IJBPAS, December, 2022, 11(12): 5823-5841

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

TYPES OF VARIATIONS IN EUROPE – VARIATION FILING PROCEDURE AND OVERVIEW

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Received 26th Jan. 2022; Revised 25th Feb. 2022; Accepted 12th March 2022; Available online 1st Dec. 2022

https://doi.org/10.31032/IJBPAS/2022/11.12.6650

ABSTRACT

Variations are the amendments made to an approved product's dossier after its original registration. They are the fundamental aspect of pharmaceutical product life cycle management. Variations notifications are informed to the Agency through Variation filing. According to the level of risk variations are categorized as Type IA/IA_{IN} (Minor Change – "Do and Tell procedure"); Type IB (Moderate Change - "Tell, wait and Do procedure"); and Type II and Line extensions (Major Change – "Tell, approval and Do procedure"). This article describes the variations, types of variations, regulations, and submission process of variations in Europe.

Keywords: Variations, Europe, Type IA/IA_{IN}, Type IB, Type II, Line extensions and Variation filing

INTRODUCTION

A variation is a change to a marketing authorization's terms and they are arranged by the degree of hazard to general wellbeing and the effect on quality, security and viability of the Pharmaceutical product and it is most commonly known as Post Approval Changes. Briefly saying that, when a medicinal product is authorized and placed in the market, MAH submits an application for post market approval to the Agency, together with the necessary supporting papers. Such medicinal product could be commercialized once it has received clearance for alterations **[1]**. Variations are an important aspect of pharmaceutical product life cycle

management. These changes are generally observed in: I.) Components and Composition; II.) Manufacturing Site and Process; III.) Specifications; IV.) Container Closure Systems; V.) Changes in Labelling; VI.) Miscellaneous and Multiple related Changes.

Changes that are done to the medicinal products are evaluated based on their impact on product's quality, safety and effectiveness. All the changes must be properly documented as per the guidance. Depending on the degree of impact the documents are evaluated and prepared. Various types of mechanisms are available in various jurisdictions to report these amendments, manufacturers must properly follow the guidance documents for more information and procedures about the jurisdiction **[2]**.

Variations are categorized based on their level of risk on the product's quality, safety, and efficacy **[3]**. It is commonly classified into three changes 1. Minor Changes; 2. Moderate Changes and 3. Major Changes. Minor changes – No or Minimal impact; Moderate Changes – Potential impact and Major Changes - Significant impact on the medicinal product **[4, 5]**. Based on the types of variations the approvals are granted, if it is a Minor variation we can make the change and then submit the documents, no need to wait for approval; Moderate change must notify and submit the appropriate documents before implementing and shall wait for 30 days to verify whether the notice is regarded acceptable or not, and then make the changes; Major changes must wait for the response and can implement the changes only if approval is given by the relevant authorities **[3, 15, 22]**.

In 1995, the European Medicines Agency (EMA) established a variation process for registered medicinal products and divided the variations into two types: Type - I (Minor Changes) and Type - II (Major changes). Since 2003, Type-I variation was classified into two parts: Minor changes - Type IA and Moderate Changes - Type IB. The EC regulations that were followed for the variations during the respective years are given below in **Table 1**.

Table 1: EC regulations and variation types [3]

YEAR	EC REGULATIONS	TYPES OF VARIATIONS
1995	EC 541 / 95 EC 542 / 95	• Type I, Type II (default)
1998	EC 1146 / 98 EC 1147 / 98	• Type I, Type II (default)
2003	EC 1084 / 2003 EC 1085 / 2003	• Type IA (Tell and Do), Type IB, Type II (default)
2008	EC 1234 / 2008	• Type IA (Tell and Do), Type IB(default), Type II
2012	EC 712 / 2012	• Type IA (Tell and Do), Type IB, Type II (default)

CLASSIFICATION OF VARIATIONS

Variations notifications are informed to the Agency by means of Variation filing. This procedure is applied to All Types of Applications, They are: I.) Decentralized Procedure; II.) Centralized Procedure; III.) Mutual Recognition Procedure and IV.) National Procedure.

Variations are divided into four types: 1. Type IA / $IA_{IN;}$ 2. Type IB; 3. Type II; and 4. Line Extensions.

Then they are grouped into Three Classes based on their level of risk: a.) Minor Changes – Type IA/$IA_{IN,}$ b.) Moderate Changes – Type IB, c.) Major Changes – Type II, Line extension **[3]**.

