WHITE PAPER

LIFECYCLE MANAGEMENT

European variations for medicinal products for human use

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Introduction

Variations are any change to the currently approved content of a Marketing Authorisation (MA) dossier and are essential in the lifecycle management of a medicinal product. For human use, this mainly concerns articles 8(3), 9, 10, 10a, 10b, 10c of Directive 2001/83/EC and Annex I thereto, as well as article 6(2) Regulation 726/2004/EC.

In accordance with Commission Regulation (EU) No 1234/2008 (the 'Variations Regulation'), and as amended by Regulation (EC) No. 712/2012, variations to Marketing Authorisations include Type IA, Type IA_{IN}, Type IB, Type II and extension applications.

The following applies to medicinal products for human use approved through Mutual Recognition Procedure (MRP), Decentralised Procedures (DCP) and Centralised Approved Products (CAPs), and authorisations granted following a Committee for Medicinal Products for Human Use (CHMP) full harmonisation referral.

Homeopathic and traditional medicinal products (which have no marketing authorisation but are subject to simplified registration procedures) are not concerned by this Regulation.

Definitions of the variation types

Variations are classified according to the level of risk to public health and the impact on quality, safety and efficacy of the medicinal product. Details regarding the classification of variations into the various categories can be located in the "Commission Guideline on the details of the various categories of variations".

Type IA variations are minor variations which have minimal impact, or no impact at all, on the quality, safety or efficacy of the medicinal product.

The Variations Regulation and Annexes list the changes that can be considered as minor Type IA variations. These minor variations do not require prior approval but must be notified by the Marketing Authorisation Holder (MAH) within 12 months following implementation - "Do and Tell" variations.

Type IA_{IN} variations are also minor variations but require immediate notification to the competent authroity on implementation.

The Annexes to the Variations Regulation specifies which minor Type IA_{IN} variations must be notified immediately on implementation.

Generally Type IA and Type IA_{IN} variations follow a 30 day review timetable. Type IA and Type IA_{IN} changes can be implemented prior to submission of the variation, however if the variation is rejected by an authority the MAH should immediately cease applying the rejected changes.

Type IB variations are minor variations which are not a Type IA variation nor a Type II variation nor an extension. Approval from the competent authority is required before implementation. Generally Type IB variations follow a 30 day assessment timetable.

Type II variations are major variations which may have a significant impact on the quality, safety or efficacy of the medicinal product. Approval from the competent authority is required before implementation. Generally, Type II variations follow a 60 day assessment timetable, but can be reduced to 30 days for urgent safety issues and extended to 90 days for extensions of the therapeutic indication.

Extension applications are detailed in the Variations Regulation Annex I and include changes to strength, route of administration and pharmaceutical form. Approval from the competent authority is required before implementation. Generally extension applications follow a 210 day assessment timetable.

Classification of unforseen variation. If the MAH has a variation for a MA which is not detailed in the variations classification guideline, scientific recommendation on classification of the submssion can be requested via the Coordination Group for Mutual Recognition and Decentralised Procedures (CMD) or the European Medicines Agency (EMA) under Article 5(1) of the Regulation.

Such a request is made using the Article 5 template form, where the proposed variation is described along with the MAH proposed classification with justification. CMD / EMA will consider the application and the justification and will make a recommendation on the classification of the proposed unforeseen variation to the MAH, within 45 days.

Getting it right the first time

When updating a marketing authorisation by variation it is important to ensure all submission requirements are met, to ensure a smooth validation process. Any validation errors can be time consuming and may impact on assessment timelines by delaying the start of a procedure.

