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Review Article

A Quality Centric Critical Assessment of Updated Variations Guidelines by European Medicines Agency

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ABSTRACT

The Committee for Medicinal Products for Human Use (CHMP) at EMA issues scientific guidelines to assist applicants. A variations regulation, made effective in 2008 to govern post-authorization changes, was last updated in 2013. In 2024, the European Commission (EC) proposed significant amendments and published them as Variations Guidelines 2025, with an implementation date of January 15, 2026. This comprehensive analysis is aimed at evaluating the extent and impact of these amendments on the pharmaceutical industry. A comparative study of EMA's Variations Guidelines 2013 and Variations Guidelines 2025 was conducted, focusing on Chemistry Manufacturing Control (CMC) changes impacting Quality. Key elements, including introduction of new changes, deletion of existing changes, merger of categories of existing changes etc., were evaluated. Notably, it examines high-impact changes for Biological and Herbal medicinal products and discusses their commercial implications. The amendments mainly emphasize the introduction and procedural sections i.e. guidance on grouping, super-grouping, and annual update of Type IA variations. Many variation categories have been streamlined. The updates have incorporated previous Article 5 recommendations (unforeseen variations). Post deletion of Veterinary Legislation, the updated guidelines are now solely for human products. These revisions are expected to reduce evaluation timelines for routine updates, potentially cutting processing duration by months for low-risk variations, which assists pharmaceutical companies to continue the supply of medicine without any interruption. However, there is a risk of rejection of the variation and a batch recall may be required from the market if misinterpretations of the change occur. Hence, the Marketing Authorisation holder should thoroughly understand the criticality of change by assessing the conditions and requirements of minor changes given the variation guideline before concluding the category of the variation as a minor.

Keywords: EMA, European Commission, Life Cycle Management, Regulatory Affairs, Variation Categories.

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INTRODUCTION

The registration of medicinal products is an inherently dynamic lifecycle process. It begins with a pre-marketing evaluation of drug dossiers to verify quality, safety, and efficacy based on existing data. Post-approval, modifications are frequently driven by emerging clinical or technical data during the product's lifecycle. Consequently, the Marketing Authorization Holder (MAH) must continuously integrate technical and scientific advancements. The MAH is legally obligated to implement any necessary amendments to ensure the product is manufactured and tested using universally accepted scientific methodologies.

Any subsequent modifications to registered products are defined as variations, ranging from minor administrative updates to substantial changes, and all require approval from the relevant European Union regulatory authorities. Standardized procedures for implementing these variation types are established to streamline workflows for both MAHs and regulatory bodies, ensuring that changes do not jeopardize public health. Applicable guidelines define the specific conditions applicants must meet and the documentation required for approval. Under EU legislation, these variations are classified into distinct types (Figure 1) and schedules governed by Commission Regulation (EC) No 1234/2008, which regulates variations to the terms of marketing authorizations within the EU.

EMA introduced "Variations guidelines" {(EC) No. 1234/2008 of 24th November 2008)} under the current legal system of regulation (EC) No. 726/2004 and Directive 2001/83/EC; which focuses on governing the variation procedure for medicinal products for use by humans and veterinary medicinal products.[1] These guidelines aim to streamline the process of managing

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post-authorization changes, which are necessary to adapt to scientific and technological advancement.[2]

Afterwards, in response to the global covid pandemic of 2021, a specific addendum was introduced in 2021, highlighting the guidelines for the active substance of coronavirus vaccines.[3]

Further, the EC proposed significant amendments to the existing guidelines compatible with the current legal context. EMA, the Heads of Medicines Agencies (HMA) and the EC solicited the comments of pharmaceutical industry representatives and interested parties on the proposed amendment until 23rd August 2024.[4] The revised Variations Guidelines were published in the Official Journal on 22nd September, 2025 by EMA.[5] The changes support the implementation of Regulation (EU) 2024/1701 and will be applied to variation applications, specifically for medicinal products for human use submitted by MAH to EMA/ European Union regulatory authorities from 15th January, 2026 onwards, and are expected to facilitate quicker and more efficient processing of variations, benefiting both MAHs and regulatory authorities.[7] The revisions aim to streamline post-authorization lifecycle management for medicinal products, reducing administrative burdens while maintaining a risk-based approach to changes in MAs.

