EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 June 2017
EMA/220707/2017
Procedure Management and Committees Support Division

Guidance for applicants for the preparation of the ‘precise scope’ section of the variation application form

Introduction

This guidance aims at supporting marketing authorisation holders (MAHs) in completing the 'Precise scope and Background for a change, and Justification for grouping, worksharing and classification for unforeseen changes (if applicable)' (hereinafter called the 'Precise scope') section of the Application Form for Type I and Type II variations.

It provides guidance on the information to be included in this section and some examples of changes applied for each of the scopes listed in the 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 (hereinafter called 'the Variations Guidelines').

It also aims at improving the description clarity of the exact change(s) applied for and, ultimately, to facilitate the EMA validation and review process of the applications.

This guidance is not mandatory, it is rather meant as support for the preparation of applications for variations in addition to the EMA/CMDh explanatory notes on variation application form, the CMDh Q/A-List for the submission of variations according to Commission Regulation (EC) 1234/2008, the EMA guidance on application form for centralised Type IA and Type IB variations and the published checklists for Type IAs, Type IBs and Type II variations.

Content of the section

As detailed in EudraLex Volume 2B - Presentation and content of the dossier, the ‘Application for Variation to a Marketing Authorisation’ Form includes a free text section to detail the ‘Precise Scope’.

This section should include a brief explanation of the change(s) applied for. When the change(s) is/are submitted as a consequence of a previous regulatory procedure (e.g. recommendation), a reference should be provided. The precise scope aims at providing a complete and concise description of the change(s) applied for. Some examples of wordings that could be used are detailed in the Annex of this guidance.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

For grouped applications (more than one scope), MAHs are encouraged to add the classification indents from the Variations Guidelines to the description of each change applied for, e.g.:

B.II.b.3.z - {description of the change}
B.II.b.3.b - {description of the change}
B.II.b.5.z - {description of the change}

When additional changes not requiring a variation (i.e. editorial changes) are proposed within a variation, these should also be reflected in the precise scope. The following wording may be used:

'In addition, the applicant has taken the opportunity to <update> <amend> <Sections of the CTD module(s)>'.

For variations affecting the Annexes, if the MAH takes the opportunity to bring them in line with the latest QRD template and/or to make updates to list of local representatives and/or implement minor editorial changes in the PI, this should be reflected in the precise scope. The following wording may be used:

'In addition, the applicant took the opportunity to <update the list of local representatives in the PL> <and> <implement minor editorial changes in <section<s> X, X and X of the SmPC> <Annex II> <Labelling> <and> <PL>.'

'Furthermore, the PI is being brought in line with the latest QRD template (version xx).'

For acceptability of editorial changes within a variation application for centrally approved products please refer to the EMA Post-Authorisation guidance on Classification of changes: Q&A.

- For groupings of variations, a justification for its acceptability should be provided including, as appropriate, e.g. either the relevant reference in Annex III of the Commission Regulation (EC) No 1234/2008, reference to examples published by CMD or the Agency, or to the pre-submission agreement with the Agency on the proposed grouping.
- For worksharing procedures, the justification should refer to the pre-submission contacts with the Agency.
- For default Type IB variations i.e. 'z'- category (except Type IB variations classified as 'z'- category following a CMDh Art.5 recommendation), a justification for the proposed classification has to be given.

ANNEX

EXAMPLES OF 'PRECISE SCOPE' SECTION WORDINGS FOR EACH CATEGORY OF THE VARIATION CLASSIFICATION GUIDELINE

EXAMPLES OF 'PRECISE SCOPE' SECTION WORDING FOR EACH CATEGORY OF THE VARATION CLASSIFICATION GUIDELINE

The list below provides some examples of wordings and details that may be considered by MAHs for each of the categories of the variation classification guideline.

ADMINISTRATIVE CHANGES

A.1

To change the <name> <and> <address> of the marketing authorisation holder from {current name and/or address} to {new name and/or address}. <The address remains unchanged.> It is hereby confirmed that the legal entity remains unchanged.

A.2.a

To change the (invented) name of the medicinal product from {old name} to {new name}.

A.3

To change the name of the <active substance><excipient> from {old name} to {new name}.

A.4

To change the name of the <site responsible for <<{activity/ies} of> <supplying> the active substance {active substance}>> <supplying the <starting material> <reagent> <intermediate> {substance}> <manufacturing the novel excipient {excipient}> <ASMF Holder> from {current name} {(address)} to {new name}. The address remains unchanged.

To update the address of the site responsible for <<{activity/ies} of> <supplying> the active substance {active substance}>> <supplying the <starting material> <reagent> <intermediate> {substance}> <manufacturing the novel excipient {excipient}> <ASMF Holder>, {name of site}, from {current address} to {new address}. There is no change in the location of the site.

A.5

To change the name of the <site responsible for {activity/ies}> <importer> of the finished product from {current name} {(address)} to {new name}. The address remains unchanged.

To update the address of the <site responsible for {activity/ies}> <importer> of the finished product, {name of site}, from {current address} to {new address}. There is no change in the location of the site.

A.6

To include the ATC Code {(code)} in Section 5.1 of the Summary of Product Characteristics (SmPC).

To change the ATC Code of {active substance} from {current ATC Code} to {new ATC Code}.

A.7

To delete the ASMF Holder {name and address}.

To delete {name and address} as a site responsible for <{activity/ies} of the <active substance {active substance}> <finished product> <intermediate {intermediate}>> <supplying the <active substance {active substance}> <starting material> <reagent> <intermediate> {substance}>> <manufacturing the novel excipient {excipient}>.

To delete the following manufacturing sites:

- {name and address} as a site responsible for <{activity/ies} of the <active substance {active substance}> <finished product> <intermediate {intermediate}>> <supplying the <active substance {active substance}> <starting material> <reagent> <intermediate> {substance}>> <manufacturing the novel excipient {excipient}>;

- {name and address} as a site responsible for <{activity/ies} of the <active substance {active substance}> <finished product> <intermediate {intermediate}>> <supplying the <active substance {active substance}> <starting material> <reagent> <intermediate> {substance}>> <manufacturing the novel excipient {excipient}>.

A.8

To provide an updated QP declaration to reflect the change in the date(s) of the audit(s) to verify GMP compliance of the manufacturer(s) of the active substance {active substance(s)}, {name of site(s)}.

A.z (CMDh Art. 5 Recommendation)

To change the nomenclature of the container material for immediate packaging of the finished product.

ACTIVE SUBSTANCE

B.I.a.1.a

To add {name and address} as an alternative site responsible for {activity/ties} of the <active substance {active substance}> <<intermediate> <starting material> <reagent> {substance} used in the manufacturing process of the active substance {active substance}>.

To replace {name and address} with {name and address} as a site responsible for {activity/ties} of the <active substance {active substance}> <<intermediate> <starting material> <reagent> {substance} used in the manufacturing process of the active substance {active substance}>.

B.I.a.1.b

To add {name and address} as a site responsible for {activity/ties} of the active substance {active substance} supported by an ASMF (<EU/ASMF/ {#}> <EMEA/ASMF/ {#}>).

To replace {name and address} with {name and address} as a site responsible for {activity/ties} of the active substance {active substance} supported by an ASMF (<EU/ASMF/ {#}> <EMEA/ASMF/ {#}>).

B.I.a.1.c

To add {name and address} as an alternative site responsible for {activity/ties} of the <active substance {active substance}> <<intermediate> <starting material> <reagent> {substance}> using a substantially different route of synthesis.

To replace {name and address} with {name and address} as a site responsible for {activity/ties} of the <active substance {active substance}> <<intermediate> <starting material> <reagent> {substance}> using a substantially different route of synthesis.

B.I.a.1.d

To add {name and address} as an alternative site responsible for {activity/ties} of the starting material {substance} used in the manufacturing process of the active substance {active substance} for which an assessment of viral safety and/or TSE risk is required.

To replace {name and address} with {name and address} as a site responsible for {activity/ties} of the starting material {substance} used in the manufacturing process of the active substance {active substance} for which an assessment of viral safety and/or TSE risk is required.

B.I.a.1.e

To add {name and address} as an alternative site responsible for {activity/ties} of the <active substance {active substance}> <<intermediate> <starting material> <reagent> {substance} used in the manufacturing process of the active substance {active substance}>.

To replace {name and address} with {name and address} as a site responsible for {activity/ties} of the <active substance {active substance}> <<intermediate> <starting material> <reagent> {substance} used in the manufacturing process of the active substance {active substance}>.

B.I.a.1.f

To add {name and address} as an alternative site responsible for quality control of the active substance {active substance}.

To replace {name and address} with {name and address} as a site responsible for quality control of the active substance {active substance}.

