



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Variation eAF v1.24.0.0

Changes introduced in v1.24.0.0 of the variation form (to NCA users)

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Go-live of the new version 15th September 2020

Mandatory use from 15th of December 2020





- The v1.24.0.0 provides **a major technical change in the variation application form** (H&V)
- The change **mainly affects the applicants** as the way of **selecting** the variation types and scopes has changed significantly
- The change to the EMA and NCAs is less, however, opening of received forms should be much faster as the form has become much lighter and shorter as the variation scopes are now selected using controlled terminology lists (from RMS) instead of hard coded list
- The main change for the receiving authorities is in the **'Conditions and Documentation'** which are now **integrated in to the form** and are inherent part of the scopes that have been selected. This means that **there is no longer a need for a separate Annex** to provide these. The applicant can include justification/details why certain condition is not met/document is not provided or to provide any other details as necessary directly in the eAF section 3.
- Unfortunately, at the time of go live the, due to RMS system limitation, **the conditions and documentations integrated into the eAF are not in the same order as in the Classification Guideline**. The system **does not allow manual ordering** of the items and hence they are displayed in a different order. The numbers referred to in the Classification Guideline are **not** displayed, however, we are discussing if these should be added to RMS. These may provide ease of seeing which condition/documentation is in question, however, they may not appear in numerical order.

These points are very important to the applicants filling in the forms, however, it is good to be aware of this points in case you are asked or come across a form with an issue;

- The eAFs should only be edited using adobe editing tools as using any other editing tools may lead to issues when the forms are received and may lead to rejection. **If the received form appears not signed or is signed but is not properly locked, it may have been edited using Adobe Acrobat/Acrobat Pro or other non adobe tool**
- Please note that the forms must be signed using an image of a signature or a signature snippet. **Adobe sign or other digital signature tools cannot** be used
- Please note that imports of data from an older version do not work when there are significant changes to the form from the previous version. For example, it is not possible to import data from v1.23.x.x due to very extensive DES changes
- In general, if you experience any issues with the forms – please report these to the [EMA Service Desk](#) portal immediately
- If you notice that there is an error in the newly introduced RMS variations list, for example a typo, a missing scope, error in the Conditions or Documentation etc, please follow the updated eAF new term request process

Please see example of a filled in, locked form section 3 using in v1.24.0.0 on the right.

Please note that the following slides provide details to the applicant on how to fill in the form and may not be so much interest to the EMA users, however, these could be useful in understanding the user experience of the applicant and the business rules.

3. TYPES OF CHANGE(S)

Variations included in this application: Please follow instructions below to add variation
All Section 1 of the form first, so as for the proper variations to be loaded. Navigate through the dropdown lists, in order to show the variation.
You can select the variation by clicking the relevant checkbox of the variation box.
Note: Any change in Type of Application in Section 1, will delete any selected variation!

| Variation | Selected |
|-----------|-------------------------------------|
| B.1.b.2.b | <input checked="" type="checkbox"/> |
| B.1.b.2.a | <input type="checkbox"/> |

Show Selected Variations

Show Variation Lists

Grouping of variations is being selected. You may choose variation changes/types that are selected on section 1.

B.1.b.2.b - QUALITY CHANGES - ACTIVE SUBSTANCE - Control of active substance - Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance - Deletion of a test procedure for the active substance or a starting material/reagent/intermediate, if an alternative test procedure is already authorized. + - Clone

Procedure Type: IA IB

Conditions:

An alternative test procedure is already authorized for the specific parameter and this procedure has not been added through a related notification.

Notes:

Documentation:

Amendment of the relevant action(s) of the dossier (presented in the e-CTD format or SDA's clone as format for medicinal products, as appropriate), including a description of the analytical methodology, a summary of substance data, revised specifications for impurities (if applicable).

Notes:

B.1.b.2.a - QUALITY CHANGES - FINISHED PRODUCT - Manufacture - Change to importer, batch release arrangements and quality control testing of the finished product - Replacement or addition of a site where batch control/testing takes place. + - Clone

Procedure Type: IA IB

Implement. Date: Implement. Note:

Conditions:

The site is appropriately authorized.