TYPE IA VARIATION

- Commonly known as "Do and Tell" Procedure. (Has No or only a Minimal impact) **[6]**.
- In accordance with Article 2(2) of EC Regulation No 1234/2008 **[7]**.
- Prior approval is not required before implementing the change **[8]**.
- Administrative changes corresponds to this Type of Variation **[9]**.
    a. Type IA – Do not require immediate notification but MAH must notify within 12 months from implementing.
    b. Type IA_{IN} – Requires immediate notification to the Agency within 14 days after implementing **[8]**.

TYPE IB VARIATIONS

- Commonly known as "Tell, Wait and Do" Procedure. (Has Potential impact) **[6]**.
- In accordance with Articles 2(5) and 3(2) of EC Regulation No 1234/2004 **[7]**.
- Must notify and submit the appropriate documents before implementing and shall wait for 30 days to verify whether the notice is regarded acceptable or not, and then make the changes **[8]**.

TYPE II VARIATIONS

- Commonly known as "Tell, Approval and Do" Procedure. (Has significant impact) **[6]**.
- In accordance with Articles (7) of EC Regulation No 1234/2004 **[7]**.
- Requires Prior approval before implementation.
- Changes are implemented after 6 months if approval is given **[8]**.

LINE EXTENSIONS (NEW APPLICATION)

- Commonly known as "Tell, Approval and Do" Procedure. (Has significant impact) **[6]**.
- In accordance with Article (19) of EC Regulation No 1234/2008 **[7]**.

- Some amendments that impact the foundations of the authorization's conditions are filed as a "line extension application" rather than a variation **[10]**.
- The extension might be issued as a separate marketing authorisation or as part of the original marketing authorization to which it pertains **[3]**.

TYPES OF VARIATION CHANGES

- ❖ Administrative changes;
- ❖ Quality changes;
  - ✓ Active Substance,
  - ✓ Finished Product,
  - ✓ Certificate of Suitability/ Transmissible Spongiform Encephalopathies Monographs,
  - ✓ Medical Devices,
  - ✓ Changes to marketing authorisation resulting from other regulatory procedures.
- ❖ Safety, Efficacy and Pharmacovigilance;
- ❖ Specific changes to Plasma Master Files (PMF) and Vaccine Antigen Master Files (VAMF) **[2]**.

TYPE IA NOTIFICATION PROCEDURE

A. Pre-Submission Phase

i. Holder will communicate with the RMS at a minimum of seven days before the submission to get the Type-IA Variation Notification process number.

ii. If there is any doubt, in the variation type number and sub-division, MAH will clarify it with RMS.

B. Submission Phase

i. The following documents should be submitted to RMS as well as to CMS by MAH along with an application at once. They are:-

- Cover Letter
- Application Form (having the variation process number, details of the variations description and the implemented date).
- Duplicate of the related Article 5 Recommendation that has been published.
- Supporting attestation as suitable.
- Variations which have an impact on the Labelling or PL, Samples are submitted in accordance with the guidelines.

ii. Also, should post the delivery dates schedules to RMS, dates when the applications were submitted,

then finally affirmation of the applicable prices that were paid.

iii. CMS should verify whether respective fees and application form has been received.

iv. If the notification is accepted, it shows that the files are submitted concurrently and applicable costs are paid.

C. Start of notification Phase (Day 0)

i. If RMS gets the delivery schedule, applicable fee and application form then on day 0 notification process begins, then completes the CTS record and CMS is informed only through CTS.

D. Validation Phase (Day 0 to 30)

i. Notification is checked by the RMS to ensure that all relevant documents have been received and that the notification may be approved. The data in the eAF will aid in the verification process. It must contain definitive proof that all of the required information have been met and that all data has been provided.

ii. CMS need to no longer ask the Marketing holder or Reference state whether Notification's content has been accepted or rejected, they'll give the feedback only when there is failure of payment of fees or failure to submit the documents. Rapporteur is not involved in the review process of notification.

iii. RMS Cannot further ask the MAH for explanation, more details and evidence in Type IA and there is no way to stop the clock or postpone the procedure.