This article aims to analyse and comment on the impact of the revised Variations regulations on the pharmaceutical industry/ MAHs.

METHODOLOGY

This study utilizes a systematic, qualitative comparative review of the European Medicines Agency (EMA) 2013 variation guidelines and new variation guidelines published in 2025 to identify the key areas of regulatory alignment and divergence. The analytical framework is specifically tailored to actively evaluate updates in Chemistry, Manufacturing and Controls (CMC) quality modifications. To ensure a reproducible and objective assessment, data extraction and findings interpretation were structured around three core regulatory vectors: the introduction/upgradation of novel variation codes, the deletion of legacy requirements, and the consolidation or merger of existing change categories. These elements were subsequently correlated with their practical regulatory impacts to ensure a robust, reliable evaluation of the changing landscape.

DISCUSSION

The recent revision of EMA variations guidelines is expected to overhaul post-authorization change procedures, as this amendment has been introduced to fasten processing for low-risk changes in MAs. This practice completely aligns with the pharmaceutical strategy of the EU to improve efficiency and progress while maintaining quality, safety, and efficacy of medicinal products without unnecessary delays.

Significant amendments

Key changes are summarized below and notable ones are highlighted in Figure 2, having been selected based on their prevalence and impact across the pharmaceutical industry.

Administrative changes

The major change is the deletion of references to the veterinary legislation, i.e. the updated guidelines only provide the direction to file the variations in terms of MAs for human use products, and on the documentation to be submitted in such procedures. Additionally, many references to the legislative framework are now updated to reflect current regulations.

Streamlining of information

Changes to procedural aspects in the updated guidelines are mainly focused on streamlining the process. Some of the information has been deleted from the updated version, i.e. the information that is available in the Variations regulations or Directive 2001/83/EC. For example, timetables available in the previous version are shifted to EMA/CMDh guidance.[2] Moreover, repetitive information is now being merged across sections. Such changes would definitely reduce the complexity and ease the variation process.

Updated information

The updated variations guidelines also counsel on the application of Article 7a, along with other articles, which was available in the previous guideline. Under Article 7a of the variations regulations, there is an introduction of super-grouping, i.e. a set of minor changes of Type 1A which can be notified simultaneously for several marketing authorizations, granted in accordance with different procedures in various Member States.[8]

It is now mandatory to submit an annual update to notify minor Type IA changes as part of grouping or super-grouping, fulfilling the conditions as per variations guidelines, i.e. changes should be identical.[9]

Furthermore, under Article 21 of the variations regulations, human coronavirus has also been included in the present guidelines for a special urgent procedure (fast-track); previously it was only for human influenza, based on Regulation (EU) 2022/2371 of the European Parliament and of the Council.[10] Table 1 summarizes the comparison of changes w.r.t variation procedure between variations guidelines 2013 and 2025.

The following are the updates w.r.t document requirements for different types of quality changes:

In case of minor change of an active substance manufacturing process, a new document requirement is introduced to provide a declaration from MAH that due to the proposed change, quality, safety or efficacy of the active substance and finished product are not impacted. This addition reinforces MAH responsibility

and reassures the Agency that a thorough internal review was conducted prior to filing the change as a minor variation.

For batch size increase change for an active substance, now minimum two batches Certificate of Analysis (COA) of non-biological active substance and three batches COA for biological active substance are required, instead of previously asked one batch data. This additional data provides greater assurance to the Agency for approval, aligned with the procedural relaxation of this category to a Type IA variation (Table 2).

To extend the re-test period/shelf-life and storage conditions of active substance and finished product, it is now mandatory to submit real-time data on three batches, instead of the previously asked two batches of data at the time of submission. This enhanced data requirement is introduced because the type of variation has been relaxed to Type IA (Table 2).

If there is a change in therapeutic indication, posology, or maximum daily dose, guidance has been provided to review its impact on quality. Earlier, there was no scope for updating the quality sections (3.2.P sections of dossier) while submitting safety variations. Now, the updated guidelines have given the flexibility to evaluate the impact on quality section simultaneously.