Notes:

The product concerned is not a sterile ophthalmic medicinal product.

Notes:

Method transfer from the old to the new site or new test laboratory has been successfully completed.

Notes:

Details on the documentation provided that the applicant wishes to provide for the regulatory authority the application is addressed to. This text does not have to be free text and the field is wrapped for ease of reading.

At least one batch control/testing site remains within the EU/EEA in a country where an operational and suitable signed user mutual recognition agreement (see A) exists between the country concerned and the EU/EEA in order to carry out product testing for the purpose of batch release within the system.

Notes:

Documentation:

Amendment of the relevant action(s) of the dossier (presented in the e-CTD format or SDA's clone as format for medicinal products, as appropriate) including revised product information as appropriate.

Notes:

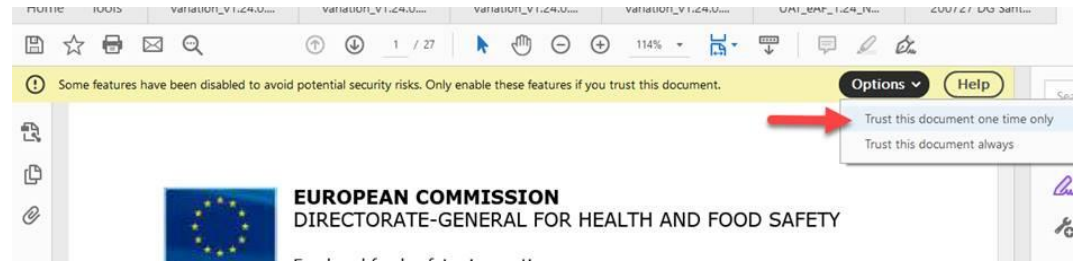
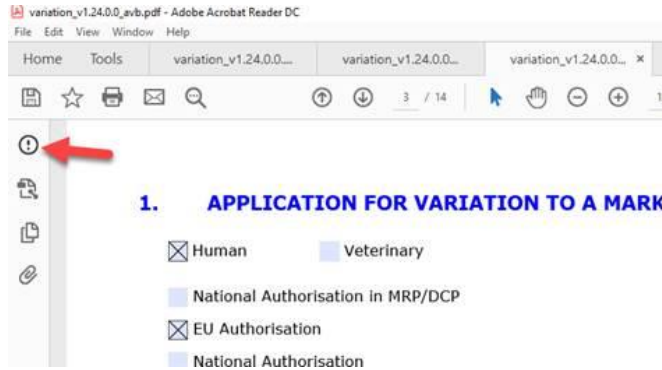
The variation application form should clearly define the present and proposed finished product manufacturer, importer, batch control/testing and batch release sites as listed in section 2.a of the application form for marketing authorisation.

Notes:

For sites within the EU/EEA, attach copy of manufacturing authorisation(s) or where no manufacturing authorisation exists a certificate of compliance issued within the last 1 year by the relevant competent authority, for a manufacturing site outside the EU/EEA, where an operational user mutual recognition agreement (UMA) exists between the country concerned and the EU/EEA, attach certificate, issued within the last 1 year by the relevant competent authority.

Notes:

- In order to access the control terminology lists, the forms **must be trusted** first
- Please save the form on your local drive – potentially with another name – and open the saved form using **adobe reader**. It is **important to use adobe reader to edit the forms** instead of adobe acrobat or acrobat pro **as using these will result in issues with locking the forms and may lead to rejection**
- Once you open the form, there should be an **exclamation mark** on the top of the left hand pane
- When you click this with your mouse, a yellow banner will open across the top, please select trust this document one time only



The selections made in section 1 'Type of Application' will now directly affect the section 3 and depending on the selection, only the relevant scopes are available for selection in section 3.

