ICH Q12 Workshop

Value of Fundamental Scientific Approaches to Understanding Stability in Lifecycle Change Management

Ron Ogilvie, presenting for

Pfizer Inc., Sandwich , Kent

Stability and Lifecycle Change Management

ICH Q12 will OPTIMISE lifecycle change management.
The best change management approaches currently are SCIENCE-BASED –
- For a specific product, based on specific understanding (c.f. IVIVC)
- For groups of products, underpinned by broad scientific understanding (c.f. BCS class change management)

STABILITY data is expected to support the introduction of many changes.

Understanding stability at a fundamental level can support different approaches to manage changes to a specific product AND provide approaches that can be used to manage changes to multiple products. Let's consider how

- Stability understanding can change the basis of ESTABLISHED CONDITIONS
- Stability understanding for a product can change stability data expectations - PACMPs
- Stability science can provide approaches to change management across multiple products - EXPANDED PACMPs

PACMPs to agree different approaches to manage change may be valuable to manufacturers of small molecule DS / DPs

Approaches to Optimising Lifecycle Change Management

Increase clarity around regulatory commitments / established conditions and enable different ways of setting established conditions
Empower the inspectable quality system – balance submission content and inspectional assurance
Move from 'Tell and Do' to 'Do and Tell' then on to 'Explain and Do' and - ULTIMATELY - 'Understand and Do'
Allow different classes of changes to be managed in a TIERED manner
Link product and process understanding to DIFFERENTIATED post-approval change management expectations
• Applicants demonstrate ENHANCED product and process understanding, allowing for more specific approaches to change management for well-understood products
• Development of FUNDAMENTAL scientific approaches that can be used for more than one product
• Ideally, applicable to any product GLOBALLY – new / existing; inc. bios

High Value Focus Area for Post Approval Change Optimisation – STABILITY

It makes sense to optimise management of changes management that happen most frequently (and the data most commonly needed to support significant changes) AND changes that are most resource-intensive / time-consuming to prosecute.

A key area for consideration is the STABILITY DATA expected to support change – such data is needed for many changes, expectations differ, and generation of the data is time-intensive.

EU Stability for Variations EMA/CHMP/CVMP/QWP/441071/2011rev.2 contains elements of 'risk based' change management – **'understanding-based' approaches can be extended**

There are ways to use FUNDAMENTAL approaches to UNDERSTANDING STABILITY to provide different and more efficient approaches to stability change management –

- PACKAGING CHANGE MANAGEMENT - STABILITY RISK ASSESSMENTS - ACCELERATED STABILITY TESTING

Packaging Change Management – e.g. can a fundamental attribute be defined as the ESTABLISHED CONDITION ?

Packaging change can have adverse impact on product stability and real time stability data can be needed to support a packaging change.
Not all packaging changes are EQUAL – EU guidance already allows for consideration of equivalence of packaging materials (based on comparative permeability data) ☺. THIS USEFUL CONCEPT CAN BE TAKEN FURTHER

The CRITICAL aspects of a product's packaging can be understood at a FUNDAMENTAL level – allowing critical attributes of a new container closure to be determined and described at the fundamental level.

- If the new CC is more protective (e.g. by MVTR) wrt. the critical driver of instability then NO stability data might be needed – SUCH UNDERSTANDING CAN BE APPLIED ACROSS MANY PRODUCTS

- If the new CC is less protective, product-understanding can allow prediction of degradation kinetics and predict what stability data would be needed – ACCELERATED rather than RT data

- The original shelf-life can be maintained for well–understood packaging changes with NO further stability data requirement

The ESTABLISHED CONDITIONS of packaging specifications can be determined and specified in DIFFERENT WAYS – rather than stating a 'packaging condition' one could e.g. ESTABLISH A MINIMUM MVTR (manage changes in the Quality System)

ENHANCING THE VALUE OF POST-APPROVAL CHANGE MANAGEMENT PROTOCOLS –

Stability Risk Assessment –

At present, generation of stability data involves providing results from 'all specification testing' for a period of time, for some number of (full scale) batches. UNDERSTANDING STABILITY can optimise such approaches –

