EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Evaluation Division

European Medicines Agency post-authorisation procedural advice for users of the centralised procedure
Grouping of variations

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

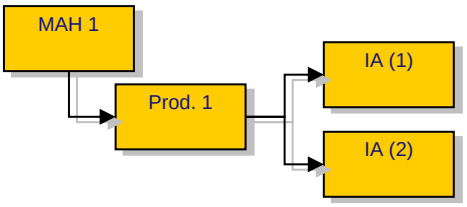
1. Grouping of variations

1.1. What types of variations can be grouped? ~~Rev. Oct 2013~~

Article 7.2(a) of the Variations Regulation, as amended, sets out the possibility for a marketing authorisation holder to group several Type IA/ IA_{IN} variations to the terms of the same marketing authorisation under a single notification to the same relevant authority:

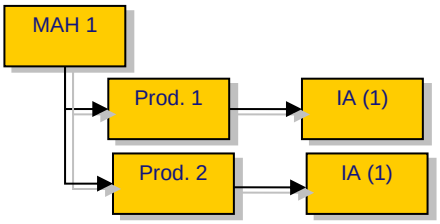
- **Several** Type IA or IA_{IN} affecting **one** medicinal product.

  This means for instance that a Type IA variation which is normally not subject to immediate notification can be included in the submission of a Type IA_{IN} variation.

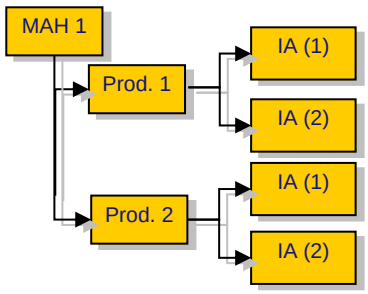


Article 7a of the Variations Regulation, as amended, sets out the possibility for a marketing authorisation holder to super-group the same or several Type IA/ IA_{IN} variations to the terms of more than one marketing authorisation under a single notification to the same relevant authority:

- **one** Type IA or IA_{IN} affecting **several** medicinal products from the same MAH authorised through the centralised procedure, provided that the variation is the same for all medicinal products.



- **several** Type IA and/or IA_{IN} affecting **several** medicinal products from the same MAH authorised through the centralised procedure, provided that those variations are the same for all medicinal products ~~and are submitted to the same relevant authority~~.



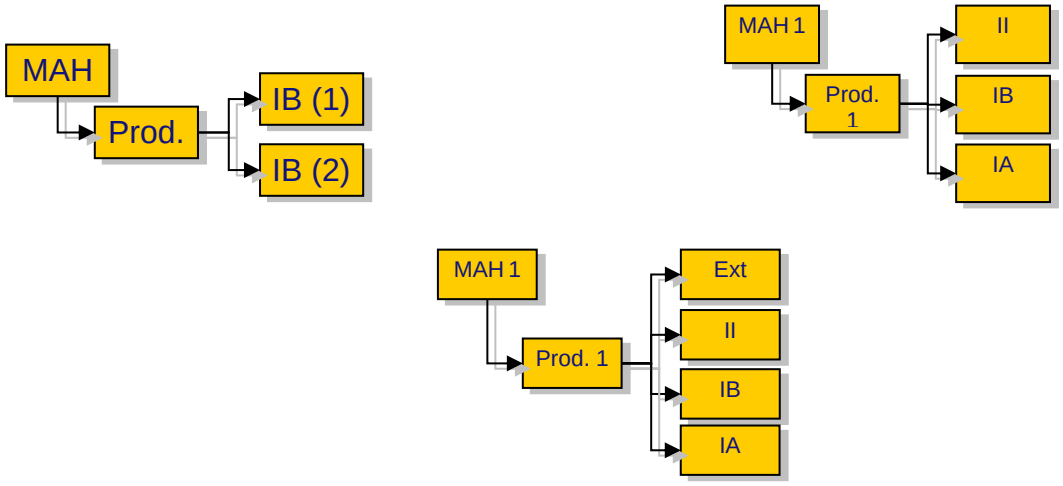
Applicants belonging to the same mother company or group of companies and applicants having concluded agreements or exercising concerted practices concerning the placing on the market of the medicinal product(s) concerned, have to be taken as "the same marketing authorisation holder".[1]