B.I.a.1.g

To add {name and address} as an alternative site responsible for {activity/ties} of the active substance {active substance}.

To replace {name and address} with {name and address} as a site responsible for {activity/ties} of the active substance {active substance}.

B.I.a.1.h

To add {name and address} as an alternative site responsible for sterilisation (using a Ph.Eur. method) of the active substance {active substance}.

To replace {name and address} with {name and address} as a site responsible for sterilisation (using a Ph.Eur. method) of the active substance {active substance}.

B.I.a.1.i

To add {name and address} as an alternative site responsible for micronisation of the active substance {active substance}.

To replace {name and address} with {name and address} as a site responsible for micronisation of the active substance {active substance}.

B.I.a.1.k

To add {name and address} as an alternative site responsible for storage of the <Master Cell Bank> <and> <Working Cell Banks>.

To replace {name and address} with {name and address} as a site responsible for storage of the <Master Cell Bank> <and> <Working Cell Banks>.

To add {name and address} as an alternative <site responsible for storage of the active substance {active substance}> <manufacturer of the <starting material> <intermediate> {substance} used in the manufacturing process of the active substance {active substance}>.

B.I.a.2.a

Minor changes in the manufacturing process of the active substance {active substance} to {brief description of the change}.

B.I.a.2.b

Substantial changes to the manufacturing process of the active substance {active substance} to {brief description of the change}.

B.I.a.2.c

Changes to the manufacturing process of the biological/immunological active substance {active substance} to {brief description of the change}.

B.I.a.2.d

Changes to the manufacturing process of a herbal medicinal product to {brief description of the change}. There is no change to the geographical source, manufacturing route or production.

B.I.a.2.e

Minor changes to the restricted part of the {name of holder} ASMF (<EU/ASMF/{#}> <EMEA/ASMF/{#}>) to {brief description of the change}.

B.I.a.2.z (CMDh Art. 5 Recommendation)

To delete one of the approved manufacturing processes of the active substance. The deletion is not due to critical deficiencies concerning manufacturing.

B.I.a.3.a, B.I.a.3.d

To increase the batch size <range> of the <active substance {active substance}> <intermediate {intermediate} used in the manufacturing process of the active substance> <manufactured at {name of site, if the change is site-specific}> from {approved batch size} to {proposed batch size}.

To include an alternative batch size of {proposed batch size} for the <active substance {active substance}> <intermediate {intermediate} used in the manufacturing process of the active substance {active substance}> <manufactured at {name of site, if the change is site-specific}> in addition to the currently approved batch size(s) of {currently approved size(s)}.

B.I.a.3.b

To decrease the batch size <range> of the <active substance {active substance}> <intermediate {intermediate} used in the manufacturing process of the active substance {active substance}> <manufactured at {name of site, if the change is site-specific}> from {approved batch size} to {proposed batch size}.

B.I.a.3.c

To <increase> <decrease> the batch size <range> of the <biological> <immunological> active substance {active substance} <manufactured at {name of site, if the change is site-specific}> from {approved batch size} to {proposed batch size}.

B.I.a.3.e

To <increase> <decrease> the scale of the <biological> <immunological> active substance {active substance} <manufactured at {name of site, if the change is site-specific}> from {approved batch size} to {proposed batch size}.

B.I.a.4.a

To tighten the {test} in-process limits, applied during the manufacture of the active substance {active substance}, from {current value} to {proposed value}.

B.I.a.4.b

To add {test} as <a new> <an alternative> in-process test applied during the manufacture of the active substance {active substance}. <The limit is set to {limit}.>

B.I.a.4.c

To delete the non-significant in-process test {test} applied during the manufacture of the active substance {active substance}.

B.I.a.4.d

To widen the {test} in-process limits, applied during the manufacture of the active substance {active substance}, from {current value} to {proposed value}.

B.I.a.4.e

To delete the {test} in-process test, applied during the manufacture of the active substance {active substance}.

B.I.a.4.f

To add the {test} in-process test, applied during the manufacture of the active substance {active substance}, as a results of a <safety> <quality> issue.

To replace the {test} in-process test, applied during the manufacture of the active substance {active substance}, with {alternative test} as a result of a <safety> <quality> issue.

B.I.a.4.z (CMDh Art. 5 Recommendation)

Minor change to the {procedure} analytical procedure for the {test} in-process test to {brief description of the change}.

B.I.a.5.a

Seasonal update of the composition of the vaccine strains officially recommended by WHO and CHMP for the season {proposed season}, which are the following: {proposed strains}.

B.I.a.z (CMDh Art. 5 Recommendation)

To re-arrange and amend equipment in the plasma pooling line of the active substance {active substance} with no changes in the manufacturing process, manufacturing site or construction of the new equipment.

B.I.b.1.a

To tighten the <active substance {active substance}> <<starting material> <intermediate> <reagent> {substance} used in the manufacturing process of the active substance {active substance}> specification limits for {test} from {current value} to {proposed value}.

B.I.b.1.b

To tighten the <active substance {active substance}> <<starting material> <intermediate> <reagent> {substance} used in the manufacturing process of the active substance {active substance}> specification limits for {test} from {current value} to {proposed value}.

B.I.b.1.c

To add {parameter} to the specifications of the <active substance {active substance}> <<starting material> <intermediate> <reagent> {substance} used in the manufacturing process of the active substance {active substance}>. <The limit is set to {value}.>

B.I.b.1.d

To delete the non-significant parameter {parameter} from the specifications of the <active substance {active substance}> <<starting material> <intermediate> <reagent> {substance} used in the manufacturing process of the active substance {active substance}>.

B.I.b.1.e

To delete the significant parameter {parameter} from the specifications of the <active substance {active substance}> <starting material> <intermediate> <reagent> {substance} used in the manufacturing process of the active substance {active substance}> <which has a significant effect on the overall quality of the <active substance> < finished product>.

B.I.b.1.f

To change the {test} specification limits from {current value} to {proposed value} in the specifications of the active substance {active substance}>.

B.I.b.1.g

To widen the {test} specification limits for the <starting material> <intermediate> {substance} used in the manufacturing process of the active substance {active substance}> from {current value} to {proposed value}.

B.I.b.1.h

To add {parameter} to the specifications of the <active substance {active substance}> <<starting material> <intermediate> <reagent> {substance} used in the manufacturing process of the active substance {active substance}> as a result of a <safety> <quality> issue.

To replace {parameter} with {alternative parameter} in the specifications of the <active substance {active substance}> <<starting material> <intermediate> <reagent> {substance} used in the manufacturing process of the active substance {active substance}> as a result of a <safety> <quality> issue.

B.I.b.1.i

Change in the specifications for the active substance {active substance} from in-house to a <non-official Pharmacopoeia> <Pharmacopoeia of a third country> where there is no <monograph in the European Pharmacopoeia> <national pharmacopoeia of a Member State>.

B.I.b.2.a

Minor changes to the {test} test procedure for the <active substance {active substance}> <<starting material> <intermediate> <reagent> {substance} used in the manufacturing process of the active substance {active substance}> to {brief description of the change}.

B.I.b.2.b

To delete the {test} test procedure for the <active substance {active substance}> <<starting material> <intermediate> <reagent> {substance} used in the manufacturing process of the active substance {active substance}>.

B.I.b.2.c

To add the {test} test procedure for the reagent {reagent} used in {clarify use of reagent}.

To replace the {test} test procedure with {alternative test} for the reagent {reagent} used in {clarify use of reagent}.

B.I.b.2.d

To introduce substantial changes to the <biological> <immunological> <immunochemical> {test} test procedure for the biological active substance {active substance} to {brief description of the change}.

To replace the <biological> <immunological> <immunochemical> {test} test procedure with {alternative test} for the biological active substance {active substance}.

B.I.b.2.e

To add the {test} test procedure for the <active substance {active substance}> <<starting material> <intermediate> {substance} used in the manufacturing process of the active substance {active substance}>.

To replace the {test} test procedure with {alternative test} for the <active substance {active substance}> <<starting material> <intermediate> {substance} used in the manufacturing process of the active substance {active substance}>.

B.I.b.z (CMDh Art. 5 Recommendation)

To remove from section(s) {section(s)} of the dossier information on the level of testing performed by the finished product manufacturer on receipt of the active substance batches, as already present in the approved registration dossier. The active substance specifications applied by the finished product manufacturer continue to be stated in the dossier.

B.I.c.1 (CMDh Art. 5 Recommendation)

To remove one of the authorised <bulk> <final container>.

B.I.c.1.a

Change in the <qualitative> <and> <quantitative> composition of the immediate packaging of the active substance {active substance} from {currently approved packaging} to {proposed packaging}.

