11 October 2022
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Procedures Office
Committees and Quality Assurance Department

European Medicines Agency practical guidance on the application form for centralised type IA and IB variations

This document is intended as guidance to facilitate the completion of the application form for type IA and IB variations to be submitted in the Centralised Procedure and should be read in conjunction with the EMA/CMDh Explanatory Notes on Variation Application Form (CMDh/EMA/133/2010).

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EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Health Systems and products

September 2021

NOTICE TO APPLICANTS

APPLICATION FOR VARIATION TO A MARKETING AUTHORISATION

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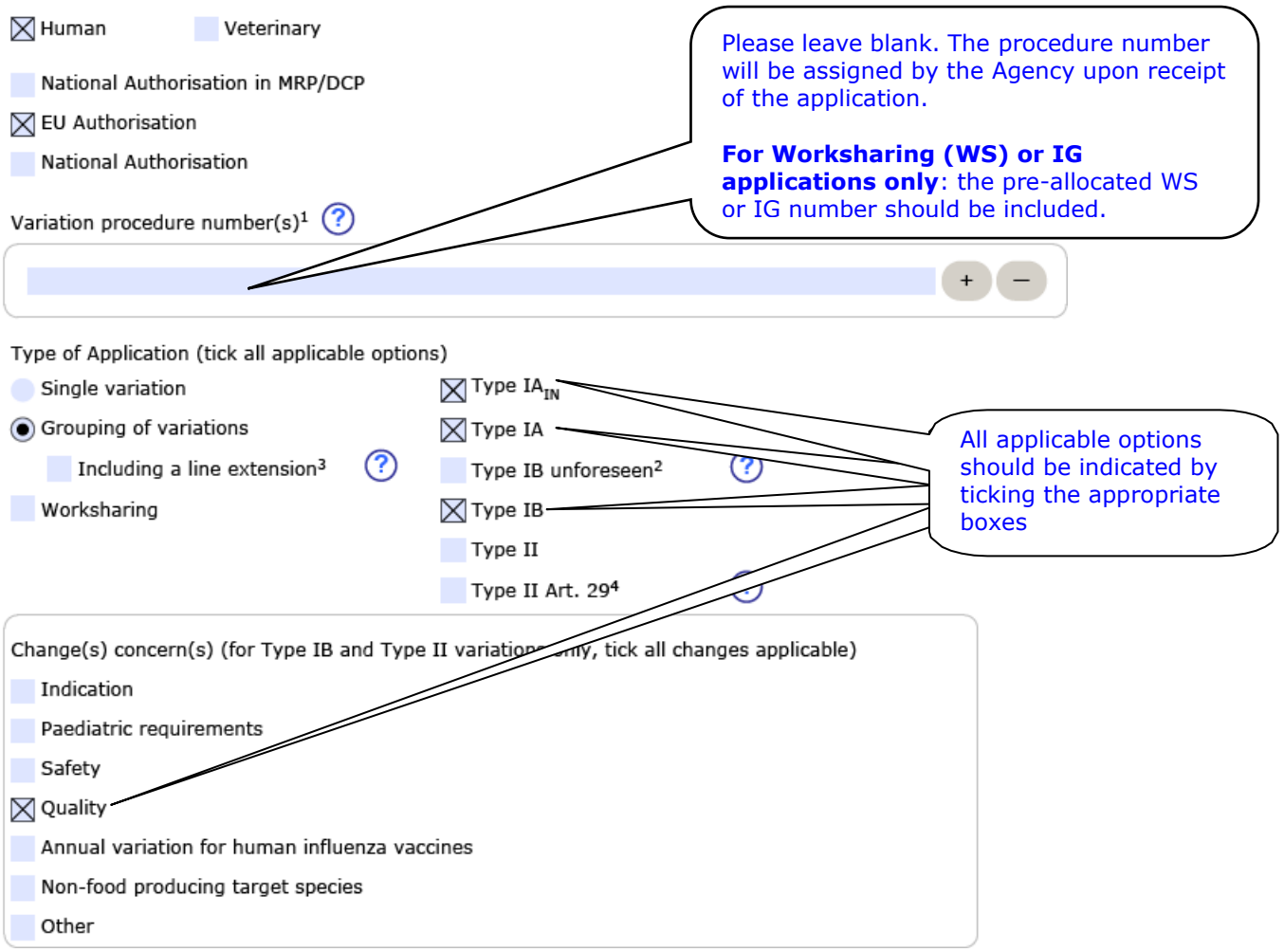
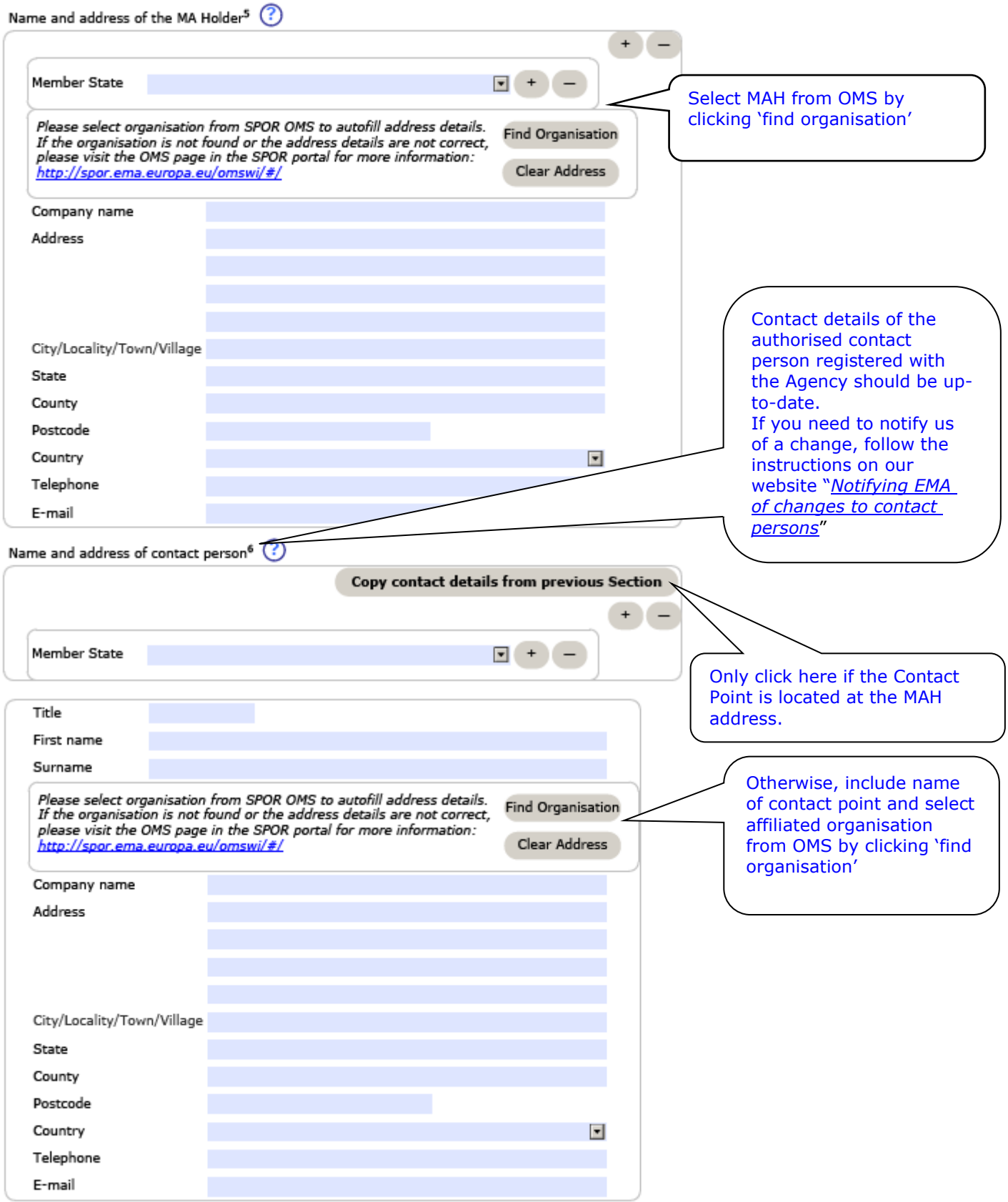
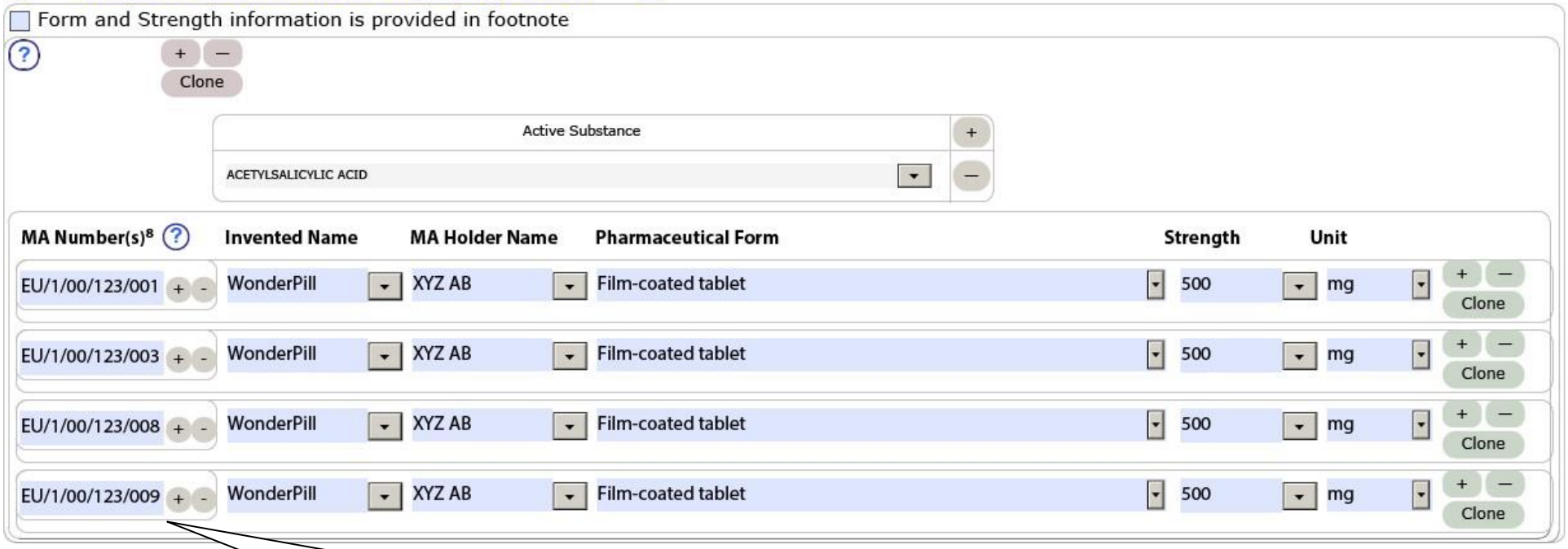
1. APPLICATION FOR VARIATION TO A MARKETING AUTHORISATION