~~All medicinal products concerned should be authorised through the centralised procedure.~~

Please note that currently it is not operationally possible to have super-grouping of Type IA variations including simultaneously marketing authorisations approved via the centralised procedure and non-centralised procedure. Additional cases taking into account the experience acquired may be identified in the future and appropriate operational guidance will be provided in Agency and CMDh websites accordingly.

[1] See Commission Communication 98/C 229/03 OJ C 229, 22.7.1998, p. 4.

Articles 7.2(b) and 7.2(c) of the Variations Regulation set-out the possibility for a marketing authorisation holder to group several types of variations affecting **one medicinal product**, under a single notification/application.



Article 7.2(b) applies for groupings that are listed in Annex III of the Regulation whilst article 7.2(c) applies for groupings of variations which are not listed in Annex III, but which have been agreed with the Agency.

In the case of groupings under Article 7.2(c) it is recommended that the grouping is agreed between the holder and the Agency at least 2 months before submission.

Where the same Type IB or Type II variation, or group of variation(s) affect several medicinal products from the same MAH, the MAH shall ~~may choose to~~ submit these variations as one application for 'worksharing'. Please also refer to "What is worksharing and what types of variations can be subject to worksharing?"

References

- Regulation (EC) No 726/2004
- Commission Regulation (EC) No 1234/2008 (OJ L334 of 12 December 2008)
- Commission Regulation (EU) No 712/2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products
- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures

1.2. What groups of variations would be considered acceptable? ~~Rev. Dec 2019~~

There are no conditions for the grouping of Type IA/ IA_{IN} variations concerning one medicinal product.

It must be noted however, that when submitting Type IA/ IA$_{IN}$ variations as part of a group, the legal deadlines for submission of each variation should be respected i.e. a Type IA$_{IN}$ should always be submitted immediately, whether or not it is grouped with other variations, and any Type IA variation should always be submitted within 12 months following its implementation.

For further information see also *When shall I submit my Type IA/IAIN variation(s)*

When super-grouping one or more Type IA/ IA$_{IN}$ variations affecting several centrally authorised medicinal products from the same MAH, the variation or group of variations must be the same for all medicinal products concerned.

Grouping of non-Type IA ~~other types of~~ variations is only acceptable when they fall within one of the cases listed in Annex III of the Regulation, or, if they do not fall within one of those cases, when the grouping of the variations has been agreed between the Agency and the MAH before submission.

MAHs are advised to inform the Agency at least 2 months in advance of the submission of a group of variations which are not listed in Annex III of the Regulation, together with a justification as to why the holder believes that the proposed group should be acceptable.

When reviewing MAH proposals for grouping of variations, the Agency will consider the following general principles:

- Changes should be consequential and/or related i.e. **meaningful to be reviewed simultaneously**, although a proposal to submit a grouped application cannot be based on convenience alone (e.g. the following cases would not in principle be acceptable: both variations result in changes to the PI or all variations affect the RMP). However, applicants are generally encouraged to group related variations whenever possible e.g. variations affecting clinical safety, variations including only non-clinical studies or variations including only drug-drug interaction studies. In these cases, the scopes are related, and it would be meaningful for the respective variations to be reviewed simultaneously.
- Quality, Non-clinical and Clinical changes can normally not be grouped unless exceptionally justified.
- CHMP-led and PRAC-led type II variations can normally not be grouped unless exceptionally justified (i.e. the scopes are closely interlinked).
- Quality variations to the active substance can normally not be grouped with finished product variations, unless justified
- Grouping should not delay the submission and implementation of updates to the safety information for the medicinal product.
- Studies undertaken in different patient populations should in general not be grouped unless the applicant can justify why it would be beneficial to assess them together (e.g. supportive of overall clinical safety).

