Annex 3 of the Guideline for Variation

Quality Changes, Finished Pharmaceutical Product (FPP) or drug product

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
3.2.P.1 Description and composition of the FPP				
22				
22 a	Change in the composition of a solution dosage form	1–6	2, 4, 7, 9–10	**IN**
22 b		None	1–10	**Vmaj**
	Conditions to be fulfilled 1 The affected excipient(s) does/do not function to affect the solubility and/or the absorption of the API 2 The affected excipient(s) does/do not function as a preservative or preservative enhancer 3 No change in the specifications of the affected excipient(s) or the FPP 4 No change in the physical characteristics of the FPP (e.g., viscosity, osmolality, pH) 5 The change does not concern a sterile FPP 6 The excipients are qualitatively the same. The change in the amount (or concentration) of each excipient is within ±10% of the amount (or concentration) of each excipient in the originally prequalified product			
	Documentation required 1 Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current MCA *Guideline for the Investigation of Bioequivalence* 2 (P.1) Description and composition of the FPP 3 (P.2) Discussion on the components of the proposed product (e.g. choice of excipients, compatibility of API and excipients, suitability studies on the packaging system for the changed product) 4 (P.3) Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation 5 (P.4) Control of excipients, if new excipients are proposed 6 (P.4.5) If applicable, either a CEP for any new component of animal origin susceptible to TSE risk or, where applicable, documented evidence that the specific source of the TSE risk material has been previously assessed by an NMRA in the ICH region or associated countries and shown to comply with the scope of the current guidelines in the countries of the ICH region or associated countries. The following information should be included for each such material: name of manufacturer, species and tissues from which the material is derived, country of origin of the source animals, and use of the material.			

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
	7 (P.5) Copies of FPP release and shelf-life specifications and certificates of analysis for a minimum of two pilot- or production-scale batches. If applicable, data to demonstrate that the new excipient does not interfere with the analytical procedures for the FPP 8 (P.8.1) Results of stability testing generated on at least two pilot- or production- scale batches with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing 9 (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of each strength of the proposed product into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified) 10 (R.1) Copies of relevant pages of blank master production documents with changes highlighted, as well as relevant pages of the executed production document for one batch and confirmation that there are no changes to the production documents other than those highlighted			
23	**Change in the colouring system or the flavouring system currently used in the FPP involving:**			
23 a	reduction or increase of one or more components of the colouring or the flavouring system	1–3, 6	1, 4, 6–7	**AN**
23 b	deletion, addition or replacement of one or more components of the colouring or the flavouring system	1–6	1–7	**IN**
	Conditions to be fulfilled 1 No change in the functional characteristics of the pharmaceutical form e.g. disintegration time or dissolution profile 2 Any minor adjustment to the formulation to maintain the total weight is made using an excipient which currently makes up a major part of the FPP formulation 3 Specifications for the FPP are updated only with respect to appearance, odour and/ or taste or if relevant, deletion or addition of a test for identification 4 Any new component must comply with section 3.2.P.4 of the WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product* 5 Any new component does not include the use of materials of human or animal origin for which assessment of viral safety data is required, or is in compliance with the current WHO *Guidelines on transmissible spongiform encephalopathies in relation to biological and pharmaceutical products* (www.who.int/biologicals) or EMA's *Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy*			

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
	agents via human and veterinary medicinal products (www.emea.europa.eu/ema) or an equivalent guide from the ICH region and associated countries 6 Where applicable, the change does not affect the differentiation between strengths and for paediatric formulations it does not require submission of results of taste acceptability studies			
	Documentation required 1 Sample of the FPP 2 (P.2) Discussion on the components of the FPP (e.g. compatibility of API and qualitative composition of the colouring or flavouring system if purchased as a mixture, with specifications, if relevant) 3 (P.4.5) Either a CEP for any new component of animal origin susceptible to TSE risk or, where applicable, documented evidence that the specific source of the TSE risk material has been previously assessed by an NMRA in the ICH region or associated countries and shown to comply with the scope of the current guidelines in the countries of the ICH region or associated countries. The following information should be included for each such material: name of manufacturer, species and tissues from which the material is derived, country of origin of the source animals, and use of the material 4 (P.5) Copies of revised FPP release and shelf-life specifications and certificates of analysis for a minimum of two pilot- or production-scale batches 5 (P.5.3) If applicable, data to demonstrate that the new excipient does not interfere with the analytical procedures for the FPP 6 (P.8.1) Results of stability testing generated on at least two pilot- or production- scale batches with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing 7 (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documents for one batch and confirmation that there are no changes to the production documents other than those highlighted			
24	**Change in weight of tablet coatings or capsule shells involving:**			
24 a	immediate release oral FPPs	1–3	2–5	**AN**
24 b	gastro-resistant, modified or prolonged release FPPs	None	1–5	**Vmaj**
	Conditions to be fulfilled 1 Multipoint in vitro dissolution profiles of the proposed version of the product (determined in the routine release medium on at least two batches of pilot- or production-scale), are similar to the dissolution profiles of the biobatch 2 Coating is not a critical factor for the release mechanism			

