ICH Q12 – adopting greater flexibility in product lifecycle management

AUTHORS

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KEYWORDS

ICH Q12; Post-approval changes; Established conditions (ECs); Post-approval change management protocol (PACMP); Pharmaceutical quality system (PQS); Product lifecycle management (PLCM); Quality by design (QbD); Flexibility; Industry; Regulators.

ABSTRACT

This article focuses on flexible approaches for the management of post-approval changes through the use of ICH Q12 tools (established conditions, post-approval change management protocol etc). It includes details around how scientific understanding of the drug product process, control strategy with application of ICH Q12 tools in regulatory dossiers for new as well as marketed products could result in fewer post-approval submissions. This will ensure timely access of well-tolerated, high quality, compliant medicines to patients and reduce unnecessary cost, time and burden on industry and regulators.

Introduction

The ICH Q12 guideline provides a globally harmonised framework to facilitate the management of post-approval chemistry, manufacturing and controls (CMC) changes in a more transparent, predictable and efficient manner across the product lifecycle. This guideline addresses the commercial phase of the product lifecycle, and is intended to complement the existing ICH Q8 to Q11 guidelines. Together the International Council for Harmonisation (ICH) guidelines aim to provide greater opportunities for an increased science- and risk-based approach for assessing changes, and thereby achieving flexibility in management of post-approval changes. Furthermore, this will promote manufacturing innovation and continual improvement and will allow regulatory authorities to better understand companies' pharmaceutical quality systems (PQS) for management of post-approval CMC changes.[1,2]

ICH Q12 applies to new drug substances and drug products (both chemical and biological), marketed products and drug-device combination products that meet the definition of a pharmaceutical or biological product.[1,2]

ICH Q12 development globally

The implementation of ICH Q12 tools and enablers across the US, EU, Japan, Canada, Switzerland and other ICH member countries is under way. The ICH Q12 guideline was first endorsed by the ICH Steering Committee in September 2014, with public consultation ending in December 2018. Step 4 Adoption was entered in November 2019.[3,4]

The ICH Q12 guideline introduces regulatory mechanisms such as established conditions (ECs) and the post-approval change management protocol (PACMP) to simplify and speed up post-approval change implementation and to encourage continual product improvement. The concepts behind some of the ICH Q12 tools (ECs, product lifecycle management [PLCM]) are fairly new, while the PACMP concept is more than a decade old for post-approval filings in the US and EU. There has been significant progress made on the implementation of ECs and PACMP tools by the US FDA and the Pharmaceuticals and Medical Devices Agency, Japan.[4,5]

United States

In May 2015 the FDA published draft guidance on ECs, and in May 2019 started the ECs pilot programme whereby sponsors can propose ECs as part of regulatory applications. The FDA accepted nine requests from the applicants to gain experience receiving, assessing, and engaging with applicants regarding proposed ECs. The pilot programme on ECs was successful and received positive feedback from industry and the FDA.[7] The PACMP tool presented in the ICH Q12 guideline is aligned with FDA Comparability Protocols,[8] which have been used in the US since 2003.

Europe

According to the "EMA note on EU implementation of ICH Q12 (EMA/CHMP/ICH/78332/2020)", ECs and PLCM are not currently recognised in the EU variations guidelines and will be considered with the next review of the EU legal framework. There are currently no defined timelines for when the EU legal framework will be reviewed.[9]

However, the concept of a PACMP was introduced in 2010 through "EU variations classifications guideline (2010/C 17/01)", which allowed the marketing authorisation holder (MAH) to keep a document describing all changes planned during the lifecycle of the medicinal product. Therefore, the PACMP tool can be utilised in the EU as it is already well described in EU guidelines.[9,10]

Post Brexit, the UK has not provided any specific advice on implementation of Q12 guidance.

