Using Stability Prior Knowledge From ‘Like-molecules’ to Determine Shelf-life

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ANDREW LENNARD; AMGEN LTD, RACMC EXTERNAL ENGAGEMENT & ADVOCACY

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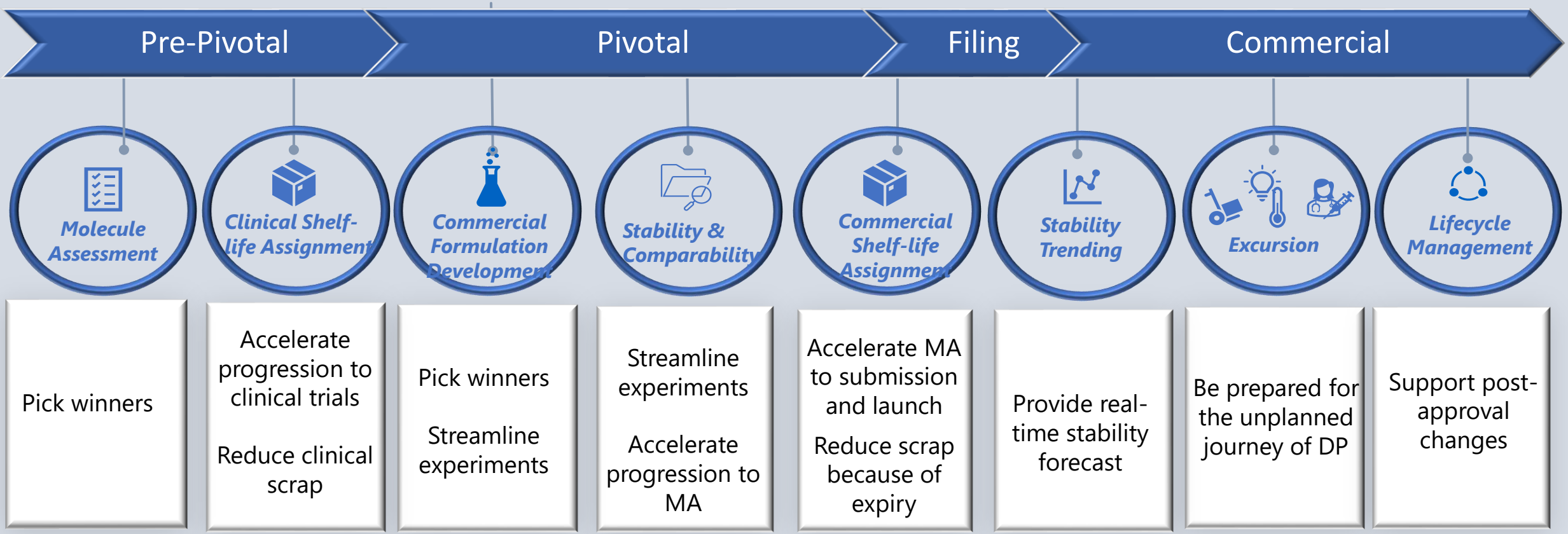
Outline

- **Introduction**
  - Why we need predictive Stability Modelling?
- **Types of Stability Model under Development**
  - Pooling of 'like-molecules'
  - Bayesian Analysis
  - Artificial Intelligence (AI) Machine Learning Models
- **Comparison of Modelling Methodologies**
- **Regulatory Landscape & ICH Stability Guideline Revision**

Predictive Stability Capability can have a Favorable Impact on the Entire Product Lifecycle



Predictive Stability Modelling using Prior Knowledge

- Focus modelling on the Stability-indicating attributes that limit shelf-life
- Accurate, empirical modelling methodologies to predict stability profile – shelf-life
  - Kinetic analysis, e.g. Arrhenius, Advanced Kinetic Modelling
  - Prior knowledge methodologies:
    - **Pooling of prior knowledge from 'like-molecules'**
    - **Stability Models using Bayesian Statistics**
      - Weighting of prior knowledge using the Power Prior
    - **Artificial Intelligence Machine Learning prediction models using prior knowledge**
    - Clustering to quantify similarity of prior knowledge to inform the Bayesian Power Prior

Selecting Stability Prior Knowledge From ‘Like-molecules’

- What is a ‘like-molecule’?
- Possible criteria to consider
- Which criteria are important for the stability profile?
- Which criteria are relevant for the model being used?

