of **prior knowledge[3]**
  - For unmet medical need (EMA)
- **AI-driven** models



[2]Two-step Kinetic Models



[3] Prior Knowledge Kinetics of IgG Drug Product HMW Species (%) in Individual IgG Lots

[1] McMahon et al. Utilization of risk-based predictive stability within regulatory submissions; industry's experience AAPS Open (2020)
[2] Clenet, *Accurate prediction of vaccine stability under real storage conditions and during temperature excursions J.E*JPB (2018)
[3] Lennard et al. *Using Prior Knowledge for Stability Modeling of Biological Therapeutic Agents to Assign Shelf Life* (2021)

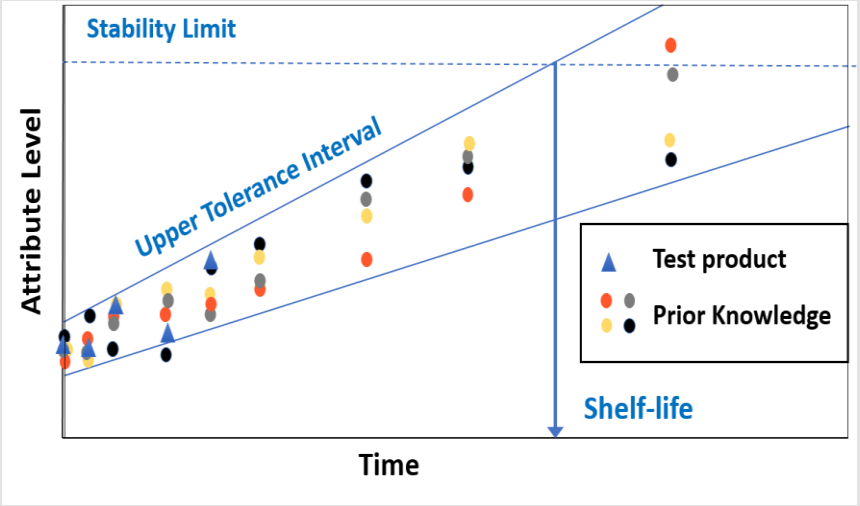
USE OF PRIOR STABILITY KNOWLEDGE FOR BIOLOGICS

The proposed approach to shelf-life setting extends from:

- EMA Prior Knowledge workshop, 2017
- EMA/FDA accelerated procedures CMC workshop, 2018

A Stability Prior Knowledge approach:

- Reference data sets for 'like molecules' CQAs
- Tolerance intervals (TI) for stability-indicating attributes
- Appropriate specification & internal stability limits
  - Aided by a patient-centric specification approach
- TI intersections with stability limits determine shelf-life
- **Lowest 'attribute' intersect used as product shelf-life**



- **When an investigated product meets pre-determined criteria, the modelled shelf-life can be applied**

Prior knowledge provides a scientific basis to extending shelf-life beyond product-specific long-term stability data

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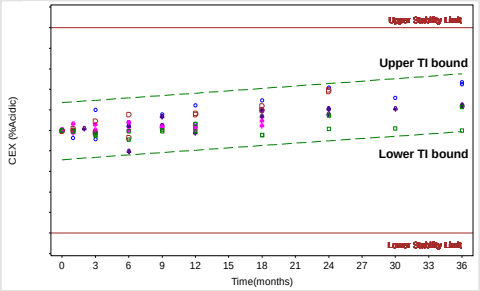
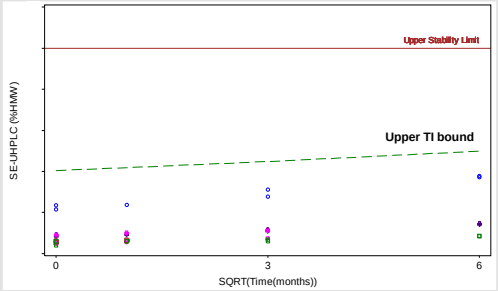
LIQUID DRUG PRODUCT ATTRIBUTES TREND WITHIN LIMITS

