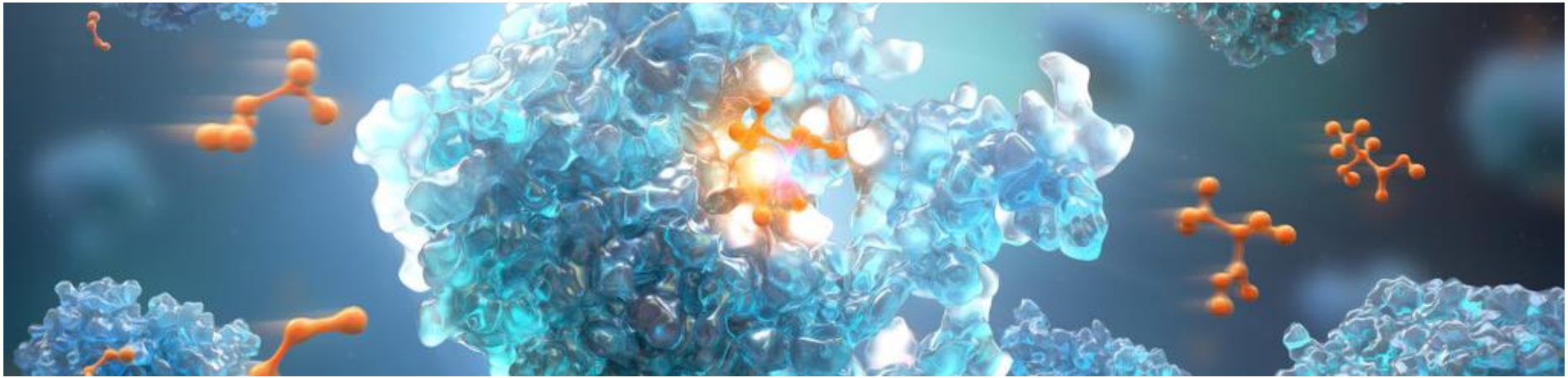
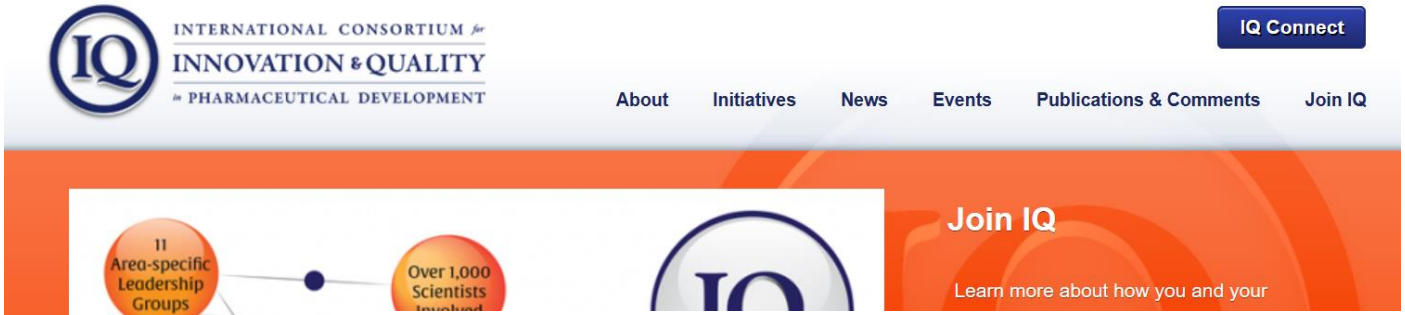
Lean Stability Case Studies

IQ Lean Stability Working Group Presentation
Science of Stability Conference 2019

Strictly Confidential
October 2019





What is IQ?

Our Work

IQ has ongoing initiatives that span the drug development process: we are active in the areas of chemistry, manufacturing and control; preclinical safety; drug metabolism; clinical pharmacology; quality; and the reduction, refinement, and replacement of animal testing. Within IQ:

- ***The IQ Board of Directors*** is responsible for strategic oversight of the Consortium's portfolio and is the Consortium's primary decision-making body.
- ***Leadership Groups*** are standing, discipline-specific forums that allow experts in major areas of pharmaceutical science to discuss and construct strategies to address key challenges. Leadership Groups are also responsible for encouraging collaboration within the organization, particularly across disciplines. For a complete list of IQ Leadership Groups, see Initiatives.
- ***Working Groups*** are project-based expert groups formed to address specific, critical, and timely issues in drug development. Working groups are sponsored and overseen by the Leadership Groups, and sunset upon completion of their work. They frequently undertake data-sharing and benchmarking activities, among others.

