TAKING STABILITY OFF THE CRITICAL PATH OF PRODUCT DEVELOPMENT

ANDREW LENNARD

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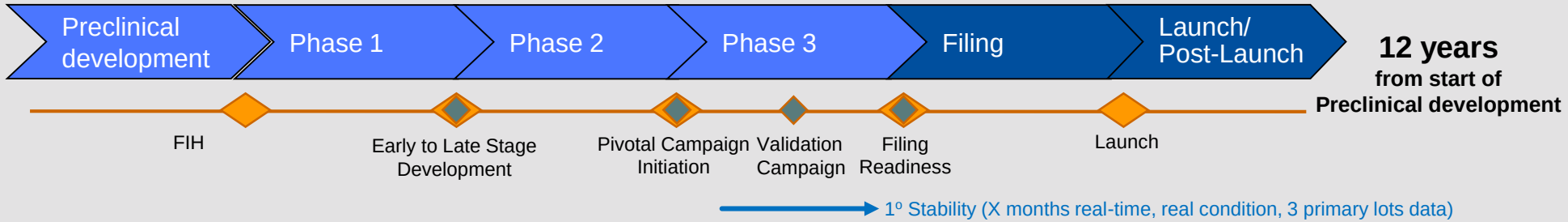
AMGEN® 40 YEARS

STABILITY DATA ARE TYPICALLY RATE LIMITING IN BIOLOGIC PRODUCT DEVELOPMENT



Acceleration of product development	• earlier patient access to new medicines
Commercial shelf-life	• Need 24m shelf-life at launch to use PPQ lots, lead time, remaining shelf-life
Clinical shelf-life	• Clinical product needs a shelf-life suited to the lifespan of the product in the program – EU CTR & labelling

A new approach to shelf-life determination is needed throughout product development

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’ (all stability-indicating CQA data)
- Tolerance intervals (TI) for stability-indicating attributes
- Phase-appropriate specification & internal stability limits
  - Aided by a patient-focused spec approach
- TI intersections with stability limits determine shelf-life
- **When an investigated product meets pre-determine criteria, the modelled shelf-life can be applied**

Shelf-life encompasses totality of knowledge

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

AN ALTERNATIVE APPROACH TO SHELF-LIFE SETTING FOR BIOLOGICS & ICH

Proposed approach is not contrary to Q5C (or Q1A)

- A reinterpretation is needed for “based on long-term, real-time, real condition stability studies”
- “Based on” means a foundation to build on

Q1A allows for alternative approaches when scientifically justified

- The proposed alternative uses stability prior knowledge that is justified as ‘transferable’

Using Prior Knowledge is not the same as conventional extrapolation

- Evaluation of Prior Knowledge is based on the described ICH Q1E Tolerance Interval approach

A current limitation in ICH is on container closure for historical data

- Agencies should accept data supporting differences – impacts available Prior Knowledge
- Comparability, stability, E/L

