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Published on IVT Network (www.ivtnetwork.com)

JVT Volume 26, Issue 6 – December 2020

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Industry One-Voice-of-Quality (1VQ) Solutions: Effective Management of Post-Approval Changes in the Pharmaceutical Quality System (PQS) - Through Enhanced Science and Risk-Based Approaches

PEER REVIEWED

SHELF-LIFE EXTENSIONS FOR PHARMACEUTICAL PRODUCTS

ABSTRACT

Post-approval changes (PACs) are inevitable and necessary throughout the lifecycle of pharmaceutical products - to implement new knowledge, maintain a state of control, and drive continual improvement.

This One-Voice-Of-Quality (1VQ) paper is part of a series of industry case studies intended to demonstrate the standard application of the principles outlined in the publication "*Effective Management of Post-Approval Changes in the Pharmaceutical Quality System (PQS) - Through Enhanced Science and Risk-Based Approaches Industry; One-Voice-of-Quality (1VQ) Solutions*" in *PDA Journal of Pharmaceutical Science and Technology*, 2020 [1].

Furthermore, this 1VQ paper provides a practical application of the concepts described in ICH Q9, *Quality Risk Management* [2], ICH Q10, *Pharmaceutical Quality System* [3], and ICH Q12, *Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* [4] to shelf-life extensions for pharmaceutical products.

In this case study, the risk associated with the extension of shelf-life was evaluated. The conclusion drawn is that shelf-life extension changes when controlled effectively as described in this paper, present a low risk to product quality, and therefore can be downgraded from a prior-approval to notification or annual reportable and managed in the PQS with immediate implementation.

KEYWORDS

CMC, Chemistry Manufacturing and Control, Regulatory, Post-approval Change, PAC, ICH Q9, Quality Risk Management, QRM, ICH Q10, Pharmaceutical Quality System, PQS, ICH Q12, Lifecycle Management, Change Control, Regulatory Considerations, Regulatory Flexibility, Science and Risk-based Approach, One-Voice-Of-Quality, Shelf-life Extensions, Pharmaceutical Products.

BACKGROUND AND CONTEXT

ICH Q10, *Pharmaceutical Quality System*, Annex 1 describes potential opportunities to enhance science and risk-based regulatory approaches to PACs as follows: When a company can *"demonstrate effective PQS and product and process understanding"* this is an opportunity to *"optimize science and risk-based PAC processes to maximize benefits from innovation and continual improvement"* [3]. Current regulatory mechanisms and guidance for PACs do not consider the company's latest product and process knowledge when determining the type of filing required to implement the change. Further, the application of ICH Q9, *Quality Risk Management*, or the effectiveness of the company's PQS to manage PACs is not considered during the assessment of individual PACs. or during inspections. Demonstrating a detailed understanding, effective implementation, and compliance with ICH Q10, will allow companies to overcome barriers to continual improvement and innovation. Additionally, it will help mitigate drug shortages in the global pharmaceutical supply chain by allowing faster implementation of PACs and reduce-the-burden on both industry and regulators.

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This specific example of shelf-life extension for pharmaceutical products demonstrates the application of the principles outlined in ICH Q9, Q10, Q12 irrespective of current national or regional reporting category and concludes that it can be managed as a notification with immediate implementation effect. It is acknowledged that different companies might be handling this example differently and may not need to pursue a regulatory downgrade for this PAC. However, companies that file this as a prior approval change, may use this position paper as a starting basis and modify scope and relevant considerations for their specific need and in accordance with their company's PQS requirements.

This PAC example and the 1VQ work in general is sponsored by the Chief Quality Officer's from more than 20 pharmaceutical companies [5].

DESCRIPTION OF CURRENT STATE FOR SHELF-LIFE EXTENSIONS FOR PHARMACEUTICAL PRODUCTS

Regulatory authority notification or prior approval with long waiting periods is required in most countries for changes associated with shelf-life extensions for pharmaceutical products, even when there are no changes to the product quality, patient safety or drug product efficacy, and the formulation, manufacturing and laboratory controls remain the same, and there are no changes to the stability acceptance criteria (*refer to Table 1*).

In certain cases, drug shortage situations that could have been avoided if a product with a longer shelf-life was available in the supply chain, is hindered by the manufacturer's inability to extend the shelf-life using product and process knowledge, sound scientific and risk-based assessment principles without prior regulatory approval.