For some variations, data requirements have been reduced, e.g. if there are minor changes in the manufacturing process of the finished product, as per updated guidelines, only a commitment to conduct the stability study has to be submitted, instead of the previously asked 3 months of stability data. This documentation relaxation aligns with the updated notification procedures for Type IA changes, which stipulate that notifications must be submitted after 9 months of implementation. However, the MAH must possess 3 months of concurrent stability data at the time of submission to ensure that product quality is not compromised.

New Requirements for Changing the Geographical Source of Herbal Starting Materials: Modifying the geographical origin of herbal raw materials introduces complex variables, as environmental factors profoundly influence a plant's composition. Unlike synthetic chemicals, identical botanical species grown in different regions can exhibit distinct chemical and safety profiles. To address these complexities, the updated guidelines introduce a new requirement. When changing a geographic source, the Marketing Authorization Holder (MAH) must now provide two distinct declarations:

1. A declaration confirming there is no change to the manufacturing process of the herbal active substance.
2. A declaration confirming compliance with Good Agricultural and Collection Practice (GACP). The mandatory content required for GACP declarations is explicitly outlined in the variation guidance.

This enhanced requirement is introduced because the type of variation has been relaxed from Major Type II to Minor Type IB (Table 2).

Consolidation and Downgrading

Numerous active substance and finished product related changes have been updated in the revised guidelines, including consolidation and downgrading w.r.t. specific change codes (Tables 3, 4). For instance, new change codes have been introduced in the updated version (change code E.5 related to deletion of sites). Some of the change codes have been merged/ consolidated to simplify the complexity of previous guidelines

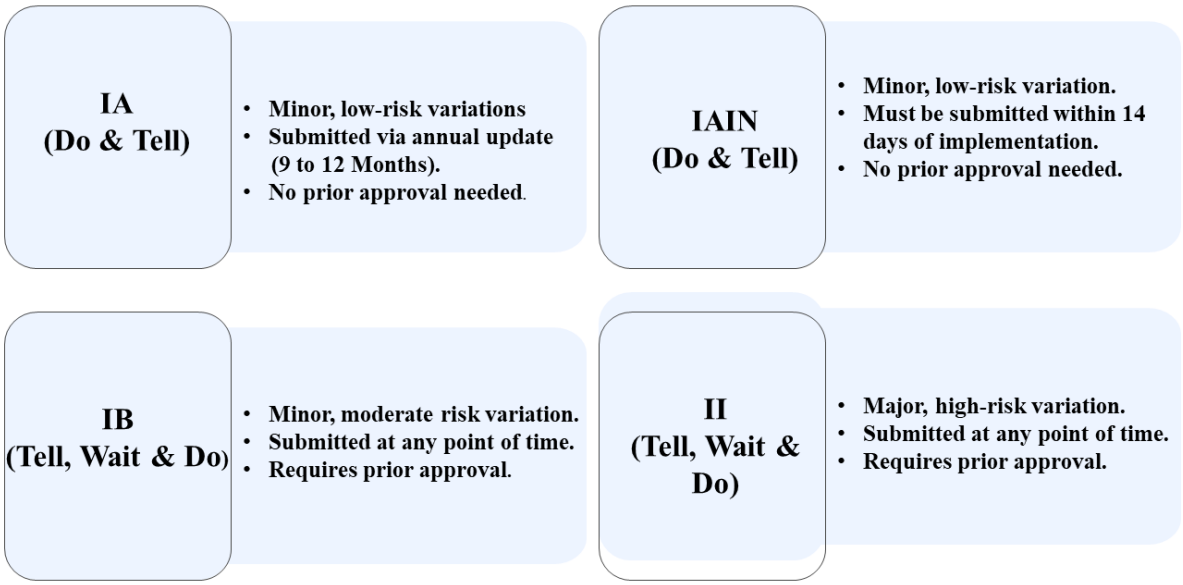

Figure 1: Types and Categorisation of changes as per EMA variation guidelines.

(e.g. for manufacturer related changes, there were 3 different types A.1, A.4 and A.5 and in the updated version all are combined under E.4).

Similarly, downgrading has been done to smoothen the variation procedure and to facilitate continuous supply of product. e.g. Q.1.a.3.a, related to change in batch size, was previously type 1B, which has now been downgraded to type 1A, remove arbitrary "10-fold" threshold and broaden the scope. Likewise, for the product shelf life extension, previously type 1B (B.II.f.1.b.1) variation has been downgraded to type $1A_{IN}$ (Q.II.f.1.b.1), i.e. immediate notification.