If a 'single' variation has been selected in section 1, it is only possible to select a single scope in section 3

Type of Application (tick all applicable options)

**Note: Any change in Type of Application, will delete any selected variation in Section 3!*

Single variation

Grouping of variations

Worksharing

Type IA_{IN}

Type IA

Type IB unforeseen²

Type IB

Type II

Type II Art. 29



3. TYPES OF CHANGE(S)

Variations included in this application: Please follow instructions below to add variation *fill Section 1 of the form first, so as for the proper variations to be loaded. Navigate through the dropdown lists, in order to show the variation.*

You can select the variation by clicking the relevant checkbox of the variation box.

Note: Any change in Type of Application in Section 1, will delete any selected variation!

| Variation | Selected |
|-----------|----------|
|-----------|----------|

Show Selected Variations

Show Variation Lists

Single Variation is being selected. You may choose only type IA variation changes and only one scope.

If a grouping has been selected in section 1, a form validation error will be raised if only single scope is selected

Type of Application (tick all applicable options)

**Note: Any change in Type of Application, will delete any selected variation in Section 3!*

- Single variation
- Grouping of variations
 - Including a line extension³ ?
 - Worksharing
- Type IA_{1N}
- Type IA
- Type IB unforeseen² ?
- Type IB
- Type II
- Type II Art. 29⁴ ?

Grouping of variations is being selected. You may choose variation changes of types that are selected on section 1.

FORM VALIDATION

Validation Errors: 1

Please select more than 1 Variations in Section 3 when Grouping of variations is selected in Section 1 and re-validate.

The selection of scopes in section 3 is done by drilling down dropdown menu which displays different available scopes based on the selections in section 1

Please note that **any changes in Type of Application in section 1 will delete any selected variations!**

Variations included in this application: Please follow instructions below to add variation fill Section 1 of the form first, so as for the proper variations to be loaded. Navigate through the dropdown lists, in order to show the variation.
You can select the variation by clicking the relevant checkbox of the variation box.
Note: Any change in Type of Application in Section 1, will delete any selected variation!

| Variation | Selected |
|-----------|----------|
|-----------|----------|

Show Selected Variations

Show Variation Lists

Single Variation is being selected. You may choose only type IB variation changes and only one scope.

| | |
|--|---|
| B. QUALITY CHANGES | ▼ |
| B.I ACTIVE SUBSTANCE | ▼ |
| B.I.a) Manufacture | ▼ |
| | ▼ |
| B.I.a.1 Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the ac | |
| B.I.a.2 Changes in the manufacturing process of the active substance | |
| B.I.a.3 Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing pro | |
| B.I.a.4 Change to in-process tests or limits applied during the manufacture of the active substance | |
| B.I.a.5 Changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza | |
| B.I.a.z Re-arrangement and amendment of equipment in the plasma pooling line of the active substance which has already | |

In order to **select** the chosen scope, it is important to tick the 'select' tick box. If this box is not ticked and you make changes in the dropdown menu, the selected options will be deleted

| Variation | Selected |
|-----------|----------|
| B.la.2.a | 1 |

Show Selected Variations

Show Variation Lists

Single Variation is being selected. You may choose only type IB variation changes and only one scope.

select B.la.2.a - QUALITY CHANGES - ACTIVE SUBSTANCE - Manufacture - Changes in the manufacturing process of the active substance - Minor change in the manufacturing process of the active substance

Procedure Types: IA IB

Conditions:

The active substance is not a biological/immunological substance.

Note:

The change is fully described in the open (applicant's) part of an Active Substance Master File, if applicable.

Note:

If only one procedure type, for example IB is possible, based on the selection in section 1, or due to classification guideline, the procedure type will be automatically ticked by the system and cannot be manually changed

For Type IA and Type IA_{IN} the implementation date and implementation note are available.

Single Variation is being selected. You may choose only type IA variation changes and only one scope.