The initial pharmaceutical product regulatory registration dossier is typically based on information and supporting data described in ICH M4Q CTD Quality Module 3. The product shelf-life with the supporting stability data is submitted for review and approval to the concerned regulatory authorities. In most cases, the concerned regulatory authority grants the applicant's initial drug product shelf-life request as conditional approval with a commitment to continue ongoing stability monitoring and provide updates as part of a post-approval commitment. The applicant then provides full stability report and supporting data to cover the entire approved shelf life of both the drug substance and drug product. An applicant based on the ongoing stability data, may request an extension of the product shelf life later as a post-approval change, and submit the required supporting information.

The table below lists the current regulatory reporting categories for shelf-life extensions of pharmaceutical products in different countries.

Table 1: Current Regulatory Reporting Categories for Pharmaceutical Products Shelf-Life Extension in ICH, PIC/S and WHO member countries

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Country	Annual Reportable	Notification	Minor Variation for EU countries- Type 1B or a 'Prior Approval' for all other countries	Major Variation for EU Countries – Type II or Prior-Approval
1. WHO*				*x*
2. Argentina				*x*
3. Armenia				*x*
4. Australia				*x*
5. Austria			*x*	
6. Belgium			*x*	
7. Brazil				*x*
8. Canada			x	
9. China				*x*
10. Colombia				*x*
11. Cuba				*x*
12. Croatia				*x*
13. Cyprus			*x*	
14. Czech Republic			*x*	
15. Denmark			*x*	
16. Estonia			*x*	
17. European Union			*x*	
18. Finland			*x*	
19. France			*x*	
20. Germany			*x*	
21. Greece			*x*	
22. Greenland			*x*	
23. Hong Kong (SAR, China)				*x*
24. Hungary			*x*	
25. Iceland			*x*	
26. India	*x*			
27. Indonesia				*x*
28. Iran				*x*
29. Ireland			*x*	
30. Israel			*x*	
31. Italy			*x*	
32. Japan		*x*		
33. Jordan				*x*
34. Kazakhstan				*x*
35. Latvia			*x*	
36. Liechtenstein			*x*	
37. Lithuania			*x*	
38. Malaysia				*x*
39. Malta			*x*	
40. Mexico				*x*

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41. Moldova				*x*
42. Netherlands			*x*	
43. New Zealand				*x*
44. Norway			*x*	
45. Poland			*x*	
46. Portugal			*x*	
47. Russian Federation				*x*
48. Romania			*x*	
49. Saudi Arabia				*x*
50. Singapore				*x*
51. Slovakia			*x*	
52. Slovenia			*x*	
53. South Africa				*x*
54. South Korea				*x*
55. Spain			*x*	
56. Sweden			*x*	
57. Switzerland			*x*	
58. Taiwan (Chinese Taipei)				*x*
59. Thailand				*x*
60. Turkey				*x*
61. Ukraine				
62. United Kingdom			*x*	*x*
63. United States**	*x*			

**World Health Organization ((WHO)* - Commercial drug products can be registered via WHO procedures in Botswana, Burkina Faso, Cameroon, Congo, Cote D'Ivore, Malawi, Namibia, Senegal, Tanzania, Uganda, Zambia, Zimbabwe, etc.

***United States* - Annual Reportable, only when there is an approved stability protocol for shelf-life extension

The following are representative pharmaceutical industry specific examples that summarize the current state of shelf-life extensions:

Industry Case 1:

- Product: Oral Solid Dosage Form 0.25mg 28ct bottle; 2mg bottle 30ct; 0.25mg Starter Pack (count)
- Initial shelf life: 18 months, 18 months, and 9 months respectively, for the three presentations
- Proposed shelf life: 24 months for all presentations
- Supporting Stability Data: 3 commercial batches manufactured at commercial scale met the approved stability specifications
- Stability Conditions: 5ºC / Ambient R.H. and 25 ºC / 60 % R.H.
- Container-Closure System: bottle; 90cc HDPE bottle with 38mm Child resistant cap; starter pack - PA/AL/PVC blister packs

- Regulatory Impact:

  ☒ *Annual Reporting* for US

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☐ *Notification*

☒ *Minor Variation for EU Type 1B and 'Prior Approval' for all other countries*

Industry Case 2:

- Product: Biological Drug Product
- Initial shelf life: 24 months
- Proposed Shelf Life: 36 months
- Supporting Stability Data: 3 Commercial batches manufactured at commercial scale met the approved stability specifications
- Stability Conditions: 2-8 °C
- Container-Closure System: 5.2 mL Lyophilized vial
- Label Storage Condition: 2-8 °C, after reconstitution up to 12 hours at room temperature (25 °C) and up to 24 hours at 2-8 °C
- Regulatory Impact:

☒ *Annual Reporting for US with approved stability protocol*

☐ *Notification*

☒ *Minor Variation for EU Type 1B and 'Prior Approval' for all other countries*

Industry Case 3:

- Product: Drug-Device Combination
- Current Shelf Life: 18 months
- Proposed Shelf Life: 24 months
- Supporting Stability Data on: 3 commercial batches manufactured at commercial scale met the approved stability specifications
- Label Storage Conditions: US - store at 20-25 °C (See USP controlled room temperature)/ EU - store below 25 °C
- Container-Closure System: 15 mL bottle (60 doses); 30 mL bottle (120 doses)
- Regulatory Impact:

☒ *Annual Reporting for US with approved stability protocol*

☐ *Notification*

☒ *Minor Variation for EU Type 1B and 'Prior Approval' for all other countries*

SCOPE

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This paper applies to shelf-life extensions for commercial drug substances and drug products (chemical, biological and biotechnological products). The principles and risk-based approach described in this paper for shelf-life extensions of pharmaceutical products, are intended to apply globally to all regulatory authorities.

INDUSTRY 1VQ POSTION FOR SHELF-LIFE EXTENSIONS OF PHARMACEUTICAL PRODUCTS

The International Council for Harmonization (ICH) has finalized Q12 "Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management" in November 2019. This guideline provides regulatory flexibility in post-approval changes to the product or its manufacturing process based on latest product and process knowledge, sound-scientific and risk-based approaches.

Shelf-life extensions for drug substance and drug product with the appropriate supporting stability can be managed within the company's Pharmaceutical Quality System (PQS) leveraging the principles outlined in ICH Q9, Q10 and ICH Q12, and be reported to the Regulatory Authorities within ICH, PIC/S and WHO member countries through Annual Reports or Notifications without prior regulatory approval. This type of change is supported by stability data that met the approved stability specifications and should not require prior approval from the regulatory authorities. This will facilitate efforts to minimize drug shortages and improve the on-time availability of products to patients worldwide.

The pharmaceutical industry's position is to utilize the above-mentioned ICH guidelines for the shelf-life extension based on acceptable risk without requiring prior regulatory approval. This will allow the industry to avoid potential supply disruptions leading to drug shortages and undue burden on patients. In addition, it will contribute towards meeting the ICH Q10 objectives of achieving product realization, establishing and maintaining a state of control, and continual improvement.

STANDARD RISK-BASED APPROACH

Figure 1 below [1] describes the risk-based approach for assessment of a PAC to shelf-life extensions for pharmaceutical products. Application of this risk-based assessment utilizing the latest product and process knowledge and supporting stability data, should demonstrate that at a minimum, the shelf-life extension does not increase the risk to product quality, efficacy and/or patient safety.

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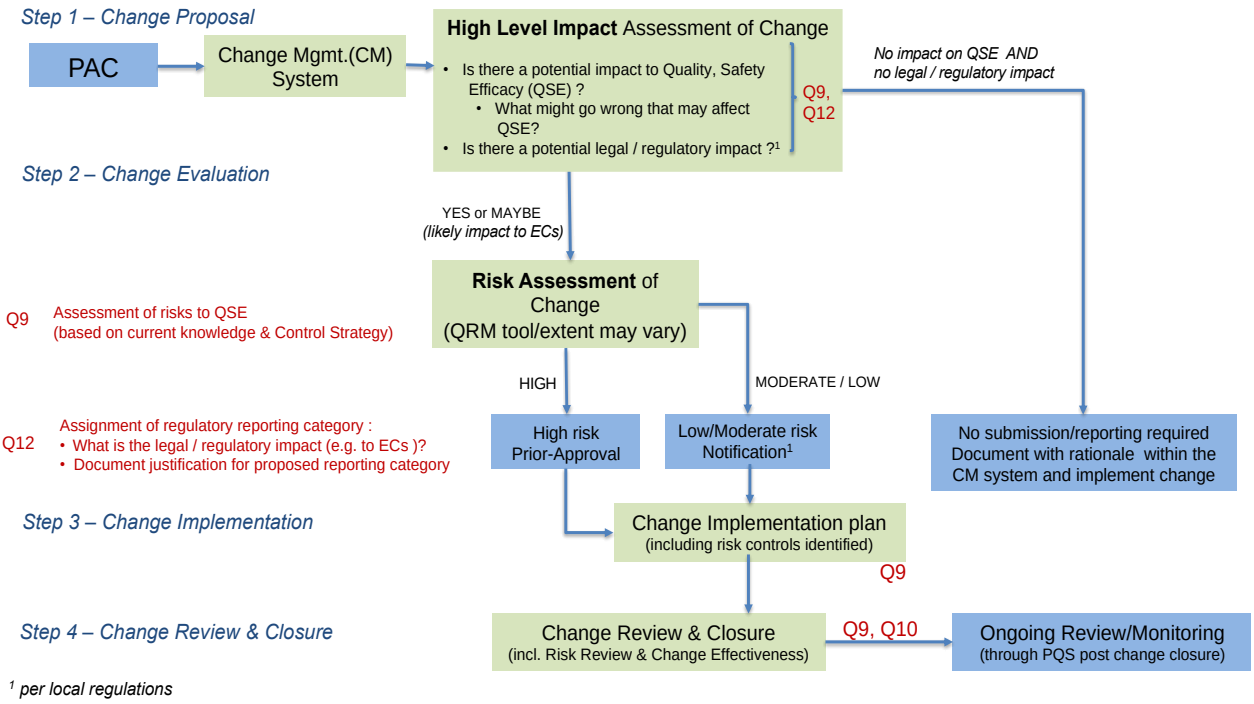

