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VARIATION FILING PROCEDURE IN EUROPE: A COMPLETE REVIEW

ABSTRACT

MAH can proceed for any post approval change implementation through variation filing to EMA agency. This approach can be applicable for all categories of applications such as Central procedure (CP), National procedure (NP), Decentralized procedure (DCP) and Mutual recognition procedure (MRP). Variation changes are classified in to four types such as 1. Administrative 2. Quality 3. Safety, Efficacy and Pharmacovigilance and 4. Specific changes to plasma master files and vaccine antigen master files. Based on the criticality of the change variations are classified as Type IA/IA_{IN}; type IB and type II variations Type-IA/IA_{IN} is for minor change; type IB is for moderate variation and type II variation is for major change. Type IA/IA_{IN} are do and tell process, type-IB is tell wait and Do process and type II is tell approval and Do process. This article is only for educational purpose.

Authors & Affiliation:

Useni Reddy Mallu*
and Anand K

Dept. of Chemistry, Sri
Krishnadevaraya
University, Anantapur,
Andhra Pradesh, India

Correspondence To:

Useni Reddy Mallu

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EMA has introduced the variation procedure in the year 1995 for approved drug product for any kind of change. In 1995, EMA has introduced the two categories of variations such as type-I for minor changes and type-II for major changes and in 2003 type-I is divided into two categories such as type-IA for minor changes and type-IB for moderate changes. Variations history has been represented in figure-1.

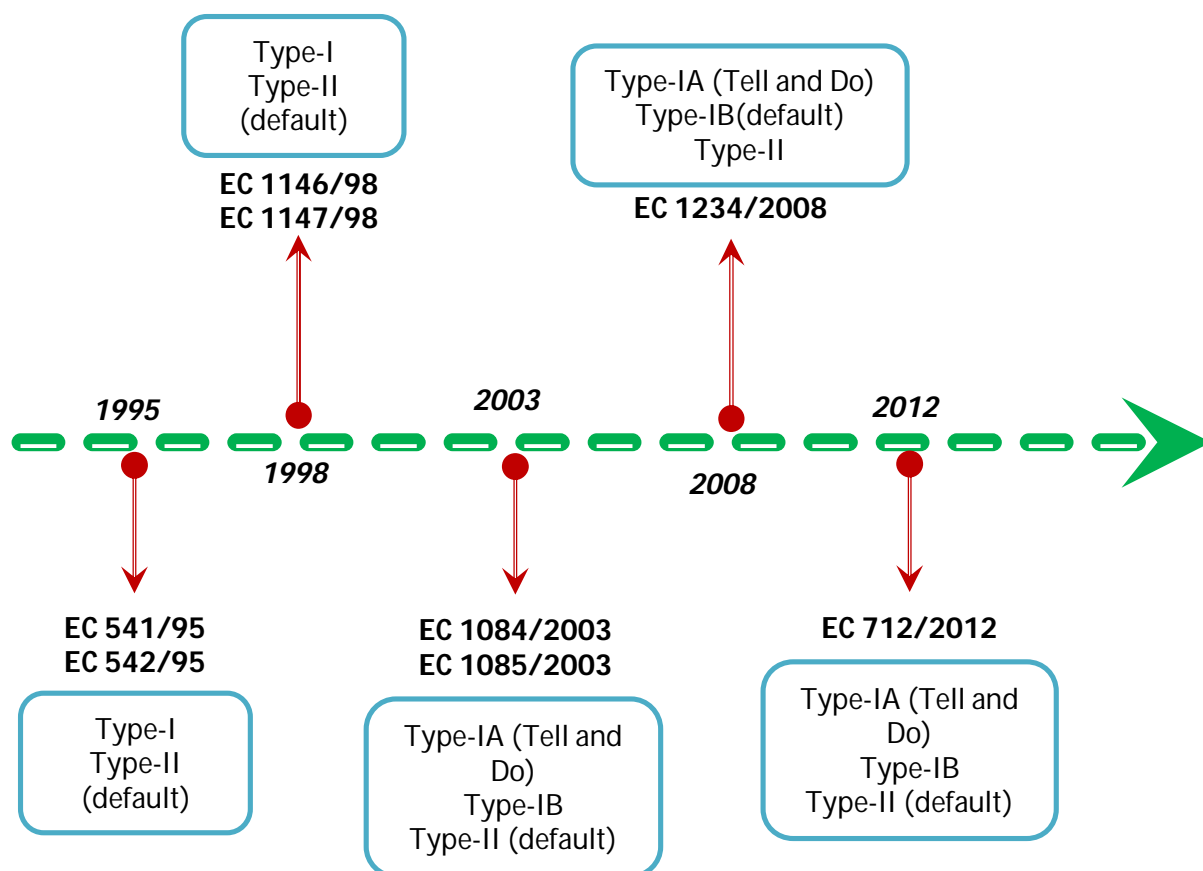


Figure-1: EMA implementation of variations

VARIATION CLASSIFICATION:

All post approval changes can be notified to the agency through variation filing. This approach can be applicable for all categories of applications such as Central procedure (CP), National procedure (NP), Decentralized procedure (DCP) and Mutual recognition procedure (MRP). Variations can be classified into four categories such as type-IA_{IN}; type-IA; type-IB; type-II and Extensions. Figure-2 represents the all categories of variations.

Minor variations of Type IA

i. Type-IA:

These variations do not require any prior approval, but MAH should notify within 12 months (“Do and Tell”).

ii. Type-IA_{IN}:

It requires immediate notification after implementation.

Minor variations of Type IB

These must be notified before implementation. The holder must wait 30 days to ensure that the notification is deemed acceptable (“Tell, Wait and Do”).

Major variations of Type II

These variations require approval of the relevant competent authority before implementation.

Extensions

These notifications will be evaluated as like initial MAA. The extension can either be granted as a new MA or will be included in the initial MA to which it relates.

