Roundtable Session - Table 4 – Predictive Stability Modelling – Current State and Best Practice

Facilitator: Karoline Bechtold-Peters, *Novartis Pharmaceutical Manufacturing GmbH*

Scribe: Salome Piuzzi, *Novartis Pharmaceutical Manufacturing GmbH*

Abstract:

Predictive stability modeling is rapidly evolving from an academic and development tool into a potential regulatory enabler for biologics and vaccines. Recent advances in advanced kinetic modeling, combined with increasing regulatory recognition in the revised ICH Q1 framework, have created new opportunities to support shelf-life assignment, comparability assessments, management of temperature excursions and lifecycle changes. At the same time, important scientific and regulatory questions remain unanswered.

This roundtable aims to complement the session on the Wednesday, and identify and discuss remaining barriers to broader adoption and to explore practical strategies for building confidence in predictive stability approaches. Practical experiences should be exchanged.

Discussion Questions:

- *What evidence is needed for predictive stability modelling to move from a promising supportive tool to a broadly accepted regulatory decision-making framework?*
- *When Is a Model Good Enough for Regulatory Decision-Making? Can a predictive stability model support a shelf-life claim as early as Phase I or Phase III, or should it initially serve only as supportive evidence?*
- *Which CQAs Are Truly Suitable for Predictive Modelling? - Are aggregation, fragmentation, and charge variants sufficient, or should potency and functional assays also be included in predictive stability models?*
- *How Should Non-Modellable CQAs Be Addressed? - Is a scientifically justified risk assessment sufficient to support quality attributes that cannot be directly modelled?*
- *Model Validation and Continuous Verification - What level of validation and ongoing verification should Health Authorities require to establish and maintain confidence in predictive stability models?*
- *Harmonization of Global Regulatory Expectations - Will FDA, EMA, MHRA, PMDA, and other regulatory authorities ultimately converge on comparable expectations and acceptance criteria for predictive stability modelling?*
- *What Is the Primary Objective: Shelf-Life or Product Understanding? - Should stability modelling be used primarily to support shelf-life determination, or should it be viewed as a broader tool for product development, process understanding, and lifecycle management?*

- *Black Box or Scientific Understanding? Must a predictive stability model be based on mechanistic understanding of degradation pathways, or is strong statistical predictive performance sufficient?*
- *Patient and Healthcare System Benefits - How can predictive stability modelling accelerate patient access to innovative therapies while maintaining product quality, safety, and regulatory confidence?*
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Notes:

The roundtable discussion highlighted that predictive stability modelling is already being explored by several companies, particularly in early-phase submissions, but experience remains limited and regulatory feedback is still evolving. Among the companies represented, some had intended to use accelerated predictive stability approaches in early development, while others had either no submission experience or had included modelling under the frame of the standard approach, therefore, without requesting any benefit compared to current regulatory acceptance. One example was shared where a standard approach incorporating predictive stability modelling was accepted, supporting a proposed shelf-life of 36 months instead of 24 months standard, in an early-phase context.

Participants noted that companies are using different modelling approaches, including Arrhenius-based models and Bayesian methods. Some companies have generated Arrhenius-based data without yet submitting it to regulators. A key point of discussion was the potential tension between predictive stability approaches and current IMPD guideline expectations. There will be a clear need to update this IMPD guideline after ICHQ1 is final, to give a frame for alternative approaches in the early phase space as well.

Model validation emerged as a central concern. Questions were raised regarding the level and type of validation data that regulators may expect, especially where companies use either commercially validated software or internally developed tools requiring their own validation. Participants emphasized that successful use of modelling requires a solid understanding of degradation mechanisms, including confidence in the reaction order and the ability to verify model suitability using specific analytical methods.

The group also discussed the role of predictive stability modelling in comparability and post-approval contexts. Questions were raised about why modelling would be needed when sufficient standard stability data are available, and whether models could support trending in annual stability programs after approval. The “sister site” concept was also discussed, with modelling potentially supporting assessment of data equivalency across manufacturing sites. However, participants acknowledged the risk that models may not work as expected and that using modelling could raise the regulatory bar, even if not intended.

Two main benefits were identified: enabling shelf-life extension and supporting submissions with less real-time stability data. The current standard expectation remains approximately six months of PPQ stability data at the time of filing, but guidelines appear open to alternative approaches if sufficiently justified with data. Regulatory acceptance may vary across regions: some agencies and industry participants see greater openness in certain mid-sized regulatory authorities, particularly where modelling is framed as part of a risk-mitigation strategy. Smaller agencies

with more limited assessment resources may be more conservative or rigid. Some regulators may not expect to assess raw modelling data directly, leaving detailed data verification to GMP inspection.

The use of prior knowledge was considered an important opportunity. Participants discussed whether prior knowledge from similar molecules, platform technologies, or related structural modalities such as IgG-based products could be integrated into predictive models or used to support risk assessments. Modelling may be especially relevant for platform technologies and complex modalities such as AOCs and ADCs. The concept of a platform master file was mentioned, as well as the need to engage regulators in the context of conjugates and related advanced modalities.

Some participants suggested starting where the degradation pathway and reaction order are well understood, verifying data with fit-for-purpose analytical methods, and selecting the model that best matches the product behavior. Beyond regulatory submissions, modelling was viewed as a valuable tool to improve product understanding.

Finally, the discussion emphasized the need for continued cross-industry dialogue. Participants referenced the IQ Consortium, ICH Q1 EFPIA sub-Team and references to publications as presented in the CASSS session materials. There is a clear need to continue discussions in appropriate forums to build shared understanding, engage further with regulators, clarify expectations, and support broader regulatory confidence in predictive stability modelling.