Criteria Considerations

Criteria for Prior Knowledge Molecules Should Focus on Molecule Characteristics that Impact the Attribute Stability Profile

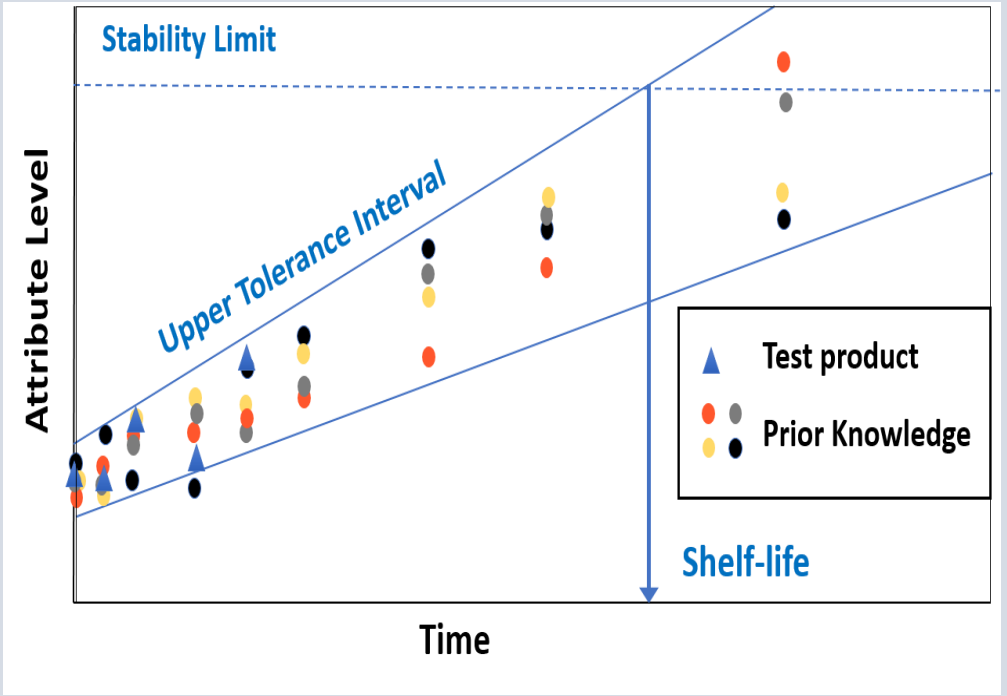
Pooling of ‘Like-molecules’: A Quality by Design Approach

Pooling of ‘like-molecule’ stability data for shelf-life setting extends from:

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

The Modelling of Stability Prior Knowledge approach:

- Reference data sets for ‘like molecules’ CQAs
- Data may be normalised for y-intercept
  - It is the trend (slope) that is important
- Non-linear kinetics may be empirically transformed
- 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**

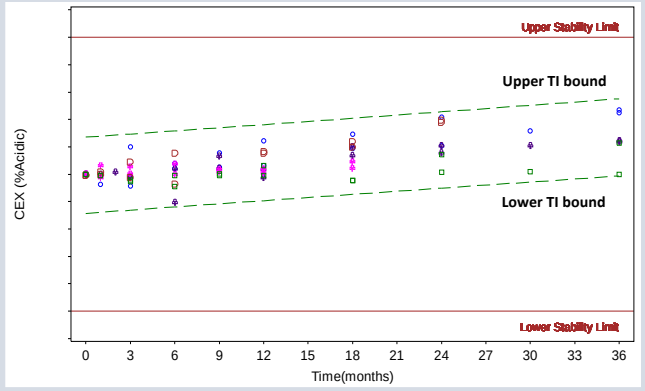


When a new product meets pre-determined criteria, the modelled shelf-life can be applied

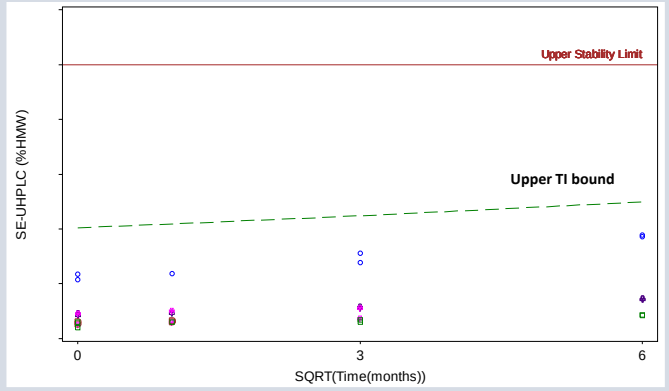
Prior knowledge provides a scientific basis to extending shelf-life beyond product-specific, long-term stability data

