Predictive Stability Methodologies: The Why, When and What

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The ‘Why’

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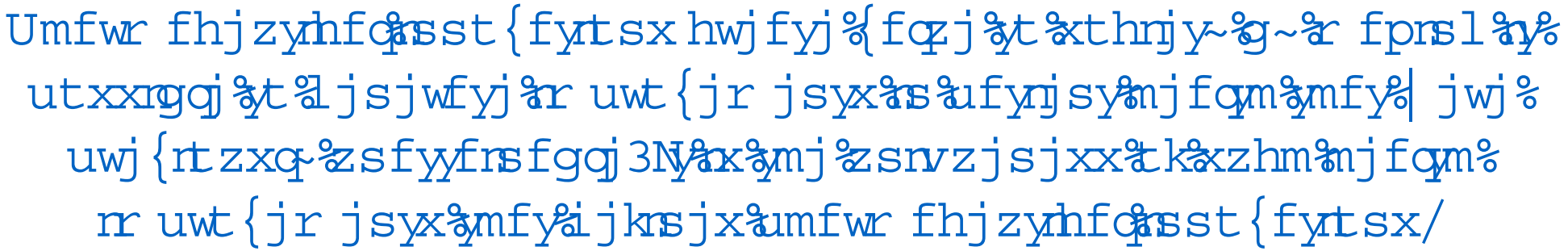

*Morgan et al. 2008. Toward a definition of pharmaceutical innovation. PMCID: PMC3091590, PMID: 21602949

The Need, Opportunity, and Knowledge Exist For Predictive Methodologies

Need – Accelerated drug development to address public health emergencies and critical medical needs

Opportunity - Regulatory environment is favorable for introduction of innovative methodologies

- 1) Precedent from kinetic modeling of small molecule stability (ASAP)
  2) EMA PRIME provisions for products with unmet medical need
  3) Precedent for vaccines and biotherapeutics during COVID emergency
  4) ICH Q1/Q5C revision (concept paper)

Knowledge - Platform manufacturing/testing strategies and extensive biologic manufacturing experience set the stage for predictive methodologies using prior knowledge

- Facilitates more rapid development of products
- Produces products with similar attribute and stability profiles
- Enables platform stability datasets for training algorithms applicable to other platform molecules

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Innovative Methodologies Enable Use of Prior Stability Knowledge for Biologics

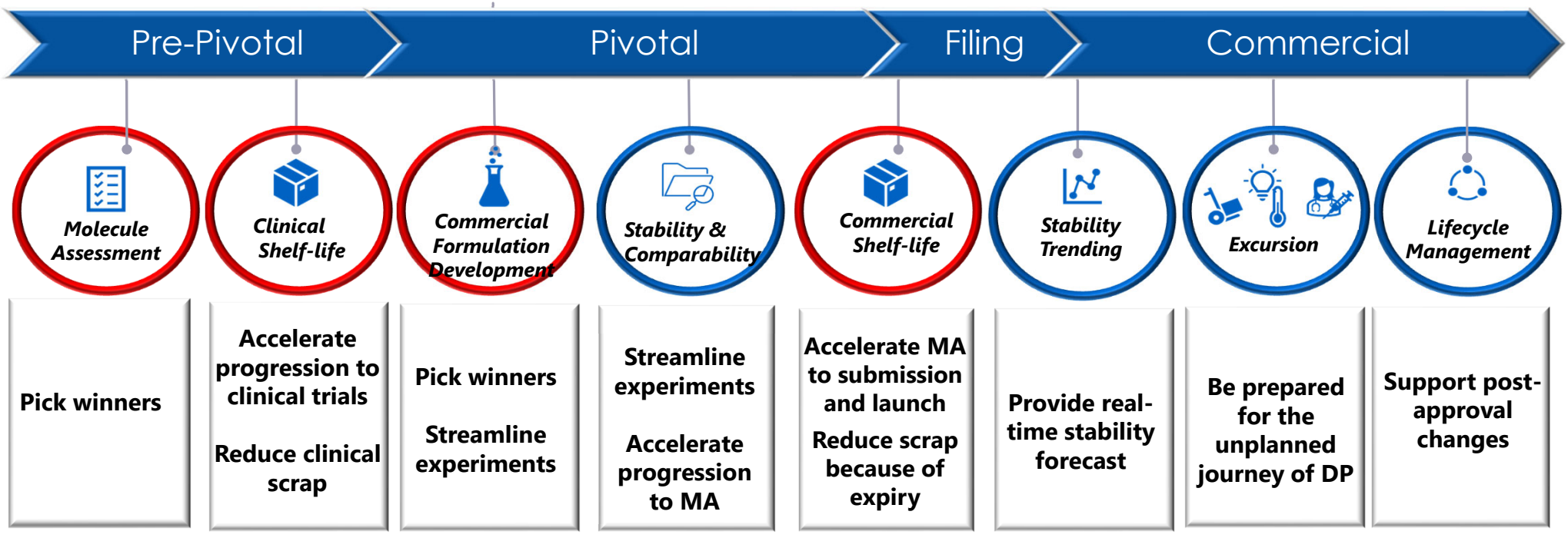
General Principles for a Stability Prior Knowledge approach:

- *Prior knowledge can be product specific or non-product specific*
- *Use of prior knowledge and predictive modelling can help 'fill in the gaps' when data is limited*
- Use of appropriate *statistical tools* to achieve accurate and robust predictions within appropriate bounds
- *Justification of prior knowledge* based on the impact that attribute differences between molecules may have on the stability profile, as appropriate
- *Qualification and/or verification of the model, as appropriate*
- *Risk assessment* — assess and mitigate the remaining (residual) risk for product stability

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

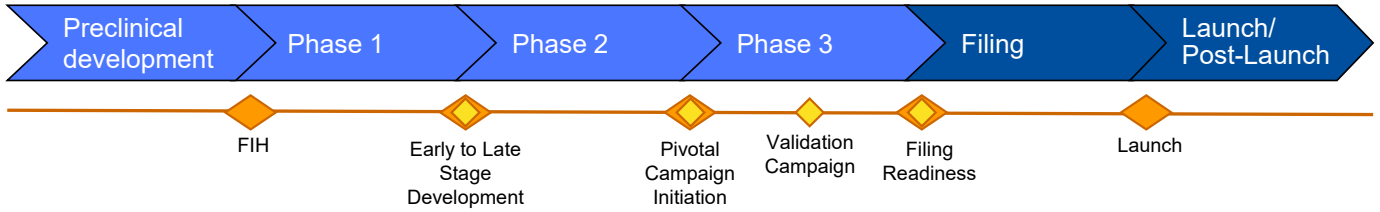
The ‘When’

A Predictive Stability Capability Can Have a Favorable Impact on the Entire Product Lifecycle



Stability Modelling Can play a Role at Multiple Points Through Commercialisation

Stability Data May Be Rate Limiting in Biologic Product Development



12 years
'Typical' development timeline

3 years
Accelerated Timeline Biosimilars

1 Year
EUA scenario

Acceleration of product development	• Shorten molecule selection and formulation development periods
Clinical shelf-life	• Clinical product needs a shelf-life suited to the lifespan of the product in the program
Commercial shelf-life	• Need at least a 24-month shelf-life at launch to use PPQ lots, lead time, remaining shelf-life, ≥ 36 months ideal for commercial product • Challenging to understand future variability based on a limited stability dataset

Predictive stability methodologies can address critical development/commercialization challenges

Predictive Stability Approaches Have the Potential to Address Critical Development Challenges

- ✓ Increasing speed to clinic: Reduce duration of stability studies for molecule selection and formulation development activities
- ✓ Establishment of a suitable clinical expiry supporting speed to clinic and reduced complexity of clinical supply chain
- ✓ Provides a more robust assessment for commercial expiry analysis and decouples stability specification from real time data

The ‘What’

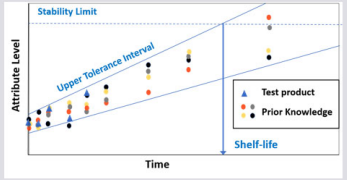
Predictive Stability Modelling using Prior Knowledge

❖ **Empirical** modelling methodologies to predict stability profile — shelf-life

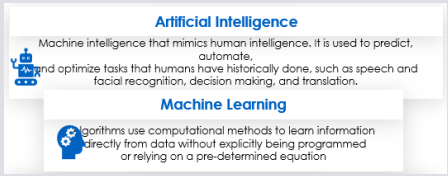
- Kinetic analysis; e.g., Arrhenius, Advanced Kinetic Modelling

❖ **Prior knowledge** methodologies:

- Pooling of prior knowledge from 'like-molecules'
- Stability models using Bayesian statistics
- Artificial Intelligence / Machine Learning prediction




Thomas Bayes 1702–1761



❖ **The tools are not intended to replace the conventional long-term stability studies**