B.I.c.1.b

Change in the <qualitative> <and> <quantitative> composition of the immediate <container closure system>/ <packaging> of the sterile and non-frozen <biological> <immunological> active substance {active substance}.

e {proposed packaging} for a sterile and non-frozen <biological> <immunological> active substance {active substance}.

B.I.c.1.c

Change in the <qualitative> <and> <quantitative> composition of the immediate packaging of the active substance {active substance}.

B.I.c.2.a

To tighten the {parameter} specification limits for the immediate packaging of the active substance {active substance} from {current value} to {proposed value}.

B.I.c.2.b

To add {parameter} to the immediate packaging specifications of the active substance {active substance}. <The limit is set to {value}.>

B.I.c.2.c

To delete the non-significant parameter {parameter} from the immediate packaging specifications of the active substance {active substance}.

B.I.c.2.d

To add {parameter} to the immediate packaging specifications of the active substance {active substance} as a result of a <safety> <quality> issue.

To replace {parameter} with {alternative parameter} in the immediate packaging specifications of the active substance {active substance} as a result of a <safety> <quality> issue.

B.I.c.3.a

Minor changes to the {test} test procedure for the immediate packaging of the active substance {active substance} to {brief description of the change}.

B.I.c.3.b

To add the {test} test procedure to the immediate packaging specifications of the active substance {active substance}.

To replace the {test} test procedure with {alternative test} in the immediate packaging specifications of the active substance {active substance}.

B.I.c.3.c

To delete the {test} test procedure from the immediate packaging specifications of the active substance {active substance}.

B.I.d.1.a.1

To reduce the <re-test> <storage> period of the active substance {active substance} from {current re-test/storage period} to {proposed re-test/storage period} <when stored at {define storage conditions}>.

B.I.d.1.a.2

To extend the <re-test> <storage> period of the active substance {active substance} from {current re-test/storage period} to {proposed re-test/storage period} <when stored at {define storage conditions}> based on the extrapolation of stability data not in accordance with ICH guidelines.

B.I.d.1.a.3

To extend the <storage> period of the <biological> <immunological> active substance {active substance} from {current storage period} to {proposed storage period} <when stored at {define storage conditions}> not in accordance with an approved stability protocol.

B.I.d.1.a.4

To extend the <re-test> <storage> period of the active substance {active substance} from {current re-test/storage period} to {proposed re-test/storage period} <when stored at {define storage conditions}>.

To introduce the <re-test> <storage> period of the active substance {active substance} of {proposed re-test/storage period} <when stored at {define storage conditions}>.

B.I.d.1.b (CMDh Art.5 Recommendation)

Change in storage conditions of the reference standard from {current storage conditions} to {proposed storage conditions}.

B.I.d.1.b.1

To introduce more restrictive storage conditions of the active substance {active substance} from {current conditions} to {proposed conditions}.

B.I.d.1.b.2

Change in the storage conditions of the <biological> <immunological> active substance {active substance} from {current conditions} to {proposed conditions}, when stability studies have not been performed in accordance with a currently approved stability protocol.

B.I.d.1.b.3

Change in the storage conditions of the active substance {active substance} from {current conditions} to {proposed conditions}.

B.I.d.1.c

Changes to the approved stability protocol of the active substance {active substance} to {brief description of the change}.

B.I.e.1.a

To introduce a new design space during {affected stage X / unit operation X} of the manufacturing process of the active substance {active substance}.

To extend an approved design space during {affected stage X / unit operation X} of the manufacturing process of the active substance {active substance}.

B.I.e.1.b

To introduce a new design space concerning the {proposed test procedures} test procedures of the manufacturing process of the active substance {active substance}.

To extend an approved design space concerning the {proposed test procedures} test procedures of the manufacturing process of the active substance {active substance}.

B.I.e.2

To introduce a post-approval change management protocol intended to {intended change in the manufacturing process / intended manufacturing site} related to the manufacturing of the active substance {active substance}.

B.I.e.3

To delete the approved change management protocol intended to {intended change in the manufacturing process / intended manufacturing site} related to the manufacturing of the active substance {active substance}.

B.I.e.4.a

To introduce major changes to the approved management protocol intended to {intended change in the manufacturing process / intended manufacturing site} including {proposed changes} related to the manufacturing of the active substance {active substance}.

B.I.e.4.b

To introduce minor changes to the approved management protocol intended to {intended change in the manufacturing process / intended manufacturing site} including {proposed changes} related to the manufacturing of the active substance {active substance}.

B.I.e.5.a

To implement changes foreseen in the approved management protocol of the active substance {active substance} to {brief description of the change }.

B.I.e.5.b

To implement changes foreseen in the approved management protocol of the active substance {active substance} to {brief description of the change }.

B.I.e.5.c

To implement changes foreseen in the approved management protocol of the <biological> <immunological> active substance {active substance} to {brief description of the change }.

B.I.z (as per Q3.4 of the CMDh Q&A on submission of variations)

Substantial updates to <Mod. 3.2.S> <the ASMF>.

FINISHED PRODUCT

B.II.a.1.a

To <add> <remove> <the imprints> <the debossing> used for marking the {specify pharmaceutical form, strength and EU#s, if needed}.

To change the composition of the ink used for marking the {specify pharmaceutical form, strength and EU#s, if needed }.

To replace the ink used for marking the {specify pharmaceutical form, strength and EU#s, if needed } with {new ink}.

B.II.a.1.b

To change the <scoring> <break line> of the {specify pharmaceutical form, strength and EU#s, if needed} to divide the tablet into equal doses.

To introduce a <scoring> <break line> in the {specify pharmaceutical form, strength and EU#s, if needed} to divide the tablet into equal doses.

B.II.a.2.a-b

Change in the <shape> <dimension> <thickness> of the {specify pharmaceutical form, strength and EU#(s), if needed} from {current shape/dimension/thickness} to {proposed shape/dimension/thickness}.

B.II.a.2.c

To add a new kit for the radiopharmaceutical preparation {specify radiopharmaceutical} with the fill volume of {specify vial capacity volume and solution volume in the container}. The strength remains unchanged.

B.II.a.3.a.1

Change in the composition of the <flavouring> <colouring> of the finished product {specify pharmaceutical form, strength and EU#(s), if needed} to <add> <remove> <replace> the {flavouring or colouring substance} <with {new flavouring or colouring substance}>.

Change in the composition of the {excipient} used in the manufacture of the finished product to {brief description of the change}.

B.II.a.3.a.2

Change in the composition of the <flavouring> <colouring> of the finished product {specify pharmaceutical form, strength and EU#(s), if needed} to <increase> <reduce> the amount of {flavouring or colouring substance} from {current value} to {proposed value}.

B.II.a.3.b.1

Minor change in the quantitative composition of the finished product {specify pharmaceutical form, strength and EU#(s), if needed} to <increase> <reduce> the amount of {excipient} from {current value} to {proposed value}.

B.II.a.3.b.2

Change in the <qualitative> <quantitative> composition of the finished product {specify pharmaceutical form, strength and EU#(s), if needed} to {describe in one sentence the changes in the composition; e.g. introduction/ replacement individual excipients, major readjustment of the quantities of excipients}.

B.II.a.3.b.3

Changes in the composition of the <biological> <immunological> finished product {specify pharmaceutical form, strength and EU#(s), if needed} to {describe in one sentence the changes in the composition; e.g. introduction/ replacement individual excipients, major readjustment of the quantities of excipients}.

B.II.a.3.b.4

Changes in the composition <of the finished product {specify pharmaceutical form, strength and EU#(s), if needed} to {describe in one sentence the changes in the composition; e.g. introduction/ replacement individual excipients, major readjustment of the quantities of excipients}> including {new substance from animal origin}, which requires an assessment of <viral safety data> <TSE risk>.

B.II.a.3.b.5

Changes in the composition of the finished product {specify pharmaceutical form, strength and EU#(s), if needed} to {describe in one sentence the changes in the composition; e.g. introduction/ replacement individual excipients, major readjustment of the quantities of excipients}, which is supported by the bioequivalence study {introduce study reference number and title}.

B.II.a.3.b.6

Change in the composition of the finished product {specify pharmaceutical form, strength and EU#(s), if needed}> to replace {excipient} with the comparable excipient {new excipient}.

B.II.a.4.a, B.II.a.4.b

Change in the <coating weight> <weight of the capsule shell> of the finished product {specify pharmaceutical form, strength and EU#(s), if needed} from {current weight} to {proposed weight}.

B.II.a.5

Change in concentration of the finished product from {current} to {proposed}. The strength is unchanged.

B.II.a.6

To remove the <solvent> <diluent container> from the pack.

B.II.b.1.a

To add {name and address} as an alternative site responsible for secondary packaging of the finished product {specify pharmaceutical form, strength and EU#(s), if needed}.

To replace {name and address} with {name and address} as a site responsible for secondary packaging of the finished product {specify pharmaceutical form, strength and EU#(s), if needed}.