The category relaxations implemented in the new variation guideline are based on a proportional, risk-based approach. Following a thorough evaluation of the conditions for Type IA changes and the corresponding increases in documentation requirements, the Agency has successfully balanced technical demands with additional supporting data, granting relaxations for low-risk changes. Furthermore, as this variation guideline represents the first major update in over a decade, these strategic decisions reflect the regulatory confidence gained over the years.

A variation package prepared with such clearly defined categories and required documentation will significantly reduce the Agency's assessment timelines. This, in turn, will ensure faster approvals and guarantee an uninterrupted supply of the active substance or finished product incorporating the proposed changes.

Upgrading

As reflected in the above sections, the majority of the variations were downgraded with regard to change in variation categories. However, a few variations were upgraded for herbal active substances, exclusively where the changes meet the condition of "*not affecting route of manufacture, extraction solvents, physical form and drug extract ratio*". In contrast to the approach in other cases where new change codes were added for streamlining, in the aforesaid cases a single change code is assigned for multiple changes solely for herbal active substances without any conditions listed (Table 4).

An upgrade to above variations enables more detailed assessment than Type IA/IAIN notifications. However, now variations involving "CEP or Ph. Eur. monograph revisions" for herbal active substances require prior Agency approval. For instance, a minor change in the CEP holder name will trigger CEP revision and consequently result in a Type IB variation for all Marketing Authorizations utilizing the material. This procedure incurs substantial regulatory costs for the MAH and may cause supply chain disruptions, which typically have a severe impact on small and medium-sized MA holders.

Addition

The current version of the guidelines is a revision in line with Article 4 of the variation regulation and takes into account the