Name and address of the MA Holder[5]
Member State
Please select organisation from SPOR OMS to autofill address details. If the organisation is not found or the address details are not correct, please visit the OMS page in the SPOR portal for more information: http://spor.ema.europa.eu/omswi/#/
Find Organisation
Clear Address
Company name
Address
City/Locality/Town/Village
State
County
Postcode
Country
Telephone
E-mail
Select MAH from OMS by clicking 'find organisation'
Contact details of the authorised contact person registered with the Agency should be up-to-date.
If you need to notify us of a change, follow the instructions on our website "Notifying EMA of changes to contact persons"
Name and address of contact person[6]
Copy contact details from previous Section
Member State
Only click here if the Contact Point is located at the MAH address.
Title
First name
Surname
Please select organisation from SPOR OMS to autofill address details. If the organisation is not found or the address details are not correct, please visit the OMS page in the SPOR portal for more information: http://spor.ema.europa.eu/omswi/#/
Find Organisation
Clear Address
Company name
Address
City/Locality/Town/Village
State
County
Postcode
Country
Telephone
E-mail
Otherwise, include name of contact point and select affiliated organisation from OMS by clicking 'find organisation'

2. PRODUCTS CONCERNED BY THIS APPLICATION[7]



Only the presentation(s) (EU number(s)) affected by the change(s) should be listed. Please do not include by default the latest Annex A with the list of all approved presentations.