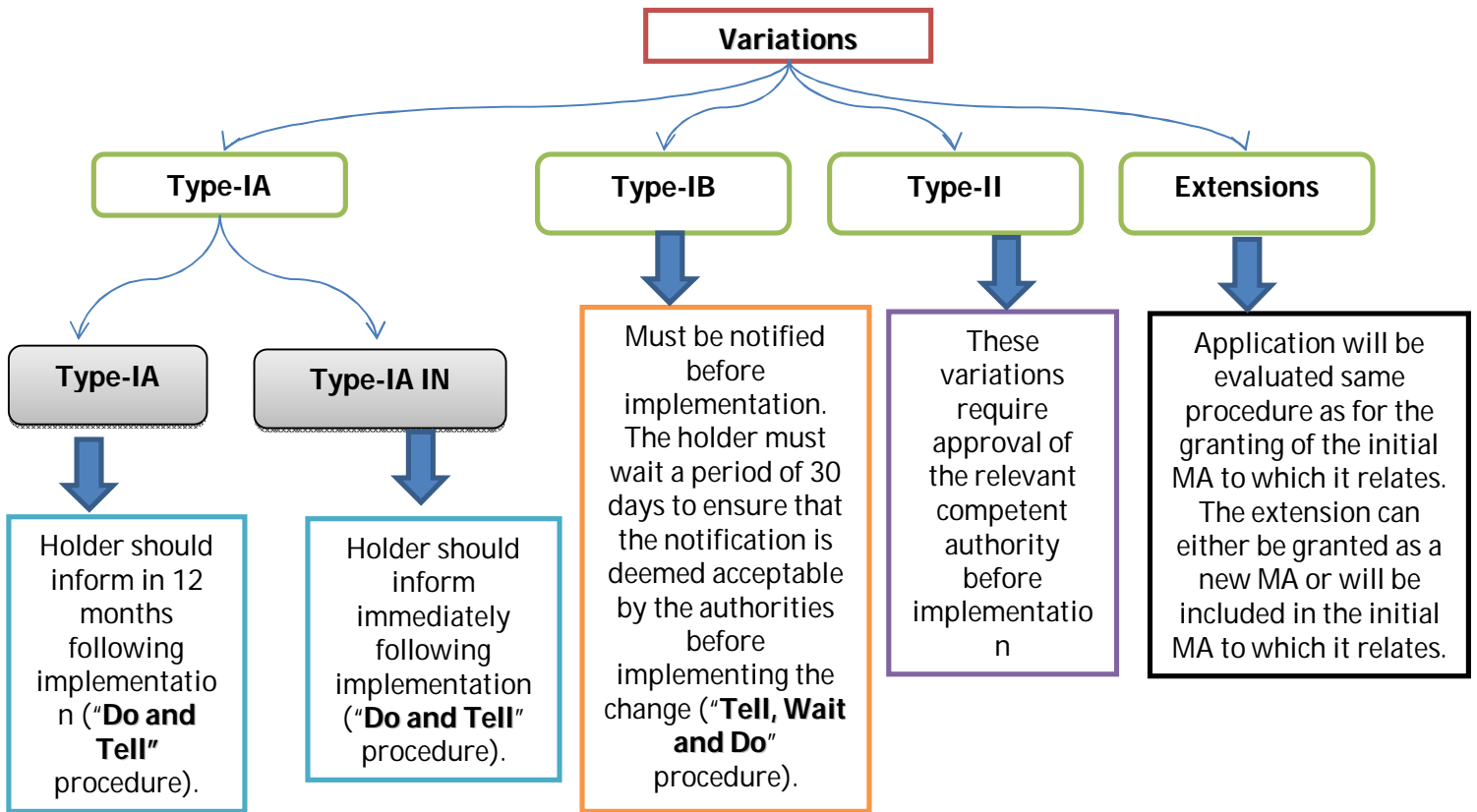


Figure-2: Classification of Variations

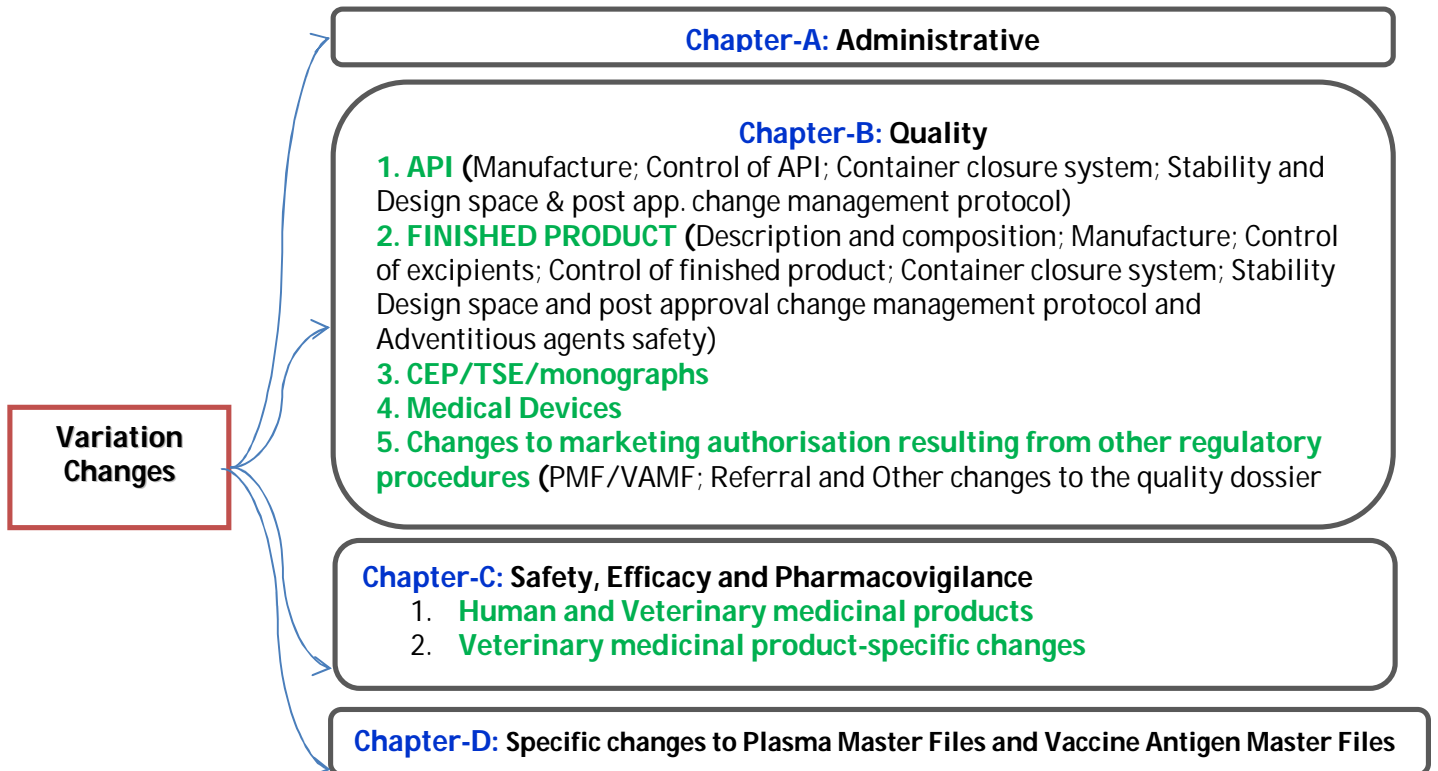


Figure-3: Variation changes

VARIATION CHANGES

Variation changes are divided in to four categories such as 1. Administrative 2. Quality 3. Safety, Efficacy and Pharmacovigilance and 4. Specific changes to plasma master files and vaccine antigen master files. Based on the change in the post approval stage, MAH should follow the EMA recommendations for document submission and implementation. Figure-3 represents the post approval changes classifications.

VARIATION GROUPING:

Variations can be submitted with a single notification to the same relevant authority, or to group them with other types of variations. MAH can group the variations such as type IA /IA_{IN} variations or type IA /IA_{IN} variations and type IB variations or all categories of variations in one drug product or in different products also. The detailed grouping approaches are represented in the below figure.

