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Targeted revision of ICH Q1s/Q5C - Opportunities with science and risk-based approaches

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Boris Zimmermann, Senior Director - Analytical Science Genentech, A Member of the Roche Group

Table of contents



- Science and risk-based approaches in pharmaceutical stability
- Stability lifecycle and application areas
- Example 1 Annual stability commitment protocol
- Example 2 Post-marketing change and shelf-life of post-change material
- Summary



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Science and risk-based approaches in pharmaceutical stability

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Introduction & current environment

- Science- and risk-based approaches in ICH Q8/11 (Development of Control Strategies) and ICH Q9 (Quality Risk Management), ICH Q10 (Quality System), and Q12 (Life-cycle Approaches)
- ICH Q1s/Q5C provide uncertainty to both industry and regulatory agencies using those approaches
- ICH (Q1A(R2), Q1D) allows for bracketing and matrixing during stability testing
- Recently established guidelines for accelerated programs (FDA BTD, EMA PRIME) facilitate the use of new approaches and innovative tools for stability - COVID-19 pandemic learnings
- Industry and regulatory agencies gained maturity with prior/platform knowledge, enhanced product-scientific understanding, and risk-based principles
- Targeted revision of ICH Q1s/Q5C started

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Talking Points

Why is Stability Testing important?

- Stability testing is important
- Determining factors such as a product's shelf life
- Optimal storage conditions
- Behavior when excursions and in-use
- Assuring a safe and efficacious product for patients

What to learn from ICH Q8 - Q11 framework?

- Structured way to define product critical quality attributes, design space, the manufacturing process process and product knowledge, and the control strategy
- Q11 clarifies principles of Q8, Q9, and Q10 and provide examples

Risk assessment

- Linking to stability Which material attributes and process parameter have an effect on stability
- 3 Fundamental questions
 - What might go wrong?
 - What is the likelihood (probability) it will go wrong?
 - □ What are the consequences (severity)?
- Enhanced product-scientific knowledge, platform knowledge/experience, and tools enable to answer the questions and is de-risking stability

What to learn from ICH Q12?

Regulatory tools and guiding principles enhance industry's ability to manage postapproval changes supporting innovation and continual improvement

Stability lifecycle and application areas

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Stability lifecycle and application areas





Consistent application of science- and risk based approaches to further debottleneck stability to avoid drug shortage, accelerate urgent medical needs and focus on innovation.





Example 1 - Annual stability commitment protocol

- Product knowledge and stability understanding highest in commercial/post-marketing phase
- Years/decades of consistent stability profile incl. experience manufacturing and analytical method changes knowledge (incl. platform knowledge)
- Non-stability indicating testing removed/reduced adequate stability information still provided
- Stability assessment integrated to change control/PQS process

mAb (IgG1) DS @-40°C, @DP 5°C 2 DS mfg sites 2 DP mfg sites +10y post-launch



DS	0y	1у	2у	Зу
Appearance	х	х	х	х
Charge -IEC	х	х	х	Х
Potency	х			х

One DS site per mfg year alternating between sites

DP	0у	1у	2у	Зу
Appearance	х	х	х	х
VP/subVis	х	х	х	х
Charge-IEC	х	х	х	х
Size -SEC	х	х	х	х
Potency	х	х	х	х
рССІ	х			х

One DP site per mfg year alternating between sites; no endotoxin, no sterility







Example 2 - Post-marketing change and shelf-life of post-change material

- Introduction of additional DS manufacturing site post-marketing
- Benefit/risk balance included Quality Risk Management, Validation, Comparability, Site Inspection Assessment
- Accelerated study with post-change material and stress comparability study w/ representative post-change vs. pre-change material to confirm know stability behavior and mode(s) of degradation
- DP stability impact assessment
- Enabled by ICH Q12 section 9. stability data approaches



Key check points:

mAb (lgG1) DS @-20°C, @DP 5°C 1 DS mfg sites 1 DP mfg sites +3y post-launch

- ✓ Low risk from benefit/risk assessment
- ✓ Scientific-sound comparability exercise successful
- ✓ No impact seen in stability-related. shelf-life limiting quality attributes
- ✓ No impact to DP manufacturing and stability - CQAs, impurities, raw materials, leachable profile





Commitment to notify about any OOT and include new DS into DP stability program for confirmation

Summary

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Summary



- Opportunity to use more science and risk-based approaches for stability
- Risk-based decision-making in stability testing needs to be encouraged in alignment with the existing ICH Q8-Q11 framework and ICH Q12
- Two examples provided Efficient, product-specific post-marketing stability studies are fully aligned with modern approaches used in product and process development and reflect gained experience/knowledge
- Encouraging support from regulatory agencies however, regulatory acceptance of these approaches is variable
- Industry to outline how the combination of scientific rationale and product knowledge has been leveraged successfully to develop stability strategies that are robust, efficient, and safe through the product shelf-life



The revised ICH Q1 stability guideline needs to have added stability-related risk-based principles that are scientifically sound, including examples

Doing now what patients need next