

EU and US variation requirements

Understanding the need for variations and avoiding unnecessary variations is core to regulatory management of product lifecycles. This continuing development supplement – the first in a quarterly lifelong learning series – looks at the most common types of variations. It covers the European procedure for Type IA, Type IB and Type II variations, including line extensions, grouping and worksharing processes, versus the US, highlighting key similarities and differences.

KEYWORDS: Lifecycle management; Post-approval; Variations; Harmonisation; Europe; US; Type IA/Type IB/Type II variations; Line extensions

Regardless of a product's route or country of registration, one constant across the pharmaceutical industry is the requirement to keep dossiers updated and current. Whether changes are driven by technical and scientific improvements or cost reduction, post-approval lifecycle management activities are a key responsibility of marketing authorisation holders (MAHs). As regulatory agencies across the world evolve, the methods of submitting and processing variations have begun to harmonise.

European variations

Alongside the European legislation that defines variation types, a guideline lays out a harmonised list of anticipated variations with classification codes.¹ A defined list of variations for European MAs has existed since implementation of the Mutual Recognition Procedure (MRP) in 1998. However, the legislation governing European variation procedures was not fully adopted at

the national level by many EU member states at that time. Legislation has periodically been updated and in the most recent update, in August 2013, implementation was made mandatory at the national level and the variation process has been completely harmonised across the EU. The classification codes are as follows:

- **Type IA/IAIN.** Changes that fall under this category are commonly referred to as “do and tell” variations because the applicant is required to implement the change and then notify the agency of the details. This level of variation is reserved for administrative changes that are anticipated to have no impact on the safety or efficacy of a product.

Variations that can be submitted as Type IA must be implemented and then the required submission made within one year of the implementation date. For changes that are categorised as Type IAIN the applicant must notify the agency

within 14 days of implementation. Multiples of these variations for a single product can be made at the same time, as long as all of them fall within the required submission deadline.

- **Type IB.** Minor variations that require assessment of supporting data and are anticipated to potentially have an impact on product safety or efficacy are classified as Type IB. These are also referred to as “tell and do” variations. The applicant must make the submission, including all required supporting data, and await agency approval before implementing the change. The process follows a defined assessment period of 30 days, but with agency questions it can often take up to three months.
- **Type II.** This classification is reserved for major variations which are expected to affect the safety and efficacy of a product and require careful assessment before the applicant can implement the change.

Key points in regulatory management of variations

- Lifecycle management of pharmaceutical products varies between the EU and US in terms of different submission requirements and assessment timelines. However, similarities do exist in regional approaches to general categorisation of post-approval changes (variations) and in many cases also the principles of implementation.
- Post-approval variations in the EU and US can be administrative in nature, simple changes requiring minor review, or major changes which are often complex.
- **Administrative:** EU regulators go as far as to define “administrative” as a category in their classification guideline, whereas in other regions they fall into the lowest variation category and have significant crossover with minor variations, eg new addresses. Many agencies accept that these changes can be implemented without the need for approval. Prior approval of administrative changes is time-consuming for agencies and costly for industry. Additionally, in certain cases such as a marketing authorisation holder (MAH) moving address, the change would actually need to take place prior to submission.
- **Minor:** Minor variations are generally considered to have either no impact on the quality of the product or have a very low chance of impact; and hence lower risk. Consequently, the level of agency review, and hence the time required is reduced. As regulatory frameworks have developed, agencies have introduced means to allow the most minor of variations to be implemented before review. For example, in the EU, when a Type IA variation is submitted the MAH must state which of a pre-defined list of conditions applies to its change, thereby reducing the amount of review required. With minor variations, many agencies have documentation requirements that are well-established and must be met before variations are submitted. This ensures that MAHs know what is expected before a submission and can prepare sufficient supporting data. This leads to faster review times as assessors have less need to request further data from applicants.
- **Major:** Where notable alterations to product registration are required, these are expected to have an impact on a product's quality and efficacy and as such are tightly controlled, requiring in-depth assessment and review. The MAH must demonstrate that the product will retain the same level of quality and efficacy. Comparative data is a significant requirement for such changes and must reliably show the proposed changes do not impair product quality. Assessment times for such variations are often much longer, as agencies carefully review submissions and frequently make requests for additional data and answers to questions and concerns.

Table 1: Summary of variations and anticipated implementation dates in Europe and US.