IQ Lean Stability Working Group

To drive industry use of stability knowledge and understanding to derive stability protocols and reduce routine non-value added stability testing. To further drive regulatory acceptance of science and risk based protocol strategies.

Goals:

- Industry alignment on how to pursue lean stability strategies
- Drive greater global regulatory consensus
- Enable speed to clinic, registration, and post-approval changes through lean strategies
- Gain understanding of complex regulatory landscape
- Removal of redundant and/or non-stability related testing from stability protocols

Initial work focused on benchmarking

- Survey distributed and data collected in 2017

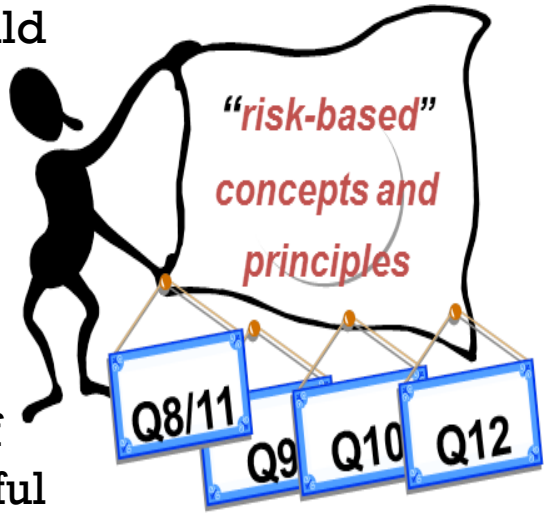
Activities

- Interpretation, discussion of survey results
- Publication of benchmarking and industry case studies

What is a Lean Stability Strategy?

- Science and risk based strategies utilize all product knowledge and understanding to develop the right stability plan for a product

- A lean stability strategy can take many forms but it should be:
  - Product specific
  - Dependent on the stage of development
  - Reflect product knowledge available

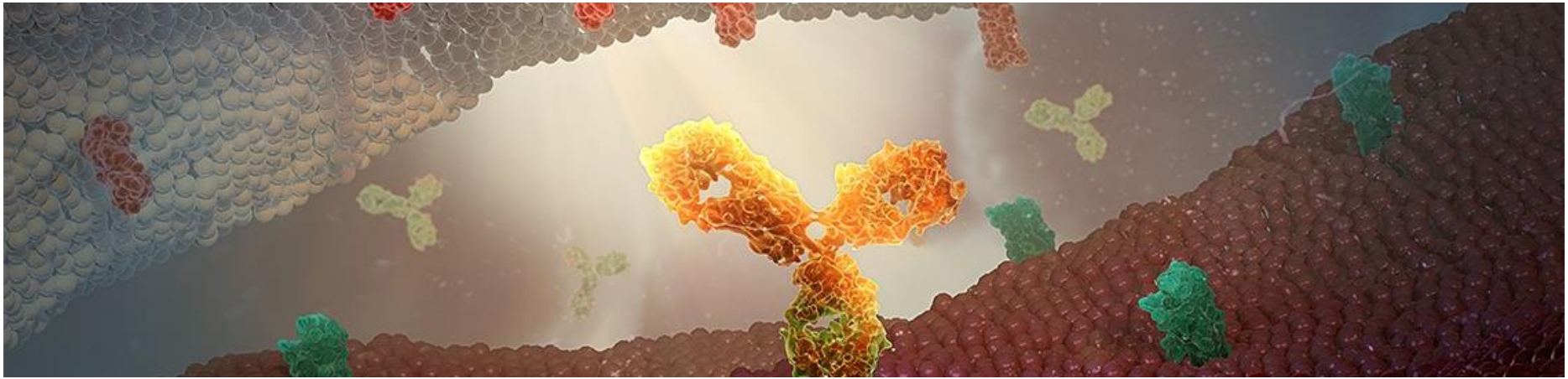


- Stability knowledge is gained in a cumulative manner throughout a product lifecycle and via different types of studies – long-term clinical, ASAP, open bottle, purposeful degradation studies, short term confirmatory, etc.

Clinical Development

Main objective for stability studies is to demonstrate that drug substance and drug product are of suitable quality throughout the retest period/shelf-life under defined storage and packaging conditions.

During this phase of development, changes and improvements are typical. Lean stability strategies may take the form of using predictive tools and/or confirmatory studies to demonstrate a change does not impact stability rather than re-initiating a long-term stability protocol.