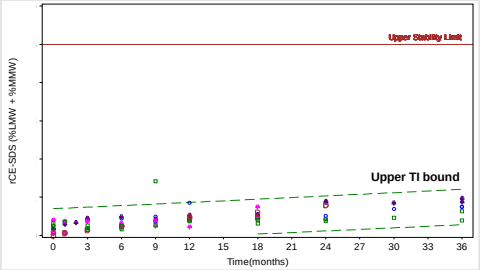
CEX-HPLC acidic peaks



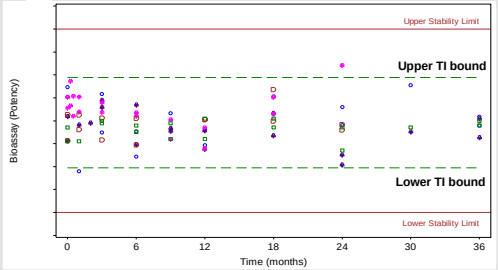
HMW species (dimer)



Fragmentation



Potency



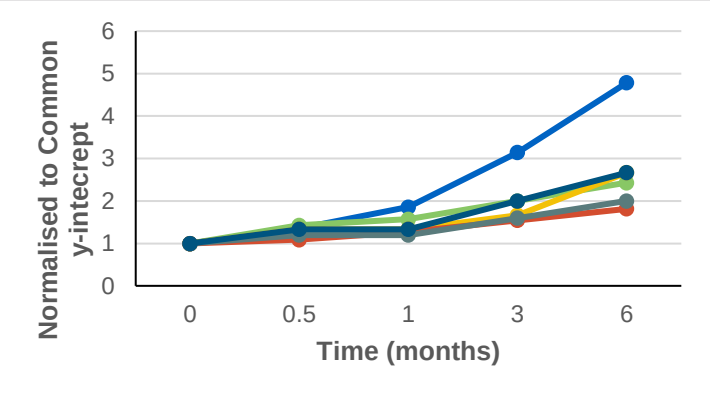
- **Stability profiles may trend through 36 months**
  - No TI intersections with stability limits within 36m
    – 36 months shelf-life assigned
- **CEX-HPLC data are normalised:**
  - It is the trend that is important
- **HMW species data are transformed for linearity**
- **Stability levels reflect phase appropriate clinical specification**

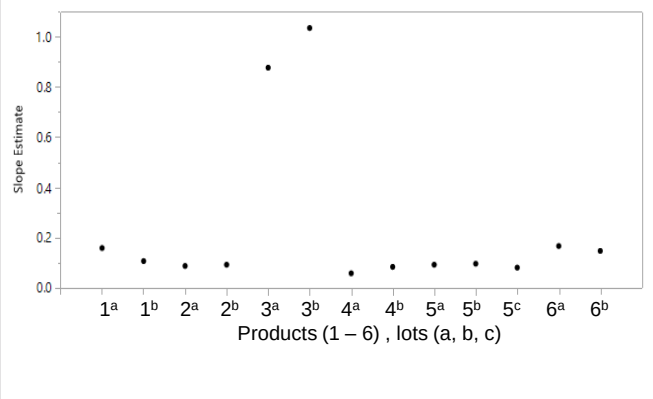
Data from 5 products meeting selection criteria

Claimed shelf-life is Highly Dependent on the Attribute Specification

SUPPORTING THE MODEL WITH ACCELERATED CONDITION STABILITY DATA

Kinetics of High Molecular Mass Species Formation under Accelerated Conditions





Accelerated condition stability data can identify non-fit molecules in:

a) Assimilating the reference data set

b) Evaluating fit of the investigated product to the model

Accelerated condition stability data is a valuable tool to support a prior knowledge derived model and its application

