9 November 2018
EMA/631179/2018
Veterinary Medicines Division

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

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's published Q&As on variations, as well as with the EC 'Variations Guidelines'. This document is not exhaustive; therefore, in case certain aspects are not covered, applicants may wish to contact vet.applications@ema.europa.eu.

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Glossary

ASMF	Active substance master file
Grouping	This refers to the number of classification scopes, not the number of products.
IG variation	So-called 'internal/informal grouping' where the same (group of) type IA/IA_{IN} variation(s) to the terms of one or more MAs owned by the same MAH are notified at the same time to the same relevant authority, submitted according to Article 7.2(a) of Commission Regulation (EC) No 1234/2008.
MA	Marketing authorisation
MAH	Marketing authorisation holder
SPOR OMS	Organisation management system
WS	Worksharing procedure [a (group of) type II and/or type IB and/or type IA/IA_{IN} variations affecting more than one product of the same MAH], submitted according to Article 20.1 of Commission Regulation (EC) No 1234/2008.

Guidance on completion of application form

EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Health Systems and products

eAF Version Number: 1.23.0.0

February 2018

NOTICE TO APPLICANTS

APPLICATION FOR VARIATION TO A MARKETING AUTHORISATION

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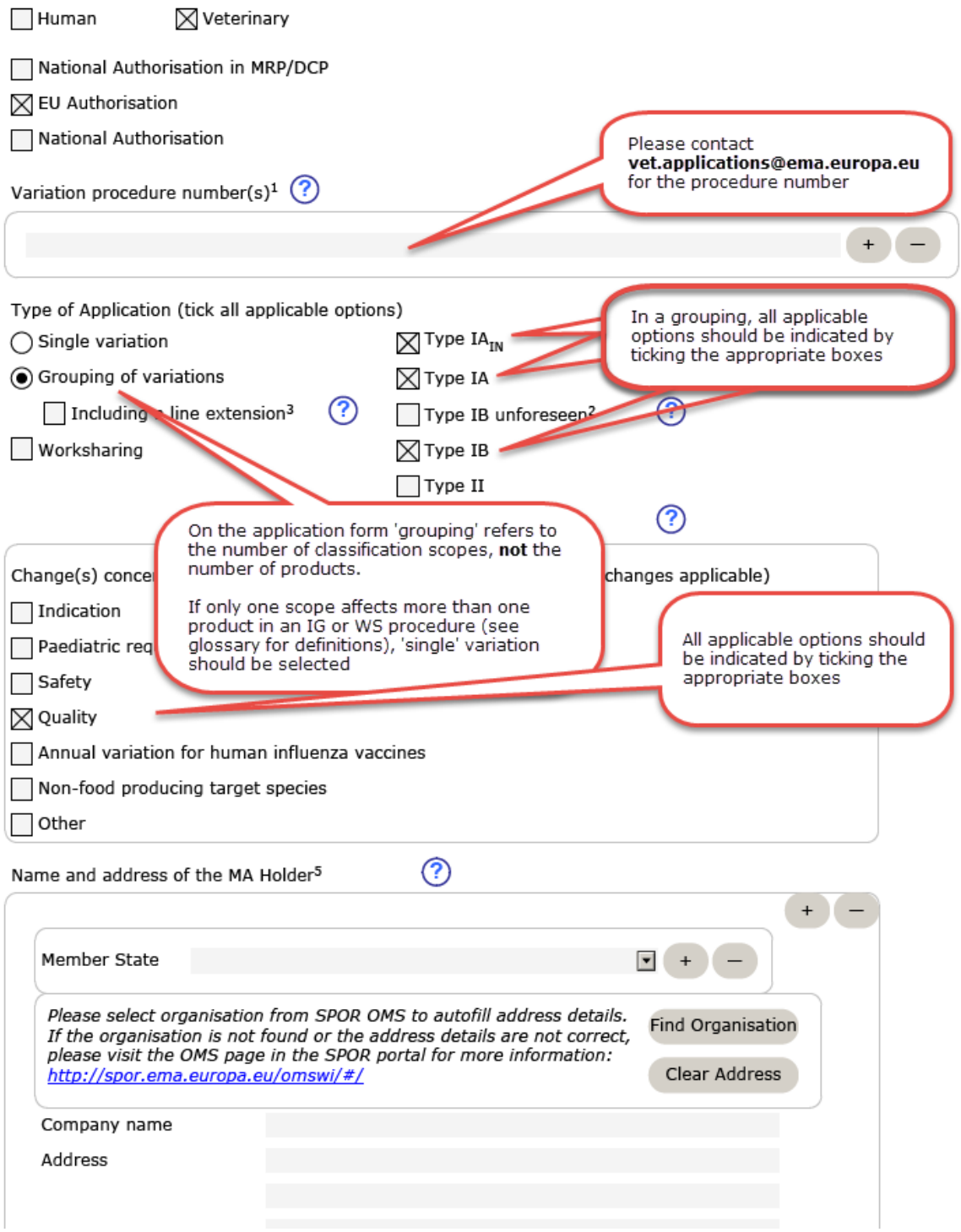
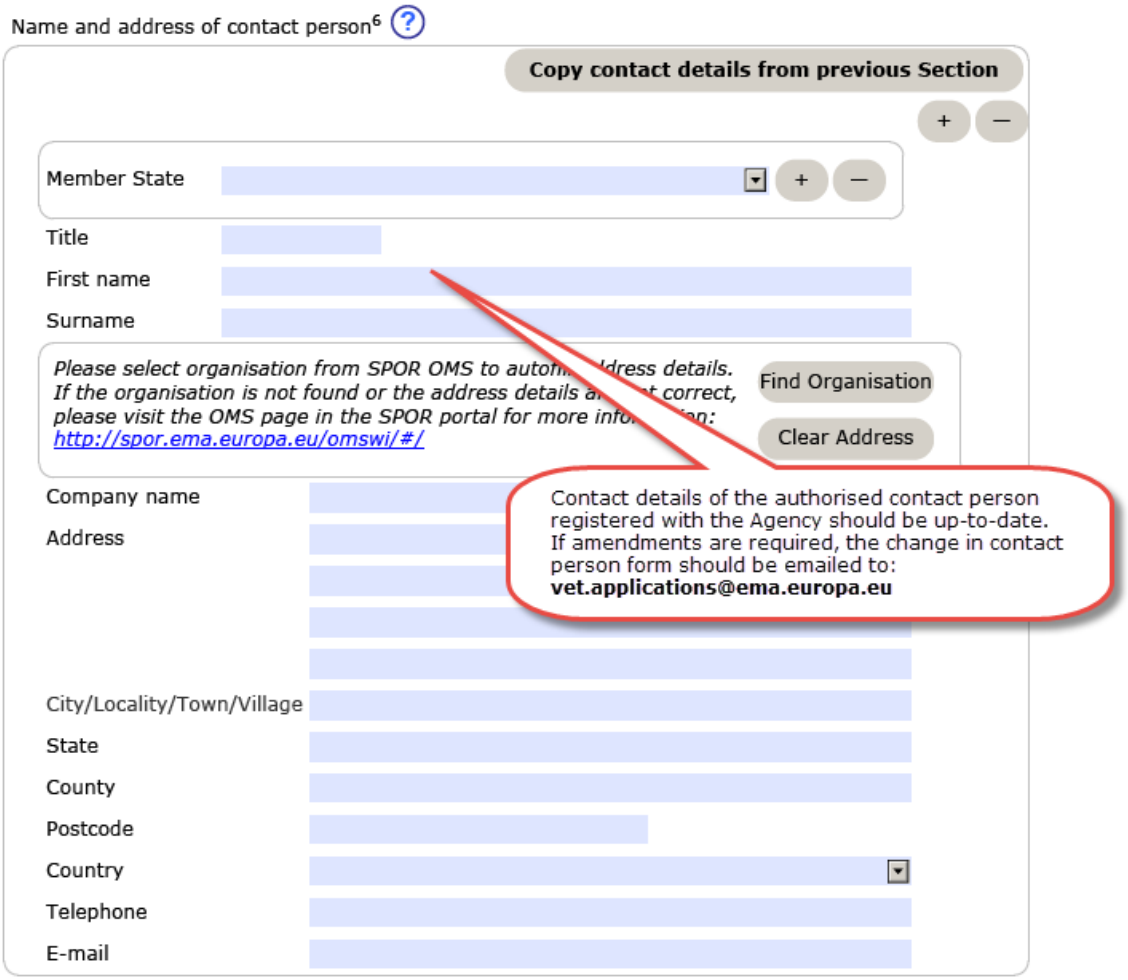
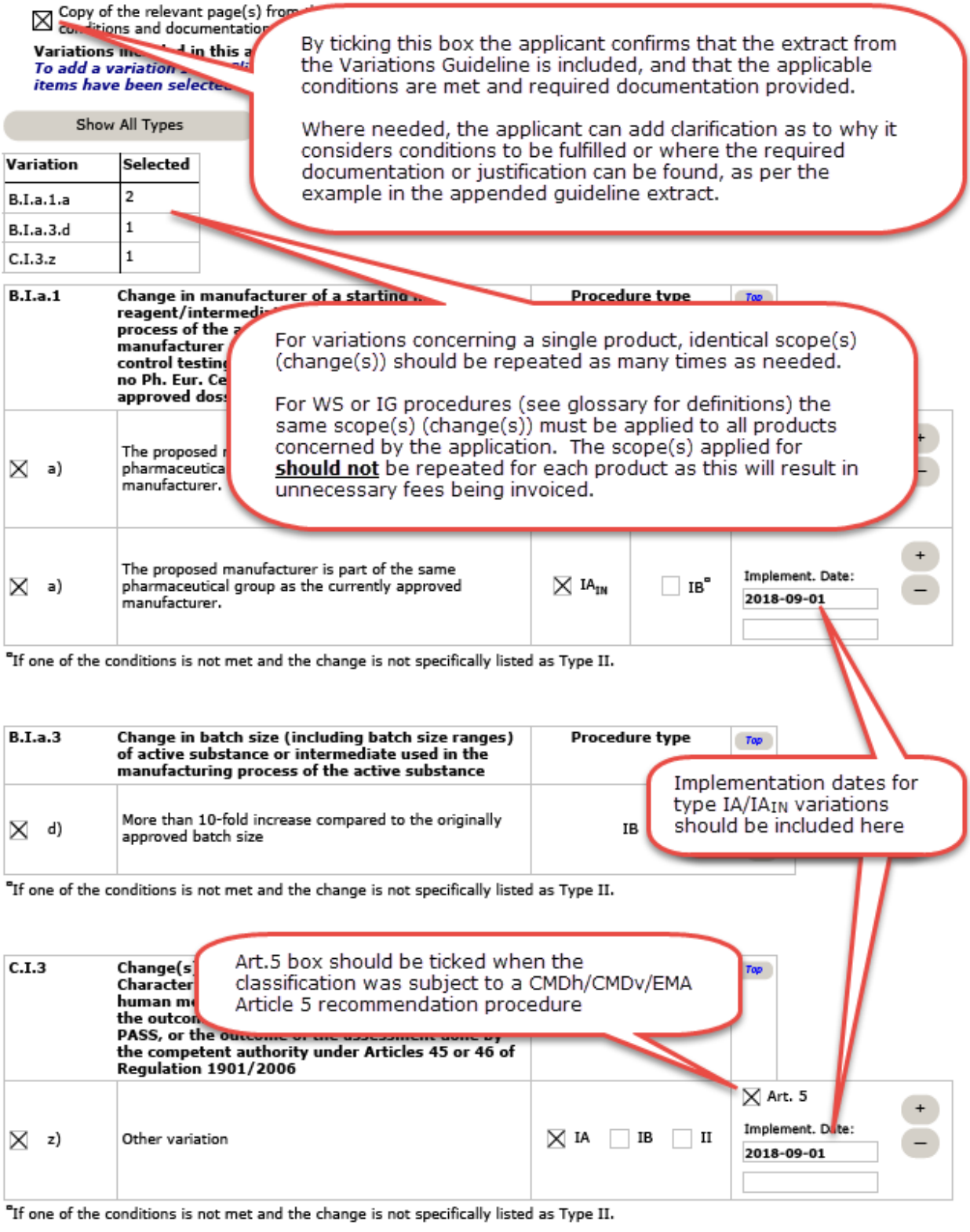
1. APPLICATION FOR VARIATION TO A MARKETING AUTHORISATION