For applications relating solely to the addition of new presentation(s), only the new presentation(s) should be indicated (EU number(s) confirmed with the Agency prior to submission).

If different changes apply to different presentations, all affected presentations should be listed in the table and a detailed description of the changes, together with an explanation of which change(s) apply/ies to which presentation(s), should be included in the 'Precise scope' section of the Application Form.

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.I.a.3.a	1
B.II.a.3.a.1	1
B.III.2.z	1
B.II.b.1.a	1

Show Selected Variations | Show Variation Lists

Grouping of variations is being selected. You may choose var

For variations concerning a single product, identical scope(s) (change(s)) should be repeated as many times as needed.

For IG applications (1 or >1 Type IA/IA$_{IN}$ variations affecting >1 product of the same MAH) or WS applications (a (group of) Type IB and/or Type II and/or Type IA/IA$_{IN}$ variations affecting >1 product of the same MAH),the same scope(s) (change(s)) must be applied to all products concernedby the application. The scope(s) applied for **should not** be repeated for each product as this will incur into unnecessary fees being invoiced.

select ☒ B.I.a.3.a - QUALITY CHANGES - ACTIVE SUBSTANCE - Manufacture - Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance - Up to 10-fold increase compared to the originally approved batch size

Procedure Types: IA ☒ IB ☐

Implement. Date: 2022-07-01 **Implement. Note:**

Implementation dates for Type IA/IA$_{IN}$ variations should be included here (see guidance for the *'Meaning of "implementation" for Type IA variations'*)

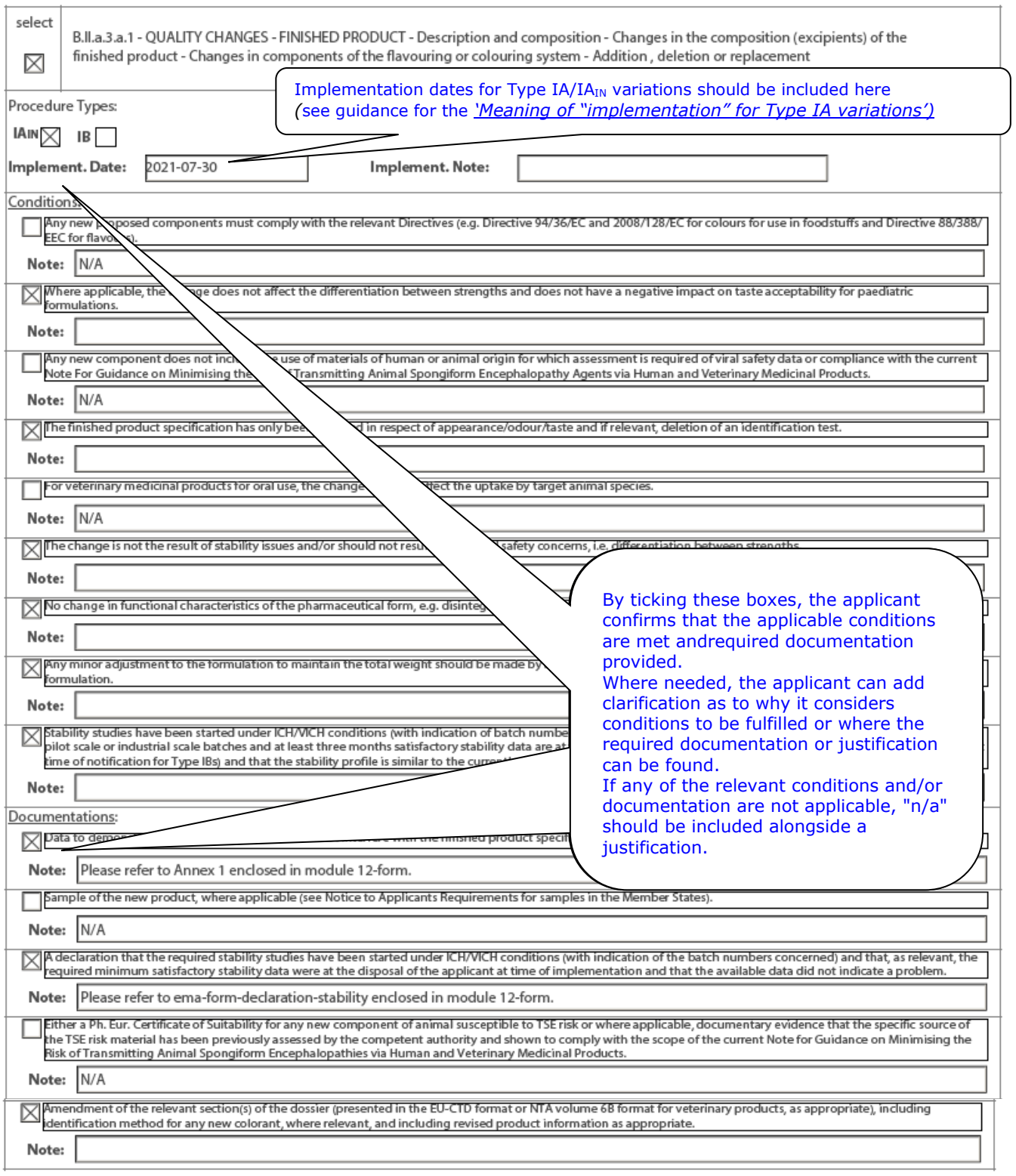
Conditions:

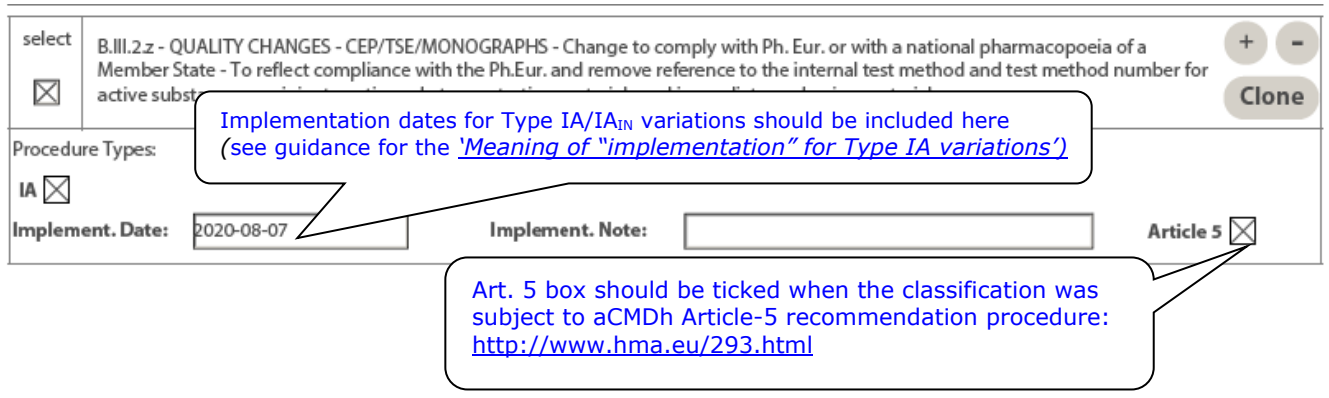
- ☒ The change does not adversely affect the reproducibility of the process.
  Note:
- ☒ The active substance is not sterile.
  Note:
- ☒ The product concerned is a biological/immunological medicinal product.
  Note:
- ☒ The batch size is within the 10-fold range as a Type IA variation.
  Note:
- ☒ Test results of at least two batches according to the specification
  Note:
- ☒ The specifications of the active substance/intermediate
  Note:
- ☒ Any changes to the manufacturing those
  Note:

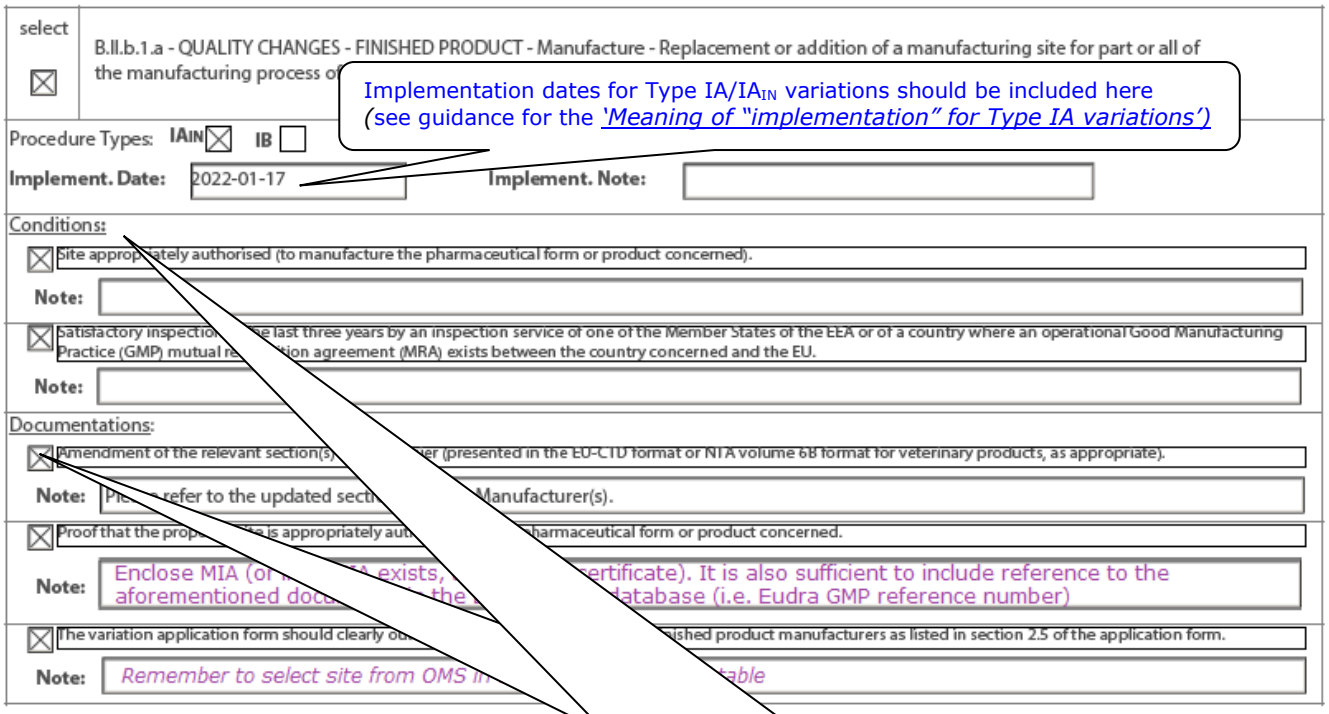
By ticking these boxes, the applicant confirms that the applicable conditions are met andrequired documentation provided.
Where needed, the applicant can add clarification as to why it considers conditions to be fulfilled or where the required documentation or justificationcan be found.
If any of the relevant conditions and/or documentation are not applicable, "n/a" should be included alongside a justification.

Documentations:

- ☒ A declaration from the marketing authorisation holder or the ASMF holder as appropriate that the changes to the manufacturing methods are only those necessitated by scale-up or downscaling, e.g. use of different-sized equipment, that the change does not adversely affect the reproducibility of the process, that it is not the result of unexpected events arising during manufacture or because of stability concerns and that the specifications of the active substance/intermediates remain the same.
  Note:
- ☒ The batch numbers of the tested batches having the proposed batch size.
  Note:
- ☒ 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).
  Note:


select
B.II.a.3.a.1 - QUALITY CHANGES - FINISHED PRODUCT - Description and composition - Changes in the composition (excipients) of the finished product - Changes in components of the flavouring or colouring system - Addition , deletion or replacement
Implementation dates for Type IA/IAIN variations should be included here (see guidance for the 'Meaning of "implementation" for Type IA variations')
Procedure Types:
IAIN
IB
Implement. Date: 2021-07-30
Implement. Note:
Conditions:
Note: N/A
Note:
Note: N/A
Note:
Note: N/A
Note:
Note:
Note:
Note:
Documentations:
Note: Please refer to Annex 1 enclosed in module 12-form.
Note: N/A
Note: N/A
Note:
By ticking these boxes, the applicant confirms that the applicable conditions are met andrequired documentation provided.
Where needed, the applicant can add clarification as to why it considers conditions to be fulfilled or where the required documentation or justification can be found.
If any of the relevant conditions and/or documentation are not applicable, "n/a" should be included alongside a justification.