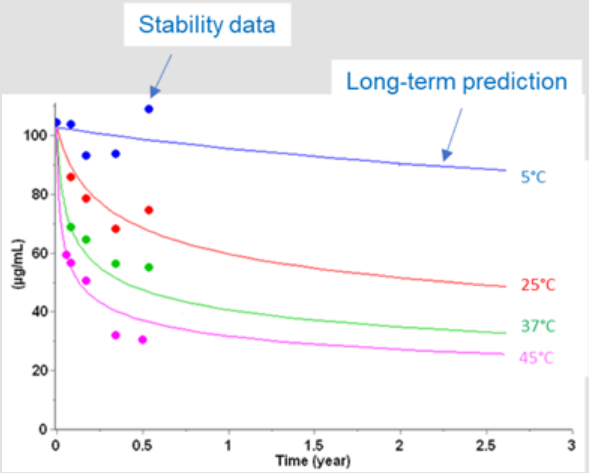
AN OPTION WHEN PRIOR KNOWLEDGE IS LACKING: ADVANCED KINETIC ANALYSIS FOR BIOLOGICS

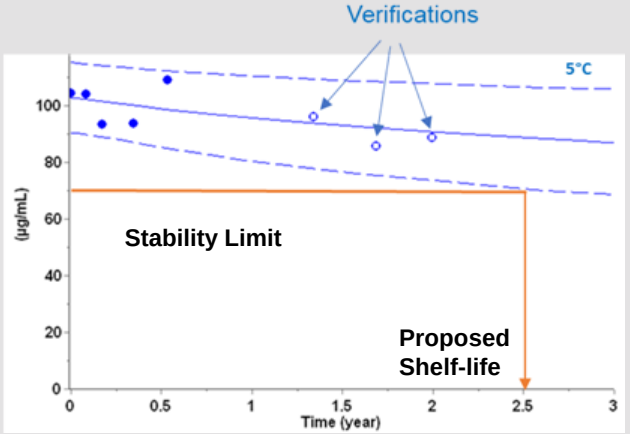
An extrapolation approach

Verifiable:

- across accelerated temperatures
- Supports temperature excursions
- Ongoing studies

Antigen adsorbed to aluminium salt adjuvant:





- **Model chosen using 20 data points to 6m at four temperatures**
- **Ongoing verification to 2 years data had good fit to prediction**

Clenet et al., J Pharm Sci., 103:3055-3064, 2014

$$\frac{d\alpha}{dt} = \exp(29.4)\exp\left(-\frac{113.6E3}{RT}\right)(1-\alpha)^{5.4}$$

Empirical kinetic analysis is an alternative approach that can be verified and does not depend on prior knowledge

SCIENCE & RISK-BASED STABILITY MODELLING

Recent Developments

- **Bayesian Statistics**
  - **Incorporating prior knowledge into a data set**

- **Use of Artificial Intelligence**
  - **Interpreting and analysing prior knowledge**
  - **What differences across molecules matter for Stability?**