Table 1 presents some examples of acceptable groups of variations listed in Annex III of the Regulation, with further clarification on how such groups will be considered in practice.

Table 2 presents some examples of other groups of variations, which the Agency would or not in principle consider acceptable. Some concrete examples are also provided to illustrate proposed groupings that could be considered acceptable or not.

These tables will be reviewed and updated regularly, in view of accumulated experience.

Table 1. Grouping examples according to Article 7.2(b) of the Variation Regulation (Cases for grouping variations listed in Annex III)

1	One of the variations in the group is an extension of the marketing authorisation.	Other clinical or non-clinical changes linked to the extension (e.g. a new indication) can be grouped with the Extension application. Quality changes affecting the drug substance and/or drug product can also be included in the group.
	Example: Extension of the marketing authorisation for a new strength/pharmaceutical form + Type II variation for new therapeutic indication concerning the already authorised strength(s)/ pharmaceutical form(s).	
2	One of the variations in the group is a major variation of type II; all other variations in the group are variations which are consequential to this major variation of type II.	"A consequential variation is regarded as a change, which is an unavoidable and direct result of another change (i.e. the 'main change') and not simply a change which occurs at the same time."
	Example: Type II for new indication + Type IB or IA for addition of a new pack size required for the use in this new indication. Grouping of non-consequential quality changes may also be acceptable, under Article 7.2(c) other groups to be agreed with the Agency.	

Table 2. Grouping examples according to Article 7.2(c) of the Variation Regulation (Cases for grouping variations agreed by the Agency)

1	*Grouping of variations relating to active substance or finished product (but not to both)*	Grouping acceptable
	Example: type IB - extension of re-test period of the active substance + type IB - changes in the storage conditions of the active substance.	
2	*Grouping of variations relating to active substance and linked variations relating to finished product*	Grouping acceptable
	Example: type IB - changes to a test procedure of the active substance + type IA - deletion of a non-significant in-process control of the finished product.	
3	*Grouping of quality and administrative variations*	Grouping acceptable (administrative change can be combined with quality change when PI Annexes are affected).
	Example: type IB - extension of the shelf life of the finished product + type IA(IN) - change in the name of a manufacturer responsible for batch release + type IA - change in ATC Code.	
4	*Grouping of several non-clinical studies*	Grouping acceptable.
	Example: Provision of final study reports for 7 non-clinical in vivo studies, one of which results in consequential changes to the SmPC. The study report affecting the PI should be submitted as part of one type II variation under category C.I.4 and the remaining 6 reports as part of 6 type II variations under category C.I.13 (one variation per study report). As all 7 studies are non-clinical the scopes are related, and it is considered meaningful for these variations to be reviewed simultaneously. Thus, the MAH should submit one grouped application including one type II variation under category C.I.4 and six type II variations under category C.I.13.	