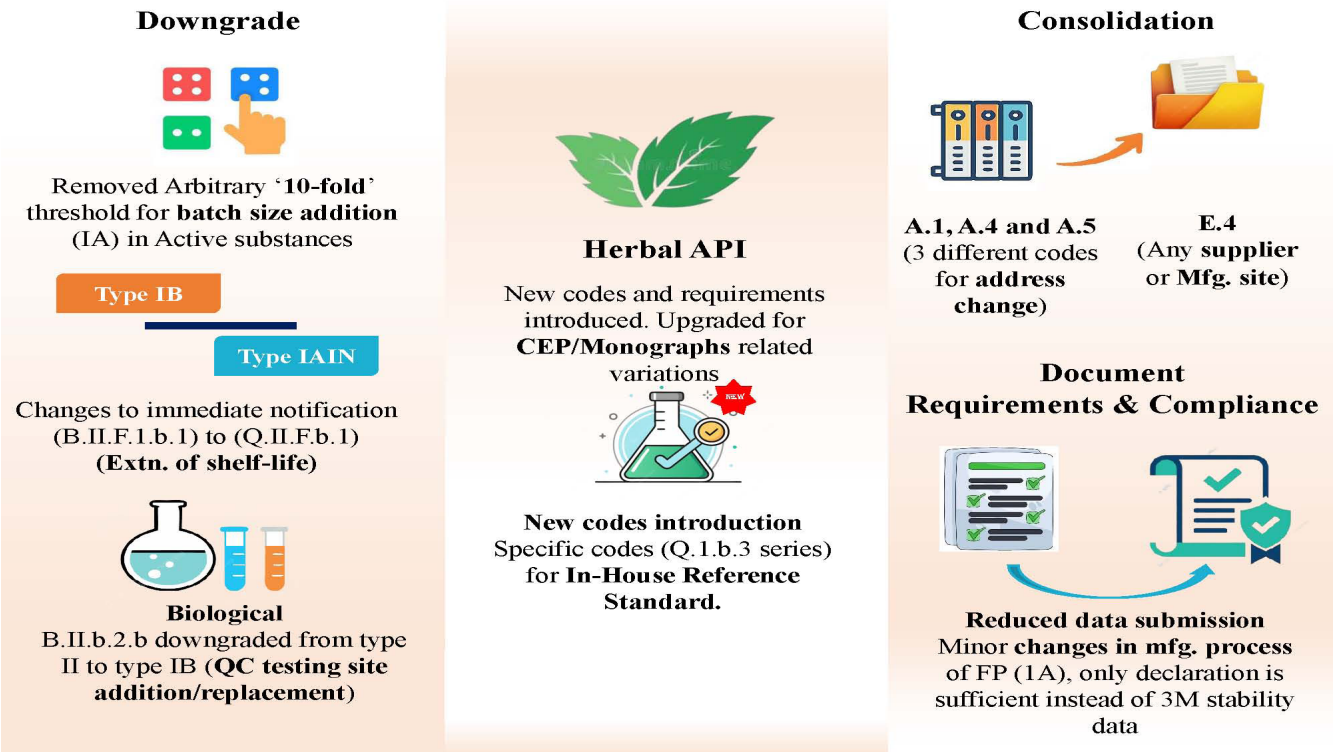

Figure 2: Notable changes having most impact and frequency.

Table 1: Comparative updates between Variations Guidelines 2013 and 2025 w.r.t variation procedure/coding system.[1, 5]

Variations Guidelines 2013	Variations Guidelines 2025
Change codes categorisation	
Administrative Changes code: A	Administrative Changes code: E
Quality Changes code: B	Quality Changes code: Q
Safety, Efficacy and Pharmacovigilance: C	Safety, Efficacy and Pharmacovigilance: C This code remains static.
Plasma Master File/Vaccine Antigen Master: D	Plasma Master File/Vaccine Antigen Master: M
Type IA variations-Annual update/Super-grouping/Grouping	
The annual update concept was not present in the guidance. However, MAH can submit even unrelated Type IA variations bundled together at any point in time within a year once the change is implemented.	The annual update concept is included in the guidance and it is made mandatory. No Type IA change can be submitted before 9 months from the implementation date. However, it must be submitted within 12 months as an annual update.
The concept of super-grouping was non-existent.	Introduces "super-grouping" to submit one or more Type IA changes in a single notification impacting several marketing authorisations of the same holder. However, the changes should be identical for all MAs. The super-grouping concept applies to all the MAs granted in mutual recognition, decentralised, or purely national licenses.
The grouping concept to submit one or more identical changes for a single marketing authorisation is followed, but there is no guidance present in this guideline.	Guidance for grouping is introduced in this new variation guideline.
Type IB Work-sharing	
Work-sharing was not mandatory for Type IB variations affecting multiple marketing authorisations.	Work-sharing made mandatory for Type IB variations affecting multiple marketing authorisations.
Vaccines and public health emergencies	
Fast-track variation procedure is available for Active substance related change for human influenza vaccines.	Fast-track variation procedure is now available for Active substance related changes for both human influenza vaccines and human coronavirus vaccines. These changes are classified as major type II and it is instructed to MAH to discuss such changes in advance with the Agency before submitting.

Agency's recommendations on unforeseen variations (Article 5), resulting in a new classification of variations.[6,7]

In case of change in the in-process tests for active substance and finished product, earlier there were no change codes available in the variation guideline. Based on the unforeseen category available in Article 5 recommendations, Type IB (B.I.a.4.z/B. II.b.5.z) variation was submitted. Now, a new change code with a relaxed category (Type IA) has been introduced with a defined set of conditions/documents under change codes Q.I.a.4.f and Q.II.b.5.f.

Other changes like deletion of a manufacturing process for active substance (Q.I.a.2.e), change in hold time or storage conditions of bulk product or an intermediate used in finished product manufacturing (Q.II.b.3.e), reduction of testing frequency of finished product test during release of batches (Q.II.d.1.i) and changing the excipient source with TSE/BSE risk (Q.II.c.3.a) are now integrated in new updated guidelines without changing the original category of respective change.

In addition to the above, many new change codes have been introduced, considering current industrial requirements, which simplified and enabled correct identification of change type in the guideline. A couple of major changes are cited below:

A new set of change codes for changing an in-house reference standard/preparation for a biological active substance under Q.I.b.3 are introduced, which gives proper direction to companies to deal with such changes.

In case of herbal medicines, a new change code (Q.I.a.1.e) is introduced for replacement or addition of a new starting material supplier or of a new herbal active substance manufacturer using the same or different plant production (i.e. cultivated or wild collection).