BAYESIAN STATISTICS

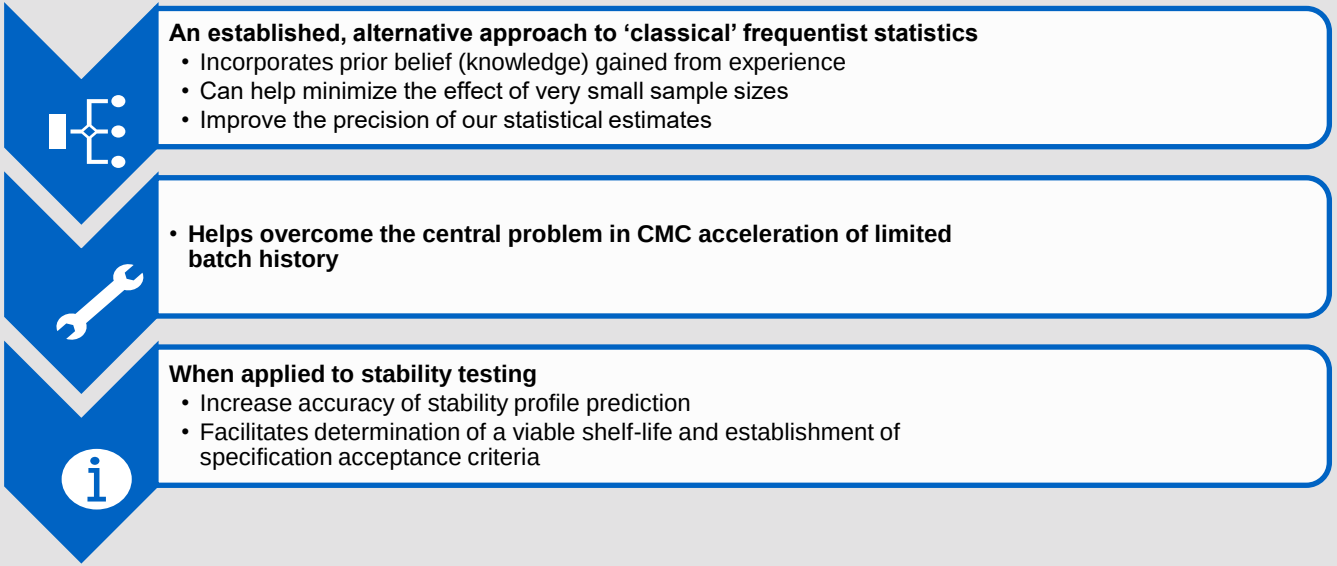
Bayesian statistics is ideally suited for the application of prior knowledge in stability modelling

- **Bayesian statistics is a theory in the field of statistics based on the Bayesian interpretation of probability where probability expresses a degree of belief in an event. The degree of belief may be based on prior knowledge about the event, such as the results of previous experiments.**
- **Bayesian statistical methods use Bayes' theorem to compute and update probabilities after obtaining new data. Bayes' theorem describes the conditional probability of an event based on actual data as well as prior information or beliefs about the event or conditions related to the event**

Thomas Bayes 1702 - 1761

A STATISTICAL METHOD DESIGNED FOR PRIOR KNOWLEDGE

Bayesian Statistics



Bayesian Statistics is an Established Method – the Challenge Focuses on 'Justifying the Prior'

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CASE STUDY:
DRUG SUBSTANCE SE-HPLC HMW SPECIES

mAb0 Original Dataset

8 Drug substance lots:
- 2 supporting (12/60 M)
- 3 primary (48/36/24 M)
- 3 validation (18 M)

-30˚C Storage
48 M expiry

mAb0 Reduced Case Study Dataset

7 Drug substance lots
- 1 supporting (24 M)
- 3 primary (24/12/6 M)
- 3 validation (6 M)

Prior Information Datasets

4 mAbs (2 IgG1s, 2 IgG2s)
- mAb1 (11 lots)
- mAb2 (8 lots)
- mAb3 (10 lots)
- mAb4 (11 lots)

All products stored at -30˚C

Note on concentration: mAb1< mAb0< mAbs 2/3/4

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BAYESIAN STATISTICS VS STANDARD (FREQUENTIST) APPROACH

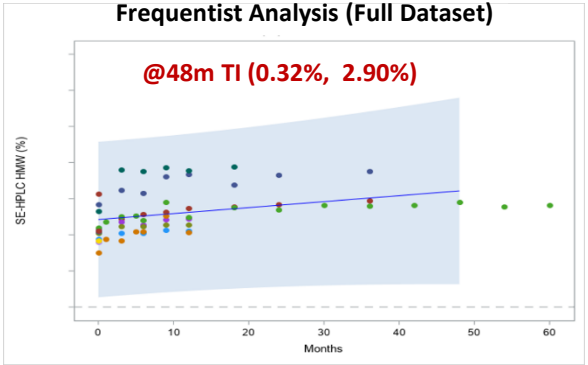
'Pressure test' of Bayesian statistics (mAb drug substance, SE-HPLC HMW species (dimer))