Japan

The PMDA is in the process of implementing ICH Q12 guidance and is utilising ECs (as approved matters) in the marketing authorisation applications (MAAs) in section 1.2 of the application form of Module 1 of eCTD (electronic common technical document). A post-approval regulatory submission is required if a MAH proposes changes in the approved matters presented in the application form.[5,11]

The PACMP pilot programme was started in April 2018, which enabled planning and implementation of future changes to approved matters in an

efficient and predictable manner.[12] The PMDA is also considering whether to incorporate the PLCM document into MAAs.[5]

Canada

Health Canada released a notice in October 2020 which set a target timeframe for implementation of ICH Q12 for the third quarter of 2021 in order to allow sufficient time for regulators and stakeholders to prepare. Health Canada will launch a stakeholder consultation in early 2021 to gather feedback on the final elements of the implementation of the Q12 guidance in Canada.[13]

Switzerland

Switzerland follows the EMA in implementing the guideline. Swissmedic applies the ICH Q12 guideline, with restrictions concerning ECs and the PLCM document to all applications submitted from 1 April 2020 onwards.[14]

Other ICH members

China and Taiwan are in the process of implementation of the ICH Q12 guideline, while Brazil, Singapore and South Korea have not yet implemented the guideline.[4]

Product lifecycle management using ICH Q12 tools and enablers

ICH Q12 guidance encourages the use of the following tools and enablers, which aims to enhance transparency between industry and regulatory authorities, and facilitate the management of post-approval lifecycle changes.

Established conditions

ECs (eg, specifications, batch formula) are legally binding information considered necessary to assure product quality and which require a regulatory submission, if changed post-approval. ECs should be determined based on the knowledge gained throughout pharmaceutical development, characterisation of drug substances/drug products, and the potential risk to product quality. MAHs should clearly identify which elements of CMC they consider as ECs, and those which they consider to be supportive information or non-ECs. The rationale for ECs with appropriate reporting categories should be provided in the appropriate sections of the CTD. ICH Q12 includes an appendix that highlights the various CTD modules in which ECs are generally located, as well as comprehensive annexes, which enables identification of ECs.[1]

Post-approval changes to ECs require different reporting categories dependent on the level of risk associated with the changes. The changes to high-risk ECs must be reported for prior approval, low-to-moderate risk ECs can be notified, whereas non-ECs do not need to be reported. The low-risk changes can be managed within an effective pharmaceutical quality system (PQS).[1]

Post-approval change management protocol

The PACMP describes specific changes that a MAH would like to implement during the lifecycle of the product with detail on how these changes will be prepared and verified. This includes an assessment of the impact of changes, proposed reporting category, specific conditions, acceptance criteria and submission requirements.[1]

As discussed in the ICH Q12 guideline, the variation category designated for reporting changes under an approved protocol is at least one category lower than would normally be the case. Therefore, a pre-approved PACMP can help with continuous improvement and flexibility which allows introduction of the latest innovations in manufacturing along with a reduction in health authority review/approval duration, thus enabling shorter timelines in the implementation of high-risk changes.[1]