Many formulations are very stable yet the same restrictions apply

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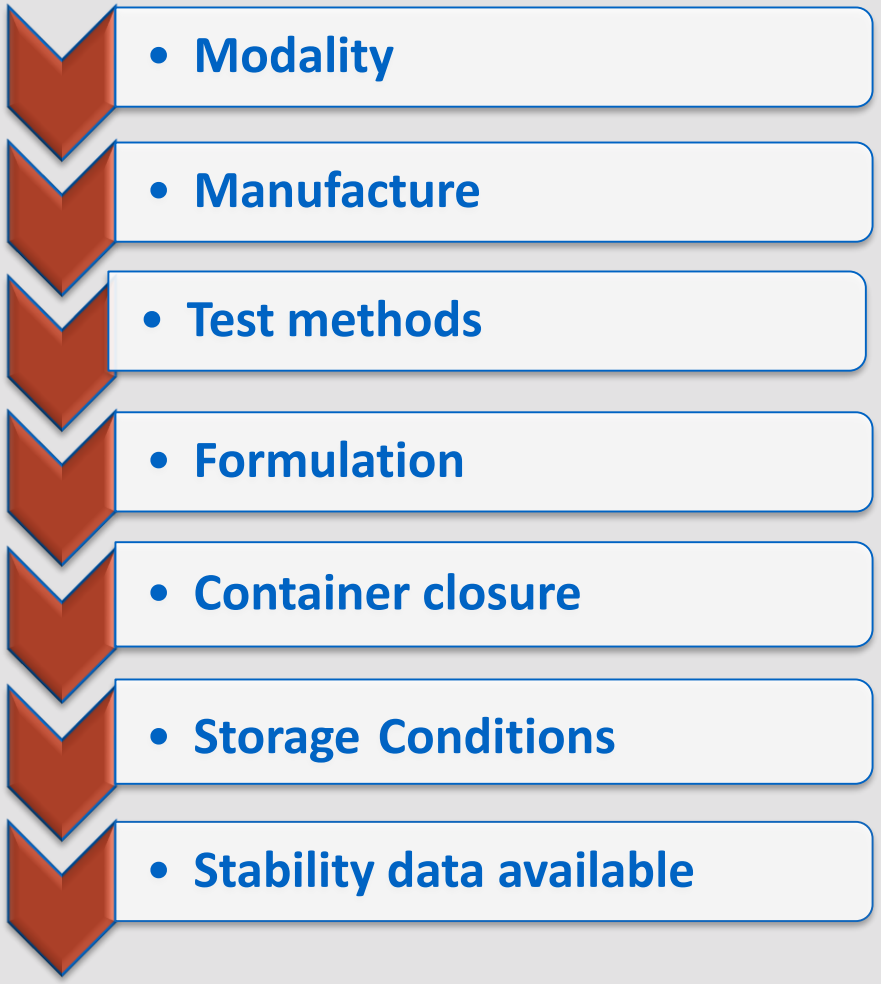
REFERENCE STABILITY DATA SET AND INVESTIGATED PRODUCT NEED TO MEET CRITERIA TO APPLY THE MODEL

- **To demonstrate transferable Prior Knowledge, the molecules selected for the Reference Data Set need to meet Predetermined Criteria.**

- **Likewise, the investigated product needs to meet the same overall criteria with modifications.**
e.g. whereas the reference data should reach the claimed shelf-life, the investigated product would have sufficient data to identify any trend notably different to the reference data

- **Differences may be justified based on a risk-based evaluation of impact to the stability profile.**
e.g. prior knowledge formulation development may show an acceptable range for excipient concentration.



Meeting Criteria is greatly assisted by Platform Product Development

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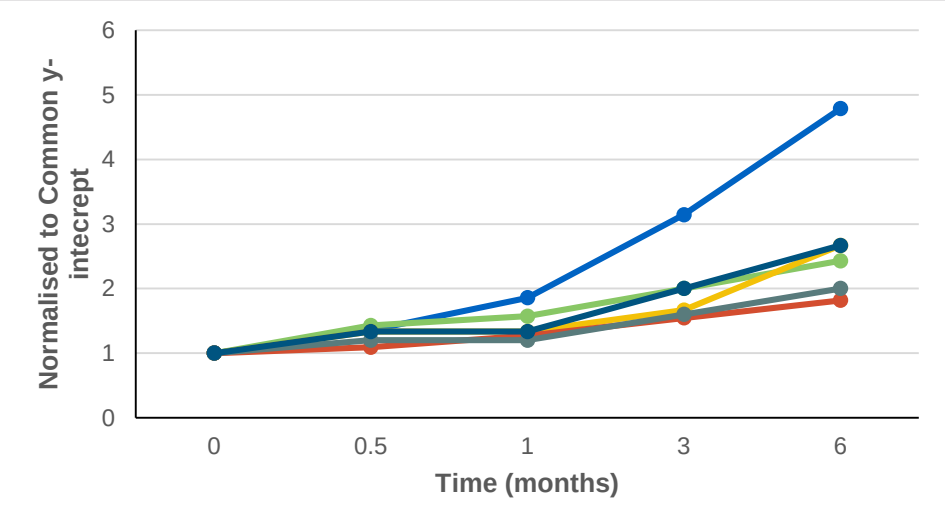
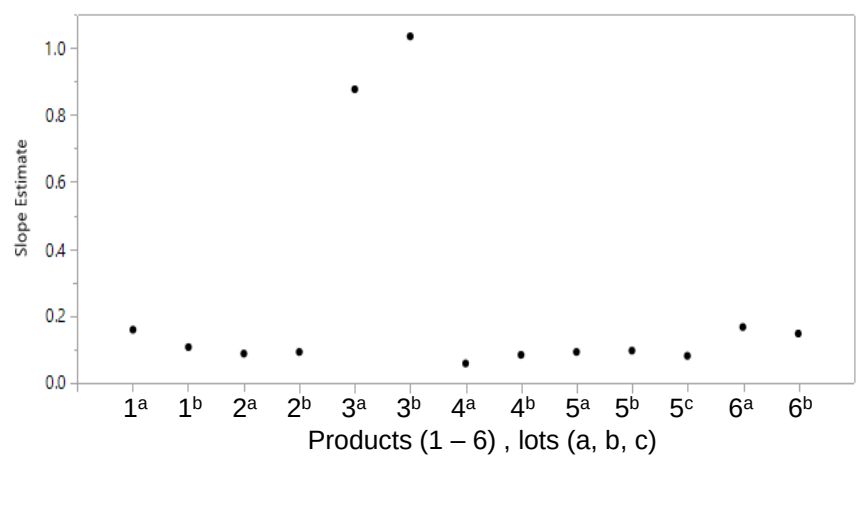
SUPPORTING THE MODEL WITH ACCELERATED CONDITION STABILITY DATA