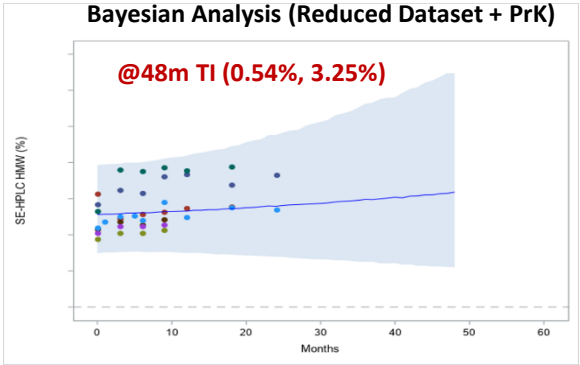
Stability data set, from a recent MA submission (mAb0), was reduced to reflect an accelerated product data set; e.g., reduce number of lots, time

Perform expiry analysis using Bayesian statistics on reduced mAb0 stability data set plus four prior knowledge mAb data sets

Compare mAb0 shelf-life analysis from marketing application using a full mAb0 dataset to that generated using Bayesian stats

Tolerance bounds predicated by Bayesian stats with reduced data set **are similar to those predicted by a Frequentist approach** using full MA data set





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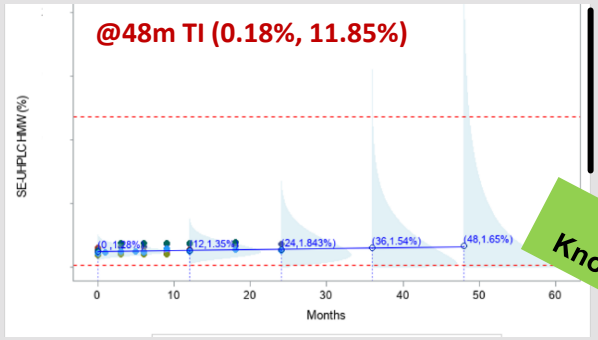
BAYESIAN ANALYSIS WITH AND WITHOUT PRIOR KNOWLEDGE (SE-HPLC HMW)

- Adding prior knowledge to small data sets greatly improves the Bayesian prediction of attribute levels over time
- Similar results were observed for a second case study performed on drug product CEX-HPLC acidic species

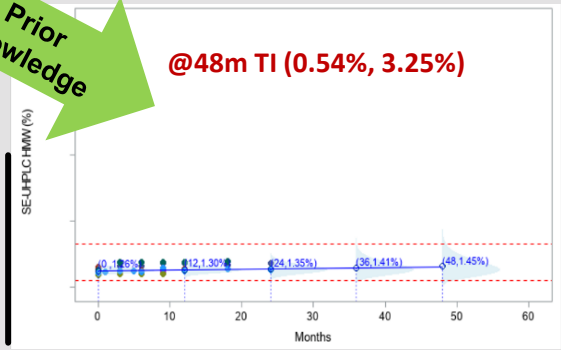


Bayesian Analysis (Reduced Data Set)

No prior knowledge

n = 7 lots

Prior Knowledge



Bayesian Analysis (Reduced Data Set)

+ prior knowledge:

$n = 7 + (1_{11m} + 1_{8m} + 1_{10m} + 1_{11m})$ lots

Bayesian Analysis of Prior Knowledge Significantly Decreases the Uncertainty of a Dataset

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REFERENCE STABILITY DATA SET AND INVESTIGATED PRODUCT NEED TO MEET CRITERIA TO APPLY THE MODEL

- **To demonstrate transferable Prior Knowledge, the molecules selected for the Reference Data Set need to meet Predetermined Criteria**
- **Differences may be justified based on a risk-based evaluation of impact to the stability profile**
  - prior knowledge formulation development may show an acceptable range for excipient concentration
- **The Justification of Transferable Prior Knowledge may be summarised in Tabular form for regulatory review and form part of the overall risk assessment for the approach**

However – what differences between products are impactful to the stability profile?