Some common validation errors could be:

- the submission of an incomplete variation application form

- incorrect variation classification / variation type

- incorrect implementation date

- incorrect fees

- missing documents that are required, as specified in the classification guidance

- missing local / nationally required documentation

- invalid certificates / licences

- non-authorised signatory

- missing Letter of Authorisation

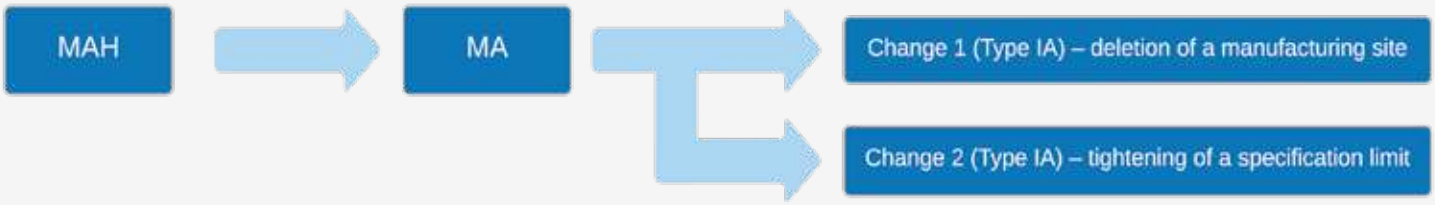
- incorrect format of submitted document e.g. Word document of Summary of Product Characteristics (SmPC) / Product Information (PI) omitted

- eCTD formatting guidelines and submission process not followed

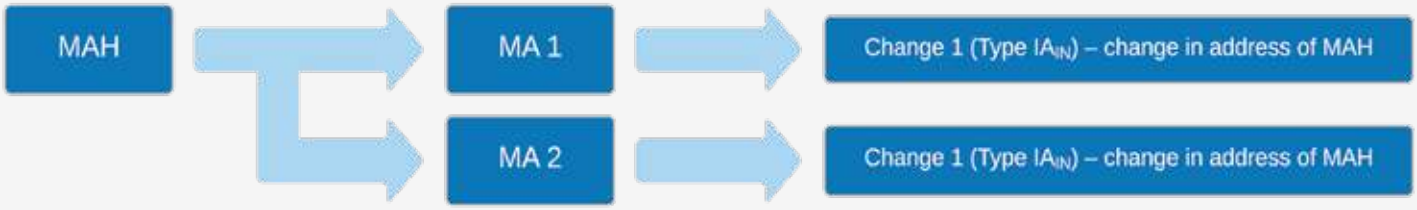
Grouping of Variations

There are certain cases where several variations can be grouped and submitted simultaneously in one application as described in articles 7(2)(a) & (b) of the Regulation:

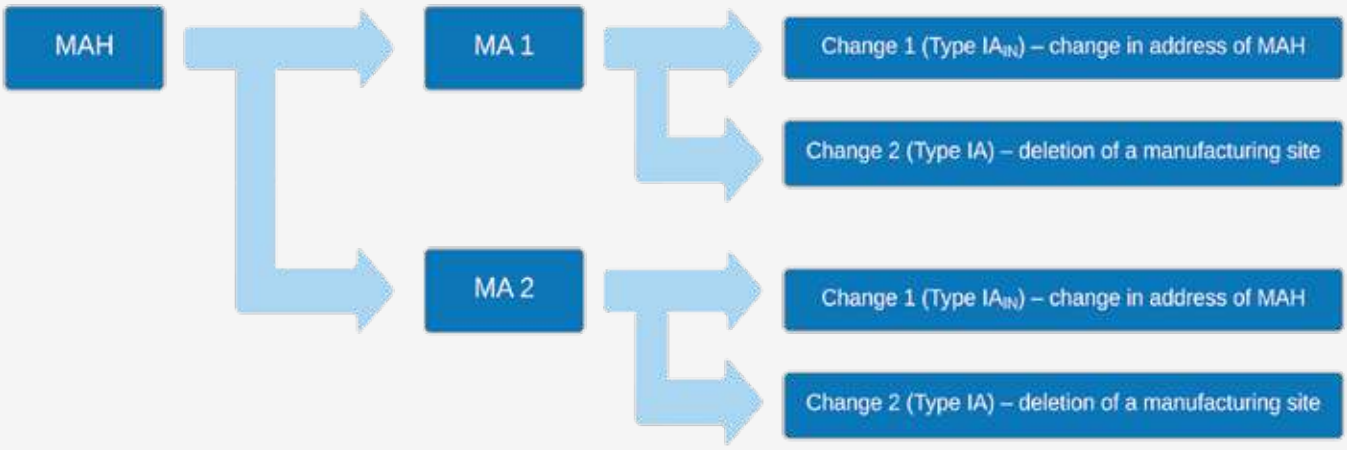
-A MAH can group several Type IA and Type IA_{IN} variations affecting one medicinal product under a single notification to the same competent authority. For example:



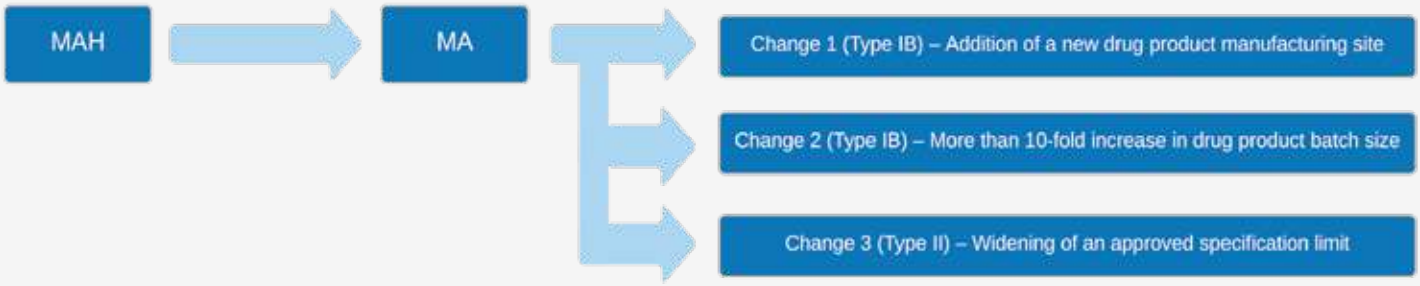
-A MAH can group one Type IA or Type IA_{IN} variation affecting several medicinal products. For example:



- A MAH can group several Type IA and Type IA_{IN} variations affecting several medicinal products, providing the variations are the same for all of the medicinal products and are submitted to the same competent authority. For example:



-A MAH can group several types of variations affecting one medicinal product under a single notification when they fall within one of the cases listed in Annex III of the Variations Regulation, or if the proposed grouping is agreed by the competent authority before submission. Such grouped submissions will follow the review procedure for the highest variation in the group. For example:



- a supergrouping may be applied for purely administrative changes and other changes that do not contain product-specific information. National, CAPs and MR/DC procedures cannot be mixed in supergroupings. The same set of Type IA variations must be submitted for all MAs covered by the supergrouping, such as a change of MAH address for example.

When a MAH is submitting a supergrouping variation for a group of products which are authorised via MRP/DCP, a lead RMS must be appointed. The lead RMS must be RMS for at least one of the MAs in the supergrouping. The lead RMS will manage the assessment and communicate with the other member states involved. In order to request agreement for a lead RMS the MAH submits a Letter of Intent for the supergrouping to the preferred lead RMS authority. If the preferred lead RMS has the capacity and expertise to take on the role they will issue the supergrouping procedure number to the MAH and the submission can proceed.

The MAH should liaise with EMA prior to the submission of a supergrouping for CAPs, and also with relevant national competent authorities for supergrouping for national MAs.

Points of note:
When submitting Type IA_{IN} variations as part of a grouped submission, the timeline for submission must be adhered to i.e. a Type IA_{IN} should always be submitted immediately, whether or not it is grouped with other variations.

The timetable of a grouped variation is dependent on the highest type of variation included in the grouping.

Variations are submitted simultaneously to the Reference Member State (RMS) and Concerned Member States (CMS) for MRP/DCP authorised medicinal products.