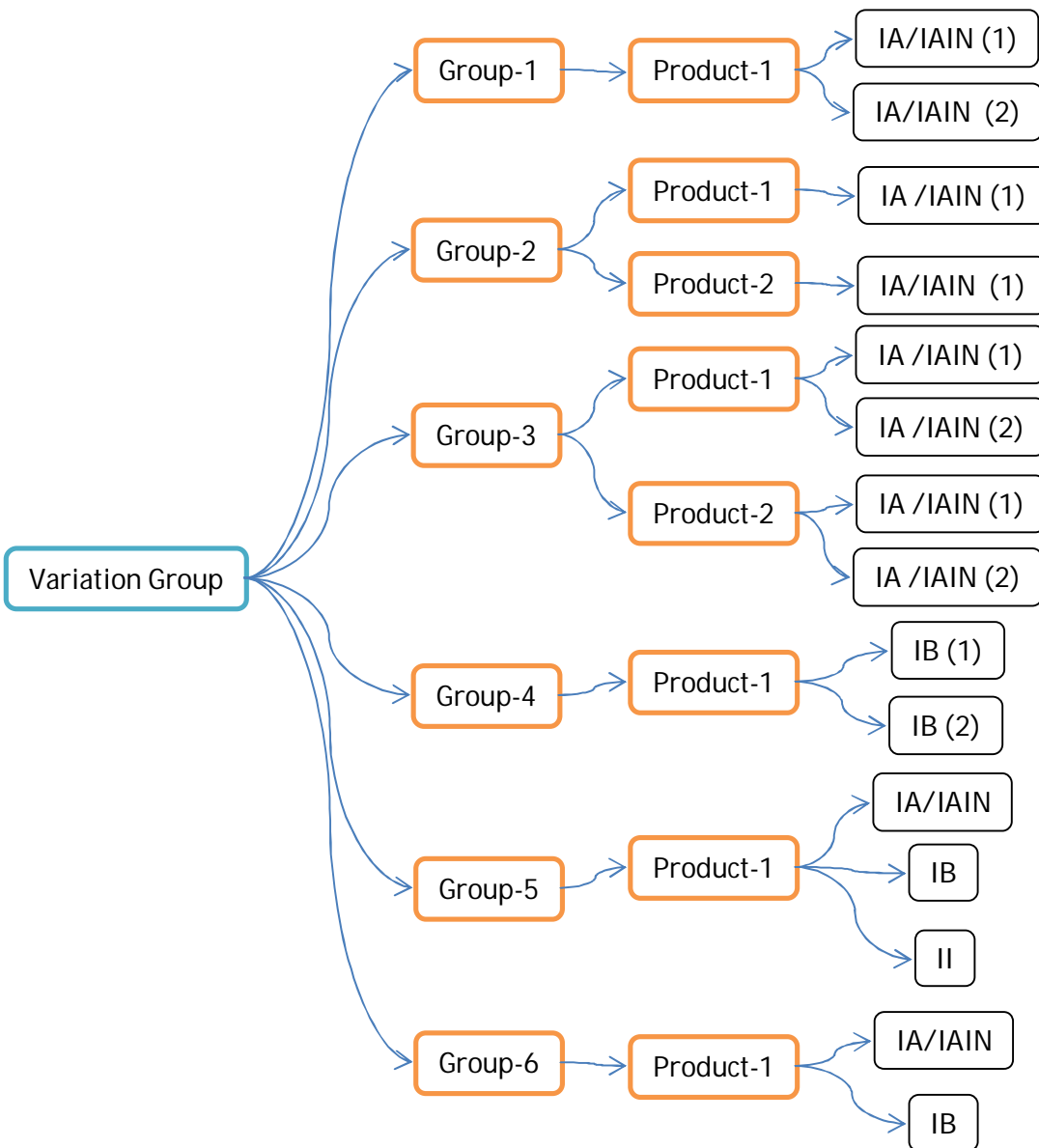


Figure-4: Variations grouping approaches

SUBMISSION OF VARIATIONS NOTIFICATION (HANDLING)

Centralized Procedure:

1. Type IA variations:

The Agency will review the notification within 30 days, without involvement of the rapporteur for the product concerned

appointed by the CHMP or CVMP. However, a copy of the Type IA notification will be submitted by the Agency to the rapporteur for information. If several minor variations of Type IA are submitted with one notification, the Agency will clearly inform the holder which variations have been accepted or rejected. While in the case of minor variations of Type IA, failure to provide all necessary documentation in the application will not necessarily lead to the immediate rejection of the variation if the holder provides any missing documentation immediately on request of the Agency, it should be highlighted that a minor variation of Type IA may in specific circumstances be rejected with the consequence that the holder must cease to apply already implemented variations concerned.

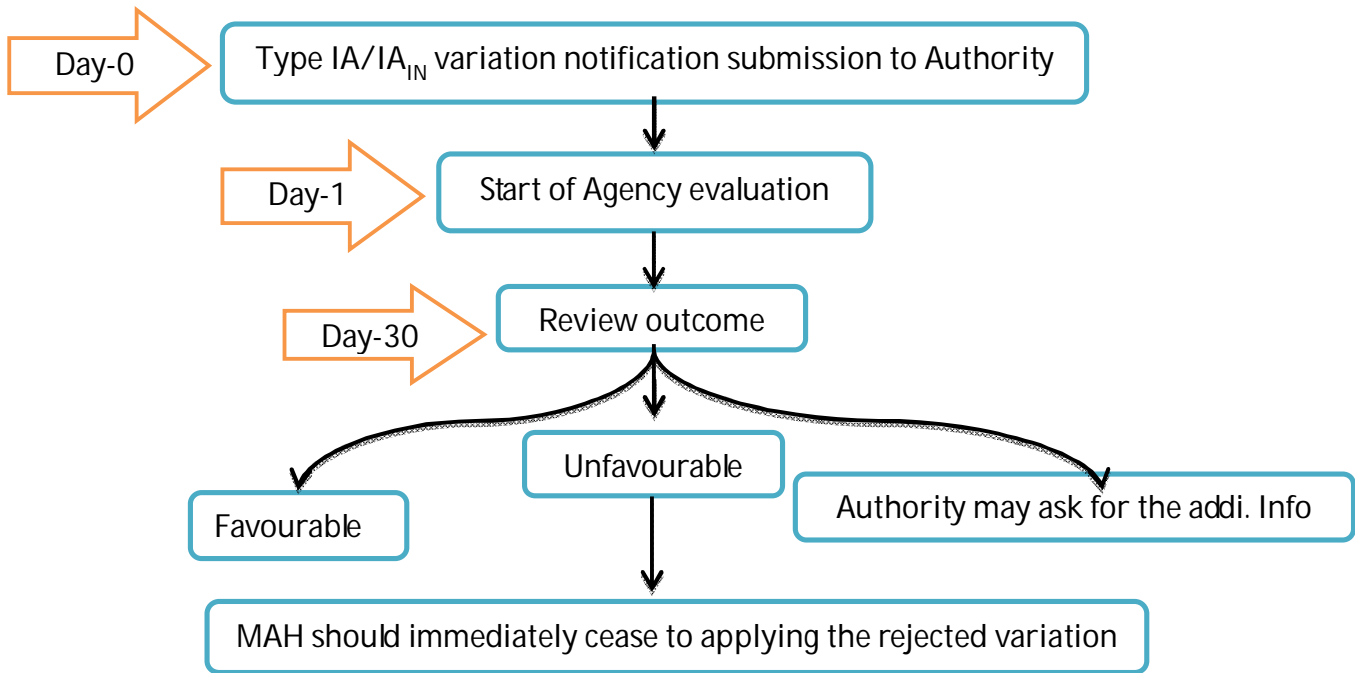


Figure-5: Type-IA variation for CP applications

2. Type IB variations

Agency acknowledges the notification within 7 calendar days. If the proposed variation is not considered a variation Type IB then the holder should request the agency to revise its application and to complete it in accordance with the requirements for a variation Type II. If the variation considered as type-IB then assessment procedure will be initiated. The rapporteur will be involved in the review and it will take 30 days. If the Agency has not sent the holder its assessment results within 30 days then the notification will be deemed acceptable. In case of an Unfavourable outcome, the holder may amend the notification within 30 days. If the holder does not amend the notification then the notification will be rejected. If amended then, Agency will inform the holder of its final acceptance or rejection. If the variation notification is grouped with other class of variations then, agency will clearly inform the holder which variations have been accepted or rejected.