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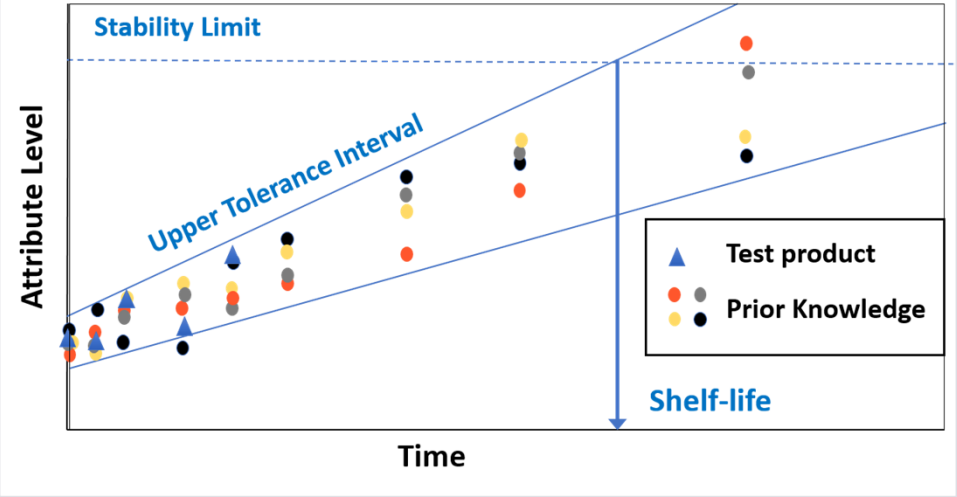
Pooling of 'Like-molecules': A Quality by Design Approach

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
- 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
- **The earliest 'attribute' intersect is 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 decouple shelf-life from real time data

Prior Knowledge and Bayesian Statistics

Bayesian Statistics

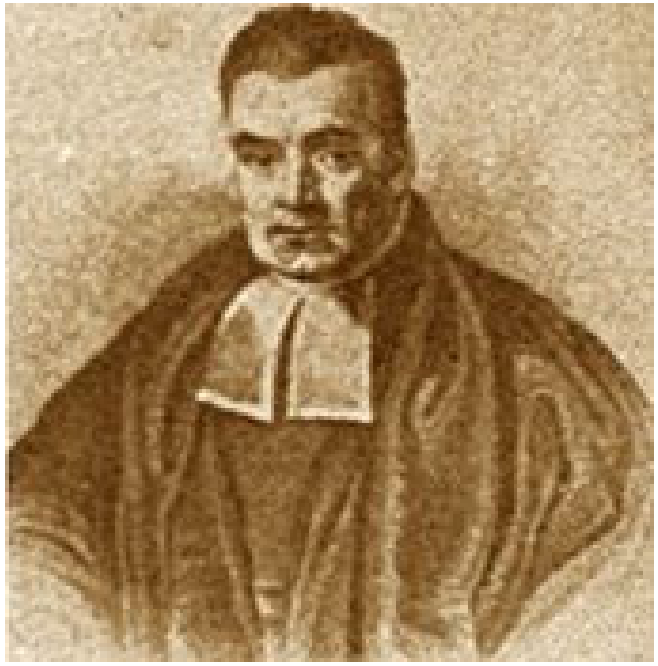
An alternative approach to 'conventional' frequentist statistics

- 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 stability specification acceptance criteria



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Bayesian Case Studies

Datasets

mAb0 DS:
- Full dataset- 14 lots up to 48M
- Reduced dataset - 7 lots up to 24M

mAb0 DP:
- Full dataset - 14 lots up to 36M
- Reduced dataset - 10 lots to 24M

mAb1 DP: 7 lots up to 24M

- **Bayesian TI's similar to Frequentist TI's after adding prior knowledge to a reduced dataset**
- **Bayesian predictions can support stability specification and/or product shelf-life, particularly for a limited dataset**

mAb0 Case Study		Frequentist (95/99% TI, Normal distribution, full dataset)	Frequentist (95/99 %TI, Normal distribution, reduced dataset)	Bayesian (95/99 %TI, Beta distribution, reduced dataset + Prior Knowledge)	Prior Knowledge Dataset (N, power prior)
mAb0	**DS**, 48M HMW SE-HPLC Spec = ≤ 3.0%	**0.32, 2.90%**	**0.18%, 11.85%**	**0.55, 3.27%**	4 products a = 0.5
	DP, 36M CEX-HPLC (acidic) Spec = ≤ 29%	**19.02 - 25.78%**	**7.80%, 47.75%**	**15.30- 32.15%**	4 products a = 0.5
	DP, 36M HC+LC, rCE-SDS	**96.65 - 97.96%**		**94.02 - 98.83%**	4 products a = 0.5