- Generation of confirmatory stability data for a MORE FOCUSSED set of attributes – e.g. for only one degradant (the shelf-life limiting attribute) OR for a SHORTER PERIOD OF TIME (if rate of degradation – under accelerated condition - is LESS than for pre-change product) OR for a LOWER NUMBER of batches (at REDUCED scale) as scientifically-justified.
- Such proposals could be made in a PACMP
- AND could be used in support of MORE THAN ONE PRODUCT and / or MORE THAN ONE CHANGE – different changes could be underwritten by the same focused stability data AND different products where SLL degradant identified can be managed under same EXPANDED PACMP

EVEN by CONTROL OF PARAMETERS, NOT generation of stability data – e.g. by understanding the fundamental drivers of instability (e.g. water content / hygroscopicity) and controlling these fundamental parameters through change

Accelerated Stability Testing -

Drug substance / product stability can be UNDERSTOOD at a mechanistic / kinetic level.
Stability kinetics can be examined at higher temperatures in a way predictive of behaviour at lower temperatures (classical Arrhenius thermodynamics). SO, ACCELERATED test conditions can be established that PREDICT the stability of the DS / DP under (various) LT storage conditions. This has consequences / presents opportunities -

- ONE STABILITY DATASET could support a range of ICH stability zones
- A maximum change rate can be established (at the accelerated condition) to ensure the DS / DP quality will be maintained across the shelflife
- Change assessment can be conducted in the accelerated model WITHOUT having LT stability data on the critical path to introducing the change

- Such proposals could be made in a PACMP
- AND the same approach could be used in support of more than one product or more than one change – GENERALISED PACMPs / INSPECTABLE QUALITY SYSTEM

Associated References – The Application of Science and Risk Based Concepts to Drug Substance Stability Strategies – J.Pharm.Innov. 7: 205-213 (2012); Lean Stability Strategies – J.Pharm Innov. (:259-271 (2014)

Using stability science differently

- Different ways of setting established conditions – **Container closure commitments based on critical attributes (e.g. MVTR)**
- Empowering the inspectable quality system – **multi-product change management approaches**
- Moving from 'Tell and Do' (**having LT stability data**) to 'Do and Tell' (**using accelerated data to underwrite change without LT data**) and on to 'Explain and Do' (**PACMPs**) and ULTIMATELY 'Understand and Do' (**making changes based on maintenance of parameters linked to stability, not based on stability data**)
- Allowing changes to be managed in a TIERED manner – **risk-assessed stability datasets**
- Development of fundamental scientific approaches that can be used for more than one product – **understanding shelf-life life limiting degradants, mechanisms and kinetics of degradation and predictive accelerated stability**
- Applicable to any product – **the science is the same**

What could Q12 guideline facilitate ?

Refresh and broaden the concept that applicants can present enhanced product and process understanding (ALLOWING FOR DIFFERENT WAYS TO ESTABLISH CONDITIONS) and make proposals for more specific approaches to change management for a well-understood product (STABILITY DESIGN SPACE)

Provide BETTER approaches to MANAGE CHANGE than current somewhat "one size fits all" approaches–

- For a specific product based on specific understanding
Shelf-life indicating degradant; kinetics of degradation (PACMP)

- For a group of products underpinned by general scientific understanding (E-PCMP)
Accelerated stability evaluations; packaging changes

Empower the inspectable quality system – balancing submission content and inspectional assurance
(INSPECTIONAL OVERSIGHT OF QUALITY SYSTEM APPROACHES)

LET'S SUCCEED - If the opportunity to optimise PAC is not taken, all stakeholders may LOSE – delay of improvements (and maybe of medicine availability), spend of resources on non-essential matters etc.

ACKNOWLEDGEMENTS

Many colleagues inside Pfizer, past and present, have contributed to our endeavours to develop and utilise fundamental understanding of stability science AND our engagement in the ICH process, to seek harmonisation and optimisation through strong scientific understanding.