Name and address of contact person[6]
Copy contact details from previous Section
Member State
Title
First name
Surname
Please select organisation from SPOR OMS to autom dress details.
If the organisation is not found or the address details a t correct,
please visit the OMS page in the SPOR portal for more info on:
http://spor.ema.europa.eu/omswi/#/
Find Organisation
Clear Address
Company name
Address
City/Locality/Town/Village
State
County
Postcode
Country
Telephone
E-mail
Contact details of the authorised contact person registered with the Agency should be up-to-date. If amendments are required, the change in contact person form should be emailed to:
vet.applications@ema.europa.eu

3. TYPES OF CHANGE(S)



Variation	Selected
B.I.a.1.a	2
B.I.a.3.d	1
C.I.3.z	1

B.I.a.1	Change in manufacturer of a starting ... reagent/intermedi... process of the a... manufacturer ... control testing ... no Ph. Eur. Ce... approved dos...	Procedure type	Top
☒ a)	The proposed m... pharmaceutica... manufacturer.		
☒ a)	The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer.	☒ IA_{IN}	☐ IB° Implement. Date: 2018-09-01

°If one of the conditions is not met and the change is not specifically listed as Type II.

B.I.a.3	Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance	Procedure type	Top
☒ d)	More than 10-fold increase compared to the originally approved batch size	IB	

°If one of the conditions is not met and the change is not specifically listed as Type II.

C.I.3	Change(s) ... Character... human me... the outcon... PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006		Top
☒ z)	Other variation	☒ IA ☐ IB ☐ II	☒ Art. 5 Implement. Date: 2018-09-01

°If one of the conditions is not met and the change is not specifically listed as Type II.

