EMA /US FDA Workshop on

support to quality development in early access approaches

Supporting Accelerated Development - STABILITY approaches

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Bio Biotechnology Innovation Organization

ebe european biopharmaceutical enterprises

efpia European Federation of Pharmaceutical Industries and Associations

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Supporting Accelerated Development

- SPEED – where it comes from …
  - Getting to clinical investigation as rapidly as possible
  - Being able to manage changes in development as quickly as possible to maintain development acceleration
  - Getting to the registration submission as rapidly as possible
  - Getting to approval as rapidly as possible
  - Being able to manage any post-approval changes to maintain robustness and supply as efficiently as possible

Supporting Accelerated Development

- Understanding product stability is essential for management of product quality
- Generation of 'real time' stability data is 'on the critical path' for a development program
  - To clinical investigational study start
  - To introduce an improved product
  - To registration

    AND to progress many post-approval CMC changes

- **Real time data can be considered to be 'necessary'**
  - **the clock ticks and the patients wait …**

- Limited allowance for alternative approaches and extrapolation in current regulatory guidelines (e.g. Q1 and EU IMPD-Q)
  - E.g. "the proposed retest period / shelf-life can be up to twice but not more than 12M beyond the period covered by long term data" (ICH Q1E)

- Scientific approaches are available to generate stability understanding under **ACCELERATED CONDITIONS** and powerful **COMPARATIVE** data support making change (and maintaining shelf-life) without 'waiting for' real time data

  - **SUPPORT RAPID DEVELOPMENT, OPTIMISATION + EXPEDITED and SUSTAINED PRODUCT AVAILABILITY to PATIENTS**

Technical Background - accelerated stability approaches

- Accelerated stability studies use data to generate mathematical models to predict the stability of materials, blends and products at long term storage conditions
- Studies are typically carried out over a short period of time at significantly elevated conditions of T and humidity (more aggressive than traditional conditions – e.g. 70C, 75% RH if appropriate)
  - Need to be within 'same manifold' of degradation
- Fundamental scientific treatments (thermodynamics + kinetics – Arrhenius etc.) allow stability at accelerated conditions of T + humidity to be modelled back to 'routine' storage conditions
  - A 'humidity-modified Arrhenius relationship' – accelerated data used to generate the temperature sensitivity (Ea) and humidity sensitivity (B) which allow extrapolation from accelerated degradation rates to LT storage conditions
  - Variable K : $\ln k = \ln A - Ea/RT$ and B (RH)
- Can be integrated with modelling of impact of other factors (e.g. packaging MVTR) to explore the protective effects of different packaging conditions
- Well-established prior knowledge – monographs and peer-reviewed publications
  - "Accelerated Predictive Stability" Edited by Qui and Scrivens (Academic Press) 2018
  - Solid state kinetics of pharmaceutical products – prior publications : Khawam and Flanagan J.Phys.Chem B 2006
  - Log-humidity relationship in ASAP – Adami and Waterson, Int.J.Pharm 2004, based on empirical experimentation – Genton and Kesselring, J.Pharm.Sci. 1977

Real Cases – 1

- The Value of Close Engagement with Regulators
  - Phase 1 studies in patients using an early development formulation were rapidly followed by pivotal clinical studies, with a consequent need to develop a practicable commercial product (and establish a shelf-life + supply chain) in a short period of time
  - Stability data generated late in development (instability under ambient conditions) impacted the considerations for the product and its storage
    - **IMPORTANT TO HAVE WAYS TO COLLABORATIVELY MANAGE UNEXPECTED EVENTS**
  - Dialogue with regulators agreed on a supply strategy utilising refrigerated storage
    - Shelf-life of 12M / 9M (mid strength) based on - single lot – bracketted batch data at 2-8C to >15M, and 3M for mid strength
      - Supported by concurrent product stability monitoring
    - Further data provided to extend shelf-life during review
  - Alternatively - Modelling (ASM*) from ambient data to refrigerated, using knowledge of degradation kinetics, would have supported 'final' shelf-life for all strengths based on original data set
    - * Clancy et al, AAPS PharmSciTech (18) 1158 (2017)