Figure 1: Risk-based Assessment of PACs and Determination of Regulatory Reporting Category

The following steps are completed to assess the impact and risks associated with shelf-life extension:

Step 1: Change Proposal

When a PAC to shelf-life extensions of pharmaceutical products is proposed and entered into the change management system, the potential Safety, Efficacy, Quality, Identity, Purity, Potency (SEQIPP) and Legal/ Regulatory impact of the change is considered including current control strategies. Utilizing existing product and process knowledge and stability data, initial impact assessment indicates that

- there is no potential SEQIPP risk associated with shelf-life extensions provided that the stability data supporting the change is readily available, assessed and met the approved stability specifications.
- there is a potential regulatory impact due to the divergent local, national and regional regulatory authorities' requirements for the reporting category of the change.

Step 2: Change Evaluation

A. Quality Risk Assessment: The initial impact assessment concluded that there is a potential impact associated with the change, therefore, a quality risk assessment should be performed for the shelf-life extension PAC. An appropriate risk assessment tool can be used to complete the risk assessment and should document current controls. Stability testing laboratory, quality control and quality assurance relevant subject matter experts should be involved in performing the risk assessment. When assessing potential risks of the change, any potential impact (direct or indirect) on the SEQIPP

of the product should be considered, based on current product/ process knowledge and the control strategy; some examples of risk questions that should be considered to assess the risks associated with a change to shelf-life extensions of pharmaceutical products include:

- Can the change impact product safety?
- Can the change potentially affect conformity of the product to current specifications?
- Can the change potentially affect the purity of the product?
- Can the change potentially impact stability of the product?

B. Assignment of Regulatory Reporting Category: Consistent with ICH Q12 [3], it is recommended that:
   - High-risk changes are categorized as prior-approval, and as such require regulatory authority review and approval prior to implementation.
   - Moderate- to low-risk changes are communicated to the regulatory authority as a formal notification, that takes place within a defined period before or after implementation, according to regional regulatory requirements.

The outcome of the risk assessment (performed in step 2A), and the available stability data, should indicate that there is no impact to product safety, purity, stability or current specifications. In such instances, a change to shelf-life extension for pharmaceutical products can be deemed to be low risk with adequate risk controls, and therefore can be managed as a notification with immediate effect for implementation through the manufacturer's PQS.

Steps 3 & 4: Change Implementation, Review and Closure

Change implementation, review and closure should be performed according to the change management process. Outcomes of the impact and risk assessments should be integrated into the overall change implementation plan. After implementation of the change, residual risks should be assessed and managed to acceptable levels prior to change closure; any unintended consequences or risks introduced as a result of the change should be evaluated, documented and handled adequately through effectiveness verification mechanisms. In case several changes are introduced at the same time or related to each other, the manufacturer should assess cumulative effectiveness of the changes.

After change closure, relevant risk assessment tools/documents should be updated, and post-effectiveness assessments documented in the PQS. Stability data trend analysis should be used for the on-going review/monitoring of the risks associated with shelf-life extensions.

The PIC/S Recommendation Paper on *How to Evaluate/Demonstrate the Effectiveness of a Pharmaceutical Quality System in relation to Risk-based Change Management*" [6] provides a practical checklist tool that can be used by the company to evaluate the effectiveness of its risk-based change management process.