- Modality
- Manufacture
- Test methods
- Formulation
- Container closure
- Storage conditions
- Stability data available

Meeting Criteria is Greatly Assisted by Platform Product Development

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ARTIFICIAL INTELLIGENCE MODEL TO PREDICT LONG-TERM STABILITY OF %HMW FOR mAbs

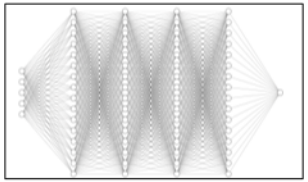
Deep Learning Model

Prototype Inputs

- Molecule Type IgG
- Concentration
- Attribute x
- Attribute y
- %HMW at 5°C @ 0 month
- %HMW at **5°C** @ a, b, c months
- %HMW at **25°**C @ d, e, f months

AI model Training:
7 IgG molecules

Model cross-validation:
'Leave-one-mAb-out'



Input → Prediction

Tool being developed to predict e.g. %HMW at 5°C, 24 months

Test: IgG xxx

INPUT

HMW % (5°C, 0-Months): 1

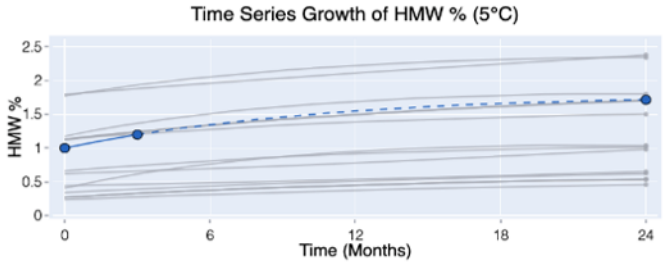
HMW % (5°C, 3-Months): 1.2

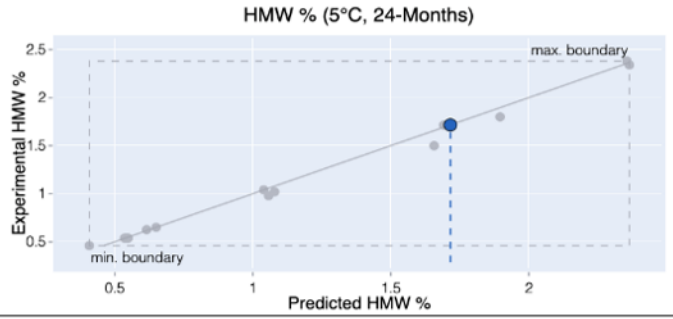
HMW % (25°C, 3-Months): 1.5

Molecule Type

Concentration

Attribute x





OUTPUT

HMW % (5°C, 24-Months): 1.716

R-Squared: 0.993

MAE: 6.28E-02

MSE: 7.32E-03

Accurate Predictions are Obtained from the Deep Learning Model and have the Potential to Identify Differences in Prior Knowledge that 'Matter'

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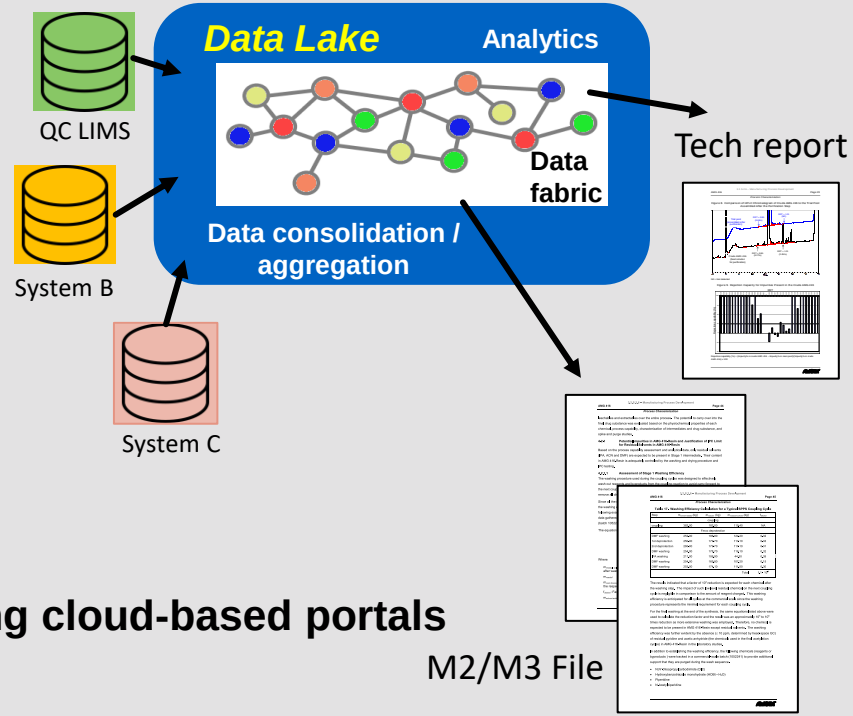
MANAGING STABILITY DATA FOR STREAMLINED, TRANSPARENT SUBMISSION AND ANALYSES.