Liquid Drug Product Attributes Trend Within Limits

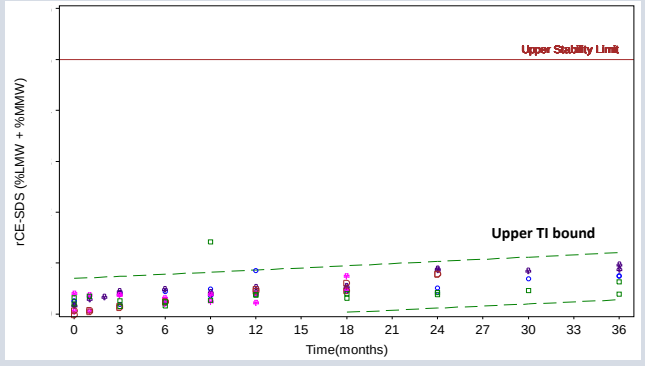
CEX-HPLC acidic peaks



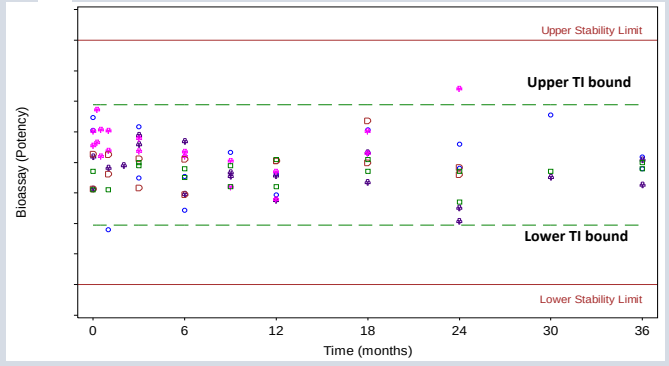
HMW species (dimer)



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

Prior Knowledge and Bayesian Statistics

Bayesian Statistics

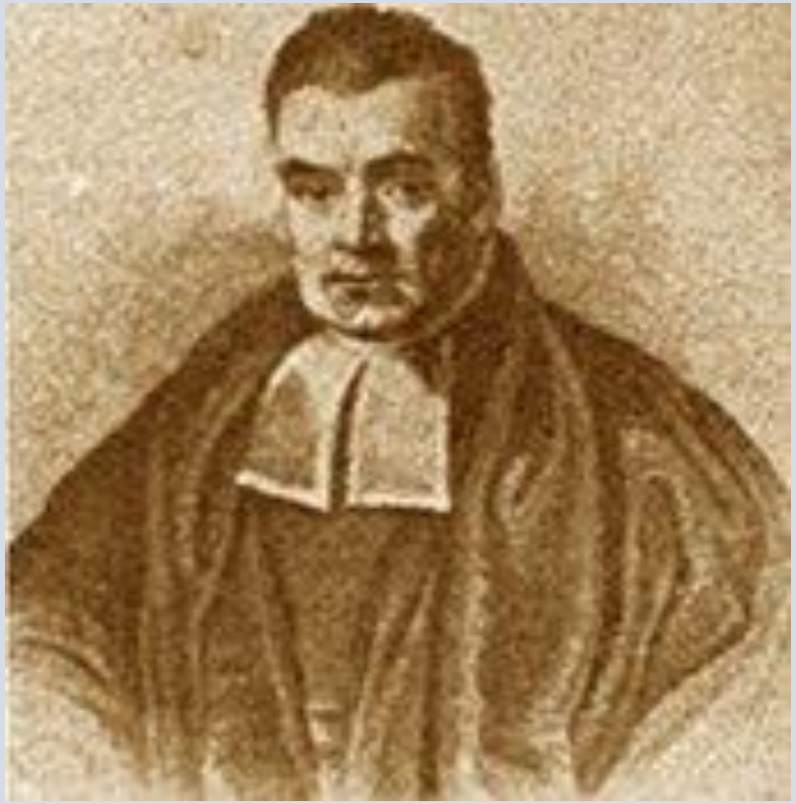
An alternative approach to 'conventional' frequentist statistics:

- Incorporates prior belief (knowledge) gained from experience
- Can help minimize the effect of very small sample sizes
- Improve the precision of our statistical estimates

- **Helps overcome the central problem in CMC acceleration of limited batch history**

When applied to stability testing:

- Increase accuracy of stability profile prediction
- Facilitates determination of a viable shelf-life and establishment of specification acceptance criteria

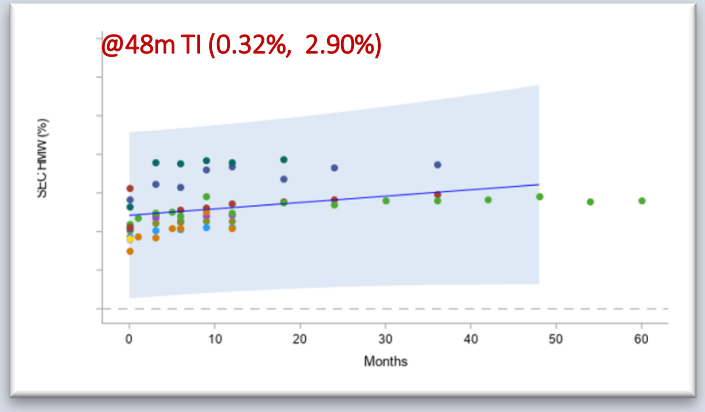


Thomas Bayes 1702 - 1761

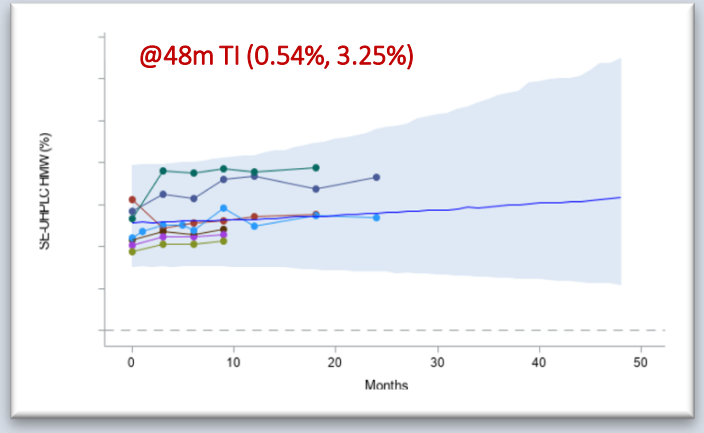
Initial Bayesian Model for %HMW Species: Titrating the Power Prior