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
	3 Specifications for the FPP are updated only with respect to weight and dimensions, if applicable			
	Documentation required 1 Justification for not submitting a new bioequivalence study according to the current MCA *Guideline for the Investigation of Bioequivalence* 2 (P.2) Comparative multipoint in vitro dissolution profiles in the routine release medium (or media), on at least two batches of pilot- or production-scale of the proposed product versus the biobatch 3 (P.5) Copies of revised FPP release and shelf-life specifications and certificates of analysis for a minimum of one pilot- or production-scale batch 4 (P.8.1) Results of stability testing generated on at least one pilot- or production- scale batch with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing 5 (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documents for one batch and confirmation that there are no changes to the production documents other than those highlighted			
25	**Change in the composition of an immediate-release solid oral dosage form including:**			
25 a 1)	replacement of a single excipient with a comparable excipient at a similar concentration	1–5	1–10	**Vmin**
25 a 2)		None	1–10	**Vmaj**
25 b 1)	quantitative changes in excipients	1–4	1–10	**Vmin**
25 b 2)		None	1–4, 7–10	**Vmaj**
	Conditions to be fulfilled 1 No change in functional characteristics of the pharmaceutical form 2 Only minor adjustments (see Appendix 2) are made to the quantitative composition of the FPP; any minor adjustment to the formulation to maintain the total weight is made using an excipient which currently makes up a major part of the FPP formulation 3 Stability studies have been started under conditions according to WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product* (with indication of batch numbers) and relevant stability parameters have been assessed in at least two pilot- or production-scale batches, satisfactory stability data covering at least 3 months are at the disposal of the MAH, and the stability profile is similar to that of the currently accepted product 4 The dissolution profile of the proposed product determined on a minimum of two pilot-scale batches is similar to the dissolution profile of the biobatch 5 The change is not the result of stability issues and/or does not result in potential safety concerns, i.e. differentiation between strengths			

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
	Documentation required 1 Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current MCA *Guideline for the Investigation of Bioequivalence* 2 (P.1) Description and composition of the FPP 3 (P.2) Discussion on the components of the proposed product (e.g. choice of excipients, compatibility of API and excipients), comparative multipoint in vitro dissolution profiles obtained on at least two batches of pilot- or production-scale of the proposed product and the biobatch (depending on the solubility and permeability of the drug, dissolution in the routine release medium or in multiple media covering the physiological pH range) 4 (P.3) Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation 5 P.4) Control of excipients, if new excipients are proposed 6 (P.4.5) If applicable, either a CEP for any new component of animal origin susceptible to TSE risk or, where applicable, documented evidence that the specific source of the TSE risk material has been previously assessed by an NMRA in the ICH region or associated countries and shown to comply with the scope of the current guidelines in the countries of the ICH region or associated countries. The following information should be included for each such material: name of manufacturer, species and tissues from which the material is derived, country of origin of the source animals and its use 7 (P.5) Copies of FPP release and shelf-life specifications and certificates of analysis for a minimum of two pilot- or production-scale batches. If applicable, data to demonstrate that the new excipient does not interfere with the analytical procedures for the FPP 8 (P.8.1) Results of stability testing generated on at least two pilot- or production- scale batches with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing 9 (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of each strength of the proposed product into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified) 10 (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documents for one batch, and confirmation that there are no changes to the production documents other than those highlighted			
26	**Change or addition of imprints, embossing or other markings, including replacement or addition of inks used for product markings and change in scoring configuration involving:**			