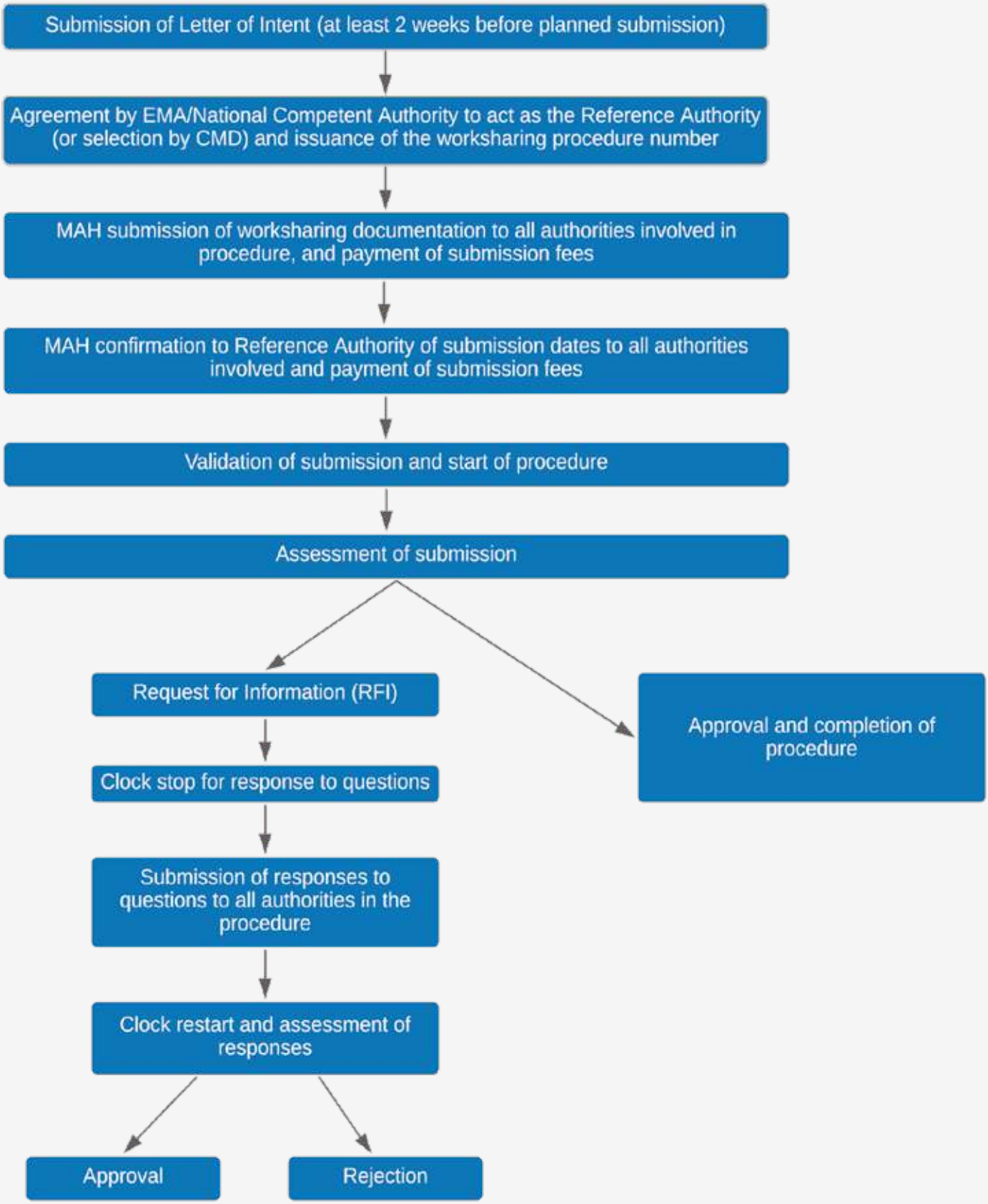
Worksharing

As per Article 20 of the Regulation, a MAH can request a worksharing procedure where the same Type IB, Type II or group of variations, affects several medicinal products. The change must be the same, with no need for product specific assessment of the change.