5	*Grouping of several drug-drug interaction studies* *e.g. type II - interaction study with Rifampicin + type II - interaction study with oral contraceptive*	Grouping acceptable; 1 type II variation scope per interaction study but type II variations can be grouped in 1 application.
6	*Grouping of several safety changes with similar implementation timelines*	Grouping acceptable, provided that the variations are to be led by the same committee
	Example 1: Update of section 4.4 of the SmPC with regard to venous thromboembolic events and haemorrhage events, and update of section 4.8 of the SmPC to include unrelated new ADRs, all following an update of the MAH's product core safety data sheet based on three different sets of data. The addition of information on venous thromboembolic events to SmPC section 4.4 is based on the analysis of one data set and requires one type II variation under category C.I.4. The addition of information on haemorrhage events to SmPC section 4.4 is based on the analysis of another data set and therefore requires one additional type II variation under category C.I.4. The addition of the new ADRs is in this case not consequential to the changes to SmPC section 4.4 above and is supported by another data set. Thus, the addition of the new ADRs to SmPC section 4.8 constitutes one additional scope and will therefore require an additional variation under category C.I.4. The applicant should in this case submit one grouped application including 3 type II variations under category C.I.4. The three variations are all related to clinical safety, they will be assessed by the CHMP and a common assessment is expected and is consequentially meaningful.	
	Example 2: Update of section 4.8 of SmPC to add three new ADRs - dyspnoea and chromaturia following a review of the MAH's safety database upon request by PRAC following a PSUSA procedure and Kounis syndrome following the MAH's own signal detection. As the three ADRs are supported by two separate data sets the MAH should submit two variations; one type II variation under category C.I.3.b to add dyspnoea and chromaturia and one type II variation under category C.I.4 to add Kounis syndrome. Both variations are related to clinical safety, but the assessment of the first variation is to be led by the PRAC while that of the second one will be performed by the CHMP; hence, the grouping is not acceptable in this case.	
7	*Grouping of several variations affecting the product information with different recommended or expected approval timelines*	Grouping <u>not</u> acceptable
	Example 1: Type IA(IN) to implement the outcome of signal assessment and type II safety variation. The implementation of the signal recommendation (which includes all language translations) is meant to allow the immediate implementation of the updated Product Information wording. Grouping with a type II variation would delay the implementation, therefore this is not acceptable.	
	Example 2: Type IB variation to implement agreed wording in the Product Information and	

	type II (non) clinical variation. In principle, the grouping is not acceptable as it would delay the implementation of the agreed wording due to longer timelines and possible need for linguistic review for the type II variation.	
	Example 3: Type II variation to propose an extension of the authorised indication. In addition, the applicant proposes an update of the SmPC regarding hepatotoxicity based on a review of the MAH's safety data base undertaken upon request by the CHMP following a previous PAM assessment, and an update of section 4.4 of the SmPC regarding pulmonary toxicity following a literature review. Given the long assessment timelines for an extension of indication application and the fact that a grouped approach would delay the implementation of new safety information, the proposed grouping would not be acceptable. Hence, the extension of indication application should be submitted as a separate stand-alone type II variation under category C.I.6.a. As the two safety topics are supported by different sets of data they should be submitted as part of two separate type II variations under category C.I.4. However, as both scopes concern clinical safety they can be submitted as one grouped application. Thus, the applicant should submit one stand-alone type II variation under category C.I.6.a and one grouped application including two type II variations under category C.I.4.	
8	*Grouping of variations affecting unrelated areas of the dossier*	Not acceptable for grouping
	Example 1: Type II variation under category C.I.4 to provide 3-year clinical data based on an interim study report from study A with consequential changes to sections 4.8 and 5.1 of the SmPC. In addition, the applicant proposed to provide the final CSR for clinical study B with consequential changes to SmPC section 5.1, and the final CSR for a drug-drug interaction study C with consequential changes to SmPC section 4.5, as well as to take the opportunity to condense the existing text in SmPC section 4.8, to align the annexes with the latest QRD templates and to implement editorial changes in the SmPC. The provision of the interim data from study A and the consequential PI changes constitutes one type II variation under category C.I.4. The provision of the final CSR from study B with a consequential update to section 5.1 of the SmPC constitutes a separate assessment and therefore a separate type II variation under category C.I.4 is required. As both studies A and B are clinical (safety and/or efficacy) and affect SmPC section 5.1 it would be meaningful for these variations to be reviewed simultaneously. The final clinical study report for study C concerns a drug-drug interaction study which is not considered consequential or related and will require different expertise for the assessment (clinical pharmacology or non-clinical, depending on the nature of the drug-drug interaction study). Therefore, a separate type II variation under category C.I.4 should be submitted. The remaining proposed changes are considered relatively minor and can be included as part of the proposed application without the need for any additional scope i.e. any additional variation. Thus, the applicant should in this case submit one grouped application including 2 type II variations under category C.I.4 and one separate stand-alone type II variation under category C.I.4.	
9	*Grouping of variations in unrelated populations*	Not acceptable for grouping
	Example 1: Data package supportive of 2 different indications e.g. renal cell carcinoma + non-	