E. Outcome of the notification Phase

i. Decision is taken by RMS, whether to accept or reject the notification. On or before 30 days, the following steps are taken:

ii. **Acceptance of the Notification:** The result of acceptance is informed by the RMS to MAH, on behalf of CMSs and issues a letter of "Acknowledgement of an acceptable Notification". The outcome is informed to

the CMS by updating the CTS record.

iii. **Notification rejection:** If the variation has been refused, then the MAH is informed by the RMS through email. CTS records are updated along with the reasons for refusal. The procedure's outcome should be described in the email's subject line.

iv. Within six months after reputation competent authorities ought to put into effect the decision nationally **[11, 12, 16, 17, 19]**. (Explained in **Figure: 1**)

TYPE IB NOTIFICATION PROCEDURE

A. Pre - submission phase

i. To get the type IB variation process number, MAH will communicate with the RMS at a minimum of seven days before the submission.

ii. If there is any uncertainty about the classification, CMDh will give the clarification.

B. Submission phase

i. The following documents should be submitted to RMS as well as to CMS by MAH along with an application at once. They are:

- Cover letter (having the type IB variation notification)
- Application form: having the variation process number; details of the variations description and MRP Variation number.
- Duplicate of the related Article 5 Recommendation that has been published.
- Supporting attestation as suitable:

✓ For variations asked by means of a NCA, example: (FUMS) - Follow-up measures; (SOs) specific obligations; therefore a cover letter is annexed with the request copy.

- Variations which have an impact on the Labelling or PL, Samples are submitted in accordance with the guidelines.

ii. Also, should post the delivery dates schedules to RMS, dates when the applications were submitted, then finally affirmation of

the applicable prices that were paid.

iii. CTS record is prepared by RMS within seven days.

C. Start of the Notification Process (Day 0)

i. Following the validation phase, CTS records are completed by RMS to notify the CMS of the timeframe and starting date. There will be no further mail to the CMS; it will only be alerted via CTS and MAH is notified of the start date by RMS.

D. Evaluation phase (Day 0 to 30)

i. The result of the procedure is informed to the MAH by RMS, in one month after it begins. In case, if RMS has no longer provided the marketing holder its view inside 30 days, then the notice is regarded as accepted.

ii. RMS is in charge of evaluating the proposed change. When making any decision, RMS must consult with appropriate CMS. When CMS has any issues, CTS should be updated and transmit the feedback to RMS inside 20 days from the procedure starting.

iii. These scenario might be used for the below changes:

- ✓ The name of the pharmaceutical product has been changed (in a CMS).
- ✓ Addition or modification of a DDPS (in a CMS).
- ✓ All C.I.1-C.I.3 and C.I.6-C.I.7 variations.
- ✓ C.II.2 and C.II.6 variations.

iv. If all MSs does not approve the notice on day 30 the reason for the rejection, is notified by the RMS to MAH and CMS. The timer will cease ticking until the MAH receives a revised notification, which must be filled to the RMS and CMS inside 30 days. Also, should post the delivery dates schedules to RMS, dates when the applications were submitted, then finally affirmation of the applicable prices that were paid. When the RMS receives the delivery date schedules it will resume the workflow and notify the MAH. The CTS is updated by RMS to inform the CMS.

v. MAH is informed about the final approval/refusal of the change by RMS through a notice on behalf of Type IB variation inside 30 days of receiving the updated notification. Suppose if MAH does not change the notice inside 30 days, the variation gets denied and CMS is notified appropriately.

E. Outcome after notification procedure:

i. Decision is taken by RMS, whether to accept or reject the notification. On or before 30 days , the following steps are taken:

ii. **Acceptance of the notification:** MAH will be notified by RMS about the acceptance of the variation along with the accepted date. CMS is notified of the outcome by updating the CTS record.

iii. **Rejection of notification:** The CMS and MAH is notified by RMS of the grounds for the variation application's denial. CTS is updated by RMS and should include the grounds for rejection.

iv. Inside six months of the procedure's conclusion, competent authorities must execute the final results on a national level. MAH on the other hand, can apply the change immediately, when the holder has been informed about the acceptance by the RMS competent authority and the appropriate document is submitted to member state **[11, 13, 17, 18, 20]** (Explained in **Figure: 2**)

TYPE II VARIATION NOTIFICATION PROCEDURE

A. Pre-Submission Phase

i. MAH prepares a schedule under the supervision of RMS. Within an appropriate timeframe set by the RMS, CMSs must accept or refuse. If the timeline is rejected then RMS must prepare a new schedule that everyone can agree on.

ii. MAH and RMS may evaluate the documents simultaneously, if it is necessary. Across all situations MAH contacts the

RMS within seven days before submission for getting acceptance of the schedule as well as to acquire Type II Notification Variation Process Number.