- **7 lots of 'test' product**
  - Open circles
  - Reduced data set
- **4 Prior Knowledge products** (8 to 11 lots each)
- **Comparison of Frequentist and Bayesian methods**
  - Each prior knowledge molecule had the same Power Prior value (0.5)
  - *Includes a dispersion effect*

Frequentist Analysis (Full Dataset)



Bayesian Analysis (Reduced Dataset)

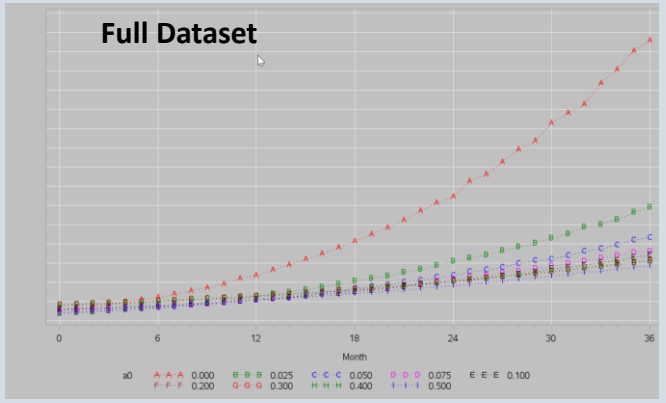


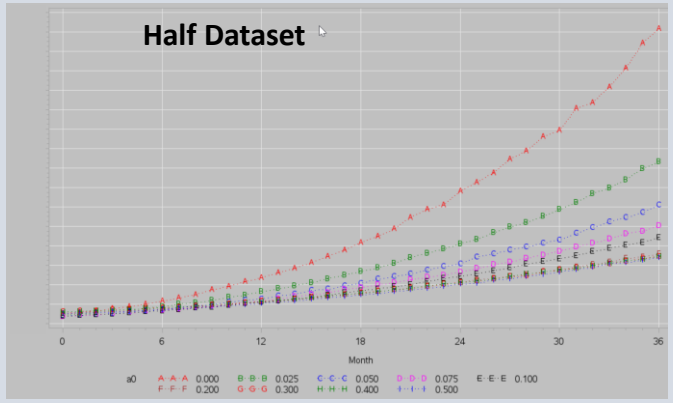
Adding prior knowledge to a reduced dataset can approach the full product dataset

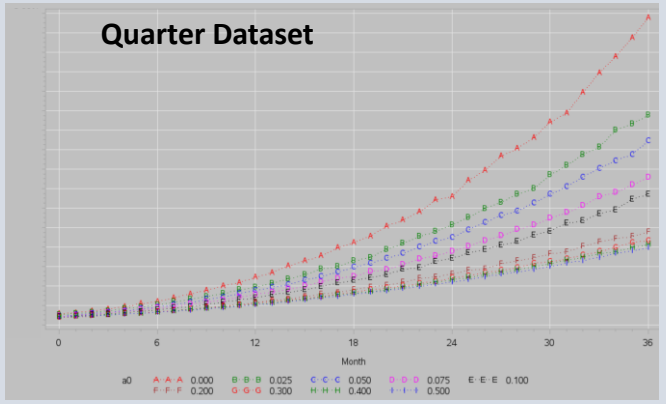
Titrating Prior Knowledge & Varying the Power Prior

Upper Tolerance Intervals (UTL) from the model simulations:

- a = 0, 0.025, 0.05, 0.075, 0.1, 0.2, 0.3, 0.4, 0.5
- Full, 0.5 and 0.25 prior knowledge data
  - No dispersion effect
  - Beta distribution
  - Linear regression
  - Monte Carlo analysis