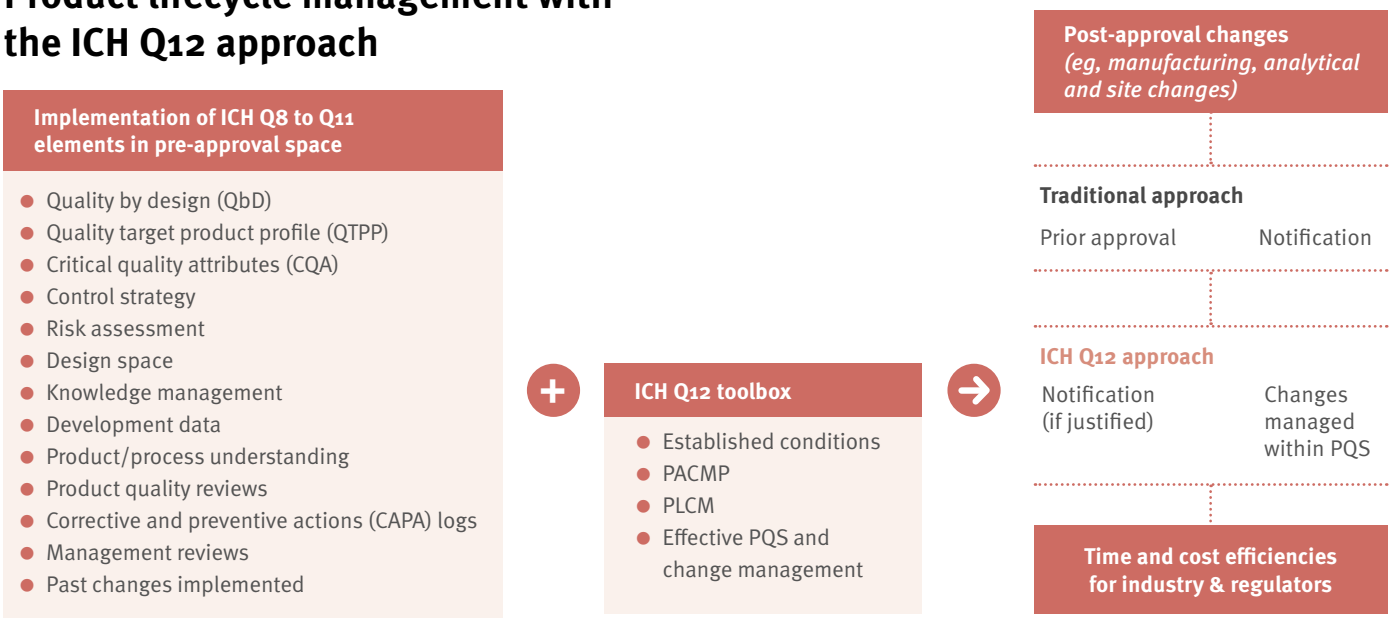
A PACMP can address one or more changes for a single product, or may address one or more changes to be applied to multiple products. The PACMP may be submitted with the initial MAA or subsequently as a standalone submission and requires approval by the regulatory authority. The PACMP document is located in CTD Module 3.2.R. The modification to the content of the protocol may require either prior approval of a protocol amendment or submission of a new protocol, as agreed on with the regulatory authority.[1]

Product lifecycle management document

The PLCM document serves as a central repository for product lifecycle management that includes the ECs, reporting categories for changes to

FIGURE 1

Product lifecycle management with the ICH Q12 approach



ECs, PACMPs (if used) and any post-approval CMC commitments. PLCM encourages prospective lifecycle management planning by the MAH and to facilitate regulatory assessment and inspection. The PLCM document is submitted in the initial MAA (in Module 3.2.R) or in a variation for marketed products and should be updated throughout the product lifecycle as needed. The MAH should follow regional expectations for maintaining a revision history for the PLCM document.[1]

Relationship between QbD, design space, control strategy and ICH Q12 tools

The effective management of post-approval CMC changes generally involves implementation of a quality-by-design (QbD) approach to product development, design space verification, continued or ongoing process verification of post-qualification batches and control strategy for continuous improvement.[15–18]

The ICH guidance on Pharmaceutical Development (Q8), Quality Risk Management (Q9), Pharmaceutical Quality System (Q10) enables science- and risk-based decision making and should be applied together to achieve the desired outcome through use of ICH Q12 tools.[1] The implementation of this guidance requires extensive experimental studies, additional assessments, collection and analysis of product/process data across the lifecycle. The QbD approach to pharmaceutical development involves extensive design of experiments and use of statistical methodologies to develop design space and establish critical quality attributes (CQAs), critical material attributes, and critical process parameters. Further, application of statistical tools ensures robustness of formulation, the reliability of the process, and predictability of the impact of potential future changes.[15–18]

Presently, there are limitations in achieving the intended flexibility to post-approval CMC changes as described in ICH Q8-Q11 guidelines. However, ICH Q12 tools provide flexible regulatory approaches and swift implementation of post-approval changes by categorisation of changes based on QbD principles and product and process understanding (ICH Q8 and Q11). Figure 1 illustrates how ICH Q12 could be used to help with PLCM.

