EMA /US FDA Workshop on support to quality development in early access approaches

8a. Stability: *Application of Predictive Stability Models to Extrapolate Shelf-life*

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Problem Statement and Up-front Requirements

- **Stability data to obtain a viable commercial shelf-life (≥24m) remains the rate-limiting factor in accelerated development programs due to process changes**
  - The use of predictive stability models to assign a viable shelf-life at MA/BLA submission for both DS and DP of any pharmaceutical form is proposed
- **Elements of ICH and EMA guidance require re-interpretation and adoption of current concepts from small molecule guidance for biologics, e.g. extrapolation of data**
- **Additional risk acceptance is needed by regulatory bodies**
  - to agree to extrapolating appropriate stability models derived from prior knowledge
  - To accept extension of product-specific stability data based on the models to assign shelf-life
  - To accept commitments from the MAH relating to post-approval stability data and reporting of new trends and other unexpected events.
- **MAH needs <u>ideally</u> to lock-down earlier the formulation, manufacturing process, SKUs, devices, analytical validation**
  - But Things Happen!
  - If needed, major process changes, commercial site and scale can be managed by PACMP

Proposed Fit of Predictive Stability Modelling with ICH Q5C

Stability Testing of Biotechnological/Biological products – a Re-interpretation

- Primary data to support a requested storage period should always be based on long-term, **real-time,** real-condition stability studies (*ICHQ5C*)
  - The model is based on long-term, **real-time,** real-condition data and justified for extrapolation to BTD/PRIME DS/DP

- Data from at least **3 representative batches** (manufacture, quality and storage); can be pilot scale with commitment
  - The **model data** uses multiple batches **considered to be representative**, in the context of stability-indicating attributes, to the BTD/PRIME product
  - At least **3 batches** of the BTD/PRIME product would be placed on stability prior to submission, during review, or post-approval with **commitments** to report trends that exceed limits defined by the model. Any OOS stability data would trigger notification to the agency with result of investigations and actions etc

- **Containers** for stability material should be representative – **same material and type** of system
  - **Containers difference may be justified as representative** through analytical comparability and primary container knowledge (prior knowledge on compatibility, stability, leachates).

- A **minimum of 6 months data** at submission when storage periods greater than 6 months requested
  - A statistically **valid minimum of data points should be provided for the stability model input products** that should not need to extend to the BTD/PRIME product given the above commitments

- **Stability specifications should be 'clinically qualified'.**
  - The stability models can be used to predict attribute levels at the proposed shelf-life and used to determine a **stability specification**, when appropriate. **Commitments** to re-evaluate post-approval. See prior workshop topic.

Generation of a Modality-specific Stability Model

- **Criteria for selection of suitable prior knowledge products for DS and DP**
  - **Same product modality with a statistically valid number of real-time data**
    - If justified, related modality data may be combined e.g. IgG1 and IgG2 data
  - **Qualitatively similar formulation**
    - Historical formulation development stability studies
  - **Similar strength**
    - No significant viscosity, HMW species, subvisible/visible particles etc impact, as justified by Sponsor
  - **Same controlled storage conditions in representative container/closure**
    - Frozen (-20C to -70C); Liquid (2C to 8C) etc
  - **Attributes monitored using the same method type**
    - Detail may vary but any offsets understood.
- **Data handling**
  - **Analysis of trends** (e.g. linear regression or, when exponential growth, asymptote and visual; with e.g. 95% TI)
  - **Identify molecules that do not trend in the same way for a given product quality attribute**
    - Assess applicability of data from outlier molecules per attribute (as justified)
  - **Normalising of data when appropriate to adjust for different time zero attribute levels**
    - It is the trends that are important – so long as data predictions are within proposed specification
  - **Pre-determined criteria for fit of BTD/PRIME data**
  - **Model switching rules**
- **BTD/PRIME would allow advanced agreement with the agency, on the model and its application**