Real Cases – 2

- Accelerating Initial Clinical Investigation
  - The acceptability of predictive / accelerated stability in support of clinical study submissions (particularly to set initial DS retest period or DP shelf-life in the absence of long-term data) **varies** between (and within) regions
    - US don't expect at expiry assignment in the IND
    - The current EU IMPD-Q guideline states particular extrapolation allowances that are 'one size fits all' and thus not optimally science-based and NOT based on specific product assessment / knowledge
      - Guidance allows a four-fold extrapolation based on accelerated data, up to 12M and +12M on LT, beyond 12M RT
      - "other schemes may be possible, but should be justified"
  - Strict enforcement of these stated extrapolations places limitations on progressing initial CTs in the most expeditious manner, necessary for developing for unmet medical need
    - More flexibility seems to be granted in some regions and countries (e.g. USA, some in EU)
      - CFR 211.166 may be more supportive "accelerated data, combined with … may be used to support expiry dates"
    - This can mean that clinical programs can be progressed more quickly in some countries than others
    - At this stage one will likely not have a PRIME / Breakthrough designation
  - The use of accelerated stability data can compress development and remove RT stability data from the development critical path

Experiences with provision of accelerated data

Investigational Phases

- Country 3 (EU) (2014) – 24M expiry approved once ASAP data supported by 3M RT/accel data
- Country 1 (EU) (2016) – 6M expiry approved with ASAP data supporting 12M
  - Shelf-life had to be extended via substantial amendment
- Country 2 (EU) (2017) – Expiry based on RT data only though ASAP provided
- Country 3 (EU) (2018) – 12M expiry based on ASAP approved – with additional discussion of certain attributes (disso, water content, physical form)
- Country 3 (EU) (2018) – ASAP 12M expiry not approved – needed RT data (1M to give 4M expiry)

- Country 4 (non-EU) (2018) – ASAP data not accepted to shorten time to **registration submission** – 12M data expected

- **In all cases commitment was made to conduct real time stability studies on clinical supplies**
- **"To date, all RT stability studies confirm ASAP predictions"**
  - No RT results lead to shorter retest / expiry periods than proposed based on ASAP

Real Cases – 3

- Management of Change – Drug Substance
  - A compound with FDA Accelerated Approval where changes to the API manufacturing process (to eliminate reprocessing) and analytical methods were introduced to control new CQAs (remove impurities) after manufacture of the primary registration stability batches
  - **Having to completely restart ICH stability program would have delayed the marketing application**
  - Comparison of 'new process' stability data, generated under accelerated conditions, was used to justify the applicability of the original API stability dataset
    - At least one stability batch of 'new process' DS was required to be tested at long term and accelerated conditions (3M data to be provided during review)
- This type of scientific approach can be used to manage process change and even more significant route change
  - The degradant pathways of the drug substance are understood and not specific to routes of manufacture
- Acceptance of accelerated stability conditions can facilitate accelerated development. Allow alternate scientifically-sound approaches in a globally-harmonised manner.
  - Such approaches can also be utilised POST-APPROVAL to expedite improvements to DS, but only optimises when accepted globally

Case Study 3: supporting process change

Changes made between primary stability set down and commercial to improve control of impurities and simplify the process meant primary stability batches with >12 months real time data were not made via a process **fully representative** of the commercial process

Batch Use	Process Changes		Impact of Process Changes
	Final chemistry steps	Final recrystallisation	
Phase III and primary stability	Same synthetic intermediates Change in process conditions to improve control of newly identified impurities (e.g. different order of addition of regents, different processing conditions such as times, temp…)	Batches re-processed (repeat of recrystallisation to address particulates)	Same potential impurities Impurity Profile for primary stability and commercial batches differ; All impurities below ICHQ3A limits (<0.15% w/w)
Commercial and Supporting stability		Single recrystallisation	

Predictive stability models support that changes made have not impacted the API stability and support the commercial retest date and equivalence of batches

Batches	ASAP/ASM Study		Results
	Conditions	Timepoints (days)	
Phase III and primary stability	70ºC/30%RH 70ºC/75%RH 80ºC/5%RH 80ºC/30%RH	0, 7, 14	Equivalent stability to primary stability batches and commercial batches Data supports >5 yrs re-test date
Commercial and Supporting stability			