Drug Substance Stability Applied to Product

Case Studies 1 & 2

- Phase I formulations of drug substance filled in capsule
- Proposal in CTAs that drug substance stability data was representative of the DiC stability
  - Section P.8 referenced Section S.7 data
- Risk assessment performed to ensure drug substance not susceptible to moisture uptake from HPMC capsule shells
- Regulatory submissions made in US, France and Spain

Regulatory response

- US and Spain requested that the DiC be placed on long-term stability
- Due to timing constraints no technical discussion was pursued and materials were placed on stability

Benefits realised

- Time savings gained by not waiting for 1 month DiC stability data prior to IND/CTA filings

Drug Substance Stability Applied to Product

Case Studies 1 & 2

- 3 weeks 70˚C/75% RH drug substance data used to justify 15 month retest period
- Phase I powder for oral solution formulation of drug substance filled in a bottle
- Drug substance data used to justify 12 month PfOS shelf life
- Commitment to complete long term drug substance studies for duration of clinical study

Regulatory response

- Successfully approved in both US and Germany

Benefits realised

- Time savings gained by compression of clinical submission time lines
- Resource savings in not conducting a drug product long term stability study

Drug Substance Route Change

Case Study 3

- Synthetic route changes on drug substance manufacturing campaigns
- Internal risk assessment performed to determine impact of synthetic route changes
- Accelerated short term comparison studies performed
  - 2 to 4 weeks duration
  - Conditions driven by prior degradation chemistry knowledge
  - Ranged from 40˚C/75% RH to 70˚C/75% RH
- Comparability data included in S.7 as justification for not placing subsequent batches on stability
- Regulatory submissions made in US and EU markets with no questions received during approval process

Excluding Tests from Stability Study

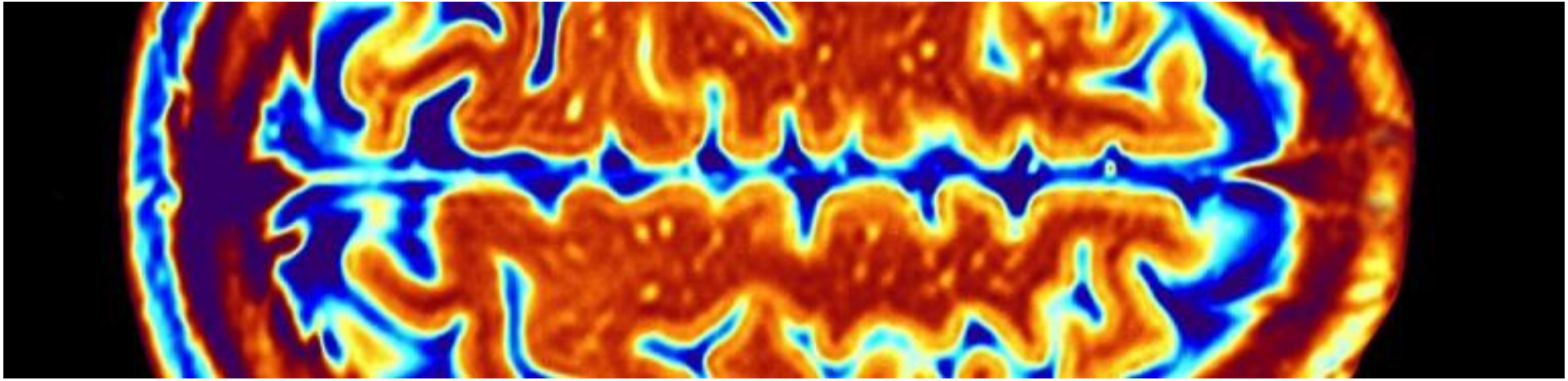
Case Study 4

- Routine exclusion of assay testing proposed in CTAs in situations where drug substance stability batch was that used as reference standard batch
- Justification stated that as stability batch and reference standard batch were stored under same conditions, assay results would only reflect method accuracy rather than degradation

- This approach was leveraged in a wide range of markets:
  - US, Canada, Czech Republic, Belgium, Hungary, Slovakia, Romania, Bulgaria, India, Philippines, Taiwan and Turkey
  - Regulatory queries received but approach widely accepted
  - Belgium requested assay is included in future submissions for a specific product
  - Czech Republic accepted mass balance approach with commitment to set up a future lot on stability and monitor assay
  - Canada did not accept this approach

Registration

In this phase of development, a lean strategy may leverage the cumulative clinical and registration stability data to justify reducing the tests, time points and/or storage conditions that are necessary to monitor stability on an annual basis.