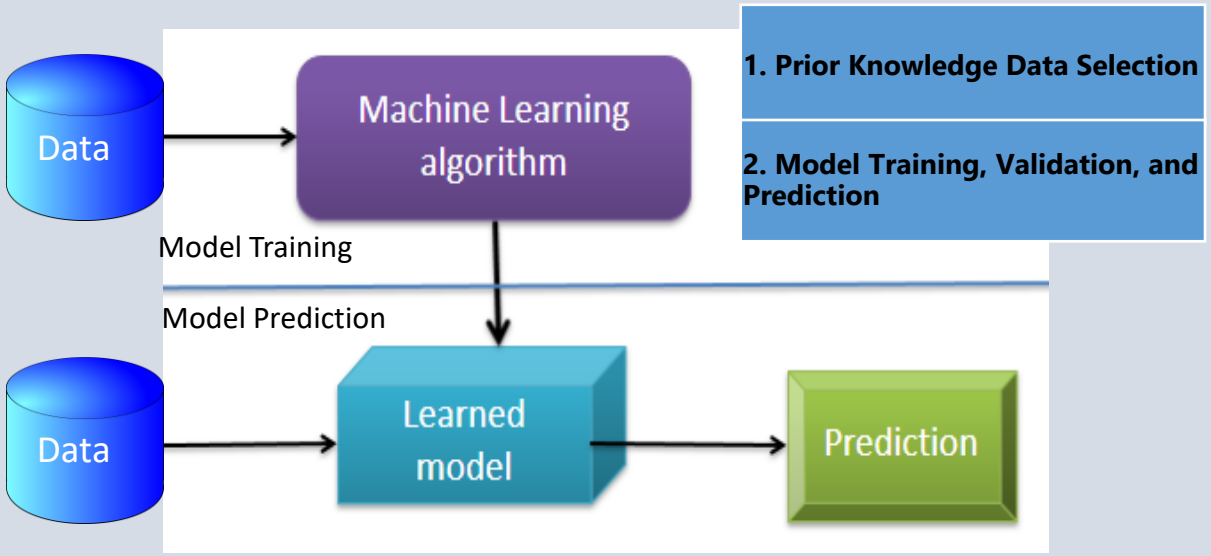


Amount of Prior Knowledge	Upper TI prediction @ 36m when a = 0.5
Full dataset	1.2
0.5 dataset	1.3
0.25 dataset	1.4

- **Tolerance intervals for test product decreases with increasing weighting for the prior knowledge**
- **How much prior knowledge is optimal?**

The Model can Empirically Balance the Amount of Prior Knowledge for Accurate Predictions that Approach Known Molecule Datasets

Why Develop an Artificial Intelligence, Machine Learning-driven approach?



AI can help us remove traditional constraints that restrict our ability to accelerate our timelines

- Ability to learn complex relations, patterns from data
- Predict future outcome with high accuracy

Clean, contextual, integrated data is required to train the model

Stability data across molecules as prior knowledge considers multiple variables / differences.
By evaluating the significance of each variable on the stability profile, the number of dimensions can be reduced to those of high impact.

AI is a critical capability of digital innovation and can provide answers to critical business questions

Data Selection for the Machine Learning Stability Model

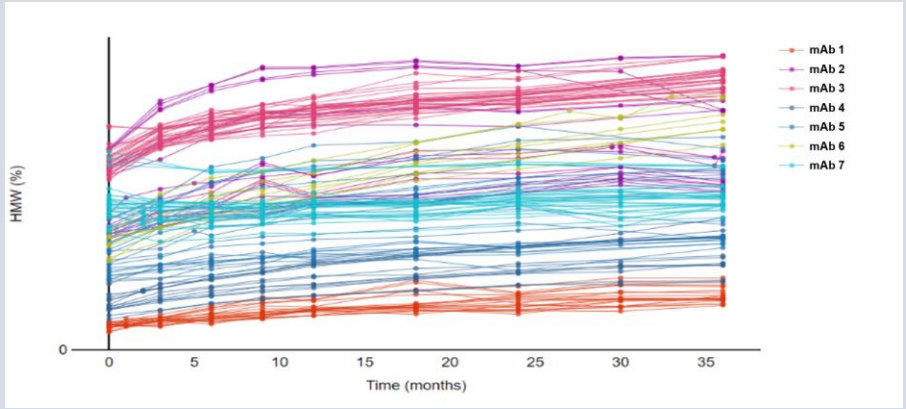
Data extraction

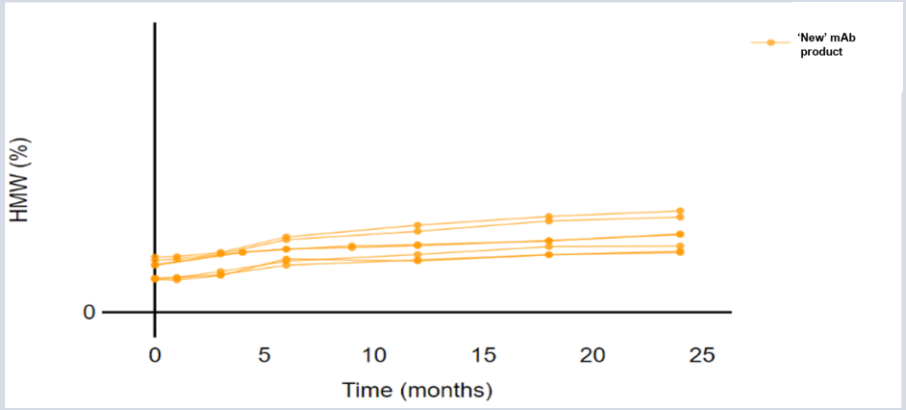
- 7 Prior Knowledge Products
- 1 ‘Hold-out’ product
- 1 ‘New’ molecule