Real Cases – 4

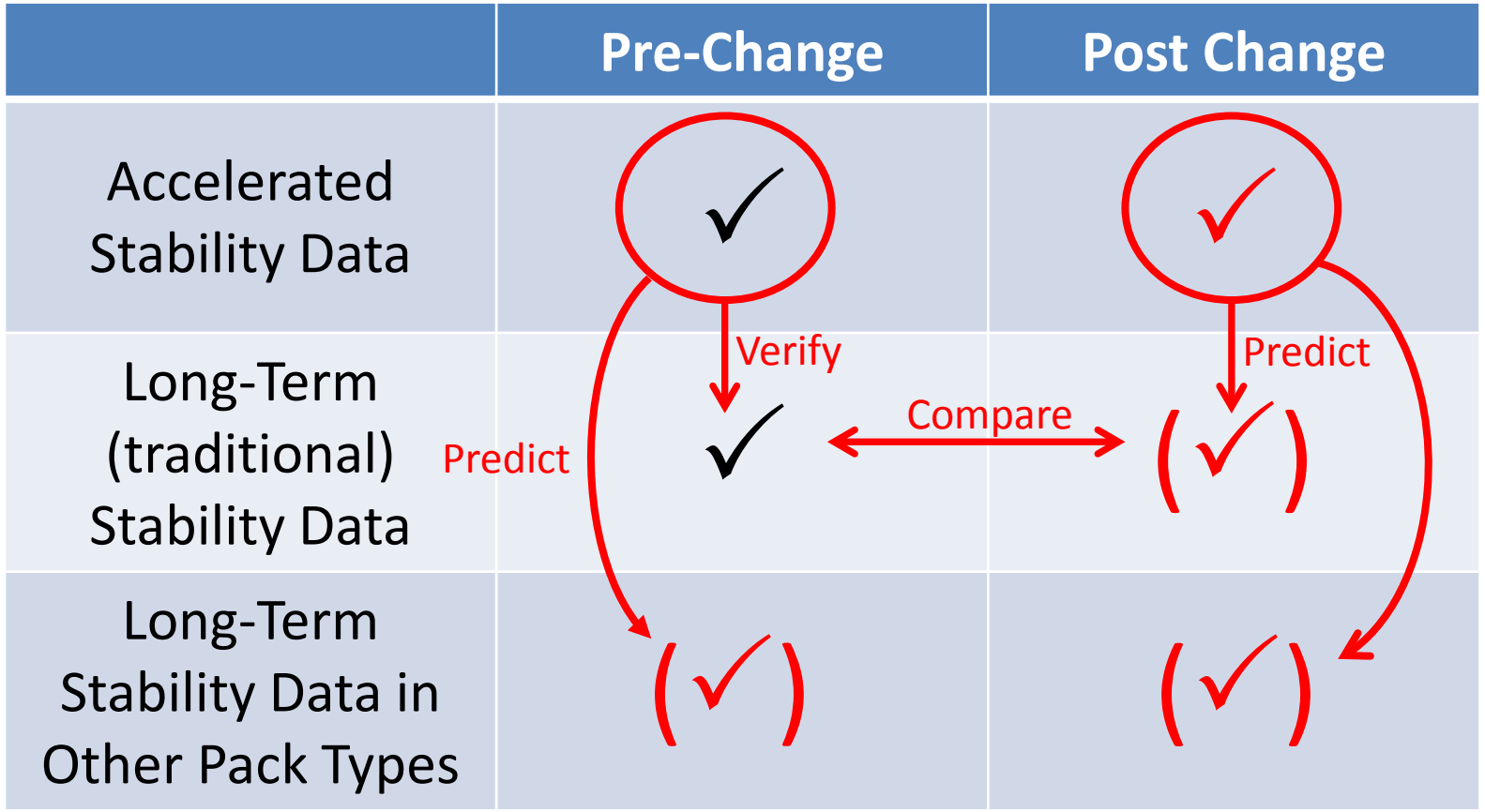
- Management of Change – Drug Product
  - An accelerated program involving CHANGES IN PRODUCT (differentiating colours) and PACKAGING for the proposed products for launch
  - **Limited time to generate long term stability data ahead of clinical dataset availability – CRITICAL PATH**
  - Managing DP change viewed as more difficult than for DS changes (as physical changes can be harder to predict) but facilitated when COMPARATIVE to prior data rather than de novo prediction
  - In this case, long term stability data existed for the similar investigational products
  - Use of predictive (including MVTR modelling) and accelerated stability data allows comparison of stability from investigational and proposed launch products
  - SUPPORTS expedited submission and application of investigational product shelf-life for the commercial products
    - How DIFFERENT can the investigational and proposed commercial products be to apply this kind of approach ?
    - **The stability dataset and control methods can allow for comparison after significant change**

Case 4 – Principles and data

- The ‘pre-change’ product used in the clinical investigations is well-studied and understood
  - RT (and ICH accelerated) stability data supporting shelflife
  - Understanding of purposeful degradation
- AND this product has been evaluated under accelerated conditions – data predictive of a longer shelf-life than assigned

- Changed products (changed colour, pack and colour + pack) can be evaluated under same accelerated conditions – data comparison key