To change the address of the site responsible for secondary packaging of the finished product {specify pharmaceutical form, strength and EU#(s), if needed}, {name}, from {current address} to {new address}.

B.II.b.1.b

To add {name and address} as an alternative site responsible for primary packaging of the finished product {specify pharmaceutical form, strength and EU#(s), if needed}.

To replace {name and address} with {name and address} as a site responsible for primary packaging of the finished product {specify pharmaceutical form, strength and EU#(s), if needed}.

To change the address of the site responsible for primary packaging of the finished product {specify pharmaceutical form, strength and EU#(s), if needed}, {name}, from {current address} to {new address}.

B.II.b.1.c

To add {name and address} as an alternative site responsible for {activity/ties} of the finished product {specify pharmaceutical form, strength and EU#(s), if needed}.

To replace {name and address} with {name and address} as a site responsible for {activity/ties} of the finished product {specify pharmaceutical form, strength and EU#(s), if needed}.

To change the address of the site responsible for {activity/ties} of the finished product {specify pharmaceutical form, strength and EU#(s), if needed}, {name}, from {current address} to {new address}.

B.II.b.1.d

To add {name and address} as an alternative site responsible for {activity/ties} of the finished product {specify pharmaceutical form, strength and EU#(s), if needed}, which requires <an initial> <a product specific> inspection.

To replace {name and address} with {name and address} as a site responsible for {activity/ties} of the finished product {specify pharmaceutical form, strength and EU#(s), if needed}, which requires <an initial> <a product specific> inspection.

To change the address of the site responsible for {activity/ties} of the finished product {specify pharmaceutical form, strength and EU#(s), if needed}, {name}, from {current address} to {new address} which requires <an initial> <a product specific> inspection.

B.II.b.1.e

To add {name and address} as an alternative site responsible for {activity/ties} of the finished product {specify pharmaceutical form, strength and EU#(s), if needed}.

To replace {name and address} with {name and address} as a site responsible for {activity/ties} of the finished product {specify pharmaceutical form, strength and EU#(s), if needed}.

To change the address of the site responsible for {activity/ties} of the finished product, {name}, from {current address} to {new address}.

B.II.b.1.f

To add {name and address} as an alternative site responsible for {activity/ties} of the finished product {specify pharmaceutical form, strength and EU#(s), if needed}.

To replace {name and address} with {name and address} as a site responsible for {activity/ties} of the finished product {specify pharmaceutical form, strength and EU#(s), if needed}.

To change the address of the site responsible for {activity/ties} of the finished product {specify pharmaceutical form, strength and EU#(s), if needed}, {name}, from {current address} to {new address}.

B.II.b.1.z (as per Q3.26 of the CMDh Q&A on submission of variations)

Change in the supplier of the sterilized primary container components, used in the aseptic manufacture of the medicinal product, from {name} to {name}.

B.II.b.2.a

To add {name and address} as an alternative site responsible for batch control/testing of the finished product {specify pharmaceutical form, strength and EU#(s), if needed}.

To replace {name and address} with {name and address} as a site responsible for batch control/testing of the finished product {specify pharmaceutical form, strength and EU#(s), if needed}.

To change the address of the site responsible for batch control/testing of the finished product {specify pharmaceutical form, strength and EU#(s), if needed}, {name}, from {current address} to {new address}.

B.II.b.2.b

To add {name and address} as an alternative site responsible for batch control/testing of the <biological> <immunological> finished product {specify pharmaceutical form, strength and EU#(s), if needed}.

To replace {name and address} with {name and address} as a site responsible for batch control/testing of the <biological> <immunological> finished product {specify pharmaceutical form, strength and EU#(s), if needed}.

To change the address of the site responsible for batch control/testing of the <biological> <immunological> finished product {specify pharmaceutical form, strength and EU#(s), if needed}, {name}, from {current address} to {new address}.

B.II.b.2.c.1

To add {name and address} as an alternative site responsible for <importation> <and> <batch release (not including batch control/testing)> of the finished product {specify pharmaceutical form, strength and EU#(s), if needed}.

To replace {name and address} with {name and address} as a site responsible for <importation> <and> <batch release (not including batch control/testing)> of the finished product {specify pharmaceutical form, strength and EU#(s), if needed}.

To change the address of the site responsible for <importation> <and> <batch release (not including batch control/testing)> of the finished product {specify pharmaceutical form, strength and EU#(s), if needed}, {name}, from {current address} to {new address}.

B.II.b.2.c.2

To add {name and address} as an alternative site responsible for <importation> <and> <batch release (including batch control/testing)> of the finished product {specify pharmaceutical form, strength and EU#(s), if needed}.

To replace {name and address} with {name and address} as a site responsible for <importation> <and> <batch release (including batch control/testing)> of the finished product {specify pharmaceutical form, strength and EU#(s), if needed}.

To change the address of the site responsible for <importation> <and> <batch release (including batch control/testing)> of the finished product {specify pharmaceutical form, strength and EU#(s), if needed}, {name}, from {current address} to {new address}.

B.II.b.2.c.3

To add {name and address} as an alternative site responsible for <importation> <and> <batch release (including batch control/testing)> of the <biological> <immunological> finished product {specify pharmaceutical form, strength and EU#(s), if needed}.

To replace {name and address} with {name and address} as a site responsible for <importation> <and> <batch release (including batch control/testing)> of the <biological> <immunological> finished product {specify pharmaceutical form, strength and EU#(s), if needed}.

To change the address of the site responsible for <importation> <and> <batch release (including batch control/testing)> of the <biological> <immunological> finished product {specify pharmaceutical form, strength and EU#(s), if needed}, {name}, from {current address} to {new address}.

B.II.b.3.a, B.II.b.3.f

Minor changes in the manufacturing process of the finished product to {brief description of the change}.

B.II.b.3.b

Substantial changes to the manufacturing process of the finished product to {brief description of the change}.

B.II.b.3.b (CMDh Art.5 Recommendation)

Change in the manufacturing process of the finished product to move the sterilizing filtration from {current location} to {new location}.

B.II.b.3.c

Changes to the manufacturing process of the <biological> <immunological> finished product to {brief description of the change}.

B.II.b.3.d

Change in the manufacturing process of the finished product to introduce the non-standard terminal sterilisation method {method}.

B.II.b.3.e

To introduce an overage of {% of overage} of the active substance {active substance} used in the manufacture of the finished product.

To increase the overage of {% of overage} of the active substance {active substance} used in the manufacture of the finished product.

B.II.b.3.z (CMDh Art.5 Recommendation)

Change in the holding time of the intermediate {intermediate} from {current holding time} to {proposed holding time}.

<Change in> <To include> <To replace> the packaging material of the bulk product not in contact with the bulk product formulation.

Minor change in the manufacturing process of the sterile finished product after the primary packaging step to {brief description of the change}.

To delete one of the approved manufacturing processes of the finished product. The deletion is not due to critical deficiencies concerning manufacturing.

B.II.b.4.a, B.II.b.4.e

To increase the batch size <range> of the finished product {specify pharmaceutical form, strength and EU#(s), if needed} <manufactured at {name of site, if the change is site-specific}> from {approved batch size} to {proposed batch size}.

To include an alternative batch size of {proposed batch size} for the finished product {specify pharmaceutical form, strength and EU#(s), if needed} <manufactured at {name of site, if the change is site-specific}> in addition to the currently approved batch size(s) of {currently approved batch size(s)}.

B.II.b.4.a, B.II.b.4.b (CMDh Art. 5 Recommendation)

To increase the batch size of the medicinal gas {name} {specify strength and EU#(s), if needed} <manufactured at {name of site if the change is site-specific}> from {approved batch size} to {proposed batch size}

To decrease the batch size of the medicinal gas {name} {specify strength and EU#(s), if needed} <manufactured at {name of site if the change is site-specific}> from {approved batch size} to {proposed batch size}

B.II.b.4.b

To decrease the batch size <range> of the finished product {specify pharmaceutical form, strength and EU#(s), if needed} <manufactured at {name of site if the change is site-specific}> from {approved batch size} to {proposed batch size}

B.II.b.4.c

To <increase> <decrease> the scale of the <biological> <immunological> finished product {specify pharmaceutical form, strength and EU#(s), if needed} <manufactured at {name of site, if the change is site-specific}> from {approved batch size} to {proposed batch size}..

B.II.b.4.d

To <increase> <decrease> the batch size <range> of the finished product {specify pharmaceutical form, strength and EU#(s), if needed} <manufactured at {name of site, if the change is site-specific}> from {approved batch size} to {proposed batch size}.

