Implementation of the regulations in compliance with timelines for national MA variation application

Field: MAs registered via the national procedure
Scope: MA variation applications

Introduction

The ANSM introduced an approach to handle MA variation applications, designed to ensure compliance with regulatory timelines, in accordance with Commission Regulation (EC) 1234/2008 of 24 November 2008 amended by the Commission delegated Regulation (EU) 2024/1701 of 11 March 2024, which came into for on 1st January 2025.

Consequently, the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) has updated the documentation in relation to variations which are available at the following website:
https://www.hma.eu/human-medicines/cmdh/procedural-guidance/variation.html

Since the 6th November 2017, the ANSM send an acknowledgement of receipt of a valid application to the Marketing Authorisation Holder (MAH). The timelines for notification of an express decision begins as of the date of this acknowledgement.

However, applications that do not receive an express decision from the ANSM within the regulatory timelines result in an implicit decision, in accordance with the regulations:

- Implicit decision to accept the variation, for variations of type IA and IB
- Implicit decision to reject the variation, for variations of type II.

Practicalities

Variation applications are processed in accordance with the procedure detailed below.

1. **Receipt of application**: For all applications, an acknowledgement of receipt is automatically sent to the applicant via the Common European Submission Platform (CESP).

2. **Application validation**: For all variations of type IB and II, an acknowledgement of receipt of a valid or an invalid application is sent to the applicant via email within 14 days of receipt of the variation application.

   If the dossier is complete and deemed compliant, the acknowledgement of receipt of a valid application marks the start of the assessment phase (procedure start or D0) and the regulatory timelines apply as of this date.

3. **Assessment of the application**: Compliance with the regulatory timelines and impact on decision

   - **For type IA variation applications**:
     If no express decision is issued within 30 days of receipt of the application via the CESP, the application is to be considered accepted.

     NB: There is no validation phase for type IA variations and no D0 is therefore issued for these applications.

   - **For type IB variation applications**:
     If no express decision is issued within 30 days from the procedure start (D0), or the re-start date where the procedure has been on clock-stop, the variation is to be considered accepted.

   - **For standard type II variation applications**:
     If no express decision is issued within 60 days from the procedure start (D0), or the re-start date where the procedure has been on clock-stop, the variation is to be considered rejected.

   - **For type II variations related to a change or addition of a therapeutic indication, and variations listed in part 2 of Annex V of the regulation**:
     If no express decision is issued within 90 days from the procedure start (D0), or within 60 days of the re-start date where the procedure has been on clock-stop, the variation is to be considered rejected.

   - **For an annual update**: The regulatory timelines applicable to type IA variation applications apply.

- **For a grouping application**: The highest variation type of the grouped application determines the rules and timelines of the grouping.

- **For a supergrouping application**: The regulatory timelines applicable to type IA variation applications apply.

- **For worksharing application**: The highest variation type (IB or II) of the variation(s) application determines the rules and timelines.

Of note, a marketing authorisation holder is now required to submit the same type IB or type II variation, or the same group of variations affecting more than one marketing authorisations from the same holder in more than one Member State (irrespective of the registration procedure), in one application via a worksharing procedure.

Harmonisation of the complete initial dossier or SmPC, PL and labelling is not a prerequisite for a worksharing procedure. However, the proposed updates to the dossier and/or Product information and outcome must be the same for all products involved in the procedure.

In justified cases agreed by the competent authorities of the Member States and the Agency, where applicable, the worksharing procedure may also include marketing authorisations owned by several holders in more than one Member State.

4. **Requests for supplementary information/clock-stop**:

MAH are reminded that supplementary information requested by the ANSM must be provided within the specified timelines. If the information is not provided within these timelines, the MA variation application is to be considered rejected.

Requests for supplementary information (RSI) are sent by email. MAH should acknowledge correct receipt within 48h by email return. Nevertheless, by default, a period of 7 days is given to the MAH to receive the RSI at the relevant department.

- **During the validation phase:**

    - If the MAH has not submitted the requested information within 15 days following the acknowledgement of receipt of an invalid application from the ANSM, the variation application is to be considered rejected.
    - If the requested information is submitted and deemed to be valid, the assessment phase can start and a D0 will be issued within 7 days of receipt of the supplementary information.

- **In the event of a clock-stop (during the evaluation phase):**
    - For type IB variations: the MAH is given 30 days to provide the requested supplementary information. If the information is not submitted within these timelines, the variation application is to be considered rejected.
    - For type II variations: the MAH is given 60 or 90 days (e.g. addition of a new therapeutic indication) to provide the requested supplementary information. If the information is not submitted within these timelines, the variation application is to be considered rejected.

5. **Confirmation of decisions: Express notification or publication**

The ANSM decision together with the amended Product information (if applicable) is sent to the MAH by email within the regulatory timelines. The electronic file containing the Product information must be used for all subsequent variation applications.

If no express decision is issued, the decision is implicit and no notification is therefore foreseen.
Where the implicit positive decision has an impact on the MA annexes, the updated Product information will be published in the Public Medicines Database ("Base de données publique des médicaments" (BDPM)) and Drug Directory ("Répertoire des spécialités pharmaceutiques" (RSP)) within two months following the end of the regulatory timelines.

The following will not be published in any way:

- Implicit decisions to accept a variation that has no impact on the MA annexes
- Implicit decisions to reject a variation, whether or not it has an impact on the MA annexes.

Implicit decisions are made without prejudice to any subsequent measures that the ANSM may need to take in the interests of public health.

To ensure that MAs are always updated fully, all subsequent variation applications can only be submitted once the regulatory timelines have expired and/or, where applicable, the updated MA annexes have been published, to ensure that the variations are based on the last approved text.

If a MAH needs to submit a variation urgently, the relevant division of the "Direction des autorisations" (varamm1@ansm.sante.fr or varamm2@ansm.sante.fr) should be contacted in advance, copying in the Department named "Direction de la Maîtrise des Flux et des Référentiels" (DMFR) (e-recevabilite@ansm.sante.fr)