When a group of variations only consist of Type IA or Type IA_{IN} variations affecting several medicinal products this is considered a group variation, not a worksharing procedure. However, Type IA and Type IA_{IN} variations can be included with a Type IB or Type II variation submitted for a worksharing procedure. In such cases the review of all the variations will be performed as part of the worksharing procedure. It should be noted that groups including an extension application are excluded from worksharing procedures.

A reference authority takes the lead in the assessment of worksharing submissions. If one of the medicinal products in the submission is authorised via the Centralised Procedure the EMA will be the reference authority. If there are no CAPs in the submission the MAH selects the preferred reference authority to lead the assessment and contacts them, using the specified email address as published in the list of CMD contact points, at least 2 weeks before the planned submission using the template for the letter of intent for the submission of a worksharing procedure. If none of the proposed reference authorities are able to lead the assessment then the MAH may forward the request to the CMD for further discussion and selection of the reference authority.

Generally, worksharing procedures follow the 60 day assessment timetable of Type II variations, but can be reduced to 30 days for urgent safety issues and extended to 90 days for extensions of the therapeutic indication.


Submission of Letter of Intent (at least 2 weeks before planned submission)
Agreement by EMA/National Competent Authority to act as the Reference Authority (or selection by CMD) and issuance of the worksharing procedure number
MAH submission of worksharing documentation to all authorities involved in procedure, and payment of submission fees
MAH confirmation to Reference Authority of submission dates to all authorities involved and payment of submission fees
Validation of submission and start of procedure
Assessment of submission
Request for Information (RFI)
Clock stop for response to questions
Submission of responses to questions to all authorities in the procedure
Clock restart and assessment of responses
Approval
Rejection
Approval and completion of procedure

Conclusions

BlueReg has extensive experience in the lifecycle management of medicinal products, including all variation types, groupings, supergroupings and worksharing procedures. Our valuable expertise can assist you by anticipating aspects which could be problematic for the different submissions and procedures, so that potential delays are mitigated against.

BlueReg can liaise with all stakeholders involved, such as manufacturing, labelling design, pharmacovigilance etc. to successfully plan and coordinate large groupings.

BlueReg expertise and high quality submissions will ensure smooth validation and timely progress and smooth running of the procedures. The complexities of European submissions and timelines will be managed, resulting in a close collaboration and development of a strong path to submission and throughout the procedure.

Definitions of the variation types

CMDh variation procedures and best practice guides:
https://www.hma.eu/96.html

CMDh Letter of Intent and Article 5 request form:
https://www.hma.eu/265.html

CMDh contact points:
https://www.hma.eu/abouthma.html

Commission Guideline on the details of the various categories of variations:
https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52013XC0802(04)&from=EN

Commission Regulation (EU) No 1234/2008:
https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:334:0007:0024:en:PDF

Directive 2001/83/EC:
https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

EMA post authorisation variation guidance:
https://www.ema.europa.eu/en/human-regulatory/post-authorisation/variations

Eudralex – Notice to Applicant:
https://ec.europa.eu/health/documents/eudralex/vol-2_en

Regulation (EC) No. 712/2012:
https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2012_712/reg_2012_712_en.pdf

Regulation 726/2004/EC:
https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32004R0726&from=EN

Unforseen variations:
https://www.hma.eu/293.html
https://www.ema.europa.eu/en/human-regulatory/post-authorisation/variations/article-5-procedure-regulatory-procedural-guidance

List of Abbreviations

CAP	Centralised approved products
CHMP	Committee for Medicinal Products for Human Use
CMD	Coordination group for Mutual Recognition and Decentralised Procedures
CMS	Concerned Member State
EC	European Commission
EMA	European Medicines Agency
EU	European Union
DCP	Decentralised Procedures
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MRP	Mutual Recognition Procedure
RFI	Request For Information
RMS	Reference Member State

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