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
26 a	changes in imprints, embossing or other markings	1–3	1–3, 5–6	**IN**
26 b	deletion of a score line	2–5	1, 5–6	**IN**
26 c 1)	addition of a score line	2–4	1, 3, 5–6	**Vmin**
26 c 2)		None	1, 3–6	**Vmaj**
	Conditions to be fulfilled 1 Any ink complies with section 3.2.P.4 of the WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product* 2 The change does not affect the stability or performance characteristics (e.g. release rate) of the FPP 3 Changes to the FPP specifications are those necessitated only by the change to the appearance or to the scoring 4 Addition or deletion of a score line from a generic product is consistent with a similar change in the comparator product or was requested by MCA 5 The scoring is not intended to divide the FPP into equal doses			
	Documentation required 1 Sample of the FPP 2 (P.1.) Qualitative composition of the ink, if purchased as a mixture 3 (P.2) Demonstration of the uniformity of the dosage units of the tablet portions, where the scoring is intended to divide the FPP into equal doses 4 (P.2) Demonstration of the similarity of the release rate of the tablet portions for gastro-resistant, modified or prolonged release products 5 (P.5) Copies of revised FPP release and shelf-life specifications 6 (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documentation for one batch and confirmation that there are no changes to the production documents other than those highlighted			
27	**Changes in dimensions without change in qualitative or quantitative composition and mean mass of:**			
27 a	tablets, capsules, suppositories and pessaries other than those stated in change no. 27b	1–2	2–6	**IN**
27 b	gastro-resistant, modified or prolonged-release FPPs and scored tablets	1–2	1–6	**Vmin**
	Conditions to be fulfilled 1 Specifications for the FPP are updated only with respect to dimensions of the FPP			

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
	2 Multipoint in vitro dissolution profiles of the current and proposed versions of the product (determined in the routine release medium, on at least one batch of pilot- or production-scale), are comparable			
	Documentation required 1 For gastro-resistant, modified or prolonged release FPPs, justification for not submitting a new bioequivalence study according to the current MCA *Guideline for the Investigation of Bioequivalence*. For scored tablets where the scoring is intended to divide the FPP into equal doses, demonstration of the uniformity of the tablet portions 2 Sample of the FPP 3 (P.2) Discussion on the differences in manufacturing process(es) between the currently accepted and proposed products and the potential impact on product performance 4 (P.2) Comparative multipoint in vitro dissolution profiles in the routine release medium, on at least one batch of pilot- or production-scale of the current and proposed products 5 (P.5) Copies of revised FPP release and shelf-life specifications 6 (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of executed production documentation for one batch and confirmation that there are no changes to the production documents other than those highlighted			
3.2.P.3 Manufacture				
28	**Addition or replacement of a manufacturing site for part or all of the manufacturing process for an FPP involving:**			
28 a	secondary packaging of all types of FPPs	2–3	1	**IN**
28 b	primary packaging site of:			
28 b 1)	solid FPPs (e.g. tablets, capsules), semi-solid FPPs (e.g. ointments, creams) and solution liquid FPPs	2–4	1, 8	**IN**
28 b 2)	other liquid FPPs (suspensions, emulsions)	2–5	1, 5, 8	**IN**
28 c	all other manufacturing operations except batch control and/or release testing	1–3, 5	1–9	**Vmin**
	Conditions to be fulfilled 1 No change in the batch formula, description of manufacturing process and process controls, equipment class and process controls, controls of critical steps and intermediates, or FPP specifications 2 Satisfactory inspection in the last three years either by MCA or an SRA 3 Site appropriately authorised by an NMRA (to manufacture the pharmaceutical form and the product concerned)			