Bracketing Study Designs

Case Studies 5 & 6

Strength		50mg			75mg			100mg		
Batch		1	2	3	1	2	3	1	2	3
Container size	15ml	T	T	T				T	T	T
	100ml									
	500ml	T	T	T				T	T	T

- Drug product with seven dosage strengths and two packaging configurations
- Bracketing stability design was proposed and accepted in pre-NDA meeting with FDA

Strength	Low			Intermediate (n=5)	High		
Batch	**1**	**2**	**3**	**1**	**1**	**2**	**3**
Packaging – 1	X	X	X	X	X	X	X
Packaging - 2	X	X	X	X	X	X	X

- Post approval stability protocol

Strength	Low			High		
Batch	**1**	**2**	**3**	**1**	**2**	**3**
Packaging – 1	X	X	X	X	X	X
Packaging - 2	X	X	X	X	X	X

Bracketing Study Designs

Case Studies 5 & 6

Strength		50mg			75mg			100mg		
Batch		1	2	3	1	2	3	1	2	3
Container size	15ml	T	T	T				T	T	T
	100ml									
	500ml	T	T	T				T	T	T

- Drug product with five strengths and one packaging configuration
- Bracketing stability design was proposed and accepted in pre-NDA meeting with FDA

Strength	**Low**			**Intermediate (n=1)**		**High**		
Batch	**1**	**2**	**3**	**1**	**2**	**1**	**2**	**3**
Packaging – 1	X	X	X	X	X	X	X	X

- Post approval stability commitment

Strength	**Low**			**High**		
Batch	**1**	**2**	**3**	**1**	**2**	**3**
Packaging – 1	X	X	X	X	X	X

Lean Proposals for Annual Batch Testing

Case Studies 7 & 8

- Complex modified release drug product with multiple strengths manufactured from common pellets
- Primary stability data supported 36 month shelf life
- No commitment to confirm shelf life as primary stability batches manufactured at commercial site and scale

- Lean proposal in annual batch commitment
  - One batch per strength per year
  - Removal of assay and water content tests as these were not stability-indicating
  - Long term storage condition only (25˚C/60% RH)
  - Reduction in time points to annual testing only

Lean Proposals for Annual Batch Testing

Case Studies 7 & 8

- FDA accepted the following proposals:
  - Long term storage condition only
  - Annual time point testing only

- Agency required batches of additional strengths be tested when manufactured from different intermediate pellet batches

- Agency required assay and water content testing be included
  - Assay
    - After sufficient product history was accrued a prior approval supplement could be submitted to remove this test from subsequent studies
  - Water content
    - Monitored at release and on stability
    - After sufficient data accrued, either acceptance criteria be proposed in CBE-30 or justification for non-inclusion provided to the agency

Lean Proposals for Annual Batch Testing

Case Studies 7 & 8

- Stable immediate release capsule drug product in 3 strengths
- Anticipated low-volume commercial product
- Traditional primary stability strategy and volume of data submitted in NDA

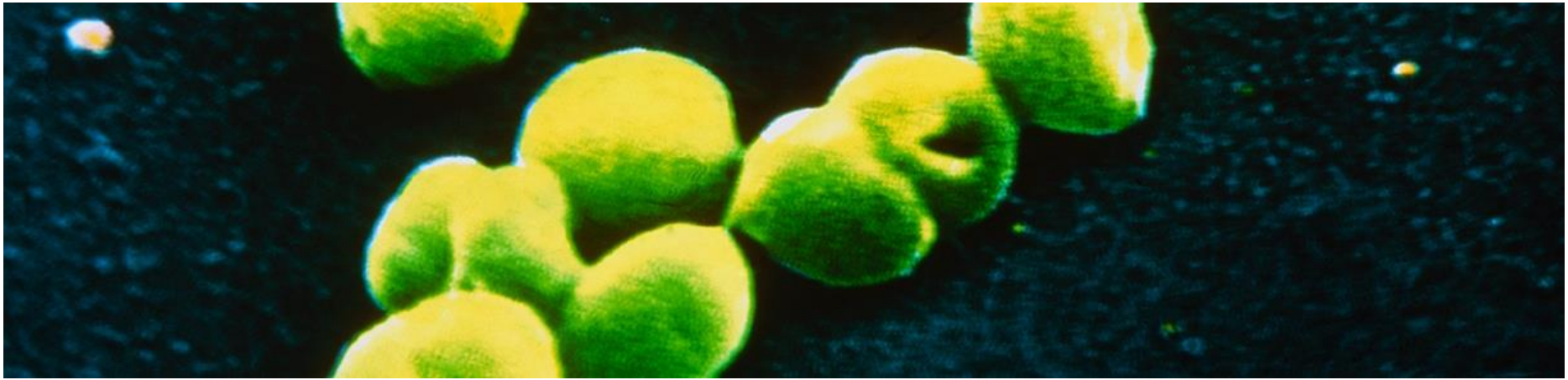
- Lean proposal in post approval commitment
  - Use non-printed capsules for 2 out of the 3 batches for 2 strengths
  - Reduced tests to appearance, assay, dissolution and degradation products
  - Long term storage condition only (30˚C/75% RH)
  - Reduction in time points to annual testing only