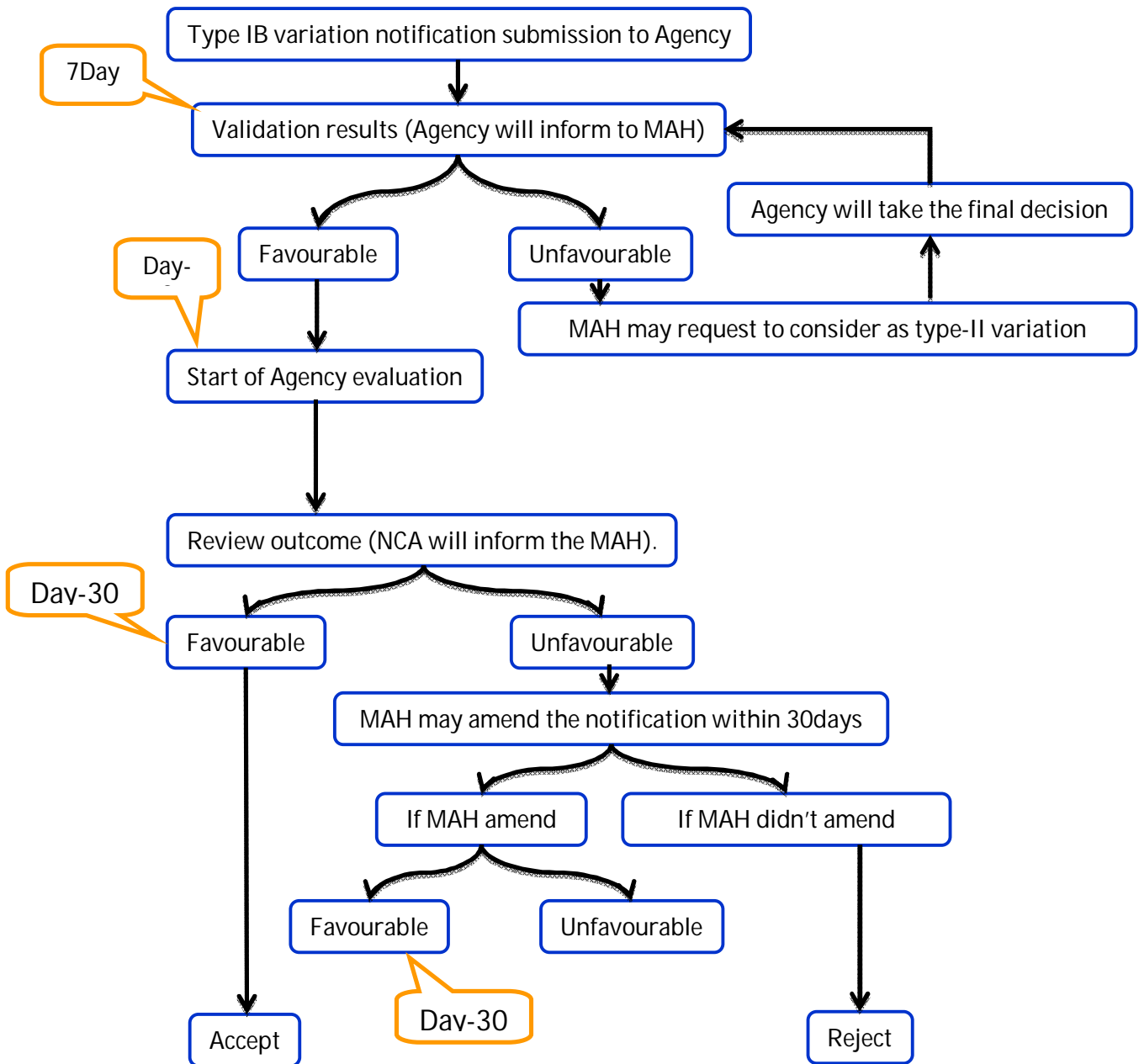


Figure-6: Type-IB variation for CP applications

3. Type II variations

Agency will acknowledge receipt of a variation notification and after this, Agency will start the assessment. In general, assessment period is 60-days and this period may be reduced by the Agency based on urgency of the matter or may be extended to 90 days. Within the assessment period, agency may request the supplementary information. The procedure will be suspended until the receipt of the supplementary information. Suspension period is up to 1 month. For extending the suspension period from 1 month, the MAH should send a justification to the Agency (Maxi. 2months)

Assessment results

Upon adoption of an opinion of the CHMP/ CVMP, the Agency will inform to MAH within 15 days as to whether the variation is accepted or rejected. Where several Type II variations, or a group of Type II variations with other minor variations have been submitted as one application, the Agency will issue an opinion reflecting the final outcome of the procedure. The holder may withdraw single variations from the grouped application during the procedure. The approved major variations of Type II requiring amendment of the Commission decision granting the MA within 2 months may only be implemented once the holder

has been informed by the Commission accordingly. Where amendment of the decision granting the MA is not required within 2 months, or where the approved variation does not affect the terms of the Commission decision granting the MA, the variation may be implemented once the holder has been informed by the Agency that its opinion is favourable. Variations related to safety issues must be implemented within a time-frame agreed between the Commission and the holder.

Extension assessment

Upon receipt of an extension application, the Agency will handle the application as for an initial marketing authorisation application in accordance with Regulation (EC) No 726/2004.