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
	4 The change does not concern a sterile FPP 5 Validation protocol is available or validation of the manufacturing process at the new site has been successfully carried out on at least three production-scale batches in accordance with the current protocol			
	Documentation required 1 Evidence that the proposed site has been appropriately authorized in the last three years, for the pharmaceutical form and the product concerned: • a copy of the current manufacturing authorisation, a GMP certificate or equivalent document issued by the NMRA • a GMP statement or equivalent issued by MCA or an SRA • date of the last satisfactory inspection concerning the packaging facilities by WHO or an SRA in the last three years 2 Date and scope (with indication as to whether scope was e.g. product-specific or related to a specific pharmaceutical form) of the last satisfactory inspection 3 (P.2) Where applicable, for semisolid and liquid formulations in which the API is present in non-dissolved form, appropriate validation data including microscopic imaging of particle size distribution and morphology 4 (P.2) For solid dosage forms, data on comparative dissolution tests in the routine release medium, with demonstration of similarity of dissolution profiles with those of the biobatch, performed on one production-scale batch each from current and proposed manufacturing sites and comparison with the biobatch results, with commitment to generate dissolution profiles on two more production-scale batches 5 (P.3.5) Process validation reports or validation protocol (scheme) for three batches of the proposed batch size, which includes comparative dissolution against the biobatch results with f2 calculation as necessary 6 (P.5.1) Copies of release and shelf-life specifications 7 (P.5.4) Batch analysis data on one production-scale batch from the proposed site and comparative data on the last three batches from the previous site 8 (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of the FPP produced at the new site into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified) 9 (R.1) Executed production documents for one batch of the FPP manufactured at the new site			
29	**Replacement or addition of a site involving batch control testing**			
29		1–2	1-3	**AN**

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
	Conditions to be fulfilled 1 Site is appropriately authorised by the NMRA and satisfactorily inspected either by MCA or an SRA 2 Transfer of methods from the current testing site to the proposed testing site has been successfully completed			
	Documentation required 1 Clear identification of the currently accepted and proposed quality control sites on the letter accompanying the application 2 Documented evidence that the site is appropriately authorized by the NMRA and satisfactorily inspected either by MCA or an SRA 3 (P.5.3) Documented evidence of successful transfer of analytical procedures from the current to the proposed site			
30	**Change in the batch size of the FPP involving:**			
30 a	up to and including a factor of 10 compared to the biobatch	1–7	2, 5-6	**IN**
30 b	downscaling	1–5	2, 6	**AN**
30 c	other situations	1–7	1–7	**Vmin**
	Conditions to be fulfilled 1 The change does not affect the reproducibility and/or consistency of the product 2 The change pertains only to immediate-release oral pharmaceutical forms and to non-sterile liquid forms 3 Changes to the manufacturing method and/or to the in-process controls are only those necessitated by the change in batch size, e.g. use of different-sized equipment 4 A validation protocol is available or validation of the manufacture of three production-scale batches has been successfully undertaken in accordance with the current validation protocol 5 The change is not necessitated by unexpected events arising during manufacture or because of stability concerns 6 The change does not require supporting in vivo data 7 The biobatch size was at least 100 000 units in the case of solid oral dosage forms			
	Documentation required 1 (P.2) For solid dosage forms: dissolution profile data, in the routine release medium, on a minimum of one representative production-scale batch and comparison of the data with the biobatch results and one production-scale batch of the previous batch size. Data on the next two full production-scale batches should be available on request and should be reported if they do not meet dissolution profile similarity (f2) requirements. For semi-solid dosage forms (e.g. lotions, gels, creams and ointments), containing the API in the dissolved or non-dissolved			

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
	form, comparative in vitro data on membrane diffusion (membrane release testing) should be submitted or be available on request 2 (P.3.5) Process validation reports for three batches of the proposed batch size or validation protocol (scheme) 3 (P.5.1) Copies of release and shelf-life specifications 4 (P.5.4) Batch analysis data (in a comparative tabular format) on a minimum of one production-scale batch manufactured to both the currently accepted and the proposed batch sizes. Batch data on the next two full production-scale batches should be available on request and should be reported immediately by the supplier of the product, if outside specifications (with proposed remedial action). 5 (P.8.2) Updated post-acceptance stability protocol (approved by authorised personnel) and stability commitment to place the first production-scale batch of each strength at the proposed scale into the long-term stability programme (bracketing and matrixing for multiple strengths and packaging components could be applied, if scientifically justified) 6 (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as relevant pages of the executed production documentation for one batch (if manufactured as required by documentation 4) (above) and confirmation that there are no changes to the production documents other than those highlighted 7 Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current MCA *Guideline for the Investigation of Bioequivalence*			
31	**Change in the manufacturing process of the FPP**			
31 a		1–9	1–4, 6–7	**AN**
31 b		1–3, 5–9	1–7	**Vmin**
	Conditions to be fulfilled 1 The change does not require supporting in vivo data 2 No change in qualitative and quantitative impurity profile or in physicochemical properties; dissolution profiles are similar to those of the biobatch 3 The manufacturing processes for the currently accepted and proposed products use the same principles (e.g. a change from wet to dry granulation, from direct compression to wet or dry granulation or vice versa would be considered a change in manufacturing principle), the same processing intermediates and there are no changes to any manufacturing solvent used in the process 4 The same classes of equipment, operating procedures, in-process controls (with no widening or deleting of limits) are used for the currently accepted and proposed products; no change in critical process parameters 5 No change in the specifications of the intermediates or the FPP			