DEMONSTRATING EFFECTIVE MANAGEMENT OF SHELF-LIFE EXTENSION PAC WITHIN THE PQS

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The following risk-control elements have been considered for ensuring effective management of shelf-life extensions within the PQS:

- Any Out-of-Trend stability results are determined not to be product related
- Statistical analysis shows the product remains within the approved stability specifications throughout the proposed shelf life extension
- No confirmed out-of-specification stability results observed
- No Formulation changes have been made for the applicable product
- No critical changes to the manufacturing process
- No critical changes to laboratory testing controls
- No changes to the approved specification limits
- Maintains ongoing follow-up stability programs on commercial batches
- No final product market container-closure system changes
- No changes to the stability-indicating analytical procedures and stability test specifications for the product except possible addition of tests

The implementation of this change will be documented and tracked within the site change management process. The outcomes of the risk assessments will be integrated into the change implementation plan. Any residual risks will be assessed and managed to acceptable levels prior to change closure. After change closure, relevant risk assessment documents will be updated as part of post-effectiveness assessments.

CONCLUSION

This 1VQ position paper provides a standard and enhanced risk-based approach within the framework of an effective PQS, that can be utilized by any company to gain regulatory flexibility, reduce the burden and global complexity, and enable faster implementation of shelf-life extensions for pharmaceutical products, without increasing risk to the patient and/or product *safety, efficacy, quality, identity, purity, and potency.*

The benefits of practical application of the principles of ICH Q9, Q10 and Q12 as described in this document are:

1. Continual improvement with timely (weeks or months vs years) implementation of many PACs
2. Enhancing product availability and mitigating potential drug shortages
3. Focusing regulatory resources on PACs that may have a potential to impact product quality as it relates to safety and efficacy
4. Reducing the regulatory approval burden for medium and low risk changes
5. Faster implementation of new knowledge and innovative technologies (if applicable for this PAC example)

About One-Voice-Of-Quality

Many post-approval changes require regulatory agency approval by individual countries before implementation. Because of the global regulatory complexity, individual post-approval changes (PACs) usually take years for full worldwide approval even when they reduce patient risk, improve compliance, or enhance the manufacturing process or test methods.

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Senior Quality Leaders (Chief Quality Officers and Heads of Quality) from more than 20 global pharmaceutical companies are speaking with "*One-Voice-Of-Quality*" (1VQ) to advocate for an effective management of specific PACs that currently are handled as a prior-approval change in some countries, but where a standard science and risk-based approach concludes that these should be downgraded to a notification or handled only in the Pharmaceutical Quality System (PQS). This benefit would be a reduction of the implementation timeline from years to months or weeks with no increased risk to patient safety or product quality.

ACKNOWLEDGEMENTS

Endorsement and active sponsorship by Chief Quality Officers/Quality Heads:

- Sean McEwen (*Abbvie)*
- Kunihiko Kobuko (*Astellas Pharma)*
- Anthony Mire-Sluis (*AstraZeneca)*
- Paul Heiden (*Bayer)*
- Juan Torres (*Biogen)*
- Lothar Halmer (*Boehringer-Ingelheim)*
- Scott Gunther (*Catalent)*
- Laura O'Brien (*CSL Behring)*
- Miyuki Arai (*Daiichi Sankyo)*
- Andi Goddard (*F. Hoffman La Roche)*
- Valerie Brown (*Gilead)*
- Paul Daly (*GSK)*
- Carol Montandon (*Johnson & Johnson)*
- Derek Glover (*Mylan Labs)*
- Maria Soler Nunez (*Novartis)*
- Flemming Dahl (*Novo Nordisk)*
- Philippe Germanaud (*Sanofi)*
- Anil Sawant (*Merck Sharp & Dohme Corp.)*
- Dirk Bissinger (*Merck Healthcare KGaA)*
- Gerard Greco (*Takeda)*
- Edith Koller-Dette (*Teva)*

The authors wish to acknowledge the following members of the IVQ team who contributed to development of this manuscript:

- Anders Vinther (*Intarcia*)
- Barry Cherney (*Amgen*),
- Becky Devine (*Consultant & PDA Board*)
- Christina Tovar (*Johnson & Johnson*)
- Denyse Baker (*AstraZeneca*),
- Emma Ramnarine (*Roche*)
- Eva Urban (*CSL Behring*)
- Fanzia Mohammed (*Roche*)
- Gopi Vudathala (*Consultant*)
- Joanna Baszczuk (*GSK*)
- Kevin Lombardi *(Novartis*)
- Kimberly Bruhin (*Johnson & Johnson)*
- Melissa Seymour (*Biogen*)
- Niraj Mehta (*Merck*)
- Nirdosh Jagota (*Merck*)
- Rich Rolke (*Merck*)
- Scott Gunther (*Catalent*)
- Sharyl Hartsock (*Eli Lilly*)
- Siobhan Ahern *(GSK)*
- Stacey Traviglia (*Biogen*)
- TG Venkateshwaran (*Merck*)
- Thierry Gastineau (*Sanofi-Pasteur*)

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest related to the content of the article.