Some new change codes for Post-Approval Change Management Protocol (PACMP) and Product Lifecycle Management document (PLCM) related to the API (Q.I.e.4, Q.I.e.6, Q.I.e.7 and Q.I.e.8) has been introduced considering ICH guideline Q12

Table 2: Notable active substance related changes.[1,5]

Variation	Change from	Change to
Manufacture		
Change to QC arrangement for biological active substance	Type II (B.I.a.1.j)	Type IB (Q.I.a.1.i)
Change in geographical location of a starting material of herbal active substance	Type II (B.I.a.2.d)	Type IB (Q.I.a.2.c)
Batch size addition; more than 10-fold	Type IB (B.I.a.3.d)	Type IA (Q.I.a.3.a)
Control of Active Substance		
Introduction of a new test with its test method, for biological/ immunological active substance	Type IB (B.I.b.1.c)	Type IA (Q.I.b.1.c)
Minor change in analytical procedure for biological/immunological active substance	Type IB (B.I.b.2.a)	Type IA (Q.I.b.2.a)
Container Closure System		
Change in immediate packaging of sterile and biological non-liquid active substance	Type II (B.I.c.1.b)	Type IB (Q.I.c.1.a)
Other changes to analytical procedure (replacement/addition) for immediate packaging for biological/immunological active substance	Type IB (B.I.c.3.b)	Type IA (Q.I.c.3.b)
Stability		
Extension of re-test period for biological active substance not in line with approved stability protocol	Type II (B.I.d.1.a.3)	Type IB (Q.I.d.1.a.4)
Common change code for extension/introduction of re-test period has now been specified for extension of re-test period.	Type IB (B.I.d.1.a.4)	Type IA (Q.I.d.1.a.5)

on technical and regulatory considerations for pharmaceutical product lifecycle management.

Overall, the introduction of these new change codes with defined conditions and requirements for documents will give prominence to companies for submission of the variation with correct documentation and implementation of changes on time as per variation category.

GAPS AND CHALLENGES

The transition from the 2013 to updated 2025 variation guidelines caused severe procedural complexities for Marketing Authorization Holders (MAHs). The guidance and newsletter published by the Agency urged the submission of all Type IA variations using the 2013 variation guidelines implemented before January 15, 2026, ahead of that specific cut-off date.[7] However, the lack of clear guidance on how to classify variations submitted after this deadline caused widespread confusion between MAHs and NCAs. Because of highly divergent NCA interpretations and to avoid rejection/potential recall of the products, MAHs voluntarily upgraded the variation to Type IB or sought assistance from the Agency. These defensive upgrade of Type IA variation incurs substantial regulatory costs and supply chain disruptions, notably to small and medium-sized pharmaceutical companies.

Switching to mandatory annual reporting demands meticulous planning for all minor updates. MAHs now face a narrowed submission window for Type IA annual reports, as filings are restricted to a strict 9 to12 month window following the first implemented change. To manage this, regulatory teams must systematically log, prepare, and consolidate all post-implementation changes within this tight annual filing window.

A significant regulatory complication would arise while consolidating multiple Type IA variations characterized by distant implementation dates. For instance, the first variation implemented in January and another in December, both could fall within a single annual update submission. This scenario introduces a notable administrative burden and shortened time for the second variation, as mentioned in the above example.

MAHs must establish contingency plans for potential rejections, including the capability to resubmit rejected variation within the strict 14-day window. These challenges are amplified if the Agency recommends upgrading the Type IA change to IB (e.g., due to complexity of changes, requires assessment, or is not satisfied with generated data and justification). Hence, there is a potential risk of product recall from the market.

Table 3: Notable finished products related changes [1,5]