To include an alternative batch size of {proposed batch size} for the finished product {specify pharmaceutical form, strength and EU#(s), if needed} <manufactured at {name of site, if the change is site-specific}> in addition to the currently approved batch size(s) of {currently approved batch size(s)}.

B.II.b.4.f

To <increase> <decrease> the scale of the <biological> <immunological> finished product {specify pharmaceutical form, strength and EU#(s), if needed} <manufactured at {name of site, if the change is site-specific}> from {approved batch size} to {proposed batch size}. There is no change in the manufacturing process.

B.II.b.5.a

To tighten the {test} in-process limits, applied during the manufacture of the finished product, from {current value} to {proposed value}.

B.II.b.5.b

To add {test} as <a new> <an alternative> in-process test applied during the manufacture of the finished product. <The limit is set to {limit}.>

B.II.b.5.c

To delete the non-significant in-process test {test} applied during the manufacture of the finished product.

B.II.b.5.d

To delete the {test} in-process test, applied during the manufacture of the finished product.

B.II.b.5.e

To widen the {test} in-process limits, applied during the manufacture of the finished product, from {current value} to {proposed value}.

B.II.b.5.f

To add the {test} in-process test, applied during the manufacture of the finished product, as a result of a <safety> <quality> issue.

To replace the {test} in-process test, applied during the manufacture of the finished product, with {alternative test}> as a result of a <safety> <quality> issue.

B.II.b.5.z (CMDh Art. 5 Recommendation)

Minor change to the {procedure} analytical procedure for the {test} in-process test to {brief description of the change}.

B.II.c.1.a

To tighten the excipient {excipient} specification limits for {test} from {current value} to {proposed value}.

B.II.c.1.b

To add {parameter} to the specifications of the excipient {excipient}. <The limit is set to {value}.>

B.II.c.1.c

To delete the non-significant parameter {parameter} from the specifications of the excipient {excipient}.

B.II.c.1.d

To change the {test} specification limits from {current value} to {proposed value} in the specifications of the excipient {excipient}.

B.II.c.1.e

To delete the significant parameter {parameter} from the specifications of the excipient {excipient}, <which has a significant effect on the overall quality of the finished product>.

B.II.c.1.f

To add {parameter} to the specifications of the excipient {excipient} as a result of a <safety> <quality> issue.

To replace {parameter} with {alternative parameter} in the specifications of the excipient {excipient} as a result of a <safety> <quality> issue.

B.II.c.1.g

Change in the specifications for the excipient {excipient} from in-house to a <non-official Pharmacopoeia> <Pharmacopoeia of a third country>.

B.II.c.1.z (CMDh Art. 5 Recommendation)

To add the alternative supplier of the excipient Norflurane/HFA with consequential differences in the specification <parameters> <and> <limits> of an excipient between the approved supplier and the new one due to the use of different test methods.

B.II.c.2.a

Minor changes to the {test} test procedure for the excipient {excipient} to {brief description of the change}.

B.II.c.2.b

To delete the {test} test procedure for the excipient {excipient}.

B.II.c.2.c

To introduce substantial changes to the <biological> <immunological> <immunochemical> {test} test procedure for the <excipient {excipient}> to {brief description of the change}.

To replace the <biological> <immunological> <immunochemical> {test} test procedure with {alternative test} for the <excipient {excipient}>.

B.II.c.2.d

To add the {test} test procedure for the excipient {excipient}.

To replace {test} the test procedure with {alternative test} for the excipient {excipient}.

B.II.c.3.a.1

To replace the <excipient {excipient}> <reagent {reagent}> <used in the manufacture of {clarify use}> with {alternative excipient or reagent}.

B.II.c.3.a.2

To replace the <excipient {excipient}> <reagent {reagent}> <used in the manufacture of {clarify use}> with {alternative excipient or reagent}.

B.II.c.3.b

To replace the TSE risk <excipient {excipient}> <reagent {reagent}> <used in the manufacture of {clarify use}> with {alternative excipient or reagent}, not covered by the TSE certificate of suitability.

To introduce the TSE risk <excipient {excipient}> <reagent {reagent}> <used in the manufacture of {clarify use}>, not covered by the TSE certificate of suitability.

B.II.c.3.z (CMDh Art. 5 Recommendation)

Change in source of the excipient {excipient}. The change does not present any risk of TSE contamination.

B.II.c.4.a

Minor change in the <synthesis> <recovery> of the <non-pharmacopoeial excipient {excipient}> <novel excipient {novel excipient}>.

B.II.c.4.b

Minor change in the <synthesis> <recovery> of the <non-pharmacopoeial excipient {excipient}> <novel excipient {novel excipient}>, with consequential changes in <specification> <and>/<or> <physico-chemical properties> of the excipient, which have an impact on the quality of the finished product.

B.II.c.4.c

Minor change in the <synthesis> <recovery> of the <biological> <immunological> <non-pharmacopoeial excipient {excipient}> <novel excipient {novel excipient}>.

B.II.c.z (CMDh Art. 5 Recommendation)

To remove from section(s) {section(s)} of the dossier information on the frequency of testing performed on the excipient {excipient}.

B.II.d.1.a

To tighten the finished product specification limits for {test} from {current value} to {proposed value}.

B.II.d.1.b

To tighten the finished product specification limits for {test} from {current value} to {proposed value}..

B.II.d.1.c

To add {parameter} to the specifications of the finished product. <The limit is set to {value}.>

B.II.d.1.d

To delete the non-significant parameter {parameter} from the specifications of the finished product.

B.II.d.1.e

To change the {test} specification limits from {current value} to {proposed value} in the specifications of the finished product.

B.II.d.1.f

To delete the significant parameter {parameter} from the specifications of the finished product <, which has a significant effect on the overall quality of the finished product.

B.II.d.1.g

To add {parameter} to the specifications of the finished product as a result of a <safety><quality> issue.

To replace {parameter} with {alternative parameter} in the specifications of the finished product as a result of a <safety><quality> issue.

B.II.d.1.h

Changes to the dossier to comply with the provisions of an updated Ph. Eur. monograph for the finished product.

B.II.d.1.i

To replace the currently registered <'Uniformity of Mass' method (Ph. Eur. 2.9.5)> <'Uniformity of Content' method (Ph. Eur. 2.9.6)> with the 'Uniformity of Dosage Units by Mass Variation' method (Ph. Eur. 2.9.40).

B.II.d.1.z (CMDh Art. 5 Recommendation)

Change in the microbiological purity specification parameters of the finished product to comply with the Ph. Eur.

To reduce the testing frequency of an analysis, from routine testing to skip or periodic testing (microbial testing of finished product).

Change in the specification parameters and/or limits of the finished product to more accurately describe the appearance of the finished product.

To replace the currently registered 'Uniformity of dosage units (by CU)' method (Ph. Eur. 2.9.40) with the <'Uniformity of content of single-dose preparations' method (Ph. Eur. 2.9.6)> <and> <'Uniformity of mass of single-dose preparations' method (Ph. Eur. 2.9.5)>.

B.II.d.2.a

Minor changes to the {test} test procedure for the finished product to {brief description of the change}.

B.II.d.2.b

To delete the {test} test procedure for the finished product.

B.II.d.2.c

To introduce substantial changes to the <biological> <immunological> <immunochemical> {test} test procedure for the finished product to {brief description of the change}.

To replace the <biological> <immunological> <immunochemical> {test} test procedure with {alternative test} for the finished product.

B.II.d.2.d

To add the {test} test procedure to the specifications of the finished product.

To replace the {test} test procedure with {alternative test} in the specifications of the finished product.

B.II.d.2.e

Changes to the {test} test procedure for the finished product to comply with the updated general monograph in the Ph. Eur.

B.II.d.2.f

Change in the {test} test procedure for the finished product to reflect compliance with the Ph. Eur. and remove reference to the outdated internal test method and test method number.

B.II.e.1.a.1

Change in the <qualitative> <and> <quantitative> composition of the immediate packaging of the finished product {specify pharmaceutical form, strength and EU#s, if needed} from {currently approved packaging} to {proposed packaging}.

B.II.e.1.a.2

Change in the <qualitative> <and> <quantitative> composition of the immediate packaging of the finished product {specify pharmaceutical form, strength and EU#s, if needed}} from {currently approved packaging} to {proposed packaging}.

B.II.e.1.a.3

Change in the <qualitative> <and> <quantitative> composition of the immediate packaging of the <sterile> <biological> <immunological> finished product {specify pharmaceutical form, strength and EU#s, if needed}} from {currently approved packaging} to {proposed packaging}.

B.II.e.1.a.4

Change in the immediate packaging of the finished product {specify pharmaceutical form, strength and EU#s, if needed} from {currently approved packaging} to a less protective packaging {proposed

packaging}. As a consequence, <the storage conditions are being changed from {currently approved} to {proposed}> <the shelf life is being reduced from {currently approved} to {proposed}>.