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
	6 The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns 7 The change does not involve packaging or labelling where the primary packaging provides a metering and/or delivery function 8 The change does not concern a gastro-resistant, modified or prolonged-release FPP 9 The change does not affect the sterilisation parameters of a sterile FPP			
	Documentation required 1 Supporting clinical or comparative bioavailability data or justification for not submitting a new bioequivalence study according to the current MCA *Guideline for the Investigation of Bioequivalence* 2 (P.2) Discussion on the development of the manufacturing process; where applicable: • comparative in vitro testing, e.g., multipoint dissolution profiles in the routine release medium for solid dosage units (one production batch and comparative data on one batch from the previous process and the biobatch results; data on the next two production batches should be available on request or reported if outside specification); • comparative in vitro membrane diffusion (membrane release testing) for non-sterile semisolid dosage forms containing the API in the dissolved or non-dissolved form (one production batch and comparative data on one batch from the previous process and the biobatch results; data on the next two production batches should be submitted or be available on request); • microscopic imaging of particles to check for visible changes in morphology and comparative size distribution data for liquid products in which the API is present in non-dissolved form. 3 (P.3) Batch formula, description of manufacturing process and process controls, controls of critical steps and intermediates, process validation protocol and/or evaluation 4 (P.5) Specification(s) and certificate of analysis for one production-scale batch manufactured according to the currently accepted process and for a batch manufactured according to the proposed process 5 (P.8.1) Results of stability testing generated on at least two pilot batches (for uncomplicated products, one pilot batch; the other one can be smaller) with a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing 6 (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of the proposed product into the long-term stability programme 7 (R.1) Copies of relevant sections of blank master production documents with changes highlighted as well as executed production documentation for one batch and confirmation that there are no changes to the currently accepted production documents other than those highlighted			

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
32	**Change to in-process tests or limits applied during the manufacture of the FPP or intermediate involving:**			
32 a	tightening of in-process limits a	1–2, 5	1.	**AN**
32 b	deletion of a test	2–3	1, 6	**AN**
32 c	addition of new tests and limits	2–3	1–6	**AN**
32 d	revision or replacement of a test	2–3	1–6	**IN**
	Conditions to be fulfilled 1 The change is within the range of acceptance limits 2 The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns 3 Any new test does not concern a novel, non-standard technique or a standard technique used in a novel way 4 The deleted test has been demonstrated to be redundant with respect to the remaining analytical procedures (e.g. colour) and does not affect the critical quality attributes of the product (e.g., blend uniformity, weight variation) 5 No change in the analytical procedure			
	Documentation required 1 (P.5.1) Copy of the proposed in-process specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications 2 (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used 3 (P.5.3) Copies or summaries of validation reports, if new analytical procedures are used 4 (P.5.3) Where an in-house analytical procedure is used and a pharmacopeial standard is claimed, results of an equivalence study between the in-house and pharmacopeial methods 5 (P.5.4) Description of the batches, certificates of analysis for at least one batch (minimum pilot-scale) and comparative summary of results, in tabular format, for one batch using current and proposed methods, if new analytical procedures are implemented 6 (P.5.6) Justification for the addition or deletion of the tests and limits			
3.2.P.4 Control of excipients				
33	**Change in source of an excipient from a TSE risk to a material of vegetable or synthetic origin**			
33		1	1	**AN**