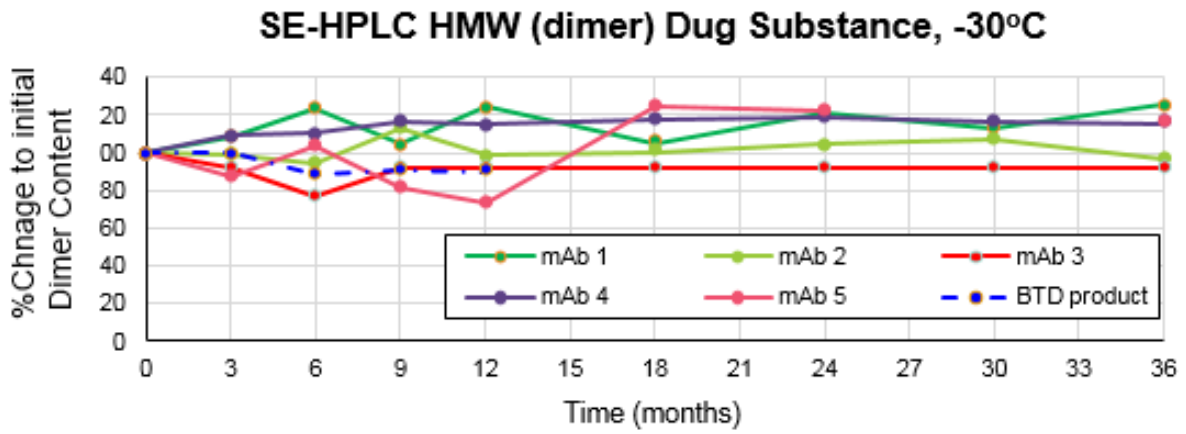
Application of the Stability Model to a Candidate BTD/PRIME/Sakigake Product

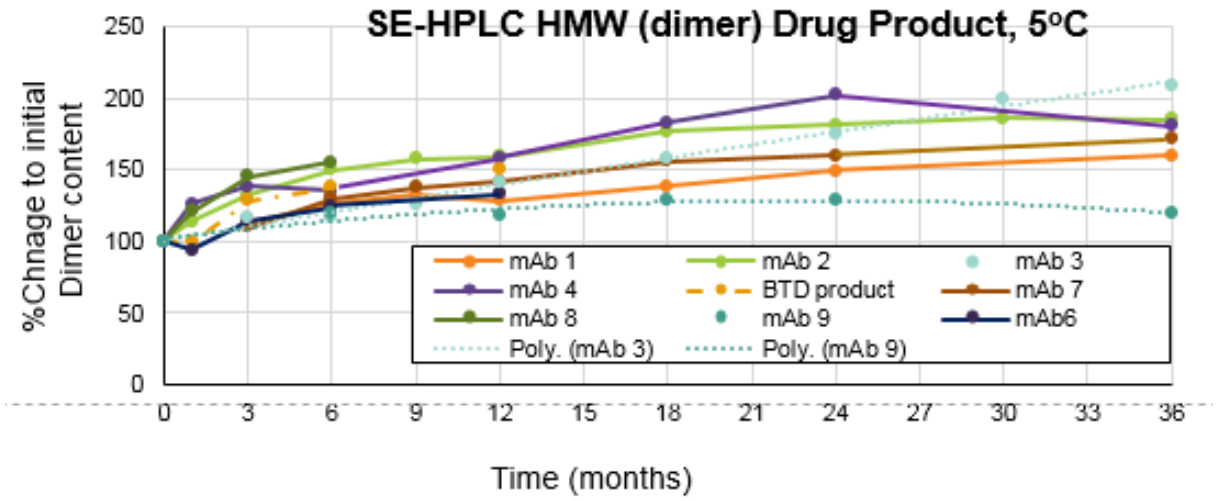
When is the Stability Model suitable for the BTD/PRIME product?

- **Analysis of fit (comparability of stability trends)**
  - **Product real-time data, real-condition**
  - **Statistical evaluation for fit to the stability model, e.g. exponential**
    - Focus on asymptote
  - **Product accelerated condition data**
    - Identifies outlier data from real-time, real-condition testing
    - Can also statistically extrapolate some attribute data to real condition
- **Interpreting the analysis combined with risk-based impact assessment on product safety & efficacy**
- **Evaluation is continuous and extends post-approval to maintain assurance of safety and efficacy**
- **Commitments**
  - **QMS for trends and actions, CAPA, reporting, annual reports (US/CA), reviews of data (per GMP) etc**

Example Stability Data Model 1

IgG mAbs stored -30C (DS) or 5C (DP) in glass vials, at same strength and formulation, analysed using same method.





Frozen drug substance does not change on storage to 36 months.