B.II.e.1.b.1

Change in the immediate packaging of the finished product {specify pharmaceutical form, strength and EU#s, if needed} to {brief description of the change}.

B.II.e.1.b.2

Change in the immediate packaging of the <sterile> <biological> <immunological> finished product {specify pharmaceutical form, strength and EU#s, if needed} to {brief description of the change / packaging}.

B.II.e.1.b.3

To delete the immediate packaging container {description of container} for the finished product {specify pharmaceutical form, strength and EU#s, if needed}.

B.II.e.2.a

To tighten the {parameter} specification limits for the immediate packaging of the finished product from {current value} to {proposed value}.

B.II.e.2.b

To add {parameter} to the immediate packaging specifications of the finished product. <The limit is set to {value}.>

B.II.e.2.c

To delete the non-significant parameter {parameter} from the immediate packaging specifications of the finished product.

B.II.e.2.d

To add {parameter} to the immediate packaging specifications of the finished product as a result of a <safety> <quality> issue.

To replace the {parameter} with {alternative parameter} in the immediate packaging specifications of the finished product as a result of a <safety> <quality> issue.

B.II.e.3.a

Minor changes to the {test} test procedure for the immediate packaging of the finished product to {brief description of the change}.

B.II.e.3.b

To add the {test} test procedure to the immediate packaging specifications of the finished product.

To replace the {test} test procedure with {alternative test} in the immediate packaging specifications of the finished product.

B.II.e.3.c

To delete the {test} test procedure from the immediate packaging specifications of the finished product.

B.II.e.4.a

Change in the <shape> <dimension> of the immediate packaging of the finished product to {brief description of the change}.

B.II.e.4.b

Change in the <shape> <dimension> of {part of the immediate packaging of the finished product} to {brief description of the change}. The change impacts the <delivery> <use> <safety> <stability> of the finished product.

B.II.e.4.c

Change in the <shape> <dimension> of the immediate packaging of the finished product to {brief description of the change}.

B.II.e.5.a.1, B.II.e.5.a.2

To add a new pack-size of {pack size} in {type of packaging} for {name of the product, strength and pharmaceutical form} (EU/{insert #})

B.II.e.5.b

To delete the {pack size} presentation (EU/{insert #}) for {name of the product, strength and pharmaceutical form}.

B.II.e.5.c

To change the fill <weight> <volume> for the sterile parenteral <biological> <immunological> medicinal product {name of the product, strength and pharmaceutical form} (EU/{insert #}).

To add the new presentation {brief description} for the sterile parenteral <biological> <immunological> medicinal product {name of the product, strength and pharmaceutical form} (EU/{insert #}).

B.II.e.5.d

To change the fill <weight> <volume> for {name of the product, strength and pharmaceutical form} (EU/{insert #}).

B.II.e.6.a, B.II.e.6.b

Change in the {part of the packaging} of {name of the product, strength and pharmaceutical form} (EU/{insert #}) to {brief description of the change}.

B.II.e.7.a

To delete the supplier(s) of the {primary packaging material or device} {name(s) and address} from Module 3.2.P.7.

B.II.e.7.a (CMDh Art. 5 Recommendation)

To delete the reference to the supplier(s) of the {primary packaging material or device} {name(s) and address} from Module 3.2.P.7.

To change the name of the supplier(s) of the {primary packaging material or device} from {current name(s)} to {new name(s)}.

B.II.e.7.b

To add {name and address} as an alternative supplier of the {primary packaging material or device}.

To replace {name and address} with {name and address} as a supplier of the {primary packaging material or device}.

B.II.e.7.c

To add {name and address} as a supplier of the spacer device for the metered dose inhaler for {name of the product, strength}.

To replace {name and address} with {name and address} as a supplier of the spacer device for the metered dose inhaler for {name of the product, strength}.

B.II.e.Z (CMDh Art. 5 Recommendation)

To remove from section(s) {section(s)} of the dossier information on the frequency of testing performed on the packaging material.

To add a calendar pack for the already registered presentation of {strength and pharmaceutical form} (EU/{insert #}).

To change the calendar pack for the already registered presentation of {strength and pharmaceutical form} (EU/{insert #}) to {brief description of the change}.

B.II.f.1.a.1

To reduce the shelf-life of the finished product {specify strength, pharmaceutical form and EU #(s) if not all presentations are affected} as packaged for sale, from {current shelf-life} to {proposed shelf-life} <when stored at {define storage conditions}>.

B.II.f.1.a.2

To reduce the shelf-life of the finished product {specify strength, pharmaceutical form and EU #(s) if not all presentations are affected} after first opening, from {current shelf-life} to {proposed shelf-life} <when stored at {define storage conditions}>.

B.II.f.1.a.3

To reduce the shelf-life of the finished product {specify strength, pharmaceutical form and EU #(s) if not all presentations are affected} after <dilution> <reconstitution>, from {current shelf-life} to {proposed shelf-life} <when stored at {define storage conditions}>.

B.II.f.1.b.1

To extend the shelf-life of the finished product {specify strength, pharmaceutical form and EU #(s) if not all presentations are affected} as packaged for sale from {current shelf-life} to {proposed shelf-life} <when stored at {define storage conditions}>.

B.II.f.1.b.2

To extend the shelf-life of the finished product {specify strength, pharmaceutical form and EU #(s) if not all presentations are affected} after first opening from {current shelf-life} to {proposed shelf-life} <when stored at {define storage conditions}>.

B.II.f.1.b.3

To extend the shelf-life of the finished product {specify strength, pharmaceutical form and EU #(s) if not all presentations are affected} after <dilution> <reconstitution> from {current shelf-life} to {proposed shelf-life} <when stored at {define storage conditions}>.

B.II.f.1.b.4

To extend the the shelf-life of the finished product {specify strength, pharmaceutical form and EU #(s) if not all presentations are affected} from {current shelf-life} to {proposed shelf-life} <when stored at {define storage conditions}> based on the extrapolation of stability data not in accordance with ICH guidelines.

B.II.f.1.b.5

To extend the shelf-life of the <biological> <immunological> finished product {specify strength, pharmaceutical form and EU #(s) if not all presentations are affected}, in accordance with the approved stability protocol, from {current shelf-life} to {proposed shelf-life} <when stored at {define storage conditions}>.

B.II.f.1.c

To change the storage conditions of the biological medicinal product {specify strength, pharmaceutical form and EU #(s) if not all presentations are affected} from {current storage conditions} to {proposed

storage conditions}. The stability studies have not been performed in accordance with the approved stability protocol.

B.II.f.1.d

Change in the storage conditions of the <finished> <diluted> <reconstituted> product from {current conditions} to {proposed conditions}.

B.II.f.1.e

Changes to the approved stability protocol of the finished product to {brief description of the change}.

B.II.g.1.a

To introduce a new design space during {affected stage X / unit operation X} of the manufacturing process of the finished product {finished product}.

To extend an approved design space during {affected stage X / unit operation X} of the manufacturing process of the finished product {finished product}.

B.II.g.1.b

To introduce a new design space concerning the test procedures {proposed test procedures} of the manufacturing process of the finished product {finished product}.

To extend an approved design space concerning the test procedures {proposed test procedures} of the manufacturing process of the finished product {finished product}.

B.II.g.2

To introduce a post-approval change management protocol intended to {intended change in the manufacturing process / intended manufacturing site} related to manufacturing process of the finished product {finished product}.

B.II.g.3

To delete the approved change management protocol of the finished product intended to {intended change in the manufacturing process / intended manufacturing site} related to manufacturing process of the finished product {finished product}.

B.II.g.4.a

To introduce major changes to the approved management protocol intended to {intended change in the manufacturing process / intended manufacturing site} including {proposed changes} related to manufacturing process of the finished product {finished product}.

B.II.g.4.b

To introduce minor changes to the approved management protocol intended to {intended change in the manufacturing process / intended manufacturing site} including {proposed changes} related to manufacturing process of the finished product {finished product}.

B.II.g.5.a, B.II.g.5.b

To implement changes foreseen in the approved change management protocol of the finished product {finished product} to {brief description of the change}.

B.II.g.5.c

To implement changes foreseen in the approved change management protocol of the <biological> <immunological> finished product {finished product} to {brief description of the change}.

B.II.h.1.a.1

To update the information in Module 3.2.A.2 on 'Adventitious Agents Safety Evaluation' to introduce a new study related to manufacturing steps and adventitious agents for the following adventitious agents: {adventitious agent for which a risk assessment is being conducted}.

B.II.h.1.b.1

To update the information in Module 3.2.A.2 on 'Adventitious Agents Safety Evaluation' to replace obsolete studies {name the studies} related to manufacturing steps and adventitious agents already reported in the dossier, including modifications in the risk assessment.