B. QUALITY CHANGES

B.II. FINISHED PRODUCT

B.II.b) Manufacture

B.II.b.2 Change to importer, batch release arrangements and quality control testing of the finished product


B.II.b.2.a Replacement or addition of a site where batch control/testing takes place

| | | |
|--------------------------|--|--|
| select | <input type="checkbox"/> | B.II.b.2.a - QUALITY CHANGES - FINISHED PRODUCT - Manufacture - Change to importer, batch release arrangements and quality control testing of the finished product - Replacement or addition of a site where batch control/testing takes place |
| Procedure Types: | IA <input checked="" type="checkbox"/> | IB <input type="checkbox"/> |
| Implement. Date: | <input type="text"/> | Implement. Note: <input type="text"/> |
| <u>Conditions:</u> | | |
| <input type="checkbox"/> | The site is appropriately authorised. | |
| Note: | <input type="text"/> | |
| <input type="checkbox"/> | The product concerned is not a biological/immunological medicinal product. | |
| Note: | <input type="text"/> | |

Where relevant the Art 5. checkbox will be automatically ticked and cannot be manually unticked.

Single Variation is being selected. You may choose only type IA variation changes and only one scope.

| | |
|--|---|
| B. QUALITY CHANGES | ▼ |
| B.I ACTIVE SUBSTANCE | ▼ |
| B.I.c) Container closure system | ▼ |
| B.I.c.1 Change in immediate packaging of the active substance | ▼ |
| B.I.c.1.z Deletion of one of the authorised bulk or final containers | ▼ |

| | |
|---|---|
| select <input type="checkbox"/> | B.I.c.1.z - QUALITY CHANGES - ACTIVE SUBSTANCE - Container closure system - Change in immediate packaging of the active substance - Change in immediate packaging of the active substance |
| Procedure Types: IA <input checked="" type="checkbox"/> IB <input type="checkbox"/> | |
| Implement. Date: <input type="text"/> | Implement. Note: <input type="text"/> Article 5 <input checked="" type="checkbox"/>  |
| <u>Conditions:</u> <input type="checkbox"/> The remaining packaging must be adequate for the storage of the bulk or final active substance at the authorised conditions. | |
| Note: | <input type="text"/> |

When grouping is selected in section 1, and different procedure types have been selected in section 1, you will need to manually select the procedure type. + and - buttons, as well as 'clone' button to add additional scopes/clone scopes you have selected are available

| | | |
|---|--|---|
| select <input checked="" type="checkbox"/> | B.II.b.2.a - QUALITY CHANGES - FINISHED PRODUCT - Manufacture - Change to importer, batch release arrangements and quality control testing of the finished product - Replacement or addition of a site where batch control/testing takes place | + - Clone |
| Procedure Types: | IA <input checked="" type="checkbox"/> IB <input type="checkbox"/> | |
| Implement. Date: | <input type="text"/> | Implement. Note: <input type="text" value="6 months after approval"/> |
| Conditions: | | |
| <input checked="" type="checkbox"/> | The site is appropriately authorised. | |
| Note: | <input type="text"/> | |
| <input checked="" type="checkbox"/> | The product concerned is not a biological/immunological medicinal product. | |
| Note: | <input type="text"/> | |
| <input checked="" type="checkbox"/> | Method transfer from the old to the new site or new test laboratory has been successfully completed. | |

The relevant Conditions and Documentation are now available directly in the form and those relevant to the selected procedure type and scope are shown as a part of the scope.

If the condition/documentation tick box is not ticked, the free text field is mandatory. The free text field is always available and any necessary information can be included in it, as previously done in the separate annex to the application form.

| | | | |
|-------------------------------------|--|--|--|
| select | <input checked="" type="checkbox"/> | B.II.b.2.a - QUALITY CHANGES - FINISHED PRODUCT - Manufacture - Change to importer, batch release arrangements and quality control testing of the finished product - Replacement or addition of a site where batch control/testing takes place | + - |
| | | Clone | |
| Procedure Types: | IA <input checked="" type="checkbox"/> | IB <input type="checkbox"/> | |
| Implement. Date: | <input type="text"/> | Implement. Note: | <input type="text" value="6 months after approval"/> |
| <u>Conditions:</u> | | | |
| <input checked="" type="checkbox"/> | The site is appropriately authorised. | | |
| Note: | <input type="text"/> | | |
| <input checked="" type="checkbox"/> | The product concerned is not a biological/immunological medicinal product. | | |
| Note: | <input type="text"/> | | |
| <input checked="" type="checkbox"/> | Method transfer from the old to the new site or new test laboratory has been successfully completed. | | |
| Note: | <input type="text" value="Details on the documentation provided that the applicant wishes to provide for the regulatory authority the application is addressed to. This text does not have size limit and the field is wrapped for ease of reading."/> | | |
| <input checked="" type="checkbox"/> | At least one batch control/testing site remains within the EU/EEA or in a country where an operational and suitably scoped GMP mutual recognition agreement (MRA) exists between the country concerned and the EU, that is able to carry out product testing for the purpose of batch release within the EU/EEA. | | |
| Note: | <input type="text"/> | | |
| <u>Documentations:</u> | | | |
| <input checked="" type="checkbox"/> | Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate) including revised product information as appropriate. | | |
| Note: | <input type="text"/> | | |