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

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

This is a grouped application to introduce changes the to manufacturer of the active substance, to increase the batch size of the active substance and to update the SPC following assessment of a PSUR

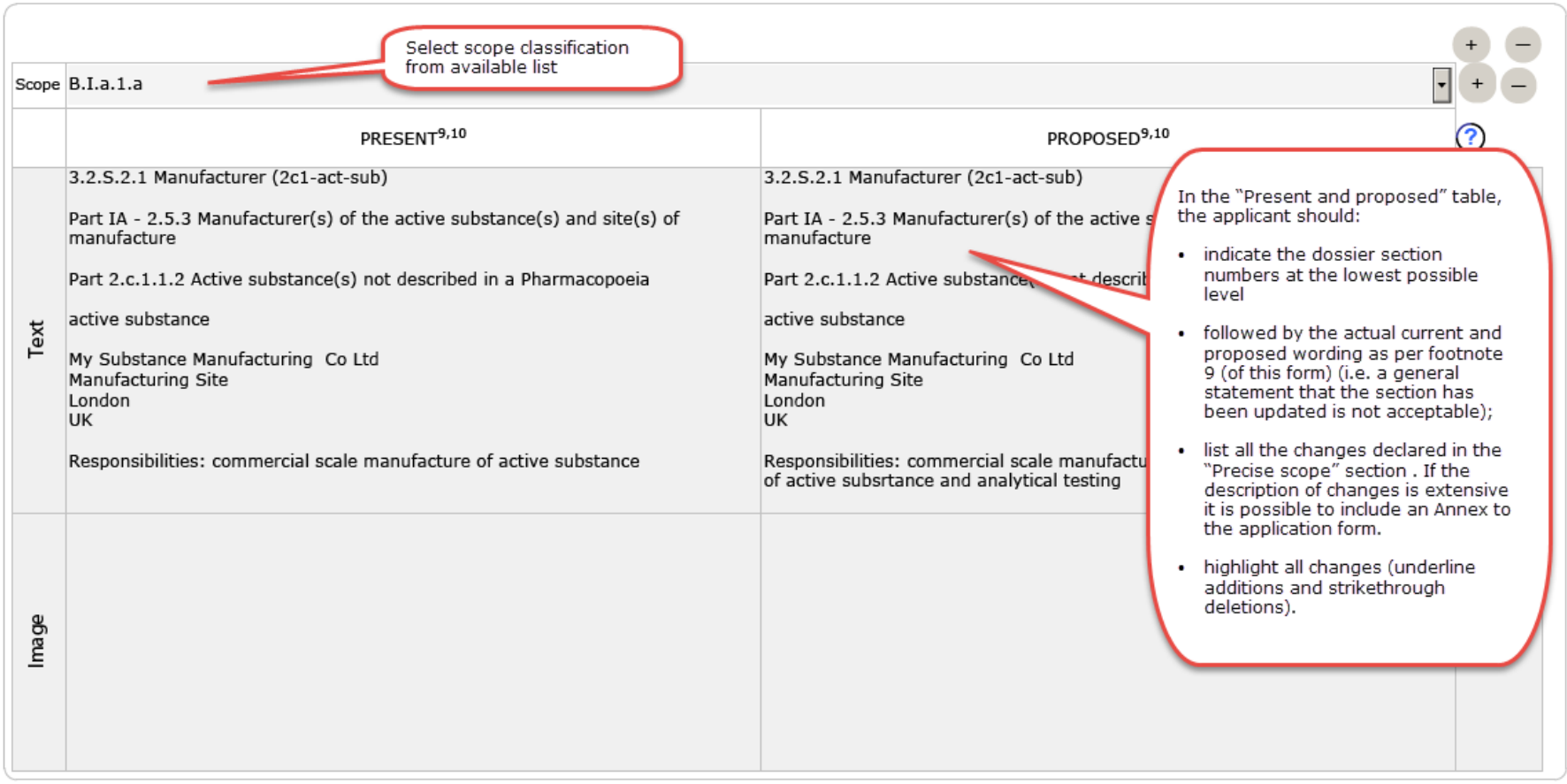
B.I.a.1.a: change in the manufacturer of the active substance (substance 1)
B.I.a.1.a: change in the manufacturer of the active substance (substance 2)
B.I.a.3.d: to increase the batch size from 50 litres to 650 litres
C.I.3.z: to implement agreed wording in the SPC following assessme... of a PSUR