mAb1 Case Study		Frequentist (95/99.9937% UTI, full dataset)	Bayesian (Beta) (95/99.9938% TI, full dataset + PrK)	Prior Knowledge Dataset (N, power prior)
mAb1	**DP, 36M** HMW, SE-HPLC	**T0: 1.17%** **T36: 1.55%**	**T0: 0.88%** **T36: 1.58%**	7 products a = 0.8

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AI/ML IS A CRITICAL CAPABILITY OF DIGITAL INNOVATION AND CAN PROVIDE ANSWERS TO CRITICAL BUSINESS QUESTIONS

Artificial Intelligence

Machine intelligence that mimics human intelligence. It is used to predict, automate, and optimize tasks that humans have historically done, such as speech and facial recognition, decision making, and translation.

Machine Learning

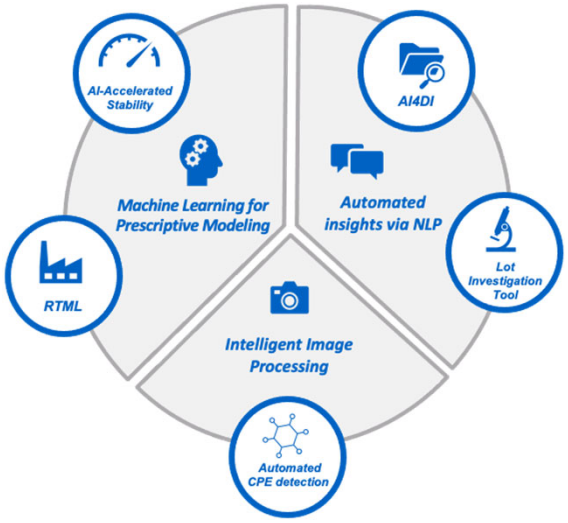
Algorithms use computational methods to learn information directly from data without explicitly being programmed or relying on a pre-determined equation

Why AI/ML?

- Ability to learn complex relations and patterns from data
- Predict future outcomes with high accuracy

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

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



Reduce COGS and manual labor to increase efficiency & reliability

Efficient drug discovery and development

Ensure quality and safety, resulting in more intelligent decision-making

Support regulatory inquiries to increase speed to patient

Reduce product complaints

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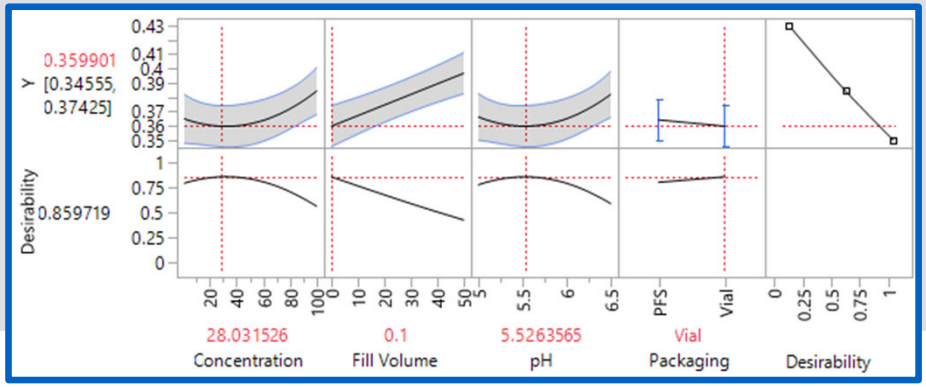
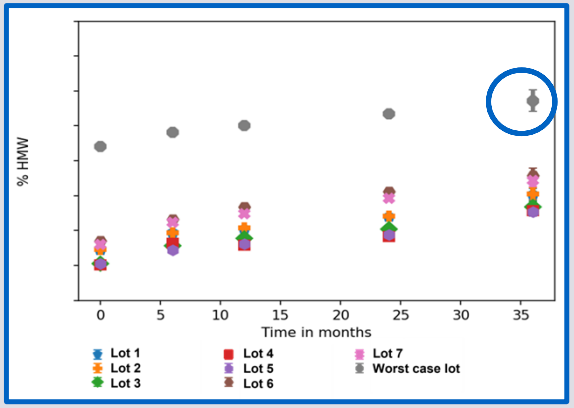
AI/ML Potential Applications