ICH Q12 encourages effective management of post-approval changes through PQS and robust knowledge management system based on process/product understanding, risk assessment, assessment of historical data, annual product reports (APRs) and any observation based on corrective action and preventive action (CAPA), etc.

CASE STUDY 1: Post-approval changes for drug substance process parameters and raw materials

Generally, high-level details are submitted within initial MAAs and there is no differentiation between critical and non-critical parameters. Any future change related to process parameters and raw materials whether it is critical or non-critical usually requires a post-approval submission resulting in huge burden to the applicant and authorities. ECs can be used to identify regulatory binding elements and supportive information in the dossier through process and product understanding and application of risk assessment tools.

Table 1 below describes some of the non-critical parameters of manufacturing process and raw materials identified in the dossier using ICH Q12 tools. The reporting categories for changes to process parameters and specification of these raw materials can be downgraded or managed within the company's PQS if justified in the dossier, leading to overall reduction in regulatory burden.[19]

TABLE 1

Application of ICH Q12 tool (ECs) in downgrading variation categories

Change	EU classification according to current procedure	US classification according to current procedure	Canadian classification according to current procedure	Japanese classification according to current procedure	Classification according to applied ICH Q12 tools
Noncritical process parameters (eg, reaction temperatures, catalyst loading, stoichiometry, solvent volume)	Type IA (B.I.a.2.a) minor change in the manufacturing process	CBE-30	Annual report	Non-approved matter	Managed within PQS
1-Octanol Refractive index n 20/D 1.4291 – 1.4300 to 1.4285 – 1.4303 (slightly widened limit)	Type IB by default B.I.b.1 z) Change in specification parameters and/or limits of a reagent	Annual report	Notifiable change submission	Partial change application	Managed within PQS
2-Butanol Deletion of test parameter "Odour – alcoholic, irritating"	Type IA B.I.b.1 d) Deletion of a non-significant specification parameter	Annual report	Annual report	Partial change application	Managed within PQS

CASE STUDY 2: Site transfer variations[21,22]

Site transfers are one of the most common types of post-approval changes which are necessary to ensure continuous supply of medicinal products. The site-related changes for a chemical/biological product are complex and time-consuming for the industry and regulators. The submission of a PACMP gives an opportunity to the authority to understand the future changes, the implications and provide feedback before the actual change is submitted through a variation. Therefore, utilisation of the PACMP tool for site transfer variations can reduce the approval and implementation timelines by approximately six months. This case study provides an insight on utilisation of a PACMP for site transfer variations.[20,21]

Step 1: The PACMP is submitted to introduce the proposed site-related changes and should contain the following information based on the nature (chemical/biological) of the product:

- Introduction and scope
- Detailed description of change
- Risk assessment
- Development and characterisation data
- Process comparison and control strategy
- Process validation strategy
- Product comparability plan – batch identification, lot release, additional characterisation studies, forced degradation, stability data (long term and accelerated conditions)
- Commitments and implementation plan.