Kinetics of High Molecular Mass Species Formation under Accelerated Conditions





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

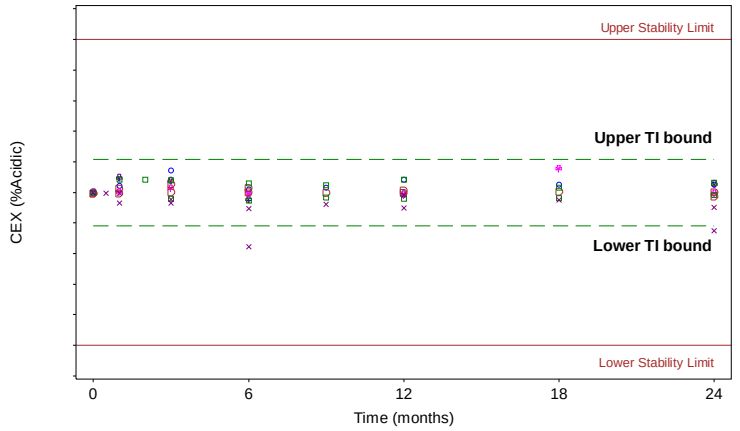
a) Assimilating the reference data set

b) Evaluating fit of the investigated product to the model

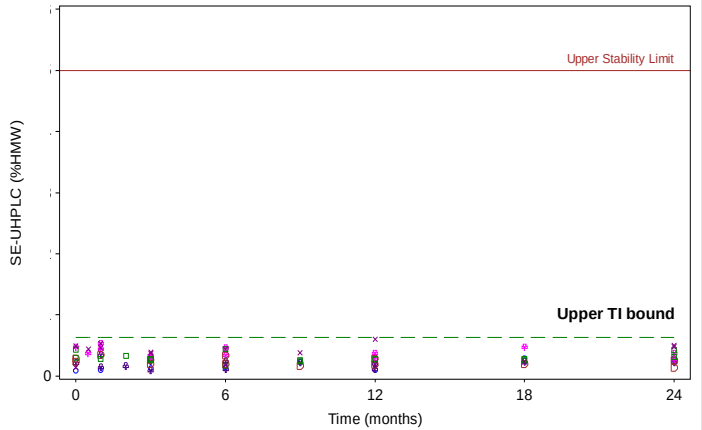
Accelerated condition stability data is a valuable tool to support a prior knowledge derived model and its application