B. Submission Phase

i. The following documents should be submitted to RMS as well as to CMS by MAH along with an application at once. They are:

- Cover letter (having the type II variation notification)
- Application form: having the variation process number; details of the variations description; and the implemented date.
- Duplicate of the related Article 5 Recommendation that has been published.
- Supporting attestation as suitable:

✓ For variations asked by means of a NCA, example: (FUMS) - Follow-up measures; (SOs) specific obligations; therefore a cover letter is annexed with the request copy.

ii. Also, should post the delivery dates schedules to RMS, dates when the applications were submitted, then finally affirmation of the applicable prices that were paid.

iii. CTS record is prepared by RMS within seven days and communicates to CMS by sending an email via MRVE inbox updating them of the new process.

C. Automatic validation

i. CMS will check the applications legitimacy, and the process should take no more than 14 days. If the application is inappropriate then CMS will notify RMS before 14 days.

ii. If MAH has any doubt, it priority discusses with RMS about the variation process number. RMS will consider CMS's opinions regarding the category and variation classification. In the event of an opposition, RMS takes the final decision.

D. Start of the Notification Process (Day 0)

i. Following the validation phase, CTS records are completed by RMS to notify the CMS of the starting date. MAH is notified of the start date by RMS.

E. The Evaluation Procedure

i. In most cases, the standard 60 day timeline is used; but, in exceptional instances, a shorter or longer timeframe is also applied.

ii. By the agreed-upon deadline, RMS makes sure whether MAH and CMSs has received the Preliminary Variation Assessment Report (PVAR). MAH and all CMSs are notified in extreme circumstances of a delay.

iii. If the variation affects one or more CMS but not the RMS, the RMS will seek assistance from anyone of the CMSs to prepare the PVAR.

iv. The RMS shall explicitly state within the PVAR, whether the variation is rejected or altered. If changes are needed, the applicant might be asked for further information. The application will be rejected if it is found to be significantly defective.

v. Suppose if the suggested amendments which were done to the SPC are deemed inappropriate by RMS, they then they must prepare a different path ahead. The applicant must provide a revised SPC/PL and Labelling version in word format.

vi. By the end of the prescribed date, the CMS must convey its decision on whether to approve or refuse the amendment to the RMS through mail. Suppose if the CMS hasn't sent any response, then RMSs PVAR is considered as acceptable by CMS. The process can also be completed at the conclusion of the initial stage, if the CMS approves the RMS's request for direct approval or refusal.

vii. CMS opinions must be divided into two different files at each and every step of the process, one holding non-confidential feedbacks and one holding confidential feedback and both the documents names should be properly labelled.

viii. If the variation is rejected by the CMS, the MAH is explained why and request for supplementary information that is needed.

ix. If CMS or RMS does not agree with the MAH's proposed variation then RMS will send MAH a request for supplementary information and the request copy to CMS. The RMS will offer the MAH a specific timeframe for sending replies to the RSI, based on the agreed-upon dates. The CMSs should always be notified of the reasons for prolonging the clock stop duration and the new schedule imposed.

x. It is advised to withdraw the variation and provide data of new variation when available if the MAH does not reply within a given period of time.

xi. Applicant will send the appropriate information for RSI by mail to RMS and it is transmitted to CMS right away. Once the requested supplementary documents are obtained, RMS compiles and distributes the PVAR to every CMSs for feedback as well as to MAH for their knowledge and the ceased time is started inside the fixed schedule.

xii. A breakthrough session can be conducted if there is a difference in opinion between both RMS and CMS. CMS must provide their feedback to RMS.

F. Outcome after notification procedure

i. Acceptance of the notification: CMS and MAH will be notified by RMS about the acceptance of the variation along with the accepted date through email. Final results must be described in the email's subject line.

ii. MAH must supply RMS the details of the referenced and clean copies of the summary product characteristics/ labelling/ PL in digital form if the outcome of the variation changes the SPC / labelling/ PL. The changed texts is reviewed by RMS. The files are distributed along with a notice stating that the revisions have been approved by RMS.

iii. Inside 7 days, it is translated to the national language and delivered by MAH at the end of procedure. Member

states shall be submitted with Mock-ups or samples as required.

iv. Inside two months of the procedure's conclusion, competent authorities must execute the final results on a national level. MAH on the other hand, can apply the change immediately, when the holder has been informed about the acceptance by the RMS competent authority after 30 days and the appropriate document is submitted to member state.

v. **Rejection of notification:** If the variation has been refused, then the MAH and CMS is informed by the RMS via email. CTS records are updated along with the reasons for refusal. The procedure's outcome should be described in the email's subject line. The databases of mutual recognition in electronic format shall be maintained by all competent authorities and make certain that the Statistics of each medicinal product is up to date **[11, 14, 16, 17, 18]** (Explained in **Figure 3**).

