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Human Medicines Division

## Executive Summary

As part of the 2020 Pharmaceutical Strategy for Europe, the Commission is reviewing the current rules governing the procedures for post-authorisation changes to the terms of a marketing authorisation for medicines products for human use, with the purpose to make the lifecycle management of medicines more efficient and future proof and ensuring the protection of public health in the European Union.

In this context, the Commission [has proposed](#) a draft delegated Regulation amending Commission Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and its annexes (Variations Regulation) within the existing legal framework of Regulation (EC) No 726/2004 and Directive 2001/83/EC.

As a next step, the Commission is reviewing the Guidelines on the details of the various categories of variations and operation of the procedures ([Variations Guidelines](#)) and, in this respect, proposed amendments compatible with the current legal context are hereby released for the stakeholders consultation with a commenting period until 23 August 2024. This document outlines the main scope and changes of the revision.

Overall, the main changes proposed to the Introduction and Procedural section of the Variations Guidelines include the addition of procedural details on the new/revised regulatory tools introduced with the proposed Variations Regulation (e.g. on super grouping of Type IA variations, annual update of Type IA variations, mandatory use of worksharing procedure, extension of update flexibility to human vaccines addressing a public health emergency in the Union).

The introduction and procedural guidance sections have been further simplified and updated to reflect the current practice of EMA and National Competent Authorities. Some operational details will be moved and/or further covered by EMA and/or CMDh guidance, as appropriate, while some provisions have been added to this document in light of the experience acquired (e.g. request for a detailed justification for unclassified ("z") Type IB variations, request of an update or addendum to quality summaries, non-clinical overviews and clinical overviews as relevant for non-complex type IB variations, recognition that certain related changes may be acceptable within a single variation application without grouping).

The Annex to the Variations Guidelines, including the different categories, conditions and documents to be submitted has also been reviewed taking into consideration the experience acquired and the scientific and technical progress. Previous Article 5 recommendations for unforeseen variations have

been integrated into the current proposal, as appropriate, and targeted proposals have been made on the administrative variations and changes affecting herbal medicinal products.

The current code system for variations has been maintained, with the deletion of the Roman numeral "I" (relating to variations for human medicines) on the C-scopes and a sequential numbering implemented.

In line with the EC proposal on the amended Variations Regulation to end automatic Type II variations for biological products, the variation framework for changes to biological active substances and finished products have been reviewed following a risk proportionate categorisation and proposals for downgrading of some Type II variations were added, where scientifically justified.

In addition, the variation framework for changes to active substances (including ASMFs and CEPs) has been updated to strengthen the requirements for the introduction of a new source of active substance to emphasize that the MAH has adequate knowledge of the quality of the active substance, and to strengthen the conditions and documentation requirements in line with the responsibilities of the MAH and finished product manufacturer. Moreover, with regards to quality changes, it is proposed to have better alignment and consistency between scopes, across several sections and between chemical and biological medicinal products, namely regarding the specification attributes and test procedures, the manufacturing and testing sites and the packaging and stability. Categories B.I.e and B.II.g on additional regulatory tools (design space, Post Approval Change Management Protocol (PACMP) and product lifecycle management document) have also been updated to allow, for example, that an extension of an approved design space could be done through a type IB variation and that changes for biological medicinal products under a PACMP could be handled by a type IA variation.

With regards to variations affecting medical devices, new scopes were proposed to cover integral, co-packaged and product information referenced devices taking into account the new requirements of the Medical Devices Regulation and the Guideline on quality documentation for medicinal products when used with a medical device. Efforts have been made to focus on impact and risk rather than type of device and a risk-based classification has been developed taking into account the impact on the delivery, quality, safety and/or efficacy of the medicinal product.

The Plasma Master File (PMF) variations have been reviewed and simplified to improve the management of changes to these medicinal products, including the downgrading of some variations and generally improving the wording of the conditions and documentation to be provided.

The chapter related to safety, efficacy and pharmacovigilance changes has been revised with some Type IB and Type II scopes added, some updated and others deleted (e.g. changes currently being made through the Article 57 database). In addition, the wording of these variations has been improved and/or some notes have been added or updated for clarity.

### **Additional information**

Guidance on the transition period between the date on which the updated Variations Regulation will become applicable (January 2025) and the date of application of the updated Variations Guidelines will be issued in due course.

A second revision of the variation framework is foreseen once the revision of the basic pharmaceutical legislation has been completed and additional provisions have been added to the legal framework, making it possible to explore additional options and further optimise the lifecycle management of medicines (e.g. digitalisation, full implementation of ICH Guidelines).