- This approach enabled capsules not used for stability testing to be used for blinded clinical studies

- Approach accepted globally

Post Approval

In the post approval phase, product knowledge and stability understanding are highest and there are many opportunities to leverage lean stability strategies to support a change.



Stable Drug Substance and Drug Product

Case Study 9

- Small molecule oral drug substance and drug product
- Lean post approval / annual stability strategy proposed
  - Long term storage condition only – no accelerated data
  - Reduced test attributes: appearance, assay, impurities/degradation products, dissolution (DP only), loss on drying (DS only)
  - Reduced time points: 6, 12, 18, 24 months and annual time points thereafter if longer dating was pursued

- Global submissions included this strategy:
  - EU, Japan, US, Canada, Switzerland, Australia, Taiwan, South Korea, Hong Kong, Brazil, India, Turkey, Russia, Mexico, UAE, Argentina & Kuwait
  - No regulatory questions received to date
  - No additional justification required in Section P.8.2

Multiple Drug Product Strengths and Presentations

Case Study 10

- Large product family separated into multiple categories based on formulation, container type and filling volume
- Historical commitment for annual testing was 1 code (formulation/container) per category.
- As there were multiple categories, this resulted in multiple batches being placed on stability each year
- Lean stability strategy was proposed:
  - Revision to product categorization based on historical data review
  - Reduction in number of time points
  - Reduction in testing at each time point
- A summary of the proposal with associated technical rationales were submitted and accepted by US with no questions

- **Benefits realised – reduction of 18 batches placed on stability per annum**

Biologic – registration stability package

Case Study 11

- Registration package
  - Drug substance:
    - 5 representative batches submitted
    - At least 36 months data at long term storage condition ≤ -60°C
    - 6 months at accelerated condition 5°C and stressed condition 25°C/60% RH
  - Drug product
    - Refrigerated product
    - Bracketing approach used
    - Time points tested were as prescribed in ICH Q5C

Strength	Low			Intermediate	High		
Batch	**1**	**2**	**3**	**1**	**1**	**2**	**3**
Prefilled syringe container	X	X	X	X	X	X	X

Biologic – post approval stability proposal

Case Study 11

- Lean post approval stability strategy proposed
  - Drug substance
    - Long term storage condition only
    - Annual time points only
    - **Approved by all agencies**
  - Drug product
    - Long term storage condition only
    - One batch per strength per annum
    - Omission of 3 and 9 month time points
    - **Agency required 6 months at accelerated conditions for each batch**
- Benefits
  - Reduction of 4 drug substance time points per annum
  - Reduction of 22 drug product time points per annum

Change in Manufacturing Site

Case Study 12

- Drug substance manufacturing site change required for a marketed small molecule solid oral dosage form product
- No change to manufacturing process and no proposed changes to drug product
- Very stable drug substance and drug product with no identified shelf-life limiting attributes
- Approved in 79 markets
- 23 of these markets required some form of stability data to support the change
  - 6 required either 6 or 12 months of drug substance data from new site
  - 17 required drug substance and drug product stability data

Change in Manufacturing Site

Case Study 12

- Lean stability strategy proposed:
  - Reduction in time points
    - 3 and 6 months at 40˚C/75% and annual time points at 30˚C/75% RH
  - Reduction in testing
    - Appearance and purity for drug substance
    - Appearance, assay, degradation products and dissolution for drug product
- Regulatory reception was mixed
  - Proposed strategy was approved by 9 markets and is under review in a further 8 markets
  - One market required additional time points and inclusion of assay test for drug substance protocol
  - Another market required additional time points for drug product
- **However, all protocols approved represent a reduction in testing burden for the sponsor**

Conclusions

- Product knowledge underpins understanding of the stability-related risks associated with the product
- Scientific rationale combined with product understanding has been used to leverage lean stability strategies throughout development
- However a unified regulatory position to science- and risk-based stability strategies does not exist at present potentially leading to conservatism within drug companies
- Although challenges remain both within companies and externally from regulators these case studies demonstrate that many scientifically sound lean strategies are acceptable from a regulatory perspective

Confidentiality Notice