Europe				US		
Variation	Type	Anticipated implementation time	Guideline approval timeline	Type	Anticipated implementation time	Guideline approval timeline
Admin	Type IA _{IN}	14 days before submission	N/A	AR	Up to 1 year before submission	N/A
	Type IA	Up to 1 year before submission	N/A			
Minor	Type IB	Up to 3 months after submission*	30 days	CBE-0	On receipt of submission by FDA	N/A
				CBE-30	30 days after receipt of submission	6 months
Major	Type II	Up to 6 months after submission*	60 days	PAS	Up to 6 months after submission*	4 months

*The noted anticipated dates are based on experience with submitting variations to the relevant agencies and incorporate the time taken for validation, application assessment, applicant's response to questions (clock stop) and assessment of responses.

They require considerable supporting documentation and must be assessed and signed off by an appropriately qualified expert in their respected field before being submitted.

- **Line Extensions.** Certain changes which affect the fundamentals of the terms of the authorisation cannot be granted via a variation and are submitted as an "extension application": changes to the active substance(s); changes to strength, pharmaceutical form and route of administration. The invented name will remain the same for the "extension".

Post-approval changes in the US

Changes to products licensed by the US FDA are achieved via the provision of supplements to the original new drug application (NDA). The supplements are as follows (see Table 1):

- **AR:** Annual Report. Changes that can be submitted in an annual report are of a minor nature and have minimal potential to effect quality, safety or efficacy of the product. The affected product can be distributed at any time after the change has been internally approved and before the details are reported in the Annual Report. At the end of a reporting period, any changes that have been implemented in the previous year are included together in a single notification to the agency.
- **CBE-0:** Changes Being Effected 0. Changes classified as CBE-0 are minor (albeit moderate) changes to the product which can be

implemented from when the FDA receives the supplemental NDA (sNDA) application. The product can also be distributed when the sNDA is received. CBE-0 changes are considered approved six months after receipt, if there are no technical issues raised by the FDA. However, if the change is not approved then distribution must cease and a product recall may be required.

- **CBE-30:** Changes Being Effected 30. Changes classified as CBE-30 are also deemed as minor (albeit moderate). Changes in this classification can be implemented and product distributed at risk, 30 days after the FDA receives the sNDA, unless the FDA notifies the applicant otherwise. Approval should be completed after six months. However, if the submission is rejected, a recall may also be required.
- **PAS:** Prior Approval Supplements. This category covers major changes that are considered to have a substantial potential to adversely affect the identity, strength, quality, purity or potency of the drug product. Product affected by these changes cannot be distributed until approval which should take up to four months, assuming there are no technical issues.

Agency comparisons

The definitions and terms used to describe variation types and processes vary across the regions, however, changes all fall into three general definitions which share many similarities: administrative, minor and major (as summarised in Table 1). The EU, in 2010, amended Type IA variations to be "do and tell" changes where the MAH may make the change before submitting a notification. When the guidelines were reviewed in 2013, certain existing Type IB variations with established requirements were downgraded to the level of Type IA where the authorities felt there was no impact on product quality. Quality implementation is when the company makes the change in its own Quality System. For product information, implementation is when the company internally approves the revised product information (which is then used in the next packaging run). In cases where the variation assessment is unfavourable, the MAH must immediately cease applying the rejected

variation. The Agency may ask the MAH to complete a suspected quality defect notification form and provide a risk assessment report for the product on the market. This concept appears to reflect the AR system seen in the US and has since been adopted by other agencies worldwide.

Submission of EU variations is also possible via Grouping and also Workshare procedures, whereas in the US, multiple changes (eg, multiple study reports) can be filed under a single sNDA.

Conclusion

Activities to improve international harmonisation of lifecycle management processes and guidelines allow agencies to share assessments and reduce individual workloads, improving their quality and speed of assessment. Such improvements are of considerable benefit to industry, seeing changes implemented faster and reducing the cost for many manufacturers. Finally, for regulatory professionals, it reduces the inevitable burden that stems from numerous national requirements and allows them to apply their skills and knowledge globally.

Reference

1 European Commission. http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm (accessed December 2016).

Additional reading

- *The Commission Regulation (EC) No 1234/2008 of 24 November 2008, concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products.* ec.europa.eu/health/files/eudralex/vol-1/reg_2008_1234/reg_2008_1234_en.pdf (accessed 05 December 2016).
- *Regulation (EU) 712/2012.* ec.europa.eu/health/files/eudralex/vol-1/reg_2012_712/reg_2012_712_en.pdf (accessed 05 December 2016).
- *Heads of Medicines, Variation Procedural Guidance.* <http://www.hma.eu/96.html> (accessed 06 December 2016).
- *EMA Procedural Advice on Variations.* http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001782.jsp&mid=WC0b01ac0580b18c7b (accessed 06 December 2016).

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Avoiding unnecessary variations

A precise description of the manufacturing process including operation conditions and details on equipment may trigger a variation procedure if these details are changed. To avoid this, the description of the manufacturing process should only include information which is considered necessary for the assessment of the procedure. It should not include, for example, details of the name of a producer of special equipment; instead, the dossier should refer to an "adequate" device.