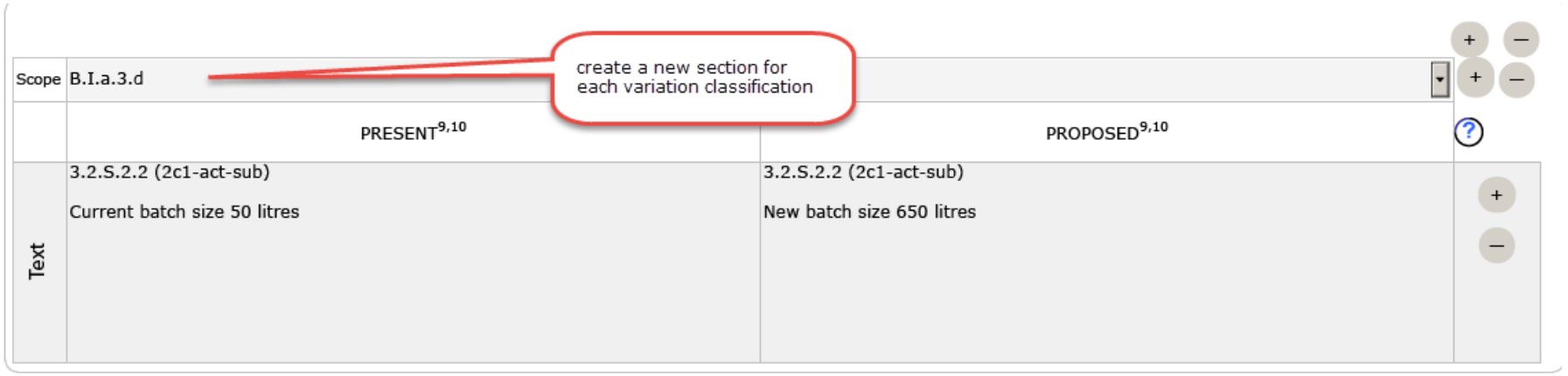
The precise scope should be clear and detailed. A 'Guidance for applicants for the preparation of the 'precise scope' section of the variation application form has been prepared to support marketing authorisation holders in completing this section for human medicinal products, which may be a useful reference

When there is a **grouped** procedure, the changes should be made clear in the 'Precise scope' section and should correspond to the 'Present and 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 or WS applications** (see glossary for definitions), the same scope(s) (change(s)) must be applied to all products concerned by the application. The scope(s) applied for **should not** be repeated for each product as this will result in unnecessary fees being invoiced.