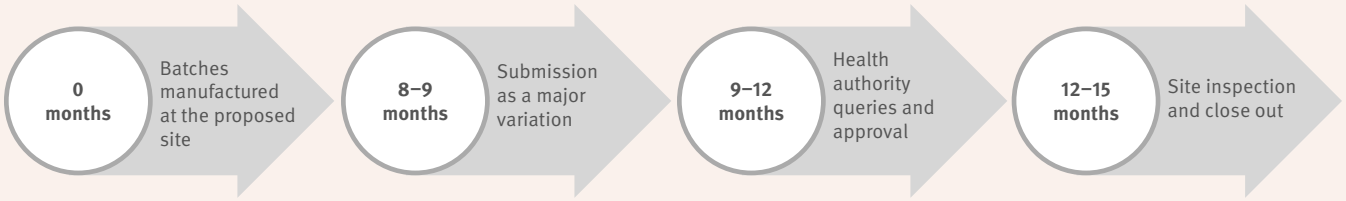
The PACMP is reviewed and approved by the regulatory authority in advance of the execution of actual changes. The good manufacturing practice (GMP) inspection of the proposed site (if required) can be performed after the PACMP is approved, and closed out before Step 2.[20,21]

Step 2: The studies outlined in the protocol are performed at the proposed site to demonstrate process performance and comparability to the registered manufacturing site. The results of these studies are submitted along with the variation package.[20,21]
Therefore, the flexible PACMP approach can be utilised to submit site-related changes under minor variations (according to the categorisation in the approved protocol) instead of submission under major variations.[20,21] Figure 2 below compares ICH Q12 PACMP management with traditional approaches for site transfer variations.

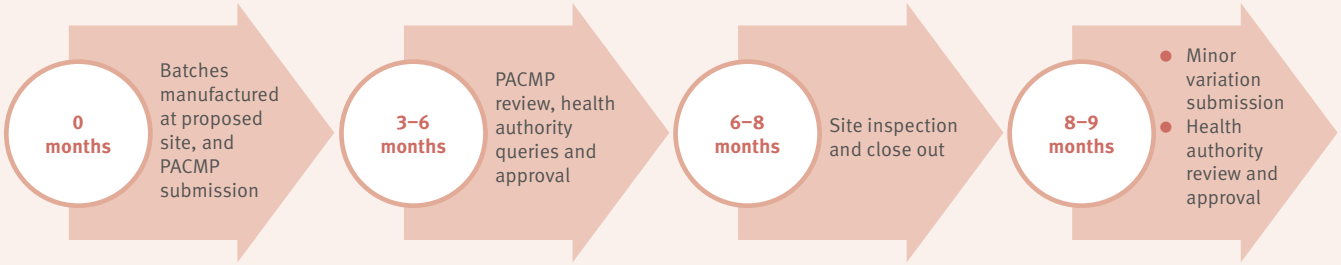
FIGURE 2

Comparison of ICH Q12 PACMP management against traditional approaches for site transfer variations

Traditional site transfer variation approach



ICH Q12 site transfer approach



The ECs and non-ECs can be proposed in the initial MAAs based on development efforts and reflected in an appropriate control strategy, which can provide clarity on regulatory submission requirements for intended post-approval changes to ECs. The submission of a PACMP helps to achieve consensus from the regulatory authority for the proposed changes, which can help in downgrading of the reporting category, shortening the review period and swift implementation of the changes.

Therefore, incorporating these ICH Q12 tools in initial dossiers for new products or through variations for marketed products helps in flexible and predictable management of changes and enables continuous improvement to allow greater innovations in pharmaceutical manufacturing sciences.[1,16–19]

Benefits

The benefits of adopting ICH Q12 are listed below.

For patients:

- Less risk of supply shortages of essential medicines
- Timely access to safe, well-tolerated, high-quality and compliant medicines.

For the industry:

- Harmonisation of a global change management system and better operational flexibility
- Reduced cost of regulatory activities through fewer variations
- Innovation and continuous improvement in manufacturing and analysis

- Optimised supply chains.

For regulators:

- Risk-based regulatory oversight with fewer number of major variations and optimisation of resources for review and inspection
- Enhanced transparency between industry and regulators.