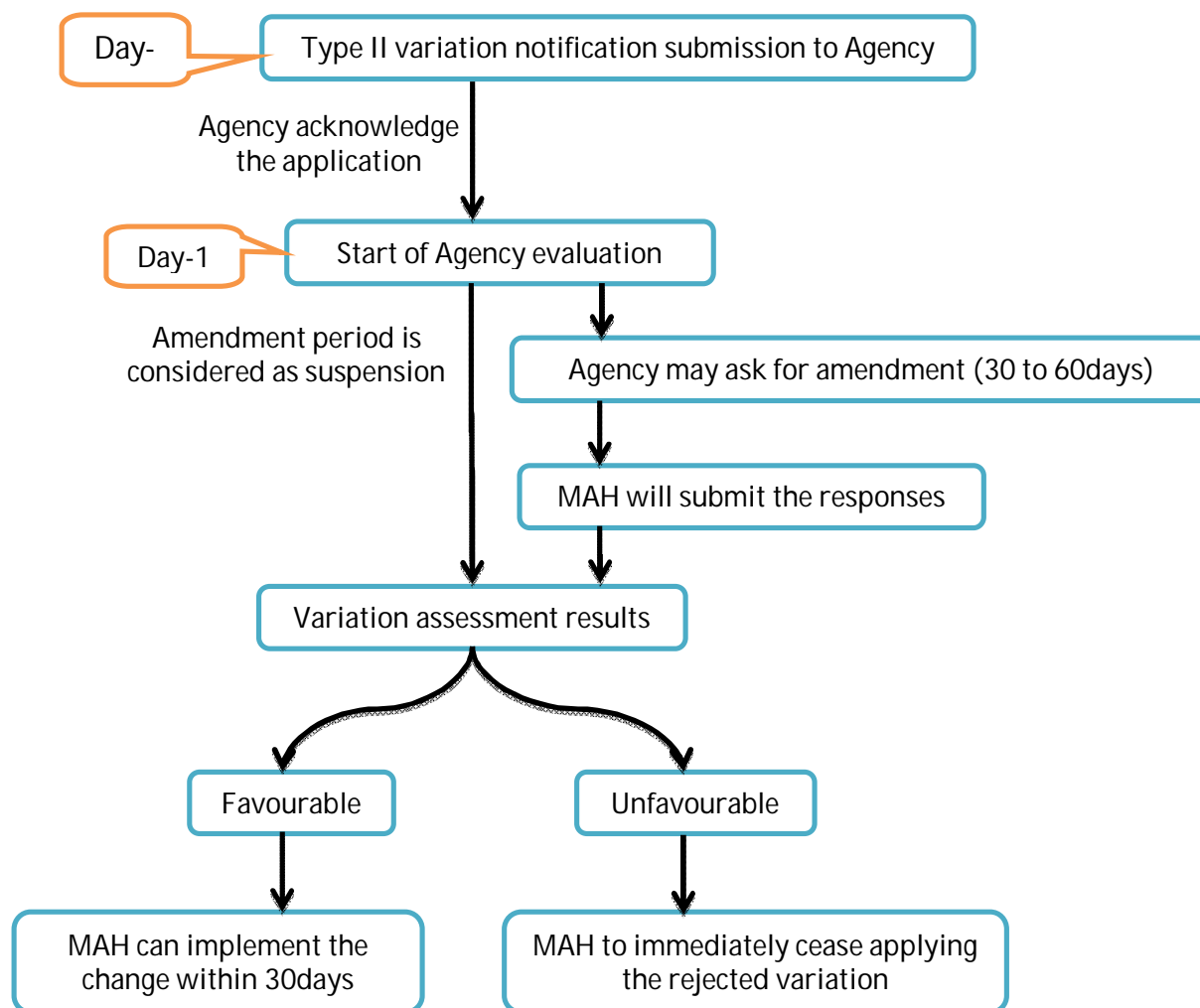


Figure-7: Type-II variation for CP applications

MRP PROCEDURE:

1. Type IA variations

Agency will acknowledge the variation notification and review within 30days. MAH can group Type IA/IA_N variations and changes can be implemented prior to submission of the notification. However, in case of un-favourable outcome, MAH should immediately cease applying the rejected variations. By Day 30, the RMS will inform the assessment results to holder and CMS. In case the MA requires any amendment to the decision granting the MA, all CMS will update the decision granting the MA within 6 months following the receipt of the outcome of the review sent by the RMS, provided that the documents necessary for the amendment of the MA have been submitted to the CMS. Where one or several minor variations of Type IA are submitted as part of one notification, the RMS will inform the holder which variations have been accepted or rejected. The MAH must not implement the rejected variations.