Formulation Development – Preliminary DoE Studies

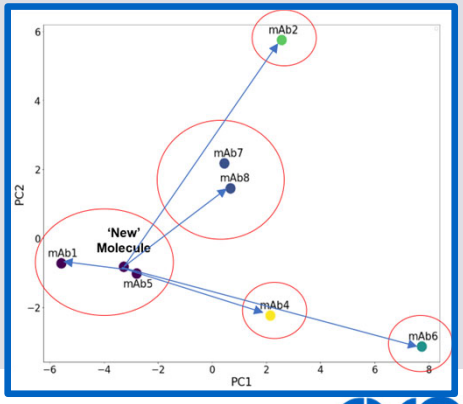
Packaging	Concentration	Fill Volume	pH	36-Month %HMW
PFS	A	2	6.5	0.41256
Vial	B	1	6.5	0.39672
Vial	A	2	5.75	0.3726
Vial	A	2	5.75	0.3726
PFS	B	1	5	0.35244
PFS	C	1	6.5	0.41976
PFS	B	3	6.5	0.4212
PFS	D	3	5	0.42012
Vial	C	3	5	0.42048
Vial	A	3	6.5	0.41904
PFS	A	2	5.75	0.39348
PFS	C	3	5.75	0.4212
Vial	C	2	6.5	0.41004
Vial	B	3	5.75	0.41508
Vial	B	1	5.75	0.39672
Vial	B	2	5	0.39168
PFS	C	2	5.75	0.39204
Vial	C	1	5	0.37512
PFS	A	1	5.75	0.3564
PFS	A	2	5	0.42372



Stability/Expiry Analyses



Molecule 'Similarity' Analysis



General Take Aways

- Predictive methodologies can be used as a product acceleration lever and overcome critical development challenges
- Predictive Stability Modelling for shelf-life is most valuable when there are insufficient real-time stability data available for the product due to an accelerated development program or small stability dataset
- An 'enhanced' level of product understanding is expected (ICH Q8, QbD)
- Models require development and 'qualification'
- If non-product specific prior knowledge is utilized, justification/support/risk assessment for relevance of molecules included in the dataset should be provided
- **The tools are not intended to replace the conventional long-term stability data**

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ICH Stability Guidance Revisions*

Concern with Current ICH Stability Guidance	Proposed Solution
Disjointed, resulting in uncertainty, confusion and mis-understanding.	A single guidance covering the general principles (concepts) of Stability and Shelf-life Setting covering all therapeutic modalities within scope, with Annexes to cover any specifics and examples.
Not reflecting current knowledge and experience in biological therapeutics.	Modernise to include science & risk-based approaches, aligned with QbD and risk management principles of ICH Q8 to Q14 (including new manufacturing methods such as Continuous Manufacturing, Q13).
Too prescriptive.	Science-driven guidance to focus on 'What' and 'Why' and less on 'How'. Annexes can provide specific examples.
Not reflecting new therapeutic modalities or integral drug-device combination products.	Future-proof the guidance by expanding scope and with general language for even newer modalities.
Lacks guidance on 'in-use Stability' .	New sections for recognised gaps in guidance.
Being applied (inconsistently) to clinical studies.	Clarify principles applicable to product development.

*From Andrew Lennard (Amgen) and Julia Claus (Pfizer). DIA Europe 2022. *Innovation in ICH and other Quality Guidance: Stability*

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Implementation of Innovation in the Pharmaceutical Industry Requires Collaboration and Communication Between Industry and Regulators

First commercially viable **light bulb** was called a 'conspicuous failure' by the Stevens Institute for Technology, and 'unworthy of the attention of practical or scientific men"

In 1902 **bikes** were thought to be unsafe, impossible to improve, and ultimately impractical for everyday use.

In 1928 Joseph Schenck, President of United Artists, **talking pictures** were a fad – dialogue was overrated

In 1985 the New York Times reported on the demise of the **laptop** – they were heavy, pricey and had poor battery life

Americans initially resisted the elevator because they didn't quite understand how it worked – they were asked to put their trust in a system they could not see*

In order to facilitate mass adoption, innovators also have to help consumers trust their [innovations] (which often means helping them understand how they work), and realize why they can provide value *

*https://medium.com/pronouncedkyle/new-technology-is-always-scary-8bf977a13773

THANK YOU!

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