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
	Conditions to be fulfilled 1 No change in the excipient and FPP release and shelf-life specifications			
	Documentation required 1 Declaration from the manufacturer of the excipient that it is entirely of vegetable or synthetic origin			
34	**Change in the specifications or analytical procedures for an excipient involving:**			
34 a	deletion of a non-significant in-house parameter	2	1-3	**AN**
34 b	addition of a new test parameter or analytical procedure	2–3	1–2	**AN**
34 c	tightening of specification limits	1-2, 4	1–2	**AN**
34 d	change or replacement of an analytical procedure	2–3	1–2	**Vmin**
	Conditions to be fulfilled 1 The change is within the range of currently accepted limits 2 The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns 3 Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way 4 No change in the analytical procedure			
	Documentation required 1 Justification for the change 2 (P.5) Comparative table of currently accepted and proposed specifications, justification of the proposed specifications and details of procedure and summary of validation of any new analytical procedure (if applicable) 3 Justification to demonstrate that the parameter is not critical			
35	**Change in specifications of an excipient to comply with an officially recognised pharmacopoeia**			
35		1	1	**AN**
	Conditions to be fulfilled 1 No change to the specifications other than those required to comply with the pharmacopoeia (e.g. no change in particle size distribution)			
	Documentation required 1 Comparative table of currently accepted and proposed specifications for the excipient			
3.2.P.5 Control of FPP				

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
36				
36 a	Change in the standard claimed for the FPP from an in-house to an officially recognised pharmacopoeial standard	1-3	1-5	**AN**
36 b	Update to the specifications to comply with an officially recognised pharmacopeial monograph as a result of an update to this monograph to which the FPP is Controlled	None	1, 3, 5	**AN**
	Conditions to be fulfilled 1 The change is made exclusively to comply with the officially recognized pharmacopoeia 2 No change to the specifications that results in a potential impact on the performance of the FPP (e.g. dissolution test) 3 No deletion of or relaxation of any of the tests, analytical procedures or acceptance criteria of the specifications. Any deletion or relaxation of the tests should meet the conditions of 37a or 37d and should follow the corresponding reporting types			
	Documentation required 1 (P.5.1) Copy of the proposed FPP specifications dated and signed by authorised personnel and a comparative table of currently accepted and proposed specifications 2 (P.5.3) Where an in-house analytical procedure is used and a pharmacopeial standard is claimed, results of an equivalence study between the in-house and pharmacopeial methods 3 (P.5.4) Description of the batches, certificates of analysis for at least one batch (minimum pilot-scale) and comparative summary of results, in tabular format, for one batch using current and proposed procedures, if new analytical procedures are implemented 4 (P.5.6) Justification for the proposed FPP specifications 5 (P.5.3) Demonstration of the suitability of the monograph to control the FPP			
37	**Change in the specifications of the FPP involving test parameters and acceptance criteria**			
37 a	deletion of a test parameter	5	1–6	**AN**
37 b	addition of a test parameter	2-4, 7	1–6	**AN**
37 c	tightening of an acceptance criterion	1–2	1, 6	**AN**
37 d	relaxation of an acceptance criterion	2, 4, 6–7	1, 5–6	**IN**

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
37 e	replacement of a test parameter	2–4, 6-7	1–6	**IN**
	Conditions to be fulfilled 1 The change is within the range of currently accepted limits 2 The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns 3 Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way 4 No additional impurity found over the ICH identification threshold 5 The deleted test has been demonstrated to be redundant with respect to the remaining tests 6 The change to the specifications does not affect the stability and the performance of the product 7 The change does not concern sterility testing			
	Documentation required 1 (P.5.1) Copy of the proposed FPP specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications 2 (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used 3 (P.5.3) Copies or summaries of validation reports, if new analytical procedures are used 4 (P.5.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalence study between the in-house and pharmacopoeial methods 5 (P.5.4) Description of the batches, certificates of analysis for at least one batch (minimum pilot-scale) and comparative summary of results, in tabular format, for one batch using currently accepted and proposed procedures, if new analytical procedures are implemented 6 (P.5.6) Justification for the proposed FPP specifications			
38	**Change in the analytical procedures for the FPP involving:**			
38 a	deletion of an analytical procedure	5	1, 6	**AN**
38 b	addition of an analytical procedure	3–4, 6–7	1–5	**AN**
38 c 1)	modification or replacement of an analytical procedure	1–4, 6–7	1–5	**AN**
38 c 2)		2–4, 6–7	1–5	**Vmin**
38 d	updating the analytical procedure with an officially recognised pharmacopeial monograph as a result of an update to that Monograph	None	1–5	**AN**