Filtered data

Product type	• Liquid
Temperature	• 5 °C
Measured attributes	• %HMW
Method	• SE-HPLC

Not a comprehensive list





Prior Knowledge Molecules have Visually Similar Rates of %HMW Species Formation

AI Model Training

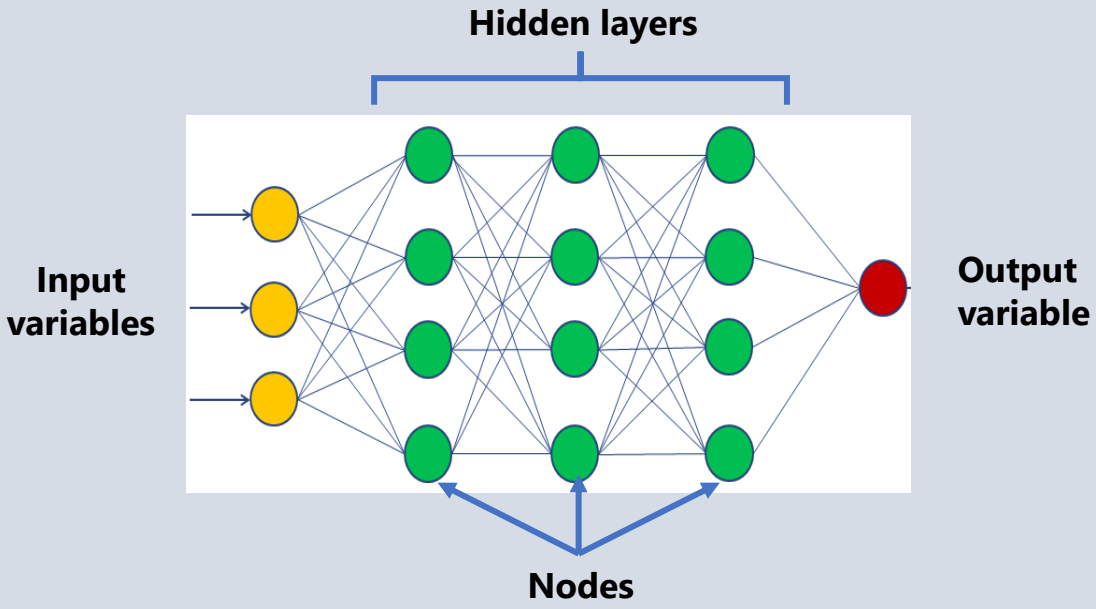
Various algorithms were initially tested as prototype models for prediction accuracy using a test product.

- Selected a neural network algorithm

Structure of a neural network model is defined by hyperparameters:

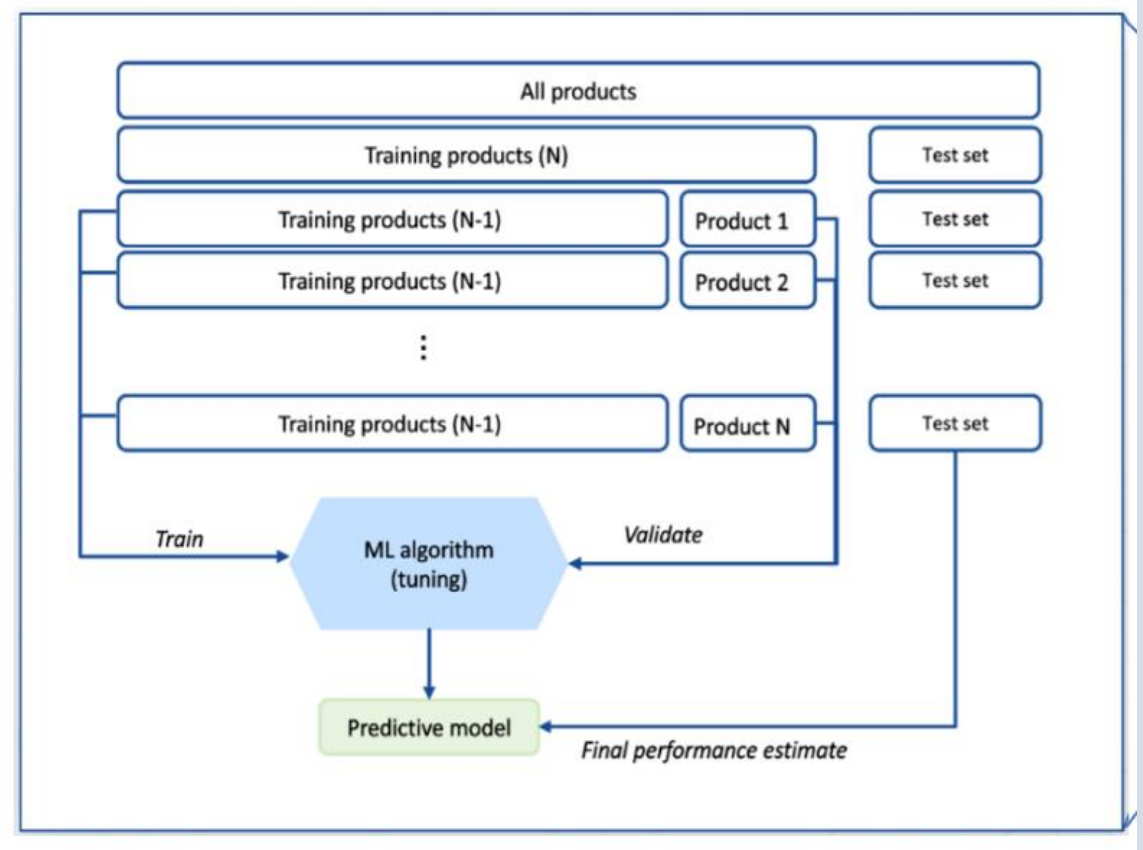
- Hidden layers size
- Number of hidden layers
- Batch size
- Loss function
- Early stopping criteria