small cell lung cancer. This would not be an acceptable grouping. Separate variations should be submitted. This is because the two indication changes may follow different timelines (i.e. number of Requests for Supplementary Information) and have different outcomes, so that the approval of one indication could be delayed because of the other.
Example 2: Provision of the final CSRs for 6 clinical phase 2 and 3 studies undertaken in the same patient population without consequential changes to the PI. The applicant should submit 6 type II variations under category C.I.13. As all 6 studies are clinical and provide safety and/or efficacy data in the same patient population, the scopes are considered related and it is considered meaningful for these variations to be reviewed simultaneously. Thus, the applicant should submit one grouped application including six type II variations under category C.I.13.

1.3. How shall I present a grouped variations application? ~~Rev. Aug 2020~~

Grouped variations applications should contain the elements listed in Annex IV of the Variations Regulation and should be presented in accordance with the appropriate headings and numbering of the EU-CTD format.

The submission requirements as set-out in the PAG sections for the different types of variations will also apply to grouped variations, but the application should be provided as one integrated submission package (i.e. one eCTD sequence) covering all changes resulting from the variations.

- One cover letter, clearly indicating that the application concerns a group of variations as well as which type of variation is the highest in the group. Indicate whether the grouping is submitted under Article 7.2(b), i.e. it falls within one of the cases listed in Annex III of the variations regulation or it is submitted under Article 7.2(c), i.e. the grouping has been agreed with the Agency. Indicate whether the (super-)grouping is submitted as an annual update of Type IA variations.
- In order to facilitate the registration of the submission, marketing authorisation holders are required to fill in all the submission attributes through the eSubmission delivery file UI.
- The completed electronic EU variation application form, declaring all variations included in the group in the section 'type of changes', as well as a justification for the proposed grouping in the 'precise scope and background' section of the application form.
- The present-proposed section of the application form should clearly identify the relevant CTD sections in support of each variation
- If the group contains an Extension, also the Module 1.2 New Application Form duly completed for the Extension should be provided (see also "How shall I present my extension application?").
- Supportive documentation for all variations concerned, submitted as one integrated package (i.e. there is no need to submit a separate documentation package for each variation in the group). For example, the clinical overview and summaries should cover all data submitted as part of a grouped application i.e. all variations included. Hence the applicant should not submit several separate overviews/summaries.
- If applicable, one revised summary of product characteristics, labelling and/or package leaflet, including all changes applied for.

- Where the overall design and readability of the outer and immediate packaging and/or package leaflet is affected, the need for the provision of mock-ups or specimens should be discussed with the Medical Information Sector of the Agency on a case-by-case basis.

Please also refer to "How shall I present my Type II Variation application?"

For a (group of) Type IA/ IA$_{IN}$ variation(s) concerning several marketing authorisations, please refer to "When shall I submit my Type IA/IA$_{IN}$ variation(s)~~How shall I present and submit my Type IA/IA IN Variation(s)?~~" and Harmonised eCTD Guidance.

References

- Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures
- eCTD Variations Q&A document
- Harmonised Guidance for eCTD Submissions in the EU

1.4. What procedure number will be given to grouped variation applications? Rev. Nov 2023

- Several Type IA/ IA$_{IN}$ variations affecting **one** medicinal product:

The usual EMA procedure number for Type IA variations will be given, with the addition of the suffix "/G".