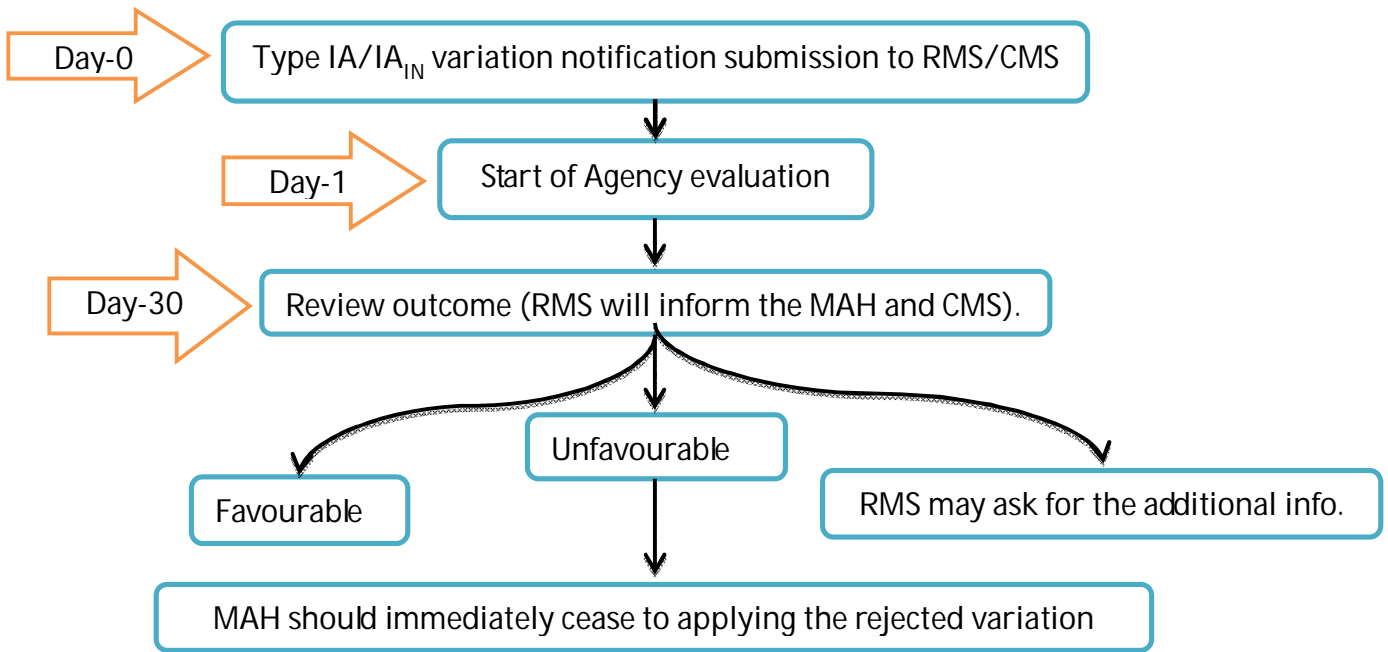


Figure-8: Type-IA variation for MRP applications

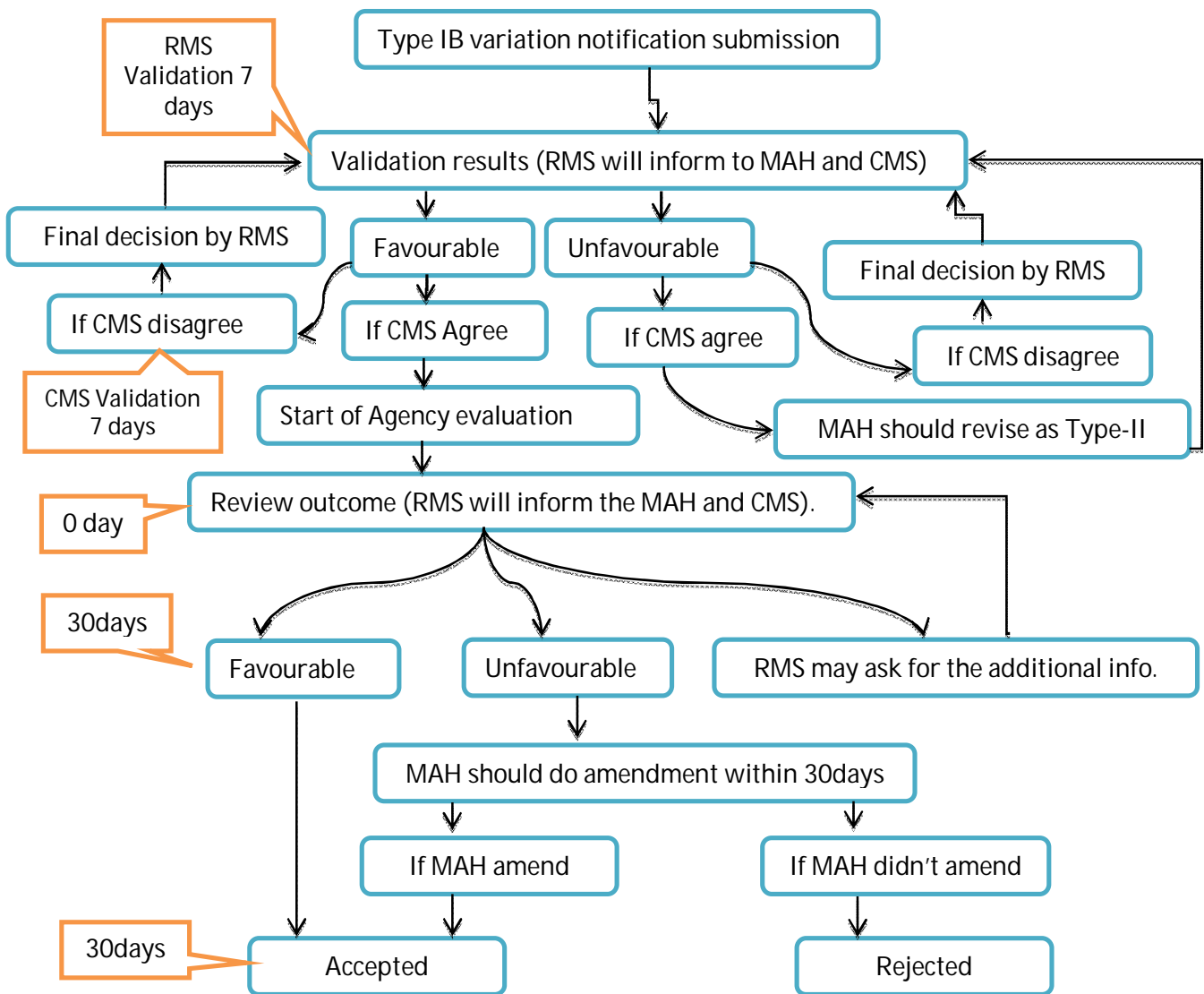


Figure-9: Type-IB variation for MRP applications

1. Type IB variations

The RMS will acknowledge the notification within the 7 calendar days. If the notification is correct and complete then assessment will start. If the notification not considered as type IB, the holder will be requested to revise its application and to complete it in accordance with the requirements for a Type II variation application. The assessment period is 30days.

If the RMS has not sent the assessment results within 30days then the notification will be deemed acceptable. In case of an un-favourable result, the holder may amend the notification within 30 days. If the holder does not amend the notification within 30 days as requested, the variation will be deemed rejected by all CMS. Within 30 days of receipt of the amended notification, the RMS will inform the holder of its final acceptance or rejection. Where a group of minor variations were submitted as part of one notification, the RMS will inform the holder and the CMS which variations have been accepted or rejected. Where necessary, the relevant authorities will update the MA within 6 months following closure of the procedure by the RMS. However, the accepted minor variations of Type IB variation may be implemented without awaiting the update of the MA.

2. Type II variations

Agency will acknowledge the notification and assessment will take 60days. This period may be reduced by the RMS based on the urgency or may be extended to 90 days. RMS will prepare a draft assessment report and a decision on the application according to the communicated timetable and will circulate them to the CMS for comments as well as to the holder for information. The CMS will send to the RMS their comments within the deadlines set out in the timetable. Within the evaluation period, the RMS may request the MAH to provide supplementary information and this period will consider as suspension. In general, a suspension time is one month and it will extend up to 2months based on the holder request to the RMS for agreement. After receipt of the holder's response, the RMS will finalize the draft assessment report and the decision on the application and will circulate them to the CMS for comments as well as to the holder for information.

Assessment Results

By the end of the evaluation period, the RMS will finalize and submit the assessment report and its decision on the application to the CMS. Within 30 days following receipt of the assessment report and the decision, the CMS will recognize the decision and inform the RMS accordingly. Where an application concerning a grouping of variations that includes at least a variation Type II is referred to the coordination group, the decision on the variations not subject to the referral will be suspended until the referral procedure has concluded. However, only the variations in respect of which a potential serious risk to human or animal health or to the environment has been identified will be discussed by the coordination group and eventually by the CHMP or CVMP. The RMS will inform the CMS and MAH about the approval or rejection. If MAH submitted the grouped variations as one application, RMS will inform the holder and the CMS which variations have been accepted or rejected. The holder may withdraw single variations from the grouped application during the procedure. After a positive decision is communicated regarding variations with changes to the summary of product characteristics, labelling or package leaflet, the holder should submit, within 7 days, translations of the product information texts to all CMS. After approval of the variations, the competent authorities of the CMS will, where necessary, amend the marketing authorisation to reflect the variations within 2 months, provided that the documents necessary for the amendment of the MA have been submitted to the CMS. The accepted major variations of Type II can be implemented within 30 days. In those cases where the application has been the object of a referral, the variations must not be implemented until the referral procedure has concluded that the variations is accepted. However, the variations in the group not subject to the referral may be implemented if so indicated by the RMS. Variations related to safety issues must be implemented within a time-frame agreed between the RMS and the holder.