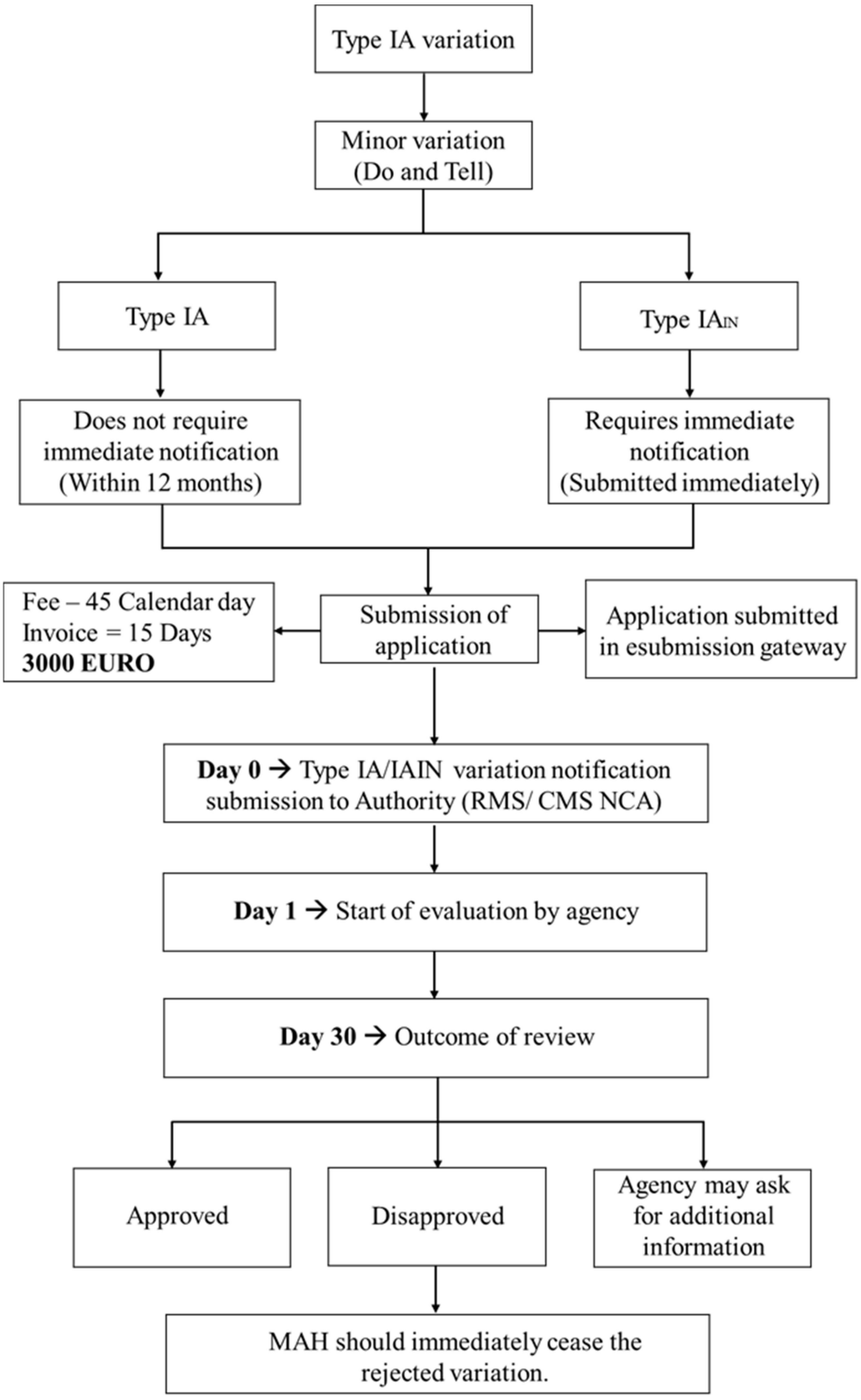

Figure 1: Process of approval of type IA variations [1, 3, 21]