select
B.III.2.z - QUALITY CHANGES - CEP/TSE/MONOGRAPHS - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - To reflect compliance with the Ph.Eur. and remove reference to the internal test method and test method number for active subst
Clone
Implementation dates for Type IA/IAIN variations should be included here (see guidance for the 'Meaning of "implementation" for Type IA variations')
Procedure Types:
IA
Implement. Date: 2020-08-07
Implement. Note:
Article 5
Art. 5 box should be ticked when the classification was subject to aCMDh Article-5 recommendation procedure: http://www.hma.eu/293.html



Implementation dates for Type IA/IA$_{IN}$ variations should be included here (see guidance for the *'Meaning of "implementation" for Type IA variations'*)

By ticking these boxes, the applicant confirms that the applicable conditions are met andrequired documentation provided.
Where needed, the applicant can add clarification as to why it considers conditions to be fulfilled or where the required documentation or justificationcan be found.
If any of the relevant conditions and/or documentation are not applicable, "n/a" should be included alongside a justification.

PRECISE SCOPE AND BACKGROUND FOR CHANGE, AND JUSTIFICATION FOR GROUPING, WORKSHARING AND CLASSIFICATION OF UNFORESEEN CHANGES (if applicable)
(*include a description and background of all the proposed changes. In case of grouping and worksha[illegible] justification should be provided in a separate paragraph. If a variation concerns an unforeseen change, in[illegible]ude a justification for its proposed classification).*

Describe details (background) of the change(s) applied for.

This is a grouped variation application to introduce changes relating to the active substance (acetylsalicylic acid) and to the finished product (500mg film-coated tablets presentations only)

B.II.a.3.a.1 - Change in the composition of the colouring of the 500 mg film-coated tablets (EU/1/00/123/001, 003, 008 and 009) to remove carnauba wax.

B.I.a.3.a - To include an alternative batch size of 150kg for the active substance acetylsalicylic acid in addition to the currently approved batch sizes of 100 and 125kg.

B.III.2.z - To reflect compliance with the Ph. Eur. and remove reference to the internal test method and test method number for the active substance acetylsalicylic acid.

B.II.b.1.a - To add ABC Packaging Ltd (6 Domenico Straat, Amsterdam, 1083HH, Netherlands) as a site responsible for secondary packaging of the finished product.

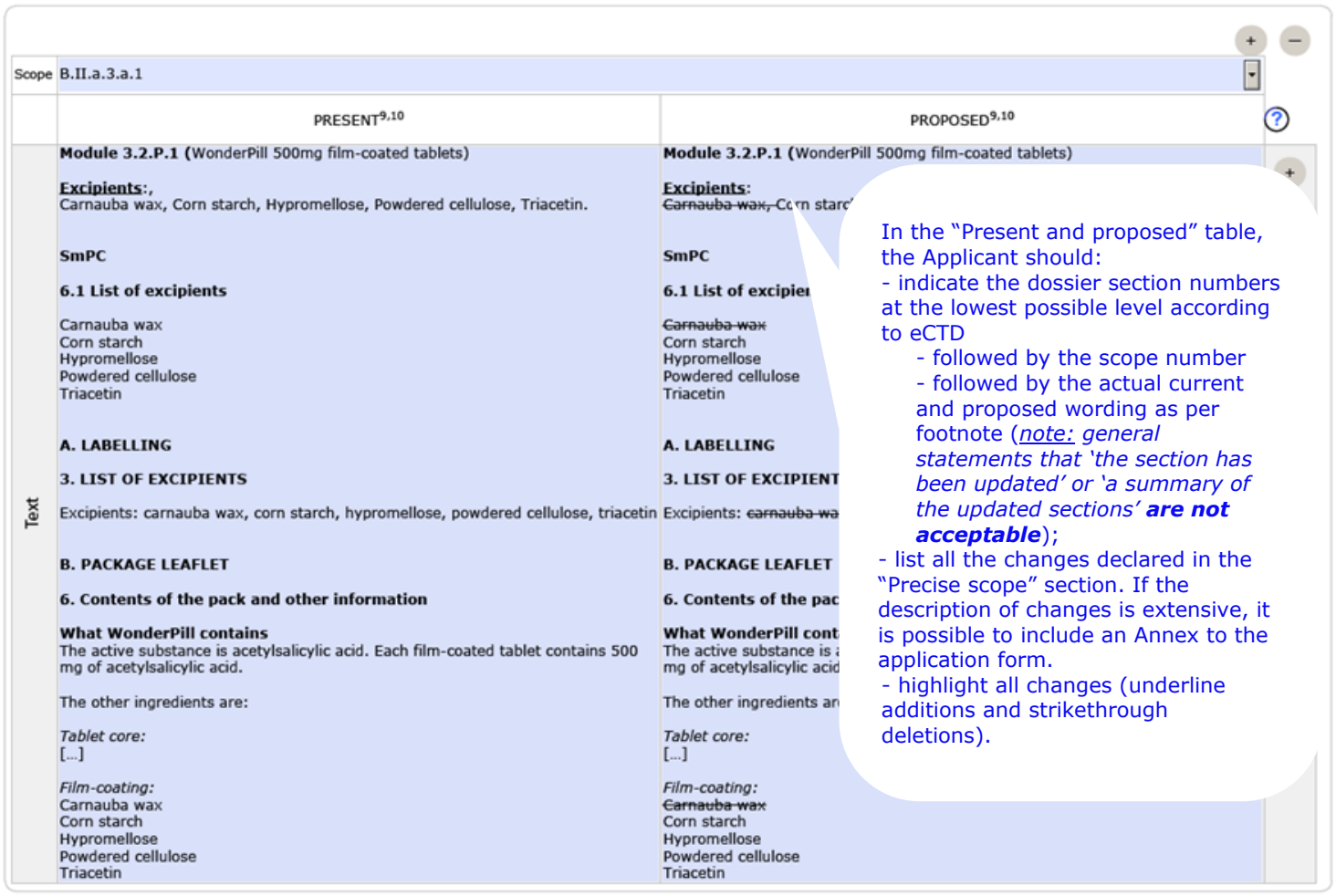
The precise scope should be clear and detailed. A 'Guidance for applicants for the preparation of the 'precise scope' section of the variation application form' has been prepared to support marketing authorisation holders in completing this section.