Example: EMEA/H/C/prod_nb/IA/nn/G

- One or more Type IA/ IA$_{IN}$ variations affecting **several** medicinal products:

The Agency will allocate a 'high-level' cross-products procedure number, which will be used for the handling of procedures which affect more than one medicinal product. A new procedure code (abbreviation) is used for groups of Type IA/ IA$_{IN}$ variations i.e. "IG". As the 'high-level' number cannot be allocated to one single product, the procedure number will therefore contain "xxxx" as a placeholder for the product number.

Example: EMEA/H/C/xxxx/IG/002

This 'high-level' procedure number should be obtained from the Agency shortly before submission. To submit your request, raise a ticket via EMA Service Desk. Please click on "Finance Services", then the Type of question to be selected is "Request for high-level procedure or ASMF number" followed by sub-option "IG Procedure Number (Type IA grouping)" and attaching a draft cover letter.

If you do not have an EMA Account, you may create one via the EMA Account Management portal.

Please note that requesting this high level number in advance is mandatory for submissions sent via the eSubmission Gateway or Web Client since this number must be included in eSubmission Gateway XML delivery file User interface.

For each medicinal product concerned by the group of variations, the following grouping number (which includes a reference to the "IG" group to which it belongs) will be given.

Example: EMEA/H/C/prod_nb/IG0002/nn which was submitted as part of a Type IA/ IA$_{IN}$ group affecting several medicinal products "IG0002")

- Several types of variations affecting **one** medicinal product:

The Agency's procedure number will reflect the highest type of variation in the group, with the addition of the suffix "/G".

Example: EMEA/H/C/prod_nb/II/nn/G (grouping of Type II + Type IB variations)

Example: EMEA/H/C/prod_nb/IB/nn/G (grouping of 3 Type IB variations)

Example: EMEA/H/C/prod_nb/X/nn/G (grouping of Extension + Type II + Type IB variations)

MAHs are reminded that EMA procedure numbers are allocated by the Agency upon receipt of the application, according to a sequential order for the product concerned which is independent from the type of regulatory procedure submitted.

1.5. ~~Can~~ Shall grouped variations be subject to a worksharing procedure? ~~Rev. Oct 2010~~

Grouped variations ~~can~~ shall be subject to a worksharing procedure, provided that the same group of variations applies to all medicinal products concerned by the worksharing procedure. However, groups including an extension application are excluded from worksharing.

Based on Articles 7a and 20 of the Variations Regulation when the grouping only consists of Type IA/ IA$_{IN}$ variations affecting several marketing authorisations, this is considered as a "super-group" of variations and not a "worksharing" procedure. However, it is possible to include a group of Type IA/ IA$_{IN}$ Variation(s) with a Type IB or Type II variation, which is submitted for a worksharing procedure.

1.6. How will grouped variation applications be handled (timetable)? What will be the outcome of the evaluation of a grouped variation application? Rev. May 2020

A grouped variation application will be handled and will follow the review procedure of the 'highest' variation type in the group.

For example:

- a group of a Type II and 3 Type IB variations will follow the timetable of the Type II variation.
- a group of an Extension and a Type II variation will follow the timetable of the Extension.

When the group follows the timetable of the Type II variation, weekly-start timetables may apply to the assessment following the same principles as those applied to the assessment of Type II variations. For more information please refer to the following questions and answers from the post-authorisation guidance for Type II variations: '*Which submission dates (weekly or monthly) are applicable for my type II variation and when shall I submit my application?*' and ' *How shall my Type II application be handled (timetable)?*'

In case of grouped Type IA/ IA$_{IN}$ variations, the Agency will issue a Notification reflecting which variations are accepted or rejected. The MAH shall immediately cease to apply the rejected variation(s) concerned.

For grouping of other types of variations, where not all of the changes applied for can be positively validated, all valid and not valid variations will be clearly listed in the validation letter.