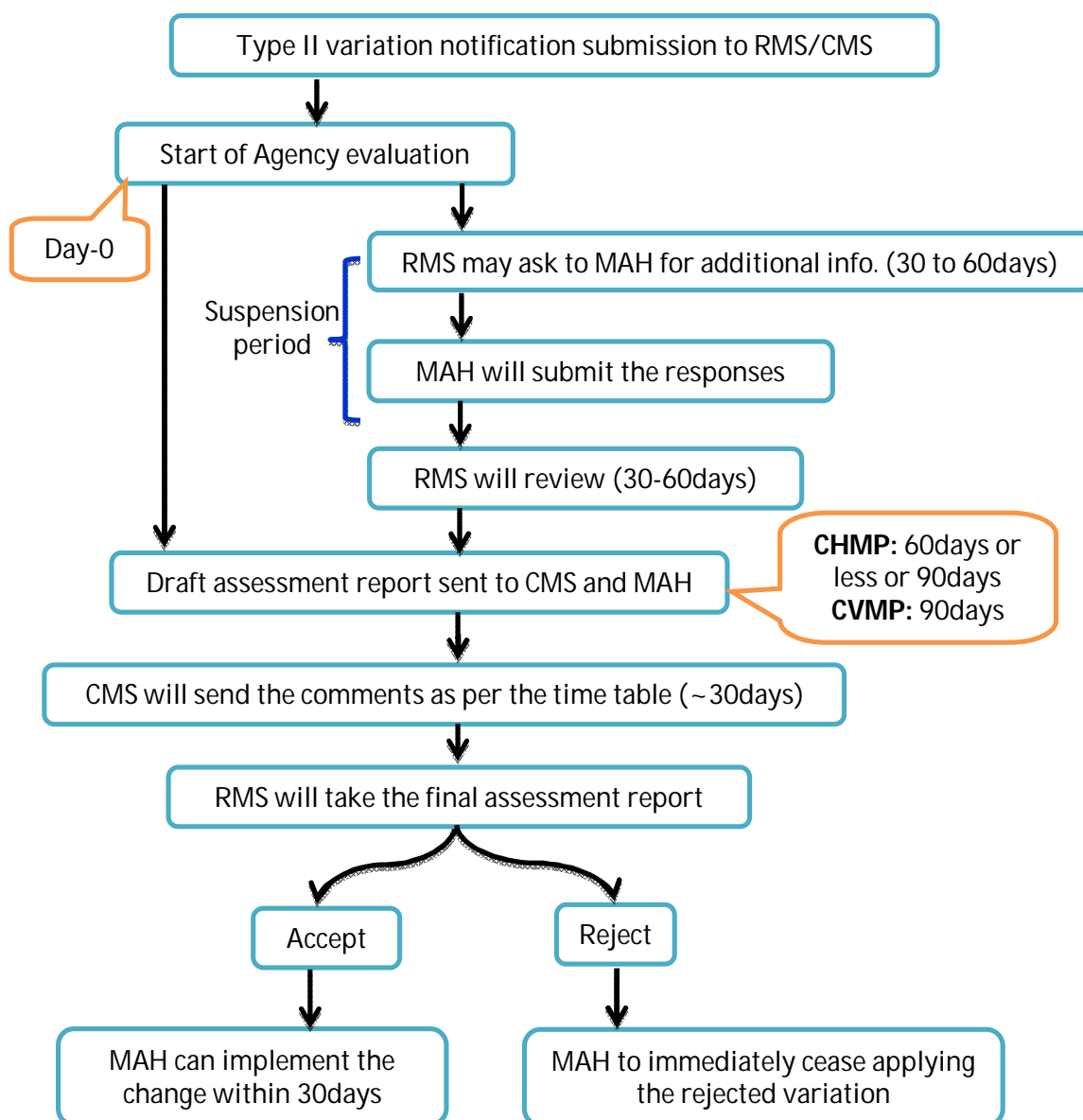


Figure-10: Type-II variation for MRP applications

NATIONAL PROCEDURE:

1. Type IA variations

NCA will review the Type IA notification within 30 days. In case the MA requires any amendment to the decision granting the MA, NCA will update the decision granting the MA within 6 months. For the grouped variation, NCA will inform the holder which variations have been accepted or rejected. If the variation has been rejected then MAH should immediately cease to apply already implemented variations.

2. Type IB variations

NCA will check whether the proposed change can be considered as Type IB variation or not. If not considered, then the holder will be requested to revise its application and to complete it in accordance with the requirements for a major variation of Type II application. The review period is 30days. If the NCA has not sent the holder its opinion on the notification within 30 days then the notification will be deemed acceptable. If rejected, then holder may amend the notification within 30 days to take due account of the grounds for the non-acceptance of the variation. If the holder does not amend the notification within 30 days as requested, the variation will be deemed rejected by the NCA. Within 30 days of receipt of the amended notification, the NCA will inform the holder of its final acceptance or rejection of the variations. Where a group of minor variations were submitted as part

of one notification, the NCA will inform the holder which variations have been accepted or rejected. However, the accepted minor variations of Type IB may be implemented without awaiting the update of the MA.