Analysis of challenges in ICH Q12 implementation for industry and regulators

The implementation of ICH Q12 tools is expected to facilitate an improved operational and regulatory flexibility for industry and regulators. However, there are some potential challenges in realising the benefits of the ICH Q12 guideline as outlined below:[8–14]

- ICH Q12 guideline is not fully compatible with present regulations/ guidelines (eg, EU variations guideline), thus implementation of ICH Q12 requires revisions in the regulatory frameworks in some regions. Further, some regulators are already using similar tools (eg, US FDA comparability protocol) for simplification of post-approval filings which will require changes to align with those of ICH Q12 tools.
- The industry will still need to manage regulatory complexities based on respective regulatory authority expectations.
- Pharmaceutical companies will need to strengthen their PQS, revise their already established standard operating procedures and look into protocols/change control systems and IT tools in order to implement ICH Q12 guidance and tools.
- Pharmaceutical companies will need to invest in their manufacturing and analytical departments to implement ICH Q8, Q9 and Q10 in order to reap the benefits of ICH Q12 tools.
- The implementation of ICH guideline will require training of health authority evaluators and industry regulatory affairs departments to apply ICH Q12 tools/concepts.
- Benefit realisation of adopting ICH Q12 for legacy products needs to be understood based on the return on investment.

Conclusion

The management of post-approval changes has always been challenging for pharmaceutical companies with respect to time, cost and resources. The ICH Q12 guideline establishes a framework for management of post-approval changes in a more productive and efficient manner, thereby helping patients, industry and regulators. The application and use of ICH Q12 tools enables risk-based categorisation of changes, advance determination of reporting categories and the data required for filing purposes. ICH Q12 is also intended to demonstrate how increased product and process knowledge can contribute to a reduction in the number of regulatory submissions. A further benefit comes from the management of CMC changes under the company PQS, which should result in reduced regulatory oversight before implementation.

The effective PQS, knowledge management system and application of risk assessment tools can be leveraged effectively to enhance operational flexibility, foster innovation and improve the supply of medicinal products benefiting patients. It is important to note that the use of ICH Q12 tools (excluding the PACMP) would also require implementation of QbD, design space, control strategy and risk assessment tools (as described in ICH Q8 to Q11 guidelines) in the MAAs.

Regulators around the world have been encouraging applicants to utilise the ICH Q12 tools (eg, US FDA, PMDA) for post-approval changes through various pilot programmes, while some agencies (eg, EMA) are planning to fully implement the ICH Q12 guideline when their legal/regulatory framework will be reviewed in future. Therefore, pharmaceutical companies should start to act now to see how they can strengthen their PQS systems, knowledge management systems, train their regulatory resources and keep an eye on the continuously changing regulatory landscape of ICH Q12 around the globe. ■