- Comparison of accelerated data can show post-change product to be
  - as stable as pre-change – PROPOSAL - investigational product shelf-life can be assigned
  - Some differences in accelerated stability – i.e. less predicted shelf-life than the investigational BUT above the assigned shelf-life.
  - Significant difference in accelerated stability – not supporting assigned investigational shelf-life – DO NOT PROGRESS THIS CHANGE


Pre-Change
Post Change
Accelerated Stability Data
Long-Term (traditional) Stability Data
Long-Term Stability Data in Other Pack Types
Verify
Predict
Compare
Predict

Drug Product Case Study – White Film Coat (pre-Change) to Blue Film Coat (Post Change)

Accelerated Raw Data – Shelf-life limiting attribute: %Deg (specified impurity)

Condition / Duration	White (Pre-Change) Strength 1	Blue (Post Change)						
		Strength 1			Strength 2	Strength 3		
		Lot 1	Lot 2	Lot 3	Lot 1	Lot 1	Lot 2	Lot 3
50°C/75%RH 14 days	0.4	0.28	0.27	0.27	0.28	0.29	0.28	0.27
60°C/40%RH 14 days	0.43	0.25	0.23	0.25	0.23	0.25	0.23	0.24
70°C/10%RH 14 days	0.6	0.28	0.27	0.29	0.29	0.29	0.28	0.29
70°C/75%RH 2 days	0.64	0.38	0.37	0.38	0.4	0.41	0.41	0.4

Comparison of predicted shelf-life:

The post-change product was same / better than pre-change product

Conclusion

- Provision of a TRADITIONAL stability dataset may **limit the rate of product development** of critical medicines and delay clinical innovation reaching patients

- Expedited development moves fast (and can encounter 'late' identification of issues needing late changes). Regulatory systems ideally will have ways to support innovative solutions to be provided that are not limited by the need to generate real-time stability datasets

- **The case examples show how alternative approaches to those in current regulatory guidelines for the evaluation and assurance of stability (use of predictive models and accelerated stability data) can provide rapid evaluation of stability and facilitate improvements to PROCESS and PRODUCTs**
  - Supported by confirmatory concurrent 'RT' stability evaluation

- Maintains delivery of a high quality product and robust supply in optimal / reduced time

- SUCH APPROACHES CAN BE WIDELY APPLICABLE to MANY and quite COMPLEX SCENARIOS

  - Ideal : widest-possible (GLOBAL) acceptability of scientifically-relevant based approaches

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- **The scientists upon whose work these science-based approaches can be based**

Back-Ups

Example 1

- Immediate release tablet
- ASAP*prime*® protocol

Condition	Time Points (days)															
	Degradation Products					Water Content					Physical Form					Dissolution	
	1	2	3	7	14	1	2	3	7	14	1	2	3	7	14	7	14
50ºC (dry)																X	X
50ºC/75%RH	X		X	X	X				X	X				X	X	X	X
60ºC/40%RH	X		X	X	X				X	X				X	X		
70ºC/5%RH	X		X	X	X				X	X				X	X		
70ºC/75%RH	X		X			X		X			X		X				
80ºC/40%RH		X					X					X					

Example 1

ASAP*prime*® Degradation Product Results

- Degradation product A

			%Area			
Condition	Day 1	Day 2	Day 3	Day 7	Day 14	
50ºC/75%RH	0.04	--	0.14	0.27	0.48	
60ºC/40%RH	0.16	--	0.36	0.78	1.41	
70ºC/5%RH	0.29	--	0.91	2.00	5.13	
70ºC/75%RH	0.78	--	2.26	--	--	
80ºC/40%RH	--	4.64	--	--	--	

- Degradation product B

			%Area			
Condition	Day 1	Day 2	Day 3	Day 7	Day 14	
50ºC/75%RH	0.00	--	0.00	0.03	0.04	
60ºC/40%RH	0.00	--	0.00	0.04	0.07	
70ºC/5%RH	0.00	--	0.10	0.09	0.24	
70ºC/75%RH	0.05	--	0.12	--	--	
80ºC/40%RH	--	0.23	--	--	--	

Example 1

ASAP*prime*® Degradation Product Results

- Degradation product C

			%Area			
Condition	Day 1	Day 2	Day 3	Day 7	Day 14	
50ºC/75%RH	0.08	--	0.14	0.26	0.47	
60ºC/40%RH	0.16	--	0.37	0.76	1.42	
70ºC/5%RH	0.34	--	0.97	2.09	5.50	
70ºC/75%RH	0.78	--	2.26	--	--	
80ºC/40%RH	--	4.70	--	--	--	