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

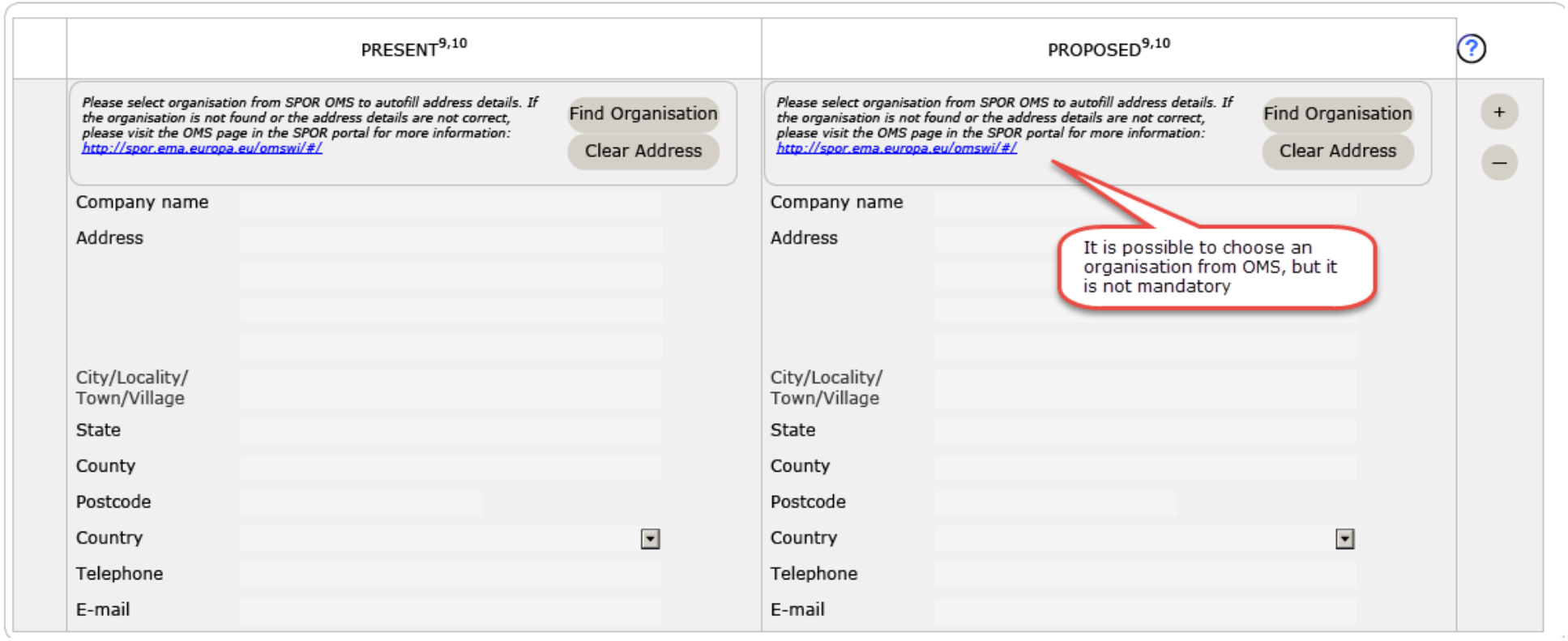

Select scope classification from available list
Scope
B.I.a.1.a
PRESENT9,10
PROPOSED9,10
Text
3.2.S.2.1 Manufacturer (2c1-act-sub)
Part IA - 2.5.3 Manufacturer(s) of the active substance(s) and site(s) of manufacture
Part 2.c.1.1.2 Active substance(s) not described in a Pharmacopoeia
active substance
My Substance Manufacturing Co Ltd
Manufacturing Site
London
UK
Responsibilities: commercial scale manufacture of active substance
3.2.S.2.1 Manufacturer (2c1-act-sub)
Part IA - 2.5.3 Manufacturer(s) of the active s
manufacture
Part 2.c.1.1.2 Active substance(
active substance
My Substance Manufacturing Co Ltd
Manufacturing Site
London
UK
Responsibilities: commercial scale manufactu
of active subsrtance and analytical testing
Image
In the "Present and proposed" table, the applicant should:
indicate the dossier section numbers at the lowest possible level
followed by the actual current and proposed wording as per footnote 9 (of this form) (i.e. a general statement that the section has been updated is 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).

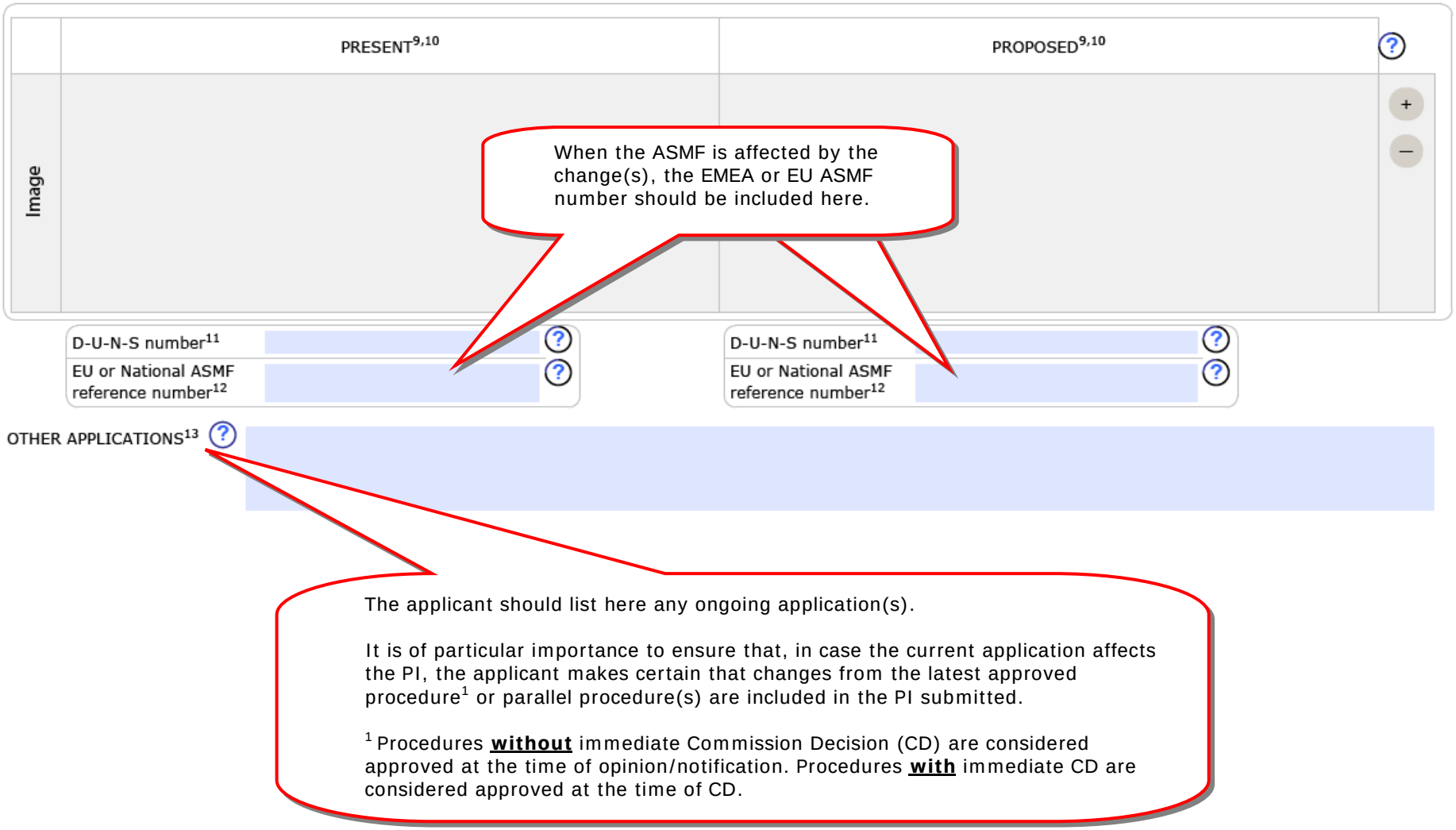


Scope	B.I.a.3.d	
	PRESENT[9,10]	PROPOSED[9,10]
Text	3.2.S.2.2 (2c1-act-sub) Current batch size 50 litres	3.2.S.2.2 (2c1-act-sub) New batch size 650 litres