- Demonstrable for all product quality attributes studied

Accelerated stability data identifies OOT products that are excluded from the applicable model

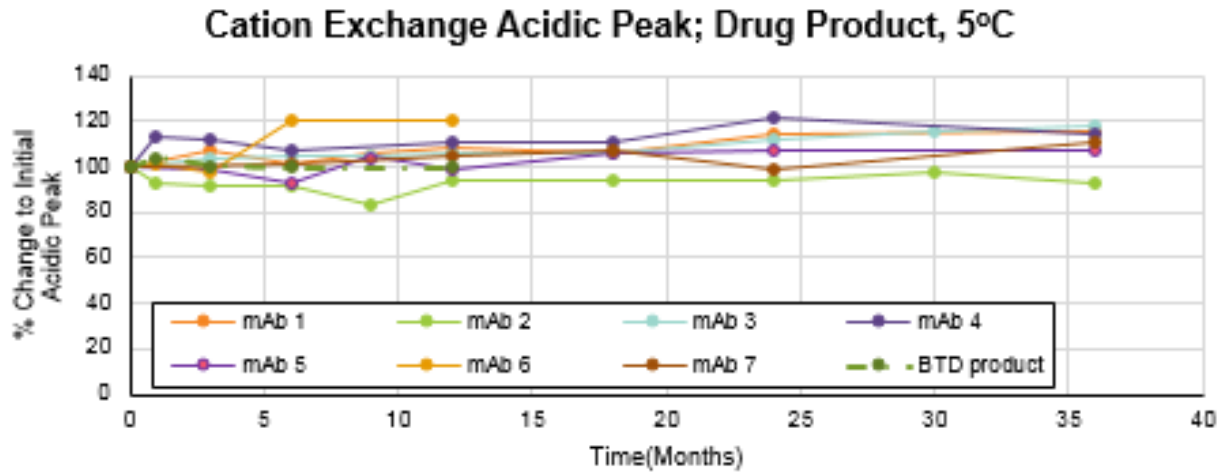
- e.g. dotted lines

Drug product rates of change are visually comparable to 36 months

Stability data support that the BTD product shelf-life can be extrapolated as needed for adequate global supply

Example Stability Data Model 2

IgG mAbs stored 5C (DP) in glass vials, at similar strength and formulation, analysed using same method.



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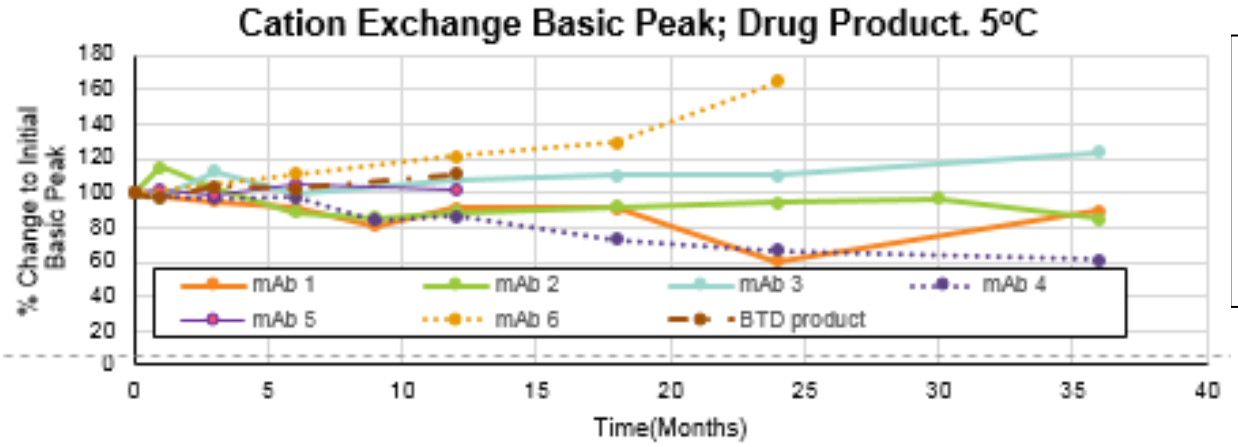