- Total degradation products

			%Area			
Condition	Day 1	Day 2	Day 3	Day 7	Day 14	
50ºC/75%RH	0.35	--	0.44	0.69	1.13	
60ºC/40%RH	0.48	--	0.89	1.78	3.14	
70ºC/5%RH	0.80	--	2.13	4.34	11.06	
70ºC/75%RH	1.74	--	4.82	--	--	
80ºC/40%RH	--	9.72	--	--	--	

Example 1

ASAP*prime*® Degradation Product Results

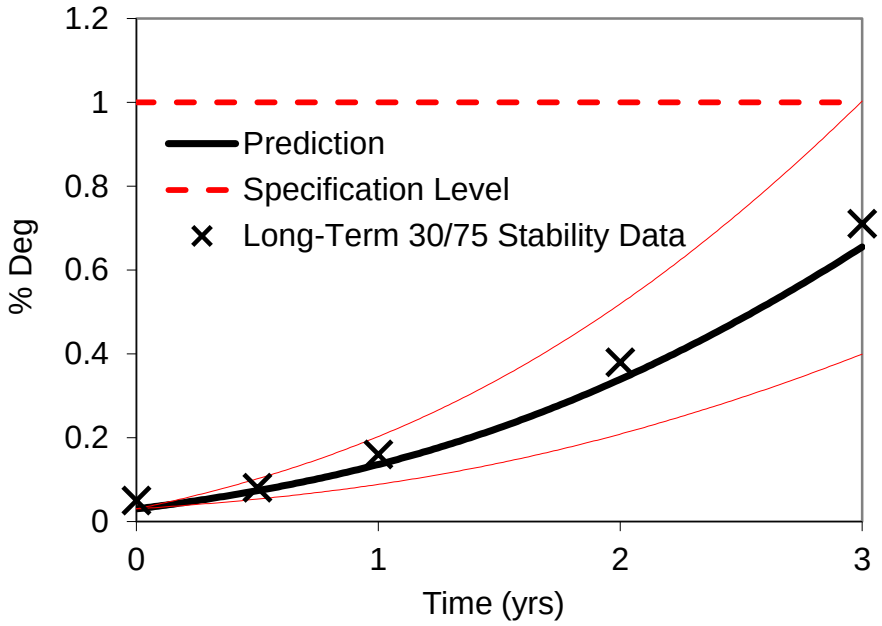
- ASAP Modeling Results

Degradation Product	Coefficient of Determination (R^2)	Probability of Passing Following 1 year at 25ºC/60%RH
A	1.00	100.0%
B	0.96	99.9%
C	1.00	100.0%
Total	1.00	100.0%

- Confirmed by at least 12 months of ICH stability at 25ºC/60%RH, 6 months at 40ºC/75%RH

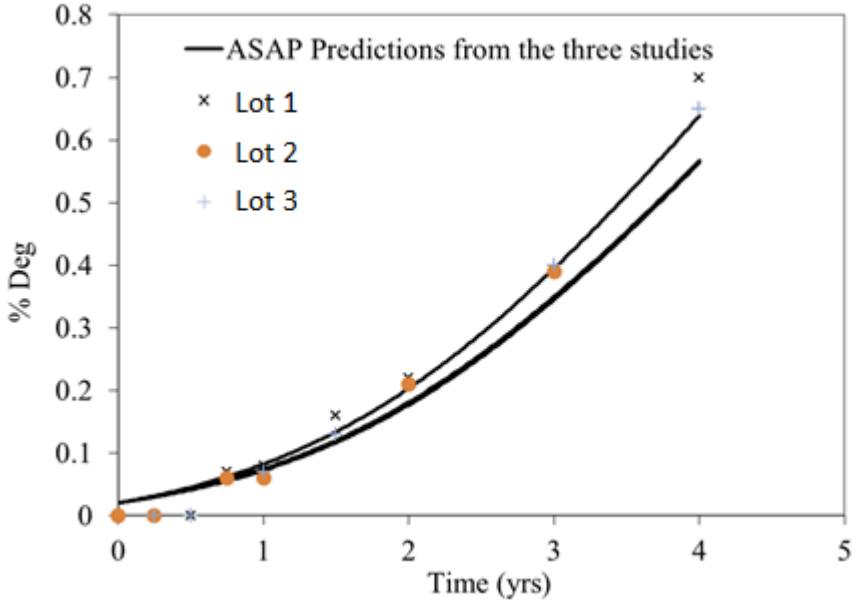
Pre-change Product

30-count HPDE bottles with 1 g desiccant



Post-change Product

7-Count HPDE bottles with 1g desiccant



Foil-foil blisters