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
38 e	change from an in-house analytical procedure to an analytical procedure in an officially recognised pharmacopeial monograph or from the analytical procedure in one officially recognised pharmacopeial monograph to an analytical procedure in another officially recognised pharmacopeial monograph	2, 7	1–3, 5	**IN**
	Conditions to be fulfilled 1 The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length and other parameters, but do not include variations beyond the acceptable ranges or a different type of column and method), and no new impurities are detected 2 Comparative studies demonstrate that the proposed analytical procedure is at least equivalent to the currently accepted analytical procedure 3 Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way 4 The change does not concern sterility testing 5 The deleted analytical procedure is an alternative method and is equivalent to a currently accepted analytical procedure 6 The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns 7 No new impurities have been detected			
	Documentation required 1 (P.5.1) A copy of the proposed FPP specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications 2 (P.5.2) Copies or summaries of analytical procedures, if new analytical procedures are used 3 (P.5.3) Copies or summaries of validation reports, including verification data for assay or purity methods, if new analytical procedures are used 4 (P.5.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalence study between the in-house and pharmacopoeial methods 5 (P.5.4) Description of the batches, certificates of analysis for at least one batch (minimum pilot-scale) and comparative summary of results, in tabular format, for one batch using currently accepted and proposed analytical procedures			

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
	6 Justification for the deletion of the analytical procedure, with supporting data			
3.2.P.7 Container-closure system				
39	**Replacement or addition of a primary packaging type**			
39 a		1	1-2, 4-6	**Vmin**
39 b		None	1-6	**Vmaj**
	Conditions to be fulfilled 1 The change does not concern a sterile FPP			
	Documentation required 1 Samples of the product as packaged in the new container-closure system 2 (P.2) Data on the suitability of the container-closure system (e.g. extractable/ leachable testing, permeation testing, light transmission) demonstrating equivalent or superior protection compared to the current packaging system. For changes to functional packaging, data to demonstrate the functioning of the new packaging 3 (P.3.5) For sterile FPPs, process validation and/or evaluation studies 4 (P.7) Information on the proposed primary packaging type (e.g. description, materials of construction of primary packaging components, specifications, and results of transportation studies, if appropriate) 5 (P.8.1) Stability summary and conclusions, results for a minimum of two batches of pilot- or production-scale, of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing and where applicable, results of photostability studies 6 (P.8.2) Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of the proposed product into the long-term stability programme, unless data were provided in documentation 5			
40	**Change in the package size involving:**			
40 a	change in the number of units (e.g. tablets, ampoules, etc.) in a package	1-2	1-2	**Vmaj**
40 b 1)	change in the fill weight or fill volume of non-parenteral multidose products	1-3	1-2	**IN**
40 b 2)	change in the fill weight or fill volume of non-parenteral multidose products	1-2	1-2	**Vmin**
	Conditions to be fulfilled 1 The change is consistent with the posology and treatment duration accepted in the SmPC			

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
	2 No change in the primary packaging material 3 No increase in the headspace or surface/volume ratio			
	Documentation required 1 Justification for the new pack-size, indicating that the new size is consistent with the dosage regimen and duration of use as accepted in the SmPC 2 (P.8.2) A written commitment that stability studies will be conducted in accordance with the MCA *Guideline for Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products* for products where stability parameters could be affected			
41	**Change in the shape or dimensions of the container or closure for:**			
41 a	non-sterile FPPs	1–2	1–3	**AN**
41 b	sterile FPPs	1–2	1–4	**Vmin**
	Conditions to be fulfilled 1 No change in the qualitative or quantitative composition of the container and/or closure 2 The change does not concern a fundamental part of the packaging material, which could affect the delivery, use, safety or stability of the FPP			
	Documentation required 1 Samples of the product packaged in the new container-closure system 2 (P.7) Information on the proposed container-closure system (e.g., description, materials of construction, and specifications) 3 (P.8.1) In the case of changes to the thickness of a packaging component or for sterile FPPs: stability summary and conclusions, results for a minimum of two batches of pilot- or production-scale, of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing and, where applicable, results of photostability studies. In the case of a change in the headspace or a change in the surface/volume ratio for non-sterile FPPs, a commitment for the above studies 4 (P.3.5) Evidence of revalidation studies in the case of terminally sterilised products. The batch numbers of the batches used in the revalidation studies should be indicated, where applicable			
42	**Change in qualitative and/or quantitative composition of the immediate packaging material for:**			
42 a	solid FPPs	1 – 3	1 – 3.	**IN**
42 b	semisolid and liquid FPPs	1 – 3	1 – 3	**Vmin**
	Conditions to be fulfilled 1 The change does not concern a sterile FPP 2 No change in the packaging type and material (an example of an allowable change is blister to blister) 3 The relevant properties of the proposed packaging are at least equivalent to those of the currently accepted material			