The same is applicable for analytical methods. If the description of an analytical method includes details on the producer of a special column, a variation procedure will become necessary on switching to another producer. For description of analytical methods, the applicant is advised to consult the *European Pharmacopoeia* for the descriptive principles.

Packaging materials for blisters or container closure systems for oral solutions should never be accompanied by details of the suppliers. This will automatically lead to a variation procedure for any change concerning the supplier, even if there is just a company name change.

Reference to monographs in the *European Pharmacopoeia* or a national member state Pharmacopoeia should always be furnished with the note to the "current edition" of the particular Pharmacopoeia – rather than a specific edition. This prevents the need to notify the competent authorities of an updated monograph.

As a general rule too many details, not required for approval of the medicinal product, should be avoided.

Example:

The changes listed in Table 1 have been proposed by the Marketing Authorisation Holder (MAH) for tablets containing morphine sulphate as an active substance. The method for determination of impurities has been revised (former method: thin layer chromatography (TLC)); proposed method: high performance liquid chromatography (HPLC). As a consequence the release specification was changed. Grouping of the different variations in Table 1 (type IB, type IB by default, 3x type IA) are possible as they are considered as consequential changes due to the replacement of the analytical method.

The following sections in the Common Technical Document (CTD) should be updated:

- **3.2.P.5.1 Specification:** Revised release and shelf life specification
- **3.2.P.5.2/5.3 Analytical Procedure/ Validation:** Description of the new method including validation data
- **3.2.P.5.4 Batch Analyses:** Batch analyses data under consideration of the revised specification
- **3.2.P.5.6 Justification of Specifications:** The limit for any other impurity is justified with reference to the Guideline on Impurities in New Drug Products, CPMP/ICH/2738/99¹ where the identification/qualification

threshold is 0.2% under consideration of the maximum daily dose of 120 mg for morphine sulphate tablets.

The limit of 1.0% for total impurities is justified by data found during stability studies.

The deletion of a non-significant parameter like the test on codeine phosphate has been justified taking into account that this impurity is not considered as a degradation product of the drug product.

Conclusion

The European variations procedures have been created to avoid the possibility that changes to a medicinal product may give rise to public health concerns. However, it should be kept in mind that any amendment to documentation, any deletion and/or any change to the content will lead to a variation procedure. In some cases it is helpful to assess information which is critical to the agencies, and update outdated or overly detailed documentation in order to avoid further variations. Analytical validation protocols included in the documentation, for example, may be important for inspections but will result in a combination of variations in the regulatory framework for an approved drug product.

Reference

- 1 *Guideline on Impurities in New Drug Products, CPMP/ICH/2738/99. Available at www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002676.pdf (accessed 9 February 2015).*

Table 1: Present situation and proposed changes.

Present situation	Proposed change	Change according to Classification Guideline
Determination of Impurities by TLC	Determination of Impurities by HPLC	Type IB with reference to B.II.d.2d) - other changes to a test procedure (including replacement or addition)
Release Specification: Pseudomorphine: NMT 0.5% Codeine Phosphate: NMT 0.5%	Release Specification: Pseudomorphine: NMT 0.4% Any other impurity: NMT 0.2% Total impurities: NMT 1.0%	Type IB by default with reference to B.II.d.1a) – Tightening of specification limits; condition 4 (test procedure remains the same) is not met. Type IA with reference to B.II.d.1d) – Deletion of a non-significant specification parameter. Type IA with reference to B.II.d.1c) – Addition of a new specification parameter Type IA with reference to B.II.d.1c) – Addition of a new specification parameter.

Acknowledgements

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- "Harmonisation of variation requirements, categorisation and implementation: A global view" by Richard O'Keeffe; and
- "A guide to the EU variation procedure from a quality viewpoint" by Cornelia Nopitsch-Mai and Susanne Winterscheid.

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1. Which types of post-approval changes are considered to be administrative in nature?

- EU Type IB + US CBE-0 + US CBE-30
- EU Type IAIN & Type IA + US AR
- EU Type IAIN & Type IA + US PAS

2. Which change is considered to be an EU line extension?

- Changes to route of administration
- Changes to the indication
- Changes to the drug product shelf-life

3. What is the anticipated implementation time of a Major EU and US post approval change?

- Up to 1 year before submission
- Up to 3 months after submission
- Up to 6 months after submission

We hope you find this CPD supplement and the assessment useful. We welcome any feedback you may have on the content, format and assessment process. If you would like to contact us about any of the above or have a CPD-related question please email publications@topra.org.



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