- **Electronic Data Lakes (EDL)**
- **Structured Content**
  - **e.g. Stability, Specifications, Batch Data**
- **Submission Authoring**
  - **Piloting Stability, Specifications, Batch Data**
- **Analytics**
  - **real-time, on-going monitoring**
  - **Link to QMS, decision-making**
- **Real-time data submission to agencies using cloud-based portals**



Refs: https://www.sciencedirect.com/science/article/pii/S0022354920300575?via%3Dihub

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POST-APPROVAL RISK MANAGEMENT

- **Both product and model reference data set would evolve as new data are obtained**
  - Ongoing product stability data to verify fit to the model
  - Adding new prior knowledge to the reference data set

- **Risk Assessment (ICH Q9; e.g. FMEA*)**
  - What are:
    - the points of failure (hazards),
    - their impact (severity)
    - likelihood of detection ?

The Stability Model would be Continuously Updated and Verified as Data Accrues

* *Failure Mode Effects Analysis*

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JUST A FEW REASONS WHY A REVISION OF THE ICH GUIDELINES IS NEEDED FOR SRBPS – ANTICIPATED TO START 2022

ICH Guidelines split across a Q1 series and Q5C for biologics

- How the various Q1 guidelines are applied to biologics is unclear

Q1A allows for alternative approaches when scientifically justified

- The proposed prior knowledge approach uses stability data from 'like-molecules' that is justified as 'transferable' through criteria but the application of Q1A to biologics is not clear
- Yet Q5C for biologics typically results in a narrow interpretation of "based on long-term, real-time, real condition stability studies" by agencies

Using Prior Knowledge is not the same as conventional extrapolation

- Q1E excludes extrapolation for refrigerated products showing decay at accelerated temperatures but the application of Q1E to biologics is unclear since other principles can be valid
- The product data are 'transposed' onto the prior knowledge derived attribute stability profile not extrapolated

Prior Knowledge provides a data-driven understanding of Stability

- The ICH Stability guidelines predate Quality by Design and Risk Management ICH Guidelines

The Science and our Understanding of Biologics has Greatly Advanced Since the ICH Stability Guidelines were Last Revised

EMA DRAFT CMC TOOLBOX - STABILITY SECTION

- Includes the use of predictive stability models derived from prior knowledge
- A means to defer long-term stability data to post-approval with ongoing verification
- The statistics used should be justified and can accommodate Bayesian statistics
- New developments need to be included e.g. Kinetic Modelling, use of AI modelling….

An outcome of the 2018 EMA/FDA workshop

A big step in the right direction but more dialogue is needed …

industry Advocates for an Extension of Scope of the EMA PRIME Toolbox to Products of 'Unmet Medical Need'

ACKNOWLEDGEMENTS

JOSÉ RAMÍREZ,
FUAT DOYMAZ
NIC ANGELL
BARBARA RELLAHAN,
SEYMA BAYRAK
SALEH ALKHALIFA
GERD KLEEMANN

SAGAR WADHWA
CAMILLA SANTOS
JETTE WYPYCH
JILL BEIERLE
MIKE ABERNATHY
NINA CAUCHON
GINO GRAMPP

DIDIER CLENET
DRAGO KUZMAN
MEGAN MCMAHON
LORI MCCAIG

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