Values determined based on iterative training



AI Model Training, Validation and Verification

- A ‘Leave One Product Out’ process was used to validate the machine learning model.
  - A form of K-fold cross-validation
  - Iteratively optimises combinations of hyperparameters
  - Each iteration validates inclusion of each product data set.
  - Hyperparameters are weighted to empirically fit known data from the ‘hold-out ‘ set – to 95% CI
  - A ‘hold-out’ product was not included in the model training data set, for use in testing the final model accuracy.
  - Model validated for accuracy of prediction from the ‘hold-out’ molecule
- Future refinement could be inclusion of higher temp stability data.
- **The model is verified as stability data for the new product are obtained**

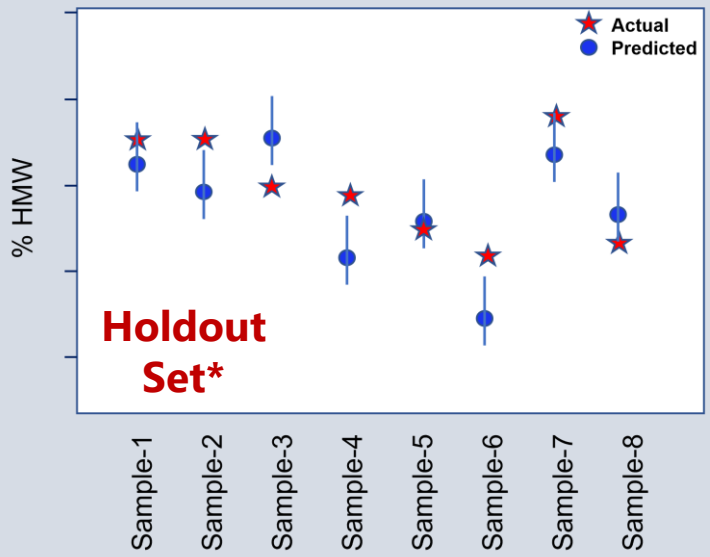


Training by ‘Leave One Out’ Avoids Overfitting of the Model to any Particular Product

Derived from Biophorum “Industry feedback on DMKA questions to critical GxP AI/ML applications”, 2021

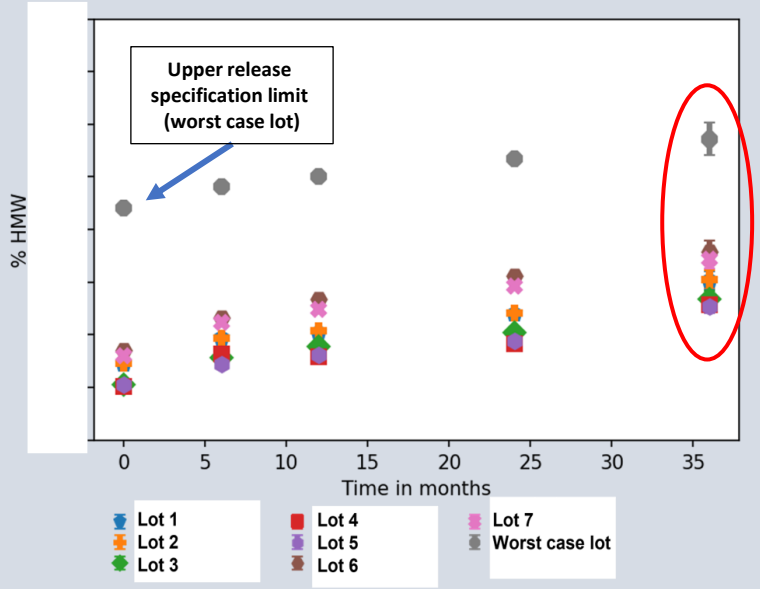
Machine Learning Model Performance Results