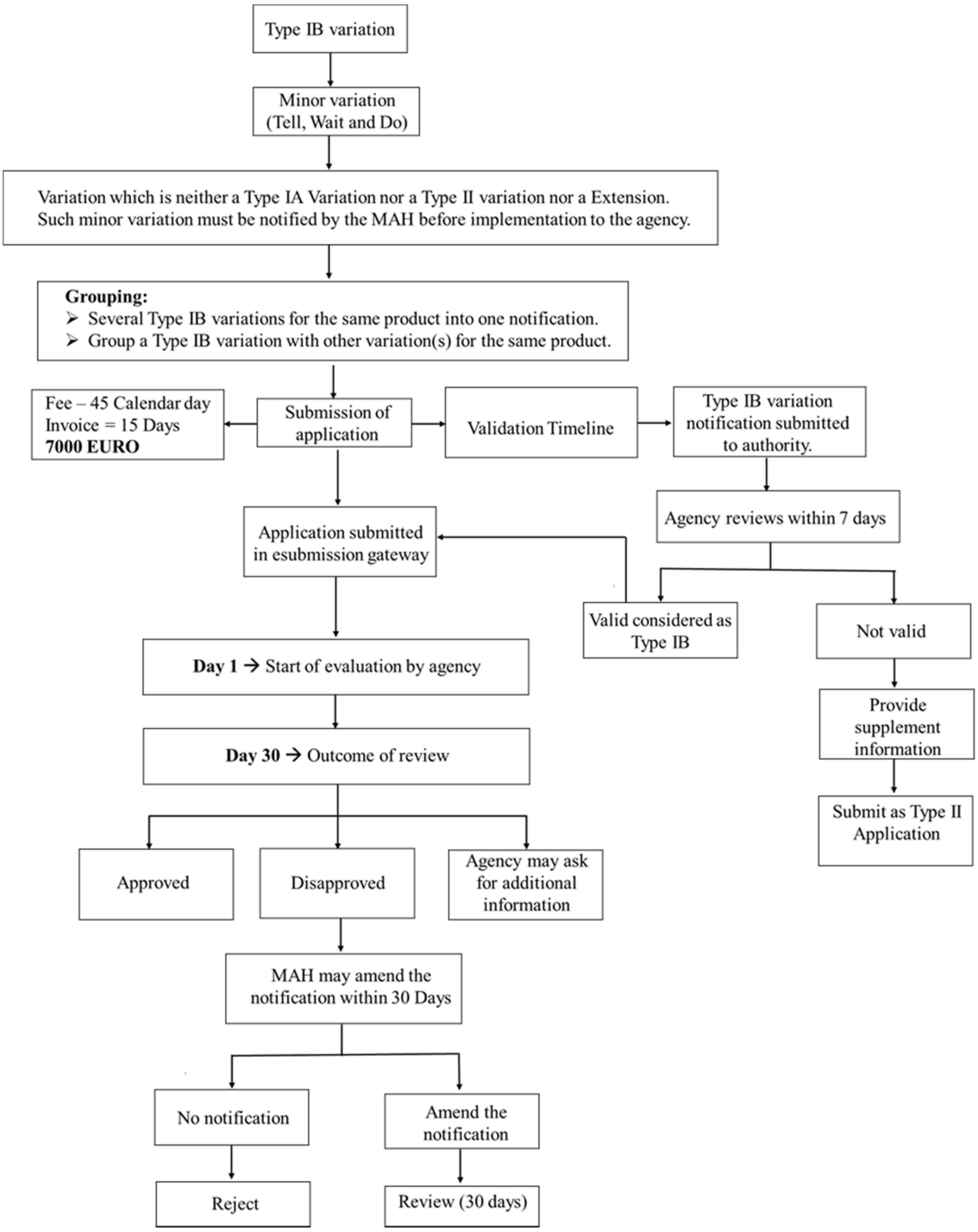

Figure 2: Process of approval of type IB variations [1, 3, 21]