When there is a **grouped** procedure, the changes should be made clear in the 'Precise scope' section and should correspond to the 'Presentand proposed' table.
For Type IB grouped applications a justification for grouping should be provided.
For type IA grouped applications, there is no need to provide a justification for grouping.

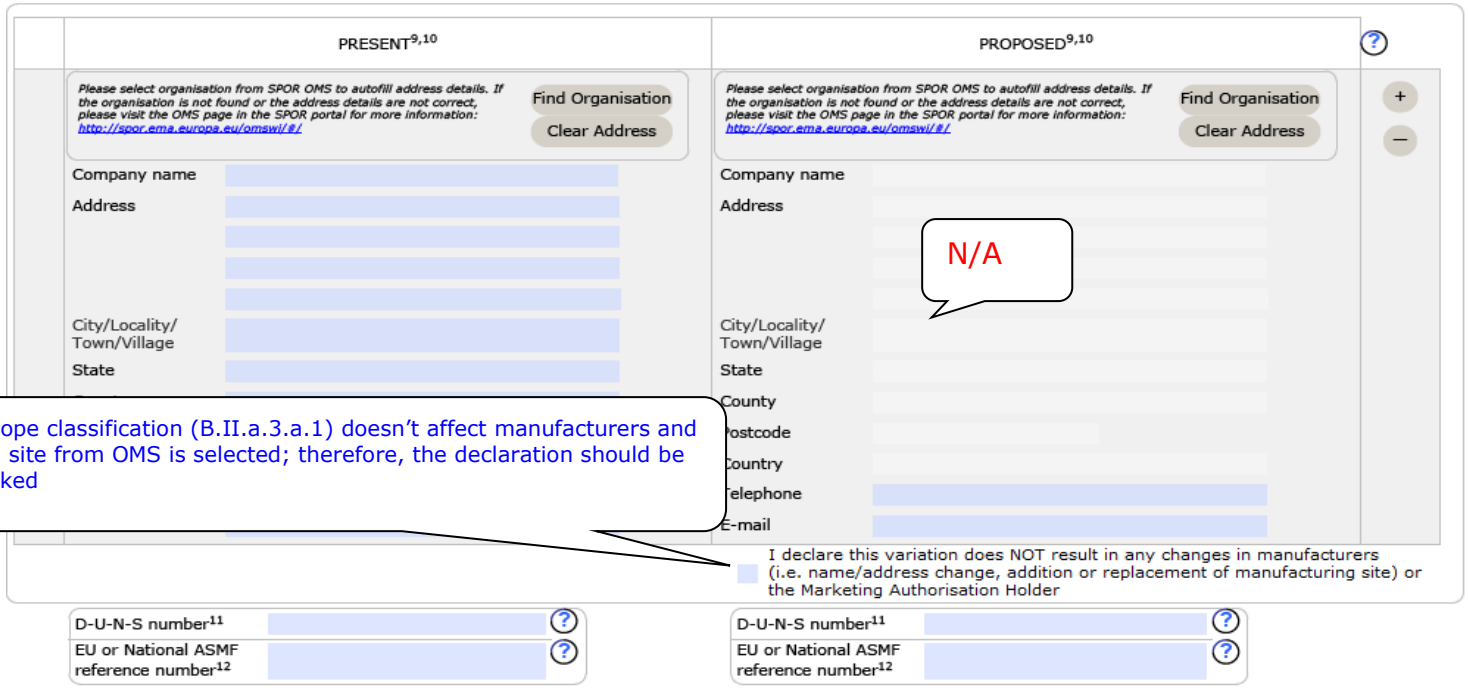
For **IG applications** (1 or >1 Type IA/IA$_{IN}$ variations affecting >1 product of the same MAH) or **WS applications** (a (group of) Type IB and/or Type II and/or Type IA/IA$_{IN}$ variations affecting >1 product of the same MAH), the same scope(s) (change(s)) must be applied to allproducts concerned by the application. The scope(s) applied for **should not** be repeated for each product as this will incur into unnecessaryfees being invoiced.

If the **product information** is updated, the sections of the SmPC should be specified along with a description of the change. In case there areadditional updates to specific languages this should also be briefly mentioned in the "Precise scope".