Upon finalisation of the review of the grouped variations, the Agency will issue an Opinion/Notification reflecting the final outcome of the procedure and in accordance with the 'highest' remaining approvable variation in the group. Such Opinion/Notification will therefore also list any variations which are not considered approvable, unless these have been withdrawn from the group by the holder during the procedure.

For example:

- Extension + Type II --> Extension evaluation procedure. Extension receives a negative assessment outcome (e.g. quality issues); Type II (e.g. new indication) is however positive.

  MAH withdraws the Extension from the group --> CHMP will adopt a positive opinion on the Type II variation only.

  MAH does not withdraw the Extension from the group --> CHMP will adopt a 'composite' opinion reflecting both the negative Extension outcome as well as the positive Type II.

- Type II + Type IB --> Type II evaluation procedure. Type II receives a negative assessment outcome; Type IB is however positive.

  MAH withdraws the Type II from the group --> Agency will issue a positive notification on the Type IB variation.

  MAH does not withdraw the Type II from the group --> CHMP will adopt a 'composite' opinion reflecting both the negative Type II outcome as well as the positive Type IB.

In any case, the assessment report will mention the initial and complete scope of the application (listing all variations initially included in the group) and will clarify the procedural timelines and steps taken during assessment.

For CHMP opinions on Extensions and Type II variations, the re-examination procedure set-out in Articles 9(2) and 34 (2) of Regulation (EC) No 726/2004 will apply. For further information please refer to the following questions and answers from the post-authorisation guidance for Type II variations 'Which post-opinion steps apply to my type II variation and when can I implement the approved changes?' and Extensions of marketing authorisations 'How shall my extension application be handled (timetable)?'

1.7. How and when will the marketing authorisation be updated for grouped variations? ~~Rev. July 2013~~

The post-opinion and decision-making process that will apply to grouped variations will generally be that of the 'highest' type of Opinion/Notification issued at the end of the procedure.

For information on the post-opinion and decision-making process for Type IA, IB and II variations, please refer to the following questions and answers '*How and when will the updated annexes become part of the marketing authorisation?'* and '*Which post-opinion steps apply to my type II variation and when can I implement the approved changes*?'

The decision granting the marketing authorisation following a grouped application will be amended, where necessary, within a year from the date of notification/CHMP opinion for the variation concerned with the exception of the following grouped variations:

- Groupings including an extension application, which will follow the decision-making process applicable to the extension application;

- Groupings including variation(s) listed in Article 23.1a(a), for which the amendments to the decision granting the marketing authorisation will follow a two-month timeframe;

Where a super-group of Type IA/ IA$_{IN}$ variations to the terms of several MAs have been approved, the Commission will update the MA with one decision per product concerned, following the yearly decision-making timeframes for Type IA/ IA$_{IN}$ variations.

1.8. What fee do I have to pay for grouped variations? Rev. Apr 2021

Grouped variations, whether consequential or not, will each attract a separate fee corresponding to the fee payable for the individual variation concerned.

Each variation applied for should therefore be declared as a separate variation on the variation application form.

The rules for reduced fees or fee reductions depending on the type of product (e.g. orphans, generics) will apply to grouped variations.

Where a grouping application is considered 'invalid' (i.e. an assessment process cannot be started), an administrative fee may be charged by the Agency.

Only one applicant will be invoiced for the grouped procedure. The details of the applicant where the invoice should be sent to should be clearly stated in the cover letter.

The fee will become due on the date of the notification of the administrative validation to the applicant and fees will be payable within 45 calendar days of the date of the said notification. After approximately 15 days an invoice will be sent to the applicants billing address held on the Agency's file.

The invoice will contain details of the product and type of procedure involved, the fee amount, the financial information and the customer purchase order number associated with the procedures invoiced (if provided in the eSubmission delivery file). The Agency does not accept stand-alone notifications of purchase order numbers that are not associated with a dossier.

Guidance on how to pay an invoice can be found on our website.

References

- More information about fees and fee payment in the Centralised Procedure