FROZEN DRUG SUBSTANCE IS STABLE THROUGH 24 MONTHS

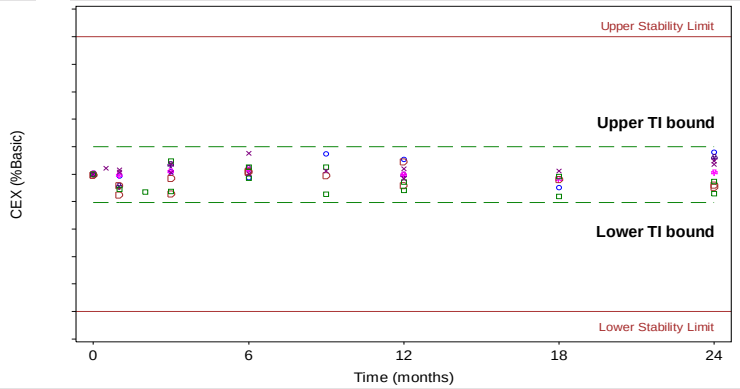
CEX-HPLC acidic peaks



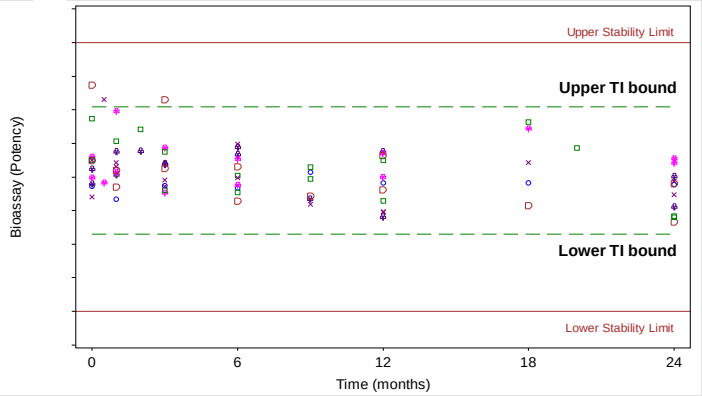
HMW species (dimer)



CEX-HPLC basic peaks



Potency



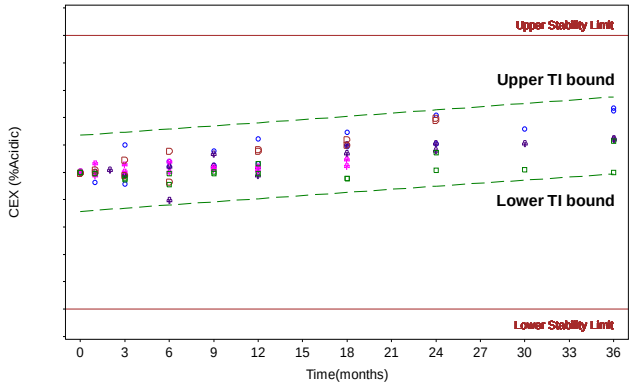
- **Stability profiles are flat through 24 months**
  - No TI intersections with stability limits – 24 months shelf-life assigned
- **CEX-HPLC data are normalised**
- **Modality forms very low levels of HMW species**
- **Stability levels reflect phase appropriate clinical specification**

Data from 6 products meeting selection criteria

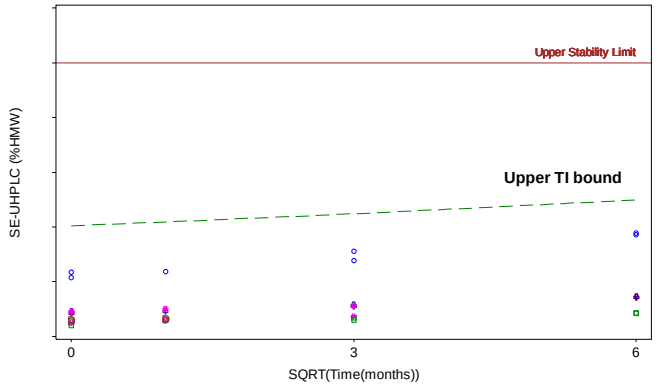
Attributes may in vary in level at time zero but it is the trend that is important