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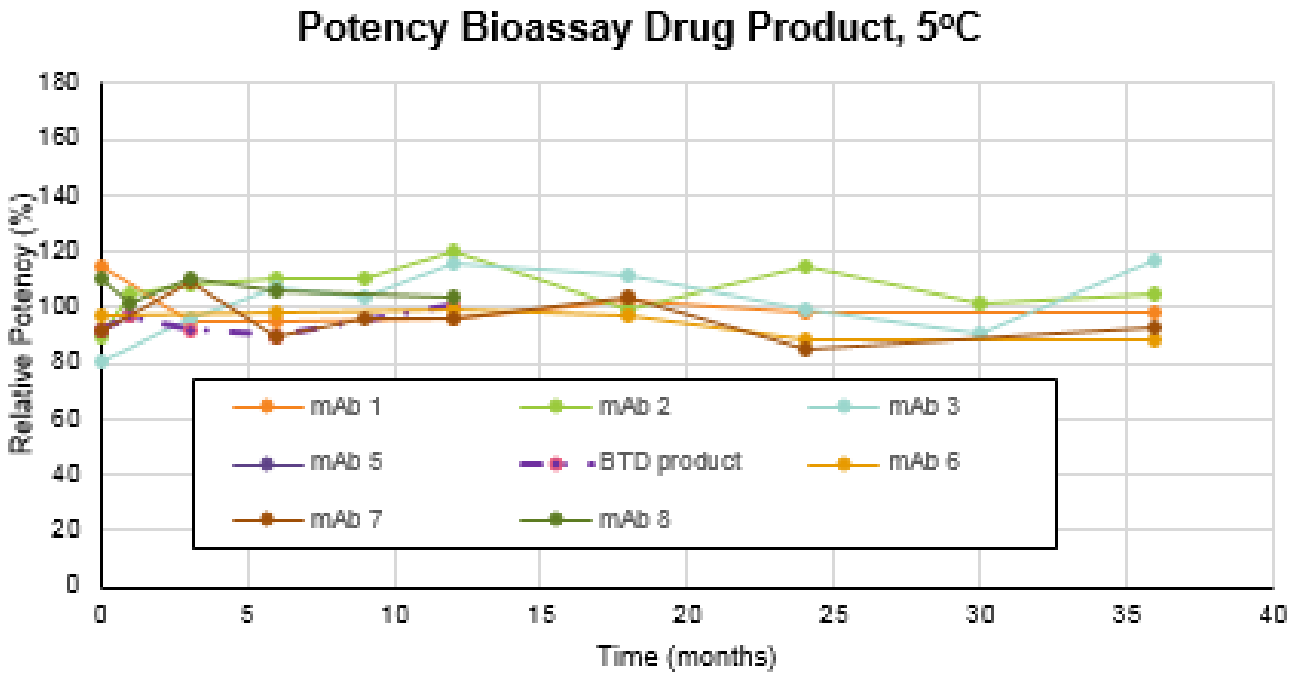

Drug product potency rates of change are visually comparable, within assay variability and no change within 36m

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Approaches when Suitable Prior Knowledge is not Available

In the case of new modalities or for SME developed products, there may not be sufficient transferable prior knowledge to create predictive stability models.

Proposals for extrapolation could be based on additional data, enhanced commitments and accelerated stability data to supplement development knowledge:

- **Where accelerated stability data identifies trends of defined kinetic models**
  - May be possible to extrapolate certain biologic attribute accelerated data back to the recommended storage condition using mathematical models for ‘n’ order kinetics
- **Additional stability timepoints**
  - Supplement ICH described timepoints to enhance detection of any changes given uncertainty
- **Additional Regulatory Commitments**
  - Formalised commitment to provide stability data at agreed timepoints (milestones)
- **Limit Extrapolation to 2-fold product RSC data**

Questions for Discussion

- **When prior knowledge is available, could the agencies allow the use of predictive stability models for monoclonal-type biologics to extrapolate stability and hence shelf-life to a Breakthrough/PRIME/ Sakigake designated product that has less data from less batches?**
  - Can be loosely interpreted as aligned to ICH
  - Criteria are provided to justify the model data its application
  - Example statistical approaches are proposed
  - Post-approval commitments for assurance of fit to model
- **Could absence of prior knowledge be supplemented by accelerated stability modelling, additional timepoints and commitments; given the benefit/risk anticipated for a BTD product, for a more restricted extrapolation?**

THANK YOU!

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