Please note:

The separate annex is no longer expected to be provided as a part of the submission.

Always ensure that you have selected the scope and ensure that the details are shown in the summary box before moving on. This is especially important for grouping variations if you need to select a different scope as this will be done by repeating the selections using the dropdown menu.

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You can select the variation by clicking the relevant checkbox of the variation box.

Note: Any change in Type of Application in Section 1, will delete any selected variation!

| Variation | Selected |
|------------|----------|
| B.II.b.2.a | 1 |

Show Selected Variations

Show Variation Lists



Grouping of variations is being selected. You may choose variation changes of types that are selected on section 1.

| | | |
|-------------------------------------|--|---|
| select | B.II.b.2.a - QUALITY CHANGES - FINISHED PRODUCT - Manufacture - Change to importer, batch release arrangements and quality control testing of the finished product - Replacement or addition of a site where batch control/testing takes place | + - |
| <input checked="" type="checkbox"/> | | Clone |
| Procedure Types: | IA <input checked="" type="checkbox"/> IB <input type="checkbox"/> | |
| Implement. Date: | <input type="text"/> | Implement. Note: <input type="text" value="6 months after approval"/> |
| Conditions: | <input type="text"/> | |



For groupings, if you have used the 'Show Selected Variations' button and wish to continue adding different scopes, please click the 'Show Variation Lists' which will display a 'fresh' dropdown menu to continue scope selection.

If you have not used 'Show Selected Variations' button and wish to continue adding other scopes, simply start over by selecting the relevant scope using the required level of detail – as long as you have selected the previous scope and can see it in the summary box, you are not overwriting the previous selection.

3. TYPES OF CHANGE(S)

Variations included in this application: Please follow instructions below to add variation
fill Section 1 of the form first, so as for the proper variations to be loaded. Navigate through the dropdown lists, in order to show the variation.
You can select the variation by clicking the relevant checkbox of the variation box.
Note: Any change in Type of Application in Section 1, will delete any selected variation!

| Variation | Selected |
|------------|----------|
| B.II.b.2.a | 1 |

Show Selected Variations

Show Variation Lists

Grouping of variations is being selected. You may choose variation changes of types that are selected on section 1.

| |
|--|
| |
| A. ADMINISTRATIVE CHANGES |
| B. QUALITY CHANGES |
| C. SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES |
| D. PMF / VAMF |

In order to **select** the chosen scope, it is important to tick the 'select' tick box. If this box is not ticked and you make changes in the dropdown menu, the selected options will be deleted

| Variation | Selected |
|-----------|----------|
| B.la.2.a | 1 |

Show Selected Variations

Show Variation Lists

Single Variation is being selected. You may choose only type IB variation changes and only one scope.

select B.la.2.a - QUALITY CHANGES - ACTIVE SUBSTANCE - Manufacture - Changes in the manufacturing process of the active substance - Minor change in the manufacturing process of the active substance

Procedure Types: IA IB

Conditions:

The active substance is not a biological/immunological substance.

Note:

The change is fully described in the open (applicant's) part of an Active Substance Master File, if applicable.

Note:

If only one procedure type, for example IB is possible, based on the selection in section 1, or due to classification guideline, the procedure type will be automatically ticked by the system and cannot be manually changed



Any questions?

Further information

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