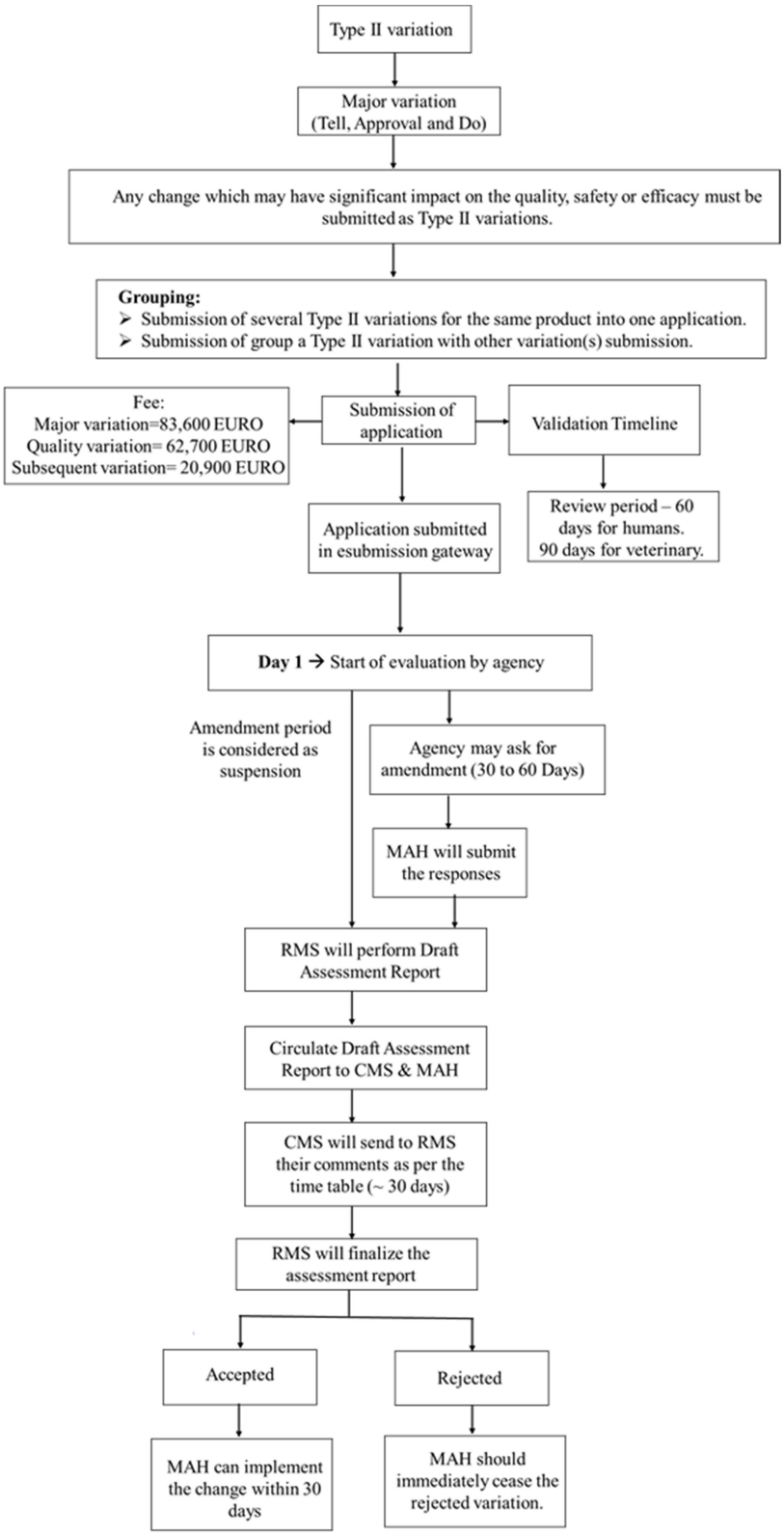

Figure 3: Process of approval of type II variations [1, 3, 21]

CONCLUSION

Variation is divided into three types based on the quality, security and viability and changes are done to the medicinal products which are evaluated based on their effectiveness. These changes are documented as per the guidance. In the year 1995, the regulation EC 541 / 95 EC 542 / 95 has a variation Type I, Type II (default); in 2003, the regulation EC 1084 / 2003 EC 1085 /2003 variation types were Type IA (Tell and Do), Type IB, Type II (default); then in 2008, the regulation EC 1234 / 2008, the variations divided into Type IA (Tell and Do), Type IB (default), Type II; finally in 2012, the regulation EC 712 / 2012 categorized the variations into Type IA (Tell and Do), Type IB, Type II (default), has been widely accepted and used.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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