B.II.h.1.b.2

To update the information in Module 3.2.A.2 on 'Adventitious Agents Safety Evaluation' to replace obsolete studies {name the studies} related to manufacturing steps and adventitious agents already reported in the dossier. The risk assessment remains unmodified.

B.II.z (CMDh Art. 5 Recommendation)

To update the information in Module 3.2.A.1 to change the meeting room indicated in the floor plans into a storage room.

B.III.1.a.1

To include the new Ph. Eur. Certificate of Suitability {new CEP number} for {substance} <to replace the ASMF issued by {ASMF Holder's name}>.

<As a consequence, the following manufacturer<s> of the active substance <and active substance intermediate> <is> <are> added in Module 3.2.S.2.1: {clearly indicate name and address of site(s)}>.

or

<As a consequence, the <name> <and> <address> of the manufacturer<s> of the active substance <and active substance intermediate> <is> <are> updated as follows: {clearly indicate changes related to name/address}>. **or**

<The name and address of the manufacturer<s> of the active substance <and active substance intermediate> remain unchanged.>

B.III.1.a.2

To update the Ph. Eur. Certificate of Suitability for {substance} from {current CEP number} to {new CEP number}.

<As a consequence, the following manufacturer<s> of the active substance <and active substance intermediate> <is> <are> added in Module 3.2.S.2.1: {clearly indicate name and address of site(s)}>. **or**

<As a consequence, the <name> <and> <address> of the manufacturer<s> of the active substance <and active substance intermediate> <is> <are> updated as follows>: {clearly indicate changes related to name/address}>. **or**

<The name and address of the manufacturer<s> of the active substance <and active substance intermediate> remain unchanged.>

B.III.1.a.3

<To add the new Ph. Eur. Certificate of Suitability {new CEP number} for {substance}>.

<To replace the Ph. Eur. Certificate of Suitability for {substance} {CEP number} with {new CEP number}> from the new <active substance> manufacturer {name and address of site}.

<As a consequence, the following manufacturer<s> of the active substance <and active substance intermediate> <is> <are> added in Module 3.2.S.2.1: {clearly indicate name and address of site(s)}>. **or**

<As a consequence, the <name> <and> <address> of the manufacturer<s> of the active substance <and active substance intermediate> <is> <are> updated as follows: {clearly indicate changes related to name/address}>. **or**

<The name and address of the manufacturer<s> of the active substance <and active substance intermediate> remain unchanged.>

B.III.1.a.4

To delete the Ph. Eur. Certificate<s> of Suitability for {substance} {CEP number<s>}. <As a consequence, <the following manufacturer<s> of the active substance <and active substance intermediate> <is> <are> removed from Module 3.2.S.2.1: {clearly indicate name and address of site(s) to be removed}.>

B.III.1.a.5

To include the new Ph. Eur. Certificate of Suitability {new CEP number} for the non-sterile active substance {substance}.

<As a consequence, the following manufacturer<s> of the active substance <is> <are> added in Module 3.2.S.2.1: {clearly indicate name and address of site(s)}.> **or**

<As a consequence, the <name> <and> <address> of the manufacturer<s> of the active substance <and active substance intermediate> <is> <are> updated as follows: {clearly indicate changes related to name/address}>. **or**

<The name and address of the manufacturer<s> of the active substance remain unchanged.>

B.III.1.b.1

To include the new Ph. Eur. TSE Certificate of Suitability {new CEP number} for {active substance}.

<As a consequence, the following manufacturer<s> of the active substance <is> <are> added in Module 3.2.S.2.1: {clearly indicate name and address of site(s)}.> **or**

<The name and address of the manufacturer<s> of the active substance remain unchanged.>

B.III.1.b.2

To include the new Ph. Eur. TSE Certificate of Suitability {new CEP number} for the <starting material> <reagent> <intermediate> <excipient> {substance}.

<As a consequence, the following manufacturer<s> of the active substance intermediate <is> <are> added in Module 3.2.S.2.1: {clearly indicate name and address of site(s)}.> **or**

<The name and address of the manufacturer<s> of the active substance intermediate remain unchanged.>

B.III.1.b.3

To update the Ph. Eur. TSE Certificate of Suitability for {substance} from {current CEP number} to {new CEP number}.

<As a consequence, the following manufacturer<s> of the active substance <is> <are> added in Module 3.2.S.2.1: {clearly indicate name and address of site(s)}>. **or**

<As a consequence, the <name> <and> <address> of the manufacturer<s> of the active substance <is> <are> updated as follows: {clearly indicate changes related to name/address}>. **or**

<The name and address of the manufacturer<s> of the active substance remain unchanged.>

B.III.1.b.4

To delete the TSE Ph. Eur. Certificate of Suitability for {substance} {CEP number<s>}. <As a consequence, the following manufacturer<s> of the active substance <and active substance intermediate> <is> <are> removed from Module 3.2.S.2.1: {clearly indicate name and address of site(s) to be removed}.>

B.III.1.b.5

To include the <new> <updated> Ph. Eur. TSE Certificate of Suitability {new CEP number} for the <active substance> <starting material> <reagent> <intermediate> <excipient> {substance}. A for the risk assessment with respect to potential contamination with adventitious agents is provided.

<As a consequence, the following manufacturer<s> of the <active substance> <active substance intermediate> <is> <are> added in Module 3.2.S.2.1: {clearly indicate name and address of site(s)}>. **or**

<As a consequence, the <name> <and> <address> of the manufacturer<s> of the active substance <active substance intermediate> <is> <are> updated as follows: {clearly indicate changes related to name/address}>. **or**

<The name and address of the manufacturer<s> of the active substance remain unchanged.>

B.III.2.a.1

Change in the specifications for the active substance {active substance} to fully comply with the <Ph. Eur.><national pharmacopoeia of the {Member State name} Member State>.

B.III.2.a.2

Change in the specifications for the <excipient> <active substance starting material> {substance} to fully comply with the <Ph. Eur.><national pharmacopoeia of the {Member State name} Member State>.

B.III.2.b

Change in the specifications of {substance} to comply with an update of the relevant <Ph. Eur. monograph> <national pharmacopoeia of the {Member State name} Member State>.

B.III.2.c

Change in the specifications of {substance} from the national pharmacopoeia of the {Member State name} Member State to the Ph. Eur.

B.III.2.z (CMDh Art. 5 Recommendation)

To reflect compliance with the Ph. Eur. and remove reference to the internal test method and test method number for the <active substance {active substance}> <<excipient> <active substance starting material> {substance}> <immediate packaging materials>.

B.IV.1.a.1

To add the CE marked {device} to be used {clarify use}.

To replace the CE marked {device} <used in the {specify pharmaceutical form, strength and EU#s, if needed}> with {new device}.

B.IV.1.a.3

To add a < spacer> {metered dose inhaler device} to be used {clarify use}.

B.IV.1.b

To delete the {device} to be used {clarify use}.

B.IV.1.c

To add the {device} to be used {clarify use}, which is an integrated part of the primary packaging of the medicinal product

To replace the {device} to be used {clarify use}, which is an integrated part of the primary packaging of the medicinal product

B.V.a.1.a

To submit a 2nd step notification procedure for the inclusion of a new Plasma Master File Certificate (EMEA/H/PMF/{number}) granted by the EMA to {PMF holder} on {date}

B.V.a.1.b

To submit a 2nd step notification procedure for the inclusion of a new Plasma Master File Certificate (EMEA/H/PMF/{number}) granted by the EMA to {PMF holder} on {date}.

B.V.a.1.c

To submit a 2nd step notification procedure for the inclusion of an updated Plasma Master File Certificate (EMEA/H/PMF/{number}) granted by the EMA to {PMF holder} on {date}.

To submit a 2nd step notification procedure for the Annual Update of the Plasma Master File Certificate (EMEA/H/PMF/{number}) granted by the EMA to {PMF holder} on {date}.

B.V.a.1.d

To submit a 2nd step notification procedure for the inclusion of an updated Plasma Master File Certificate (EMEA/H/PMF/{number}) granted by the EMA to {PMF holder} on {date}.

To submit a 2nd step notification procedure for the Annual Update of the Plasma Master File Certificate (EMEA/H/PMF/{number}) granted by the EMA to {PMF holder} on {date}.

B.V.b.1.a

To update the following quality section<s> of the dossier {indicate high level modules affected} to implement the outcome of the Union referral Art. {referral type} {procedure number} on {introduce in one sentence the scope of the Union referral}

B.V.b.1.b

To updated the following quality section<s> of the dossier {indicate high level modules affected} linked to the outcome of the Union referral Art. {procedure number} on {introduce in one sentence the scope of the Union referral}, for which harmonization of the quality section is required.