Model Accuracy from Known Data



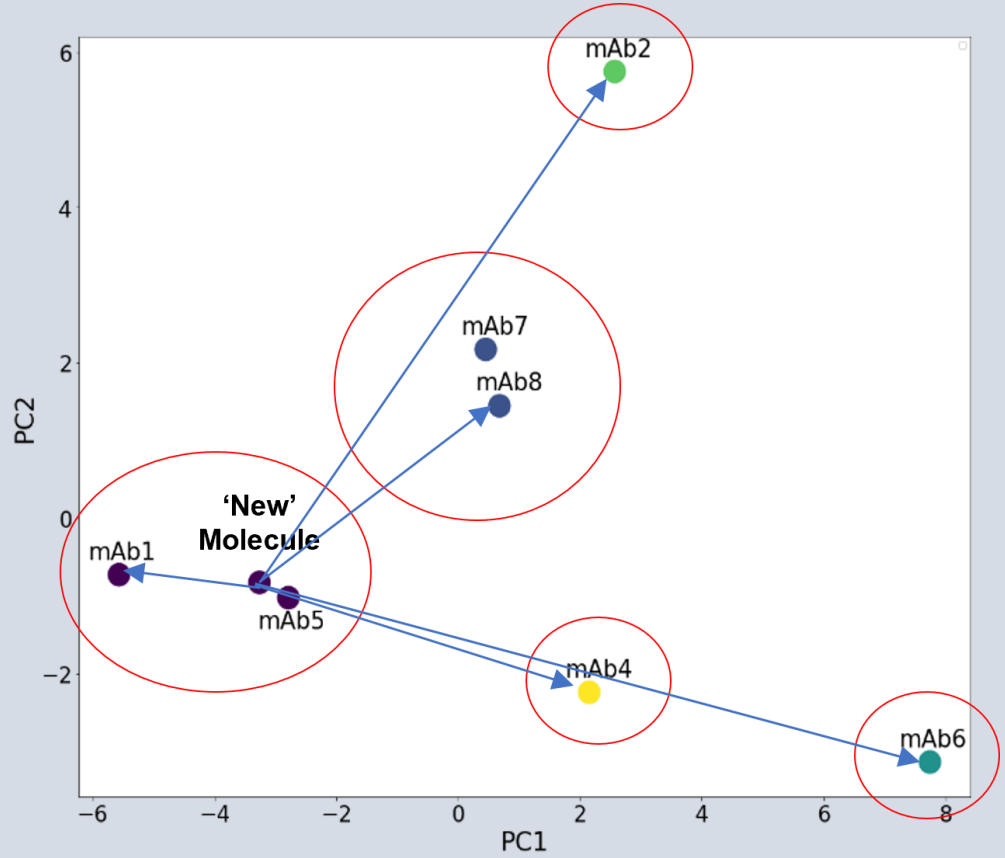
* *Illustrative data shown*

Prediction at 36 months



The Prediction can Support a Stability Specification and/or Product Shelf-life

Mean Shift Clustering to Measure Similarity of Molecules



The prior knowledge data were used for similarity modelling by Mean-shift Clustering to measure the degree of 'likeness' between the prior knowledge molecules and the 'New' Molecule

- Molecule features (variables) summed by 'Principal Component Analysis'.
- Some clustering of the prior knowledge molecules is evident
- Prior knowledge molecules are more or less distant from the 'New' Molecule = degree of similarity

Clustering Analyses Could Provide Objective Values for the Bayesian Power Prior

Comparison of Predictive Stability Modelling Tools using Prior Knowledge

Methodology	Extrapolation	Similarity	Validation	Verification
Pooling Data	No (transposition)	Criteria	e.g. ANCOVA	Yes
Bayesian	Yes	Power Prior	TBD	Yes
Machine Learning	Yes	Algorithm	Hold out product	Yes

Regulatory Landscape for Predictive Stability Modelling

EMA CMC Toolbox for PRIME and certain products meeting an 'unmet' medical need


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 April 2022
EMA/CHMP/BWP/QWP/IWG/694114/2019
Committee for Human Medicinal Products (CHMP)

Toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME and certain marketing authorisation applications targeting an unmet medical need

ICH Stability Guidance:

- **Update to current science and to align with more recent QbD and risk management ICH guidelines**
  - Recognition of alternative sources of stability knowledge to set shelf-life beyond traditional, long-term stability data
- **Science & Risk-based approaches to accelerate CMC are not described,** e.g. modelling, prior knowledge
- **Guidance considered as too prescriptive and interpretations too narrow**
- **Confusion on elements of the Q1 series that apply to biologicals**
- **Guidance for newer therapeutic modalities is lacking**
- **Identified gaps include:**
  - In-use stability
  - Short-term end user stability
  - Integral drug-device combination (iDDC) products
  - Integrated Stability Profiling – 'end-to-end' stability
- **ICH Q1/5C IWG formed , targeting Concept paper by end October**

Revision of ICH Stability Guidelines is Hoped to 'Open the Door' to Predictive Stability Modelling, Generally.

Acknowledgement thank you

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Regulatory

Developing Predictive Stability Models Requires Diverse Expertise

ありがとうございました

Arigatōgozaimashita