LIQUID DRUG PRODUCT ATTRIBUTES TREND WITHIN LIMITS

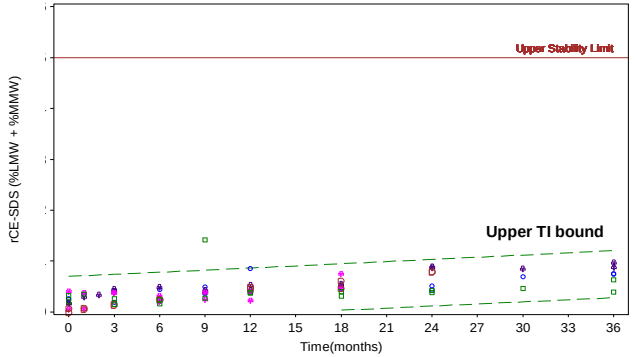
CEX-HPLC acidic peaks



HMW species (dimer)



Fragmentation



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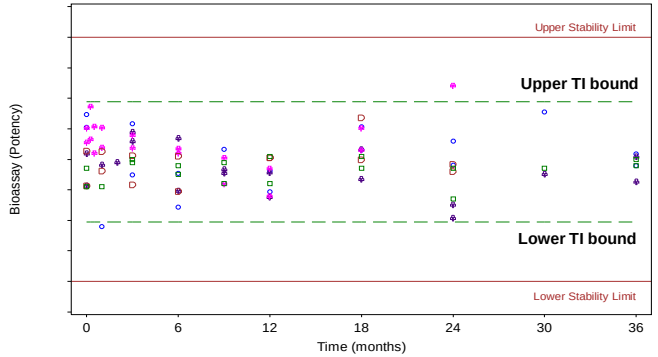

- **Stability profiles may trend through 24 months**
  - No TI intersections with stability limits within 24m
    – 24 months shelf-life assigned
- **CEX-HPLC data are normalised**
- **HMW species data are transformed for linearity**
- **Stability levels reflect phase appropriate clinical specification**

Data from 5 products meeting selection criteria

Claimed shelf-life is highly dependent on the attribute specification

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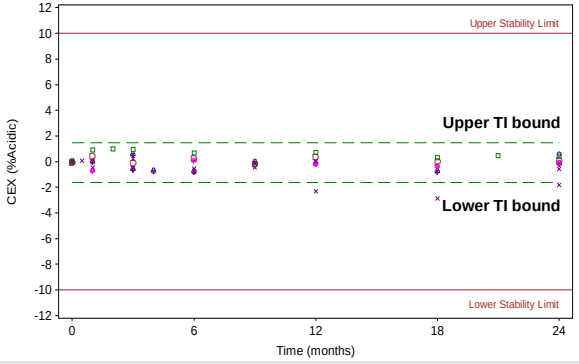
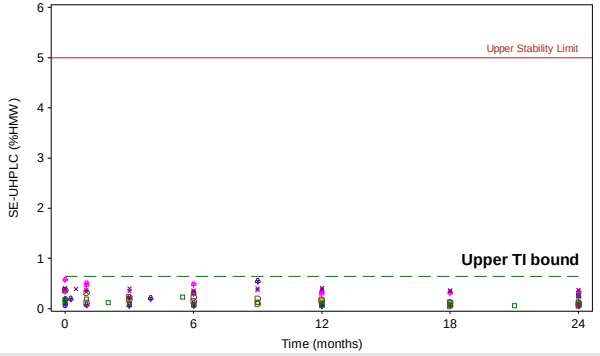
LYOPHILISED DRUG PRODUCT IS STABLE THROUGH 24 MONTHS

CEX-HPLC Acidic peaks



HMW species (dimer)