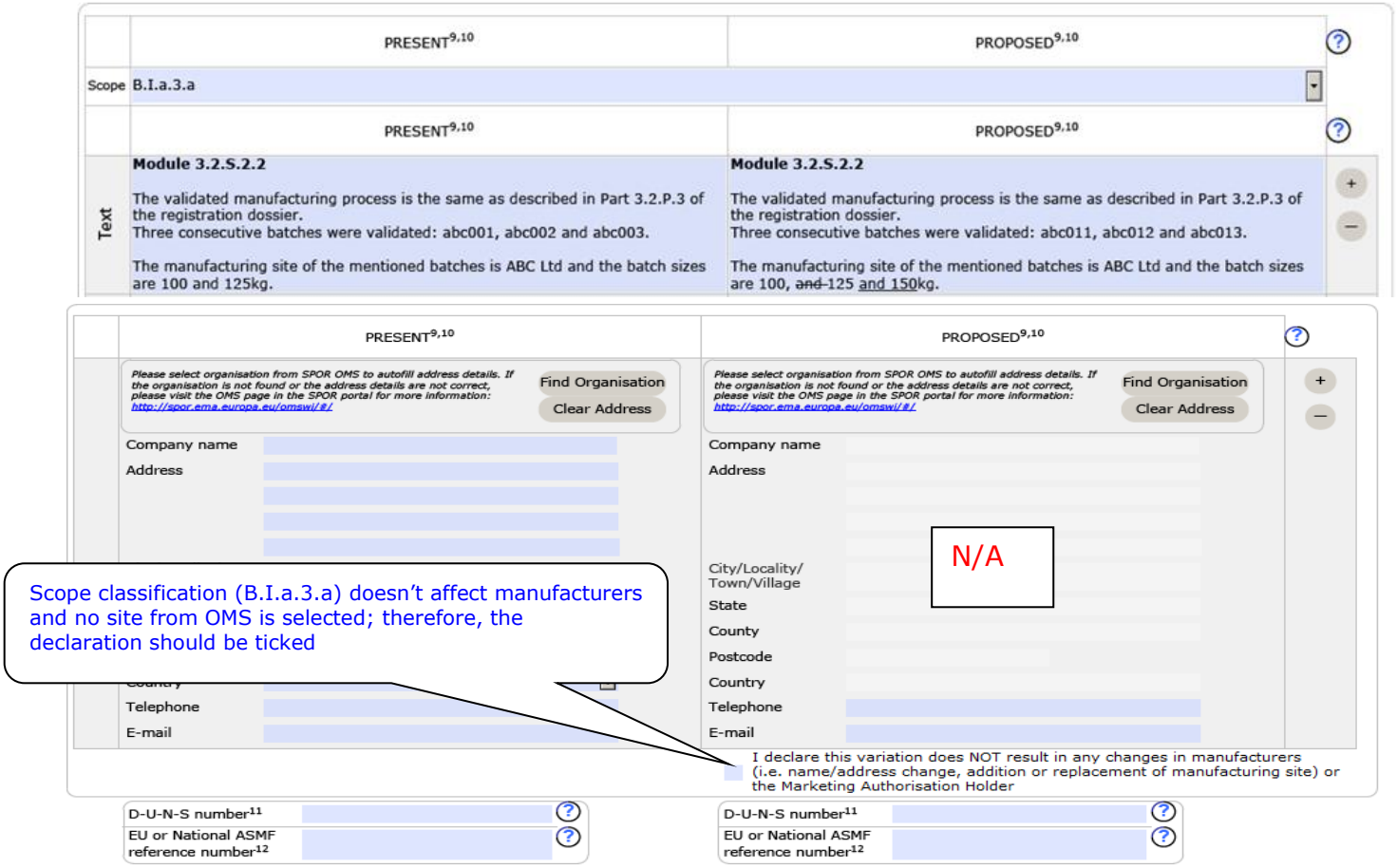
I

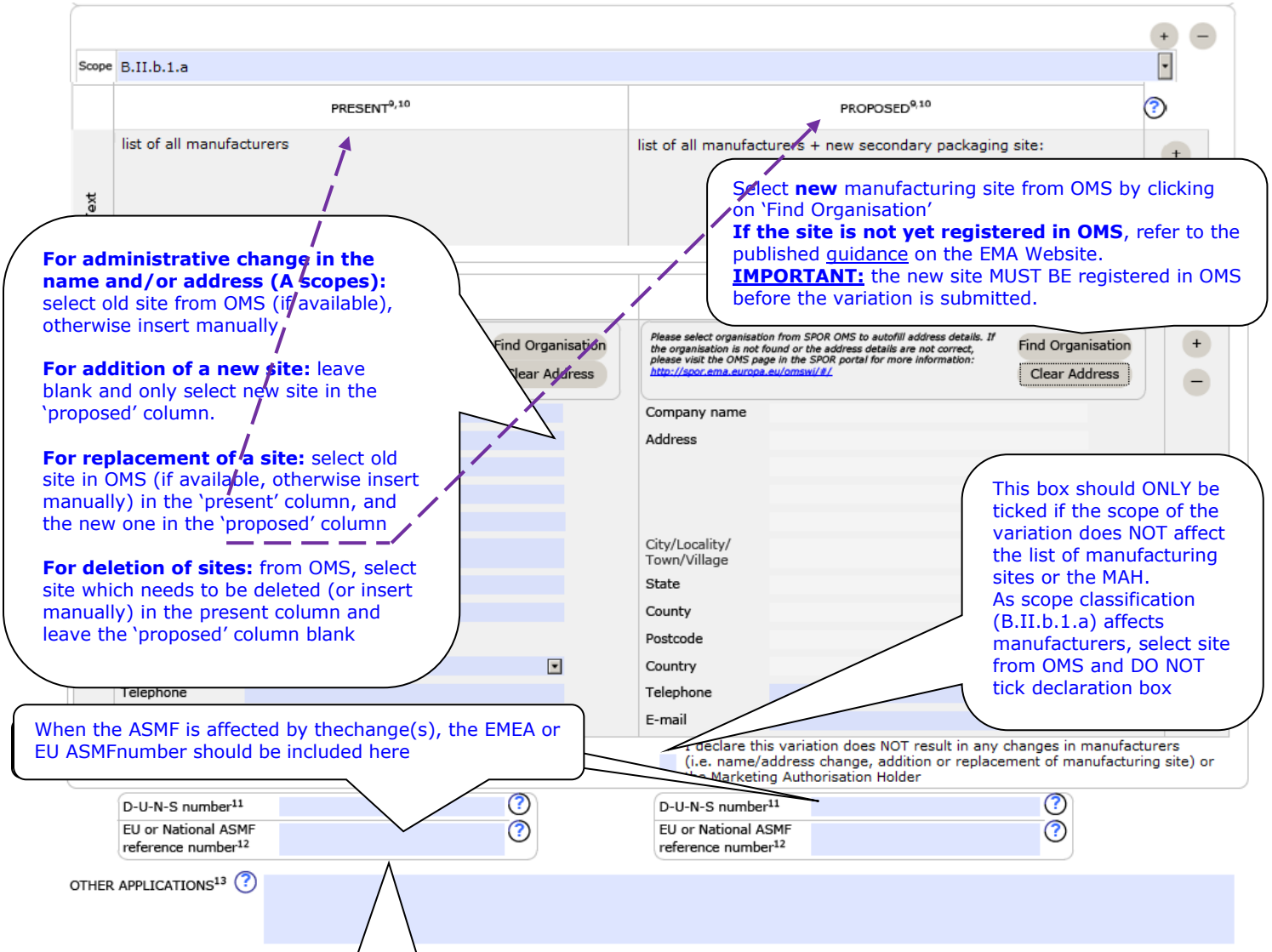


In the "Present and proposed" table, the Applicant should:
- indicate the dossier section numbers at the lowest possible level according to eCTD
  - followed by the scope number
  - followed by the actual current and proposed wording as per footnote (*note: general statements that 'the section has been updated' or 'a summary of the updated sections'* ***are not acceptable***);
- list all the changes declared in the "Precise scope" section. If the description of changes is extensive, it is possible to include an Annex to the application form.
- highlight all changes (underline additions and strikethrough deletions).



