More efficient management of post-approval change control

Post-approval change control of established marketed products is managed by the pharmaceutical quality system (PQS)1 and regulatory endorsements2. However, change control is rarely approached in a consistent manner. Whilst the ideas encapsulated in a Quality by Design (QbD) approach to the development of new chemical entities provide opportunities for more science- (ICH Q8 and Q11), quality- (ICH Q7 and Q10) and risk-based (ICH Q9) approaches for evaluating changes across the product’s lifecycle, there are several deficiencies constraining the full realisation of the envisioned benefits.

As a consequence the intended post-approval operational and regulatory flexibility has not been realised. This has resulted in misunderstandings as to what constitutes the appropriate level of information in the regulatory dossier and its subsequent influence on change management, as well as the required level of post-approval regulatory interactions. This can hinder subsequent innovation and continual improvement during this phase of the lifecycle.

ICH Q12

The guideline ICH Q122 will provide a structure to enable the management of post-approval chemistry, manufacturing and controls (CMC) changes in a more efficient manner across products’ lifecycles. It will apply to all pharmaceutical products, including currently marketed drugs. However, each individual regulatory authority will assess whether generics should also be included within the scope of this guideline. ICH Q12 is intended to work synergistically with the existing QbD guidelines, i.e., ICH Q8-Q11.3

In addition, ICH Q12 is designed to support ongoing innovation and continual improvement, strengthening the quality of the product and ensuring a consistent product supply. This should include preemptive planning of changes to the existing supply chain. This will allow regulators (both reviewers and inspectors) to better understand, and have more confidence in, the ability of a company’s PQS to manage any post-approval CMC changes in a more transparent, predictable and efficient manner.

In particular, ICH Q12 will focus on three main areas:

PQS aspects (ICH Q101)

ICH Q12 will establish those criteria that establish a consistent risk-based change management system, which will be based on product, process and/or clinical knowledge. This will effectively assess the impact of any proposed changes on quality, safety and efficacy. ICH Q12 will clarify regulatory expectations and strengthen the need to maintain a knowledge management system that will ensure ‘continuity of product and process information’ over a product’s lifecycle.

Post-approval change management plans and protocols (PACMPP)

ICH Q12 will introduce the concept of a post-approval management plan that can be used to proactively identify post-approval changes and the mechanism to submit and assess these changes by regulatory authorities (assessors and inspectors). The guideline will establish criteria for post-approval change management protocols that can be adopted by the various ICH regions. It is also intended to encourage enhanced QbD and control strategy approaches, providing opportunities for scientific and risk-based strategies for post-approval change management plans.

Regulatory dossier

ICH Q12 will explore the development of a standardised approach to regulatory commitments4. Such approaches could support an environment of continual improvement and encourage the adoption of innovative technologies. The guideline will ensure the appropriate level of detail and supporting information necessary for regulatory assessment and inspection within the dossier, creating a more empowered post-approval change management system.

Conclusion

The key to achieving the desired state of ICH Q12 and providing assurance that the majority of changes can be managed by the pharmaceutical industry, without the need for extensive regulatory oversight, is to provide guarantees that all product quality aspects are managed within a robust PQS over a product’s entire lifecycle. However, it is of significant concern to the effective implementation of ICH Q12 that the biggest finding in both good manufacturing practice and good distribution practice audits continues to be related to quality management systems.

In addition, identification of those elements of CMC information that constitute “established conditions”, i.e., those attributes of the process that are quality-critical (aligned to QbD thinking) should provide a better understanding of which CMC changes can be made solely under the PQS, without requiring regulatory approval. Both regulators and industry must integrate knowledge effectively across the lifecycle to ensure that initial established conditions have been derived using risk-based processes, thereby allowing effective post-approval control and conformance to the established conditions, and that such conditions remain relevant based on existing knowledge.

References

1. References can be found online at: www.europeanpharmaceuticalreview.com