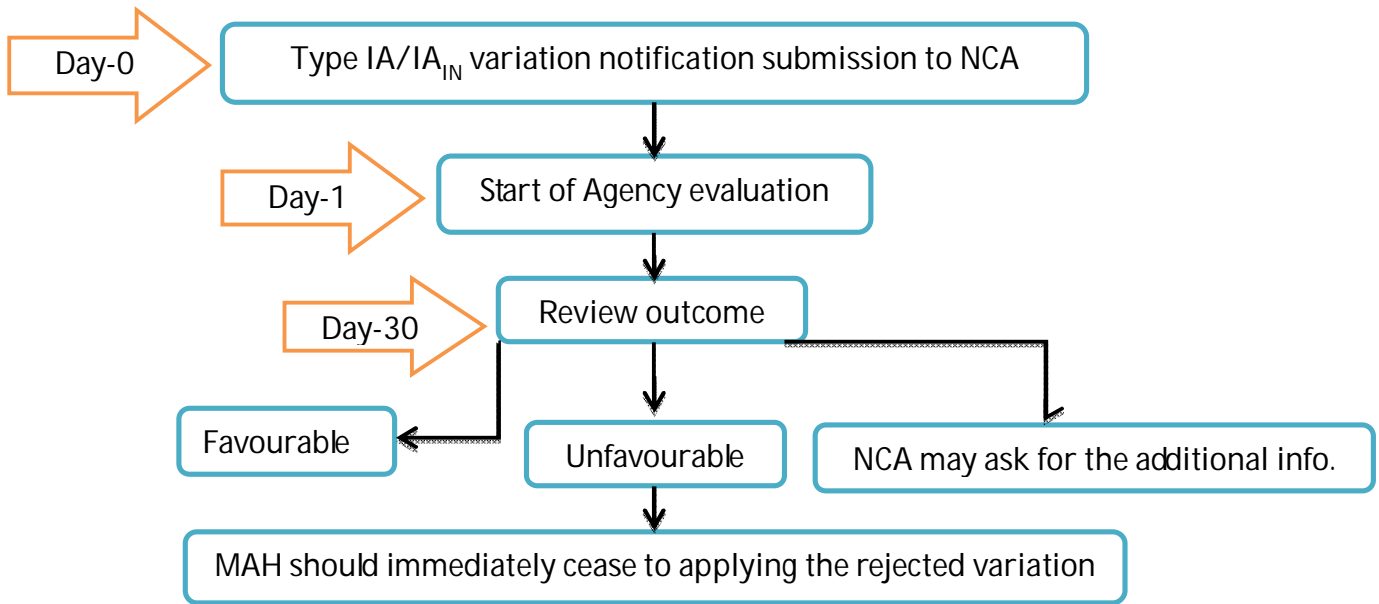


Figure-11: Type-IA variation for NP applications

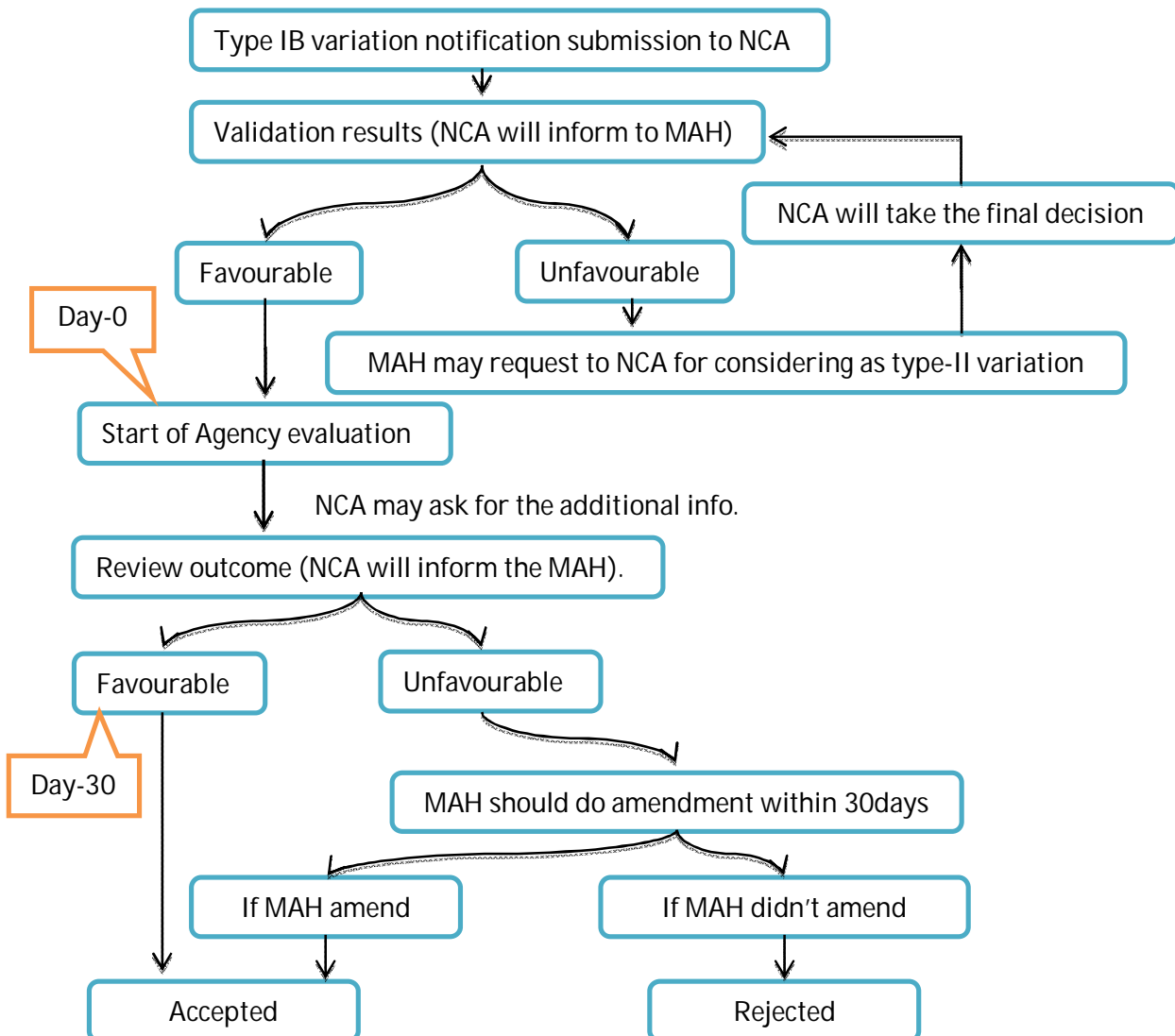


Figure-12: Type-IB variation for NP applications

3. Type II variations

NCA will acknowledge receipt of a valid variation Type II application and review starts from the date of acknowledgement. In general, the review period is 60-day for human and 90days for veterinary medicines. This period may be reduced or may be extended to 90 days. Within the evaluation period, the NCA may request the holder to provide supplementary information. The procedure will be suspended until the receipt of the supplementary information. As a general rule, a suspension of one month will apply. For longer suspension the holder should send a justified request to the NCA for agreement. The evaluation of responses may take up to 30 or 60 days depending on the complexity and amount of data requested to the holder.

Assessment Results

By the end of the evaluation period, the NCA will inform to the holder about the approval or rejection. For grouped variations, NCA will inform the holder which variations have been accepted or rejected. The holder may withdraw single variations from the grouped application during the procedure. After approval of the variations, NCA will amend the MA to reflect the variations within 2 months provided that the documents necessary for the amendment of the MA have been submitted to NCA.

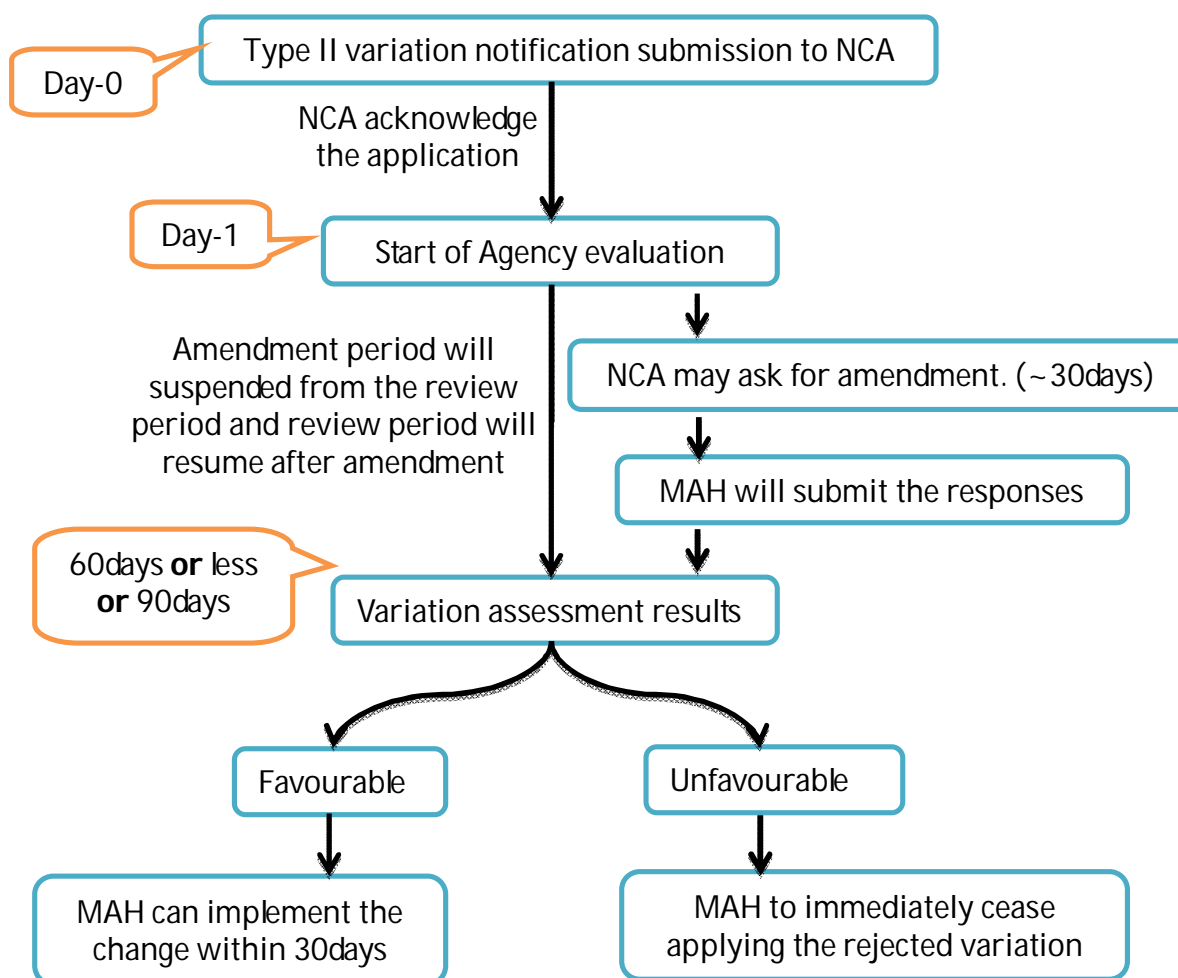


Figure-13: Type-II variation for NP applications

Accepted variations of Type II can be implemented after acceptance of the variations by the NCA, Variations related to safety issues must be implemented within a time-frame agreed between the NCA and the holder.

Extension assessment

Upon receipt of an extension application under the mutual recognition or the purely national procedure, it will be handled as an initial MAA.

REJECTED VARIATION HANDLING

In the case of a negative outcome from the agencies and not met and consequently a resubmission is needed or because documentation is deficient. If this is the case, Agency may ask the MAH to complete a suspected quality defect notification form and provide a Risk Assessment report on the impact of the product on the market via e-mail to qdefect@ema.europa.eu within 7 calendar days from the date of the rejection letter. Such requests are expected to be very exceptional.

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This article is only for the education purpose and completely from the authors experience and official websites.

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