Scope	C.I.3.z	
	PRESENT[9,10]	PROPOSED[9,10]

	PRESENT[9,10]	PROPOSED[9,10]
Text	SPC section 4.6 and Leaflet section 6: An average increase in body temperature varying between 0.5 and 1.0 ºC is a common reaction observed in dogs. It lasts not longer than 24 to 48 hours. Transient fever was observed in rare cases. Temporary local reactions occur in very rare cases at the injection site in the form of a normally painless nodule of 0.5 to 1 cm which disappears within 14 days, at the latest. Loss of appetite can occur in very rare cases.	SPC section 4.6 and Leaflet section 6: An average increase in body temperature varying between 0.5 and 1.0 ºC is a common reaction observed in dogs. It lasted not longer than 24 to 48 hours. Transient fever was observed in rare cases. Temporary local reactions can occur very rarely at the injection site in the form of a nodule of 0.5 to 1 cm which disappears within 14 days, at the latest and which may be painful. Loss of appetite can occur in very rare cases. Hypersensitivity reactions are very rarely observed.


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
It is possible to choose an organisation from OMS, but it is not mandatory


PRESENT[9,10]
PROPOSED[9,10]
Image
When the ASMF is affected by the change(s), the EMEA or EU ASMF number should be included here.
D-U-N-S number[11]
EU or National ASMF reference number[12]
D-U-N-S number[11]
EU or National ASMF reference number[12]
OTHER APPLICATIONS[13]
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 ible 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 for these 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)

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	2017-06-14
Main Signatory[21]	?

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 authorisation letter should be provided to confirm the delegation of signature.

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

Appendix

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

- **Variations Guidelines extract** should be attached to every submission for scopes foreseen in the guideline (e.g. for 'z' scopes there is no need to attach the guideline extract);
- **Letter of Authorisation** or **Power of Attorney** should be attached when the application form is not signed by the authorised contact person;
- Any other document which does not fit within the vNeeS structure, but facilitates validation (e.g. justification for deleting a finished product specification parameter).

General points to consider when completing the application form:

- In order to help marketing authorisation holders ensure that their type IA/IA_{IN} variation applications are complete and correct before submitting them to the Agency, it is strongly recommended to use the **pre-notification checklist for type IA/IA_{IN}** variations.
- 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/CMDv guidance** on variations.
- **Product information** - please do not submit Annex IV as part of the product information Annexes.

Classification guideline extract

	B.II.a.3 Changes in the composition (excipients) of the finished product	Cond. to be fulfilled	Docum. to be supplied	Proced. type
	a) Changes in components of the flavouring or colouring system			
√	1 Addition, deletion or replacement	1, 2, 3, 4, 5, 6, 7, 9, 11	1, 2, 4, 5, 6	IAIN
	2 Increase or reduction	1, 2, 3, 4, 11	1, 2, 4	IA
	b) Other excipients			
	1. Any minor adjustment of the quantitative composition of the finished product with respect to excipients	1, 2, 4, 8, 9, 10	1, 2, 7	IA
	2. Qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the medicinal product			II
	3. Change that relates to a biological/immunological product			II
	4. Any new excipient that includes the use of materials of human or animal origin for which assessment is required of viral safety data or TSE risk			II
	5. Change that is supported by a bioequivalence study			II
	6. Replacement of a single excipient with a comparable excipient with the same functional characteristics and at a similar level		1, 3, 4, 5, 6, 7, 8, 9, 10	IB
	Conditions			
√	1. No change in functional characteristics of the pharmaceutical form e.g. disintegration time, dissolution profile.			
√	2. Any minor adjustment to the formulation to maintain the total weight should be made by an excipient which currently makes up a major part of the finished product formulation.			
√	3. The finished product specification has only been updated in respect of appearance/odour/taste and if relevant, deletion of an identification test.			
√	4. Stability studies have been started under ICH/VICH conditions (with indication of batch numbers) and relevant stability parameters have been assessed in at least two pilot scale* or industrial scale batches and at least three months satisfactory stability data are at the disposal of the applicant (at time of implementation for Type IAs and at time of notification for Type IBs) and that the stability profile is similar to the currently registered situation. Assurance is given that these studies will be finalised and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action). In addition, where relevant, photo-stability testing should be performed.			
√	5. Any new proposed components must comply with the relevant Directives (e.g. Directive 94/36/EC and 2008/128/EC for colours for use in foodstuffs and Directive 88/388/EEC for flavours).			
√	6. Any new component does not include the use of materials of human or animal origin for which assessment is required of viral safety data or compliance with the current Note For Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.			
√	7. Where applicable, the change does not affect the differentiation between strengths and does not have a negative impact on taste acceptability for paediatric formulations.			