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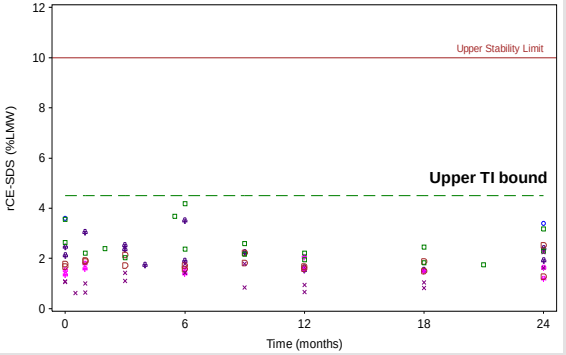
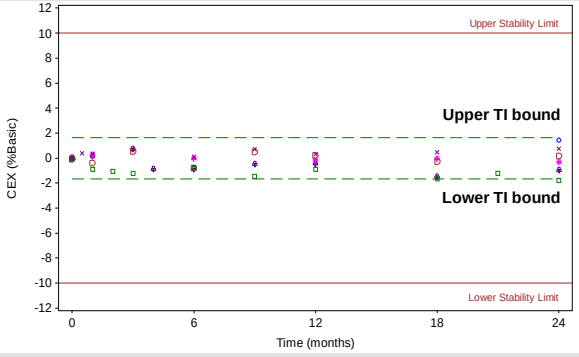
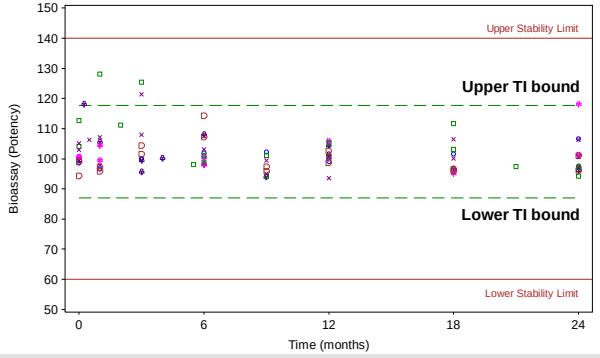


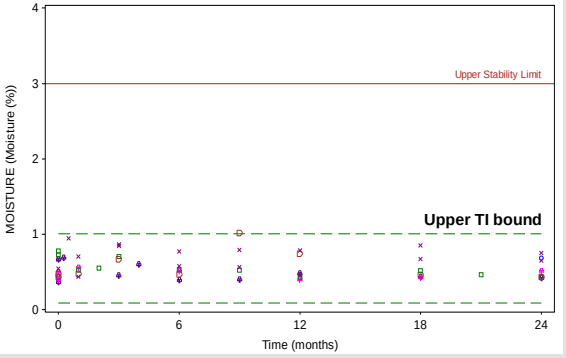
CEX-HPLC Basic Peak



Potency



Moisture



Data from 6 products meeting selection criteria

Lyophilised Drug Product is a Stable Pharmaceutical Form

APPLICATION OF PRIOR KNOWLEDGE STABILITY FOR SHELF-LIFE THROUGH PRODUCT DEVELOPMENT

In clinical applications:

based on commitments, EU national agencies allow up to 2-fold extrapolation limited to 12 months

At MA the claimed shelf-life <u>may</u> require less 'extrapolation' than at FIH

- **The proposed use of prior knowledge extends what is currently allowed to > 2-fold but on the basis of data rather than only commitments**
  - **A science-driven, risk-based approach**
- **Apply from FIH through phase 3**
  - **Increasing product specific data through development from representative lots**
  - **Increasing product attribute understanding**
  - **In accelerated development earlier decision-making allows earlier lots than usual to be justified as the primary lots used in pivotal clinical studies.**
- **'extrapolation' decreases through development as more product data are obtained**
  - depending on the clinical acceleration program and representativeness of earlier clinical lots

As greater product knowledge is gained through development, there is decreased risk in using prior knowledge from 'like' molecules

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POST-APPROVAL AND MANAGING THE UNEXPECTED

- The model reference data set would evolve as new data are obtained
  - Extending the model shelf life
  - Adding new products to the reference data set
  - Changes in platform!

- When “the unexpected happens!”
  - **In the event of a confirmed, consistent new trend:**
    - Consider impact of new trend, for example, more testing points to get a better idea of the trend
    - Assess if trend will remain within specification through expiry, with appropriate follow-up as needed

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

FUTURE DIRECTIONS FOR BIOLOGIC STABILITY

Attribute-focused Stability	• MAM to replace method-based, indirect measures e.g. CEX-HPLC acidic and basic peaks • Understanding of HMW species formation, parameters and kinetics
Prior Knowledge from a Data Lake	• Efficient, accurate management of knowledge input and output • Analytics capability for trend analyses
Direct Extrapolation	• Technically possible: balance of assay variability and data points • ICH challenges and agency acceptance
ASAP for Biologics	• Requires more attribute-focused methods • May depend on attribute interactions and understanding

THANK YOU!

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