Scope classification (B.II.a.3.a.1) doesn't affect manufacturers and no site from OMS is selected; therefore, the declaration should be ticked


PRESENT9,10
PROPOSED9,10
Scope B.I.a.3.a
PRESENT9,10
PROPOSED9,10
Text
Module 3.2.S.2.2
The validated manufacturing process is the same as described in Part 3.2.P.3 of the registration dossier.
Three consecutive batches were validated: abc001, abc002 and abc003.
The manufacturing site of the mentioned batches is ABC Ltd and the batch sizes are 100 and 125kg.
Module 3.2.S.2.2
The validated manufacturing process is the same as described in Part 3.2.P.3 of the registration dossier.
Three consecutive batches were validated: abc011, abc012 and abc013.
The manufacturing site of the mentioned batches is ABC Ltd and the batch sizes are 100, and 125 and 150kg.
PRESENT9,10
PROPOSED9,10
Please select organisation from SPOR OMS to autofill address details. If the organisation is not found or the address details are not correct, please visit the OMS page in the SPOR portal for more information:
http://spor.ema.europa.eu/omswi/#/
Find Organisation
Clear Address
Company name
Address
City/Locality/ Town/Village
State
County
Postcode
Country
Telephone
E-mail
N/A
Scope classification (B.I.a.3.a) doesn't affect manufacturers and no site from OMS is selected; therefore, the declaration should be ticked
I declare this variation does NOT result in any changes in manufacturers (i.e. name/address change, addition or replacement of manufacturing site) or the Marketing Authorisation Holder
D-U-N-S number11
EU or National ASMF reference number12



For administrative change in the name and/or address (A scopes): select old site from OMS (if available), otherwise insert manually

For addition of a new site: leave blank and only select new site in the 'proposed' column.

For replacement of a site: select old site in OMS (if available, otherwise insert manually) in the 'present' column, and the new one in the 'proposed' column

For deletion of sites: from OMS, select site which needs to be deleted (or insert manually) in the present column and leave the 'proposed' column blank

Select **new** manufacturing site from OMS by clicking on 'Find Organisation'
If the site is not yet registered in OMS, refer to the published guidance on the EMA Website.
IMPORTANT: the new site MUST BE registered in OMS before the variation is submitted.

This box should ONLY be ticked if the scope of the variation does NOT affect the list of manufacturing sites or the MAH.
As scope classification (B.II.b.1.a) affects manufacturers, select site from OMS and DO NOT tick declaration box

When the ASMF is affected by thechange(s), the EMEA or EU ASMFnumber should be included here

The applicant should list here any ongoing application(s). It is of particular importance to ensure that in case the current application affects the PI, the applicant makes certain that changes from the latest approved procedure[1] or parallel procedure(s) are included in the PI submitted.

[1] Procedures **without** immediate Commission Decision (CD) are considered approved at the time of Opinion/Notification. Procedures **with** immediate CD are considered approved at the time of CD.

ANNEXED DOCUMENTS (WHERE APPROPRIATE)

The following amended product information proposals are provided in the relevant sections of the EU-CTD format or NTA volume 6B format, where applicable:

☒ Summary of product characteristics

☐ Manufacturing Authorisation Holder res ble for batch release and conditions of the Marketing Authorisation[17]

☒ Labelling

☒ Package leaflet

☐ Mock-ups[18]

☐ Specimens[18]

Product Information (PI) - related tick boxes should indicate which sections are modified by the change(s).

DECLARATION OF THE APPLICANT

I hereby submit a notification/application for the above Marketing Authorisation(s) to be varied in accordance with the proposals given above. I declare that *(Please tick appropriate declarations)*:

☒ There are no other changes than those identified in this application (except for those addressed in other variations submitted in parallel);

☒ Where applicable, all conditions as set for the variation(s) concerned are fulfilled;

☒ For type IA notifications: the required documents as specified for the changes concerned have been submitted;

☐ Where applicable, national fees have been prepaid or will be paid in accordance with national requirements;

☒ This notification/application has been submitted simultaneously in RMS and all CMSs *(for products within the Mutual Recognition Procedure and worksharing)* or both to EMA and (Co-)Rapporteur *(for products within the Centralised Procedure) or, in case of worksharing involving the EMA, to the relevant National Competent Authorities and/or RMS/ CMS (as applicable) and the EMA;*

☐ For worksharing or grouped variations affecting more than one MA: the MAs concerned belong to the same MAH.

Chang (s) will be implemented from[19]: ☐ Next production run/next printing

☐ Date

Tick boxes should be marked as applicable.

This box should always be ticked for IG and WS submissions.

This section will only appear in case Type IB or Type II applications are ticked in Section 1 of the application form as this is where the implementation date forthese procedures should be inserted.

For Type IA/IA$_{IN}$ changes, the implementation date should be included in the appropriate field in Section 3.

SIGNATURE

☐ Proof of payment (when relevant)

Copy contact person details from Section 1

Title	Mr
First name	Thomas
Surname	Eriksson
Status (Job title)	Regulatory Affairs Specialist

☐ For worksharing/grouping for more than one MA: the main signatory confirms authorisation to sign on behalf of the designated contacts as specified in section 2.4.3 in Part IA/Module 1 Application Form for each of the MAs concerned.

Date 2022-09-16

ain Signatory[20] ?

tional Signatory +

This box should always be ticked for IG and WS submissions.

If the application form is signed on behalf of the authorised contact person, an official letter of authorisation should be provided to confirm the delegation of signature.

Please ensure that the same details appear in this section and in section 1.

The following documents are to be annexed to the Application form in order to facilitate the review of the application:

Letter of Authorization or Power of Attorney, should be attached when the application form is signed on behalf of the authorised contact person;

Any other document which does not fit within the eCTD structure, but facilitates validation (e.g. justification for deleting a finished product specification parameter).

General points to consider when completing the application form:

- The **application form** should be consistent with the cover letter. Providing confusing or contradictory information can delay the procedure;
- All changes listed under the 'Precise scope' section and in the 'Present and proposed' table should be reflected under the **Types of changes** section, by their corresponding scope indent, as per Variations Guidelines;
- Please also consult the EMA/CMDh explanatory notes on Variation Application Form for further assistance.
- **Product information** - please do not submit Annex IV as part of the Product Information Annexes.

  Please ensure to include the filled and signed Checklist for Type IA and IB PI and Annex A (europa.eu) when Product Information Annexes are affected; absence of this checklist will result in validation request for supplementary information and delay in the procedure.