	8.	The dissolution profile of the new product determined on a minimum of two pilot scale* batches is comparable to the old one (no significant differences regarding comparability, see the relevant (Human or Veterinary) guidance on Bioavailability). For herbal medicinal products where dissolution testing may not be feasible, the disintegration time of the new product is comparable to the old one.
√	9.	The change is not the result of stability issues and/or should not result in potential safety concerns i.e. differentiation between strengths.
	10.	The product concerned is not a biological/immunological medicinal product.
	Documentation	
√	1.	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 ide any new colorant, where relevant, and including revised product informa **2c1-act-sub (or module 3.2.S.1)**
√	2.	A declaration that the required stability studies have been started under I indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
	3.	The results of stability studies that have been carried out under ICH/VICH conditions, on the relevant stability parameters, on at least two pilot* or industrial scale batches, covering a minimum period of 3 months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
X	4.	Sample of the new product, where applicable (see Notice to Applicants Requirements for samples in the Member States).- N/A
√	5.	Either a Ph. Eur. Certificate of Suitability for any new component of animal susceptible to TSE risk or where applicable, documentary evidence that the specific source of the TSE risk material has been previously assessed by the competent authority and shown to comply with the scope of the current Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathies via Human and Veterinary Medicinal Products. The following information should be included for each such material: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use. For the Centralised Procedure, this information should be included in an updated TSE table A (and B, if relevant).
√	6.	Data to demonstrate that the new excipient does not interfere with the finished product specification test methods, if appropriate. **2e1-fin-prod-spec (or module 3.2.P.5.3)**
	7	Justification for the change/choice of excipients etc. must be given by appropriate development pharmaceutics (including stability aspects and antimicrobial preservation where appropriate).
	8.	For solid dosage forms, comparative dissolution profiledata[16] of at least two pilot scale* batches of the finished product in the new and old composition. For herbal medicinal products, comparative disintegration data may be acceptable.

The applicant is advised to add clarifications as these can speed up the validation of the procedure.

	B.I.a.3 Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance	Cond. to be fulfilled	Docum. to be supplied	Proced. type
√ a)	Up to 10-fold increase compared to the originally approved batch size	1, 2, 3, 4, 6, 7, 8	1, 2, 5	IA
b)	Downscaling down to 10-fold	1, 2, 3, 4, 5	1, 2, 5	IA
c)	The change requires assessment of the comparability of a biological/immunological active substance			II
d)	More than 10-fold increase compared to the originally approved batch size		1, 2, 3, 4	IB
e)	The scale for a biological/immunological active substance is increased / decreased without process change (e.g. duplication of line)		1, 2, 3, 4	IB
	Conditions			
√ 1.	Any changes to the manufacturing methods are only those necessitated by scale-up or downscaling, e.g. use of different-sized equipment.			
√ 2.	Test results of at least two batches according to the specifications should be available for the proposed batch size.			
√ 3.	The product concerned is not a biological/immunological medicinal product.			
√ 4.	The change does not adversely affect the reproducibility of the process.			
5.	The change should not be the result of unexpected events arising during manufacture or because of stability concerns.			
√ 6.	The specifications of the active substance/intermediates remain the same.			
√ 7.	The active substance is not sterile.			
√ 8.	The batch size is within the 10-fold range of the batch size foreseen when the marketing authorisation was granted or following a subsequent change not agreed as a Type IA variation.			
	Documentation			
√ 1.	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). **2b-manuf-batch-formula (or module 3.2.S.4.4)**			
√ 2.	The batch numbers of the tested batches having the proposed batch size. **2b-manuf-batch-formula (or module 3.2.S.4.4)**			
3.	Batch analysis data (in a comparative tabulated format) on a minimum of one production batch of the active substance or intermediate as appropriate, manufactured to both the currently approved and the proposed sizes. Batch data on the next two full production batches should be made available upon request and reported by the marketing authorisation holder if outside specification (with proposed action).			
4.	Copy of approved specifications of the active substance (and of the intermediate, if applicable).			
√ 5	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. **Justification attached to the Application form**			

In the “Present and proposed” table, the applicant should:

- indicate the dossier section numbers at the lowest possible level;
- followed by the actual current and proposed wording as per footnote 9 (of this form) (i.e. a general statement that the section has been updated is 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).

List of references

EC Variations Guidelines

EMA guidance on type IA variations

EMA guidance on type IB variations

CMDv guidance on variations

Guidance for applicants for the preparation of the precise scope section of the variation application form (written for human medicines, but a useful reference for veterinary medicines as same principles apply)

Pre-notification checklist for type IA/IA_{IN} variations