CLINICAL CHANGES

C.I.z - Temperature of use (CMDh Art. 5 Recommendation)

To update section 4.2 of the SmPC and section 3 of the PL to clarify a temperature of use of {temperature} and ensure the correct handling of the medicinal product.

C.I.z - ADR reporting (CMDh Art. 5 Recommendation)

To update section 4.8 of the SmPC and section 4 of the PL with the inclusion of the QRD statements to encourage ADRs reporting.

C.I.z - PRAC recommendation (CMDh Art. 5 Recommendation) (IA_{IN}, IB or II depending on whether translations have been agreed upon or not, or whether additional data is required)

To update section<s> <4.4> <and> <4.8> of the SmPC and section<s> <2> <and> <4> of the PL to implement the signal recommendations on '<{insert full title of PRAC recommendation}> (EPITT no {number})' adopted at the {DD MM YYYY} PRAC meeting.

<The implementation of the change(s) is further substantiated by new additional data on {specify} submitted by the MAH.>

C.I.z - Recommendation of Competent Authority (CMDh Art. 5 Recommendation) (IA, IB or II depending on whether translations have been agreed upon or not, or whether additional data is required)

To update section<s> {sections} of the SmPC <<and> <section<s> {sections} of the Labelling> <and section<s> {sections} of the PL> to implement the recommendation of the <CHMP> <CMDh> <PRAC> <EMA> <further to {e.g. update of the Core SmPC following the assessment of an Urgent Safety Restriction}>.

<The implementation of the change(s) is further substantiated by new additional data on {specify} submitted by the MAH.>

C.I.1.a, C.I.1.b

To update section<s> {sections} of the SmPC <<and> section<s> {sections} of the Labelling> <and section<s> {sections} of the PL> to implement the outcome of a Union referral procedure.

C.I.1.c

To update section<s> {sections} of the SmPC <<and> section<s> {sections} of the Labelling> <and section<s> {sections} of the PL> to implement the outcome of a Union referral procedure. The implementation of the change(s) is further substantiated by new additional data on {specify} submitted by the MAH.

C.I.2.a

To update section<s> {sections} of the SmPC <<and> section<s> {sections} of the Labelling> <and section<s> {sections} of the PL to {brief description of the change} following assessment of the same change for the reference product {product}.

C.I.2.b

To update section<s> {sections} of the SmPC <<and> section<s> {sections} of the Labelling> <and section<s> {sections} of the PL to {brief description of the change} following assessment of the same change for the reference product {product}. The implementation of the change(s) is further substantiated by new additional data on {specify} submitted by the MAH.

C.I.3.a

To update section<s> {sections} of the SmPC <<and> section<s> {sections} of the Labelling> <and section<s> {sections} of the PL> to implement the wording agreed by the <CHMP> <PRAC> <EMA> following the <outcome of the <PSUR procedure EMEA/H/C/PSUSA/{xxx}> <PASS protocol {protocol #}>> <assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006>.

C.I.3.b

To update section<s> {sections} of the SmPC to <add a warning> <update the safety information> […].following the <assessment of {specify}> <based on <interim> <final> results from study {include study identifier} listed as <a <specific obligation> <imposed PASS> <obligation><PAES> in Annex II> <a category 3 study in the RMP>; <this is a {copy the high-level description of study which should particularly mention whether the study is interventional or observational and whether the primary objective relates to efficacy or safety; the description can be omitted for non-clinical or PK studies, particularly when multiple small studies are submitted};>< the Package Leaflet <and Labelling> are updated accordingly.>< The RMP version {#} has also been submitted.>

C.I.3.z (CMDh Art. 5 Recommendation)

To update section<s> {sections} of the SmPC <<and> section<s> {sections} of the Labelling> <and section<s> {sections} of the PL> to implement the wording agreed by the <CHMP> <PRAC> <EMA> following the <outcome of the <PSUR procedure EMEA/H/C/PSUSA/{xxx}> <PASS protocol {protocol #}>> <assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006>.

C.I.4

To update section<s> {sections} of the SmPC to <add a warning> <update the safety information> <following> <based on> <<interim> <final> results from study {include study identifier} listed as <a <specific obligation> <imposed PASS> <obligation> <PAES> in Annex II> <a category 3 study in the RMP>; this is a {copy the high-level description of study which should particularly mention whether the study is interventional or observational and whether the primary objective relates to efficacy or safety; the description can be omitted for non-clinical or PK studies, particularly when multiple small

studies are submitted};< the Package Leaflet <and Labelling> are updated accordingly.>< The updated RMP version {#} has also been submitted.>

C.I.4 (CMDh Art. 5 Recommendation)

To include significant changes to section<s> {sections} of the SmPC <<and> section<s> {sections} of the Labelling> <and section<s> {sections} of the PL> for the medicinal product {name} containing the active substances {list all active substances}, following the assessment of the medicinal product {name}, which also contains the active substance {active substance}, via procedure EMEA/{insert # of procedure}. The same wording is used for the combination product.

C.I.5.a

Change in the legal status of {product} from {current legal status} to {approved legal status} following the approved legal status change of the reference product {product}.

C.I.5.b

Change in the legal status of {product} from {current legal status} to {approved legal status} in view of {include justification}.

C.I.6.a

To add the new therapeutic indication {new indication}. As a consequence, section<s> {insert section(s)} of the SmPC and section<s> {insert section(s)} of the PL are updated accordingly. The updated RMP version {#} has also been submitted.

To modify the approved therapeutic indication to include <new indication/population>. As a consequence, section<s> {insert section(s)} of the SmPC and section<s> {insert section(s)} of the PL are updated accordingly. The updated RMP version {#} has also been submitted.

C.I.6.b

To delete the therapeutic indication {indication}. Section 4.1 of the SmPC and section 1 of the PL are updated accordingly.

C.I.7.a

To delete the pharmaceutical form {pharmaceutical form} from the {product} marketing authorisation (EU/{#(s)}).

C.I.7.b

To delete the {strength} strength from the {product} marketing authorisation (EU/{#(s)}).

C.I.8.a (as of Feb. 1st 2016 updates can be done via Art.57 database only without the need for any further variation)

To replace the Detailed Description of the Pharmacovigilance System (DDPS, version {#}, dated {DD MM YYYY}) with the Pharmacovigilance System Master File (PSMF, version {#}, dated {DD MM YYYY}). The PSMF is located in {country}.

To introduce the Pharmacovigilance System Master File (PSMF, version {#}, dated {DD MM YYYY}). The PSMF is located in {country}.

To introduce the Pharmacovigilance System Master File (PSMF, version {#}, dated {DD MM YYYY}) and include a change in the <contact details of the Qualified Person for Pharmacovigilance (QPPV)>< and ><location of the Pharmacovigilance System Master File (PSMF). <The PSMF location is moved to {country}> <The PSMF remains located in {country}>.

To update the Pharmacovigilance System Master File (PSMF) to version {#} to include a change in the <contact details of the Qualified Person for Pharmacovigilance (QPPV)>< and ><location of the Pharmacovigilance System Master File (PSMF). <The PSMF location is moved to {country}> <The PSMF remains located in {country}>.

C.I.9.a-i (indents applicable only to veterinary products)

To update the Detailed Description of the Pharmacovigilance System (DDPS) to version {#}, to include {clarify type of change}.

C.I.10

To change the <frequency> <and> <date of submission> of the PSUR submission from {current frequency/date} to {new frequency/date}. <The new Data Lock Point (DLP) is {DD MM YYYY},> in accordance with the EURD list.> <Annex II has also been updated in line with the latest QRD template (version {#}).>

C.I.11.a

To update <Annex II> <the RMP for {product} to version {#}> to {include a concise description of the (type of) change in the RMP/Annex II}. This change has been agreed by the <CHMP> <Competent Authority> in the outcome of {indicate variation or type of assessment}>.

C.I.11.b

<To update <Annex II> <the RMP for {product} to version {#}> to {include a concise description of the (type of) change in the RMP/Annex II}. This change has been agreed by the <CHMP> <Competent Authority> in the outcome of {indicate variation or type of assessment}. The implementation of the change(s) is further substantiated by new additional data on {specify} submitted by the MAH.>

<To submit interim reports for post approval studies, which are a condition to the Marketing Authorisation.>

C.I.12

To <include in><remove from> the Product Information the black symbol and explanatory statements for medicinal products subject to additional monitoring.

C.I.13

To submit the final report from study/studies {include description of the study and study identifier(s)} <listed as a category 3 study in the RMP>. <An updated RMP version {#} has also been submitted>.

C.I.13 (CMDh Art. 5 Recommendation)

To submit the additional clinical and non-clinical studies {list studies}, including the BE-study/ies {list study/ies}. <An updated RMP version {#} has also been submitted>.