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References

1. ICH Harmonised Guideline: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management (Q12), Final version, Adopted on 20 November 2019. Available at: https://database.ich.org/sites/default/files/Q12_Guideline_Step4_2019 _1119.pdf (accessed 25 August 2020).
2. Final Concept Paper Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management, Dated 28 July 2014. Available at: https://database.ich.org/sites/default/files/Q12%20Concept%20Paper.pdf (accessed 25 August 2020).
3. Final Business Plan Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management, Dated 28 July 2014. Available at: https://database.ich.org /sites/default/files/Q12%20 Buisness%20Plan.pdf (accessed 25 August 2020).
4. ICH webpage quality guidelines. Available at: https://www.ich.org/page/quality-guidelines (accessed 28 August 2020).
5. Webber K. ICH Q12 – ready or not, here it comes! Dated 30 July 2019. Available at: https://www.lachmanconsultants.com/2019/07/ich-q12-ready-or-not-here-it-comes/ (accessed 2 September 2020).
6. US FDA Guidance for Industry: Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products, May 2015. Available at: https://www.fda.gov /media/92242/download (accessed 4 September 2020).
7. US FDA Established Conditions; Pilot Program, 15 February 2019. Available at: https://www.federalregister.gov/documents/2019/02/15/2019-02364/established-conditions-pilot-program (accessed 9 September 2020).
8. Guidance for Industry: Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information. Available at: https://www.fda.gov/ regulatory-information/search-fda-guidance-documents/comparability-protocols-human-drugs-and-biologics-chemistry-manufacturing-and-controls-information. Dated April 2016 (accessed 15 September 2020).
9. Note on EU implementation of ICH Q12 (guideline on technical and regulatory considerations for pharmaceutical product lifecycle management) (EMA/CHMP/ICH/ 78332/2020), Dated 04 March 2020. Available at: https://www.ema.europa.eu/en/ documents/other/note-eu-implementation-ich-q12-guideline-technical-regulatory-considerations-pharmaceutical-product_en.pdf (accessed 22 September 2020).
10. EMA questions and answers on post approval change management protocols (EMA/CHMP/CVMP/QWP/586330/2010), 30 March 2012. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-post-approval-change-management-protocols_en.pdf (accessed 22 September 2020).
11. Rie F. PMDA perspective on established conditions for specification in connection with Japanese application form. Available at: https://www.pmda.go.jp/files/000215709.pdf (accessed 22 September 2020).
12. Hara K. Overview of PACMP pilot program in Japan, 9 April 2019. Available at: https://apac-asia.com/images/achievements/pdf/8th/3_ATIM/5_Overview%20of%20 PACMP%20pilot%20program%20in%20Japan.pdf (accessed 22 September 2020).
13. Health Canada Notice – Interim Implementation of International Council for Harmonisation (ICH) Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management, 9 October 2020. Available at: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/quality/notice-interim-implementation-q12-technical-regulatory-considerations-pharmaceutical-product-lifecycle-management.html (accessed 30 October 2020).
14. ICH Guideline Q12: Implementation in Switzerland 9 April 2020. Available at: https://www.swissmedic.ch/swissmedic/en/home/news/mitteilungen/ich-guideline-q12.html (accessed 30 October 2020).
15. ICH Harmonised Tripartite Guideline: Pharmaceutical Development Q8 (R2), Current Step 4 Version, Dated August 2009. Available at: https://database.ich.org/sites/default/files/Q8% 28R2%29%20 Guideline.pdf (accessed 22 September 2020).
16. ICH Harmonised Tripartite Guideline: Quality Risk Management Q9, Current Step 4 Version, Dated 9 November 2005. Available at: https://database.ich.org/sites/default/files/ Q9%20Guideline.pdf (accessed 22 September 2020).
17. ICH Harmonised Tripartite Guideline: Pharmaceutical Quality System Q10, Current Step 4 Version, Dated 4 June 2008. Available at: https://database.ich.org/sites/default/files/ Q10%20Guideline.pdf (accessed 22 September 2020).
18. ICH Harmonised Tripartite Guideline: Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) Q11, Current Step 4 Version, Dated 1 May 2012. Available at: https://database.ich.org/sites/default/files/Q11%20 Guideline.pdf (accessed 22 September 2020).
19. Joint BWP/QWP/GMDP IWG – Industry European Workshop on Lifecycle Management – case studies on established conditions. Available at: https://www.ema.europa.eu/en /documents/presentation/presentation-case-studies-established-conditions_en.pdf (accessed 30 October 2020).
20. Pepper T. Post approval change management protocol (PACMP) case study: regulatory strategy considerations for biotechnology drug product site transfers. May 2013. Available at: https://cdn.ymaws.com/www.casss.org/resource/resmgr/CMC_Euro_Speaker _Slides/2013_CMCE_PepperTeresa2.pdf (accessed 30 October 2020).
21. ICH Harmonised Guideline: Technical and regulatory considerations for pharmaceutical product lifecycle management – Q12 annexes, final version, adopted on 20 November 2019. Available at: https://database.ich.org/sites/default/files/Q12_Annexes_Step4_2019_ 1119.pdf (accessed 25 August 2020).