Variation	Change from	Change to
Description and composition		
Change in coating weight or weight of cap shell for gastro resistant products where coating or cap shell is critical for release of active	Type II (B.II.a.4.b)	Type IB (Q.II.a.4.b)
Manufacturer		
Addition/replacement of QC testing site for biological products	Type II (B.II.b.2.b)	Type IB (Q.II.b.2.b)
Inclusion of batch release site including QC testing for biological products	Type II (B.II.b.2.c.3)	Type IB (Q.II.b.2.c.3)
Minor change in manufacturing process for Oral Suspension	Type IB (B.II.b.3.f)	Type IA (Q.II.b.3.a)
Control of Excipients		
Change of source of excipient from TSE risk material to non-TSE risk material for biological/immunological products	Type IB (B.II.c.3.a.2)	Type IA (Q.II.c.3.a)
Control of Finished Products		
Introduction of a new test with its test method, for biological/ immunological products	Type IB (B.II.d.1.c)	Type IA (Q.II.d.1.c)
Container Closure System		
Change of qualitative/quantitative composition for existing immediate packaging for solid biological/immunological products	Type II (B.II.e.1.a.3)	Type IB (Q.II.e.1.a.1)
Addition of a new container closure system for non-sterile biological/ immunological products	Type II (B.II.e.1.b.2)	Type IB (Q.II.e.1.b.1)
Stability		
Extension of shelf life for an IR film-coated tablet	Type IB (B.II.f.1.b.1)	Type IAIN (Q.II.f.1.b.1)

Table 4: Notable categories having upgraded change in variation guidance.[1,5]

Variation	Change from	Change to
CEP/TSE/Monographs (applicable only for herbal active substances)		
Addition of new active substance manufacturer	Type IAIN (B.III.1.a.1)	Type IB (Q.III.l.a.5)
Update in CEP of an already approved manufacturer	Type IA (B.III.1.a.2)	
Change in non - Ph. Eur. specification to comply with Ph. Eur. or national pharmacopoeia of a member state	Type IAIN (B.III.2.a.1)	Type IB (Q.III.2.d)
Update in non - Ph. Eur. specification of herbal active substance starting material to comply with Ph. Eur. or national pharmacopoeia of a member state	Type IA (B.III.2.a.2)	
To update specification and analytical test of herbal active substance to comply with changes in pharmacopoeial monograph	Type IA (B.III.2.b)	
To update specification of herbal active substance to comply with Ph. Eur. from national pharmacopoeia of a member state.	Type IA (B.III.2.c)	

CONCLUSION

The EMA's updated variations guidelines transform the post-authorization process by expediting the review of low-risk modifications. By revising the existing framework, particularly the quality chapter for CMC variations, the EMA aims to reduce administrative burdens and accelerate the implementation of minor changes. This increased efficiency allows pharmaceutical companies to adapt more quickly to market demands and patient needs.

The new Chapter Q framework achieves a highly sophisticated balance between regulatory relief and risk-based oversight. By aggressively downsizing the hurdles for traditional chemical scale-ups, routine testing, site transfers, and standard specification adjustments, the EMA has unlocked significant operational velocity for established pharmaceutical portfolios. Furthermore, embedding ICH Q12 predictive tools (PACMPs and PLCMs) marks a massive step forward in transforming variations from a reactive, piece-meal paperwork exercise into a proactive, strategic lifecycle approach.

However, the successful adoption of these guidelines will depend on the ability of stakeholders to adapt to the new requirements and effectively integrate them into their operational practices. The transition to 2025 variation guidelines has created significant procedural and financial hurdles for MAHs, including classification ambiguity, strict reporting windows, and high stakes for grouped submissions. These challenges, including defensive upgrades and potential rejections, threaten supply chain stability and increase the risk of product recalls, particularly affecting smaller and medium-sized companies. Hence, staying informed and agile in response to regulatory changes will be essential for maintaining compliance and ensuring the timely delivery of safe and effective medicines to patients.

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ABBREVIATIONS

EMA: European Medicines Agency; **EU:** European Union; **MA:** Marketing Authorisation; **CHMP:** Committee for Medicinal Products for Human Use; **EC:** European Commission; **MAH:** Marketing Authorisation Holders; **HMA:** Heads of Medicines Agencies; **CMDh:** Co-ordination Group for Mutual Recognition and Decentralised Procedures- Human; **COA:** Certificate of Analysis; **CEP:** Certificate of Suitability; **NCA:** National Competent Authority.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTIONS

DSD, AKTK, ATD: Conception and design of the study, collection and interpretation of regulatory data, and the comparative analysis. VK: Drafting the manuscript, collection and drafting, and ensuring the accuracy and integrity of all included information. PM: Review of the draft, approval of the final version for publication, accountable for all aspects of the work. The author meets the authorship criteria as defined by the International Committee of Medical Journal Editors (ICMJE).

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