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
	Documentation required 1 (P.2) Data demonstrating the suitability of the proposed packaging material (e.g. extractable/leachable testing, light transmission, permeation testing for oxygen, carbon dioxide, and moisture) 2 (P.7) Information on the proposed packaging material (e.g. description, materials of construction, and specifications) 3 (P.8.1) Stability summary and conclusions, results of (or a commitment to study in the case of demonstrated equivalent or more protective packaging) a minimum of two batches of pilot- or production-scale, of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing and, where applicable, results of photostability studies			
43	**Change in the specifications of the immediate packaging involving:**			
43 a	tightening of specification limits	1–2	1	**AN**
43 b	addition of a test parameter	2–3	1–2	**AN**
43 c	deletion of a non-critical parameter	2	1, 3	**AN**
	Conditions to be fulfilled 1 The change is within the range of currently accepted limits 2 The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns 3 Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way			
	Documentation required 1 (P.7) Comparative table of currently accepted and proposed specifications, justification of the proposed specifications 2 (P.7) Description of the analytical procedure and summary of validation of the new analytical procedure 3 Documentation to demonstrate that the parameter is not critical			
44	**Change to an analytical procedure on the immediate packaging involving:**			
44 a	minor change to an analytical procedure	1–3	1	**AN**
44 b	other changes to an analytical procedure including addition or replacement of an analytical procedure	2–4	1	**AN**

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
44 c	deletion of an analytical procedure	5	2	**AN**
	Conditions to be fulfilled 1 The method of analysis is based on the same analytical technique or principle (e.g. changes to the analytical procedure are within allowable adjustments to column length and other parameters, but do not include variations beyond the acceptable ranges or a different type of column and method) 2 Appropriate (re)validation studies have been performed in accordance with the relevant guidelines 3 Comparative studies indicate the new analytical procedure to be at least equivalent to the former procedure 4 Any new analytical procedure does not concern a novel 5 The deleted analytical procedure is an alternative method and is equivalent to a currently accepted method			
	Documentation required 1 (P.7) Description of the method and comparative validation results demonstrating that the currently accepted and proposed methods are at least equivalent 2 Documentation to demonstrate the equivalence of the deleted method and a currently accepted method			
45	**Change in any part of the (primary) packaging material not in contact with the FPP formulation (e.g. colour of flip-off caps, colour code rings on ampoules, or change of needle shield)**			
45		1	1–2	**IN**
	Conditions to be fulfilled 1 The change does not concern a fundamental part of the packaging material, which affects the delivery, use, safety or stability of the FPP			
	Documentation required 1 (P.7) Information on the proposed packaging material (e.g. description, materials of construction, and specifications) 2 Sample of the FPP			
46	**Change to an administration or measuring device that is not an integral part of the primary packaging (excluding spacer devices for metered dose inhalers) involving:**			
46 a	addition or replacement	1, 2	1–2	**IN**
46 b	deletion	3	3	**IN**
	Conditions to be fulfilled 1 The proposed measuring device is designed to accurately deliver the required dose for the product concerned in line with the posology, and results of such studies are available 2 The proposed device is compatible with the FPP			

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
	3 The FPP can be accurately delivered in the absence of the device			
	Documentation required 1 (P.2) Data to demonstrate accuracy, precision and compatibility of the device 2 Sample of the device 3 Justification for the deletion of the device			
3.2.P.8 Stability				
47	**Change in the shelf-life of the FPP (as packaged for sale) involving:**			
47 a	reduction	3	1-3	**IN**
47 b	extension	1-2	1-3	**Vmin**
	Conditions to be fulfilled 1 No change to the primary packaging type in direct contact with the FPP and to the recommended conditions of storage 2 Stability data were generated in accordance with the currently accepted stability protocol 3 The change is not necessitated by unexpected events arising during manufacture or because of stability concerns			
	Documentation required 1 (P.5.1) Copy of the currently accepted shelf-life specifications 2 (P.8.1) Proposed shelf-life, summary of long-term stability testing according to currently accepted protocol and test results for a minimum of two pilot- or production-scale batches for a period sufficient to support the proposed shelf-life 3 (P.8.2) Updated post-acceptance stability protocol and stability commitment and justification of change			
48	**Change in the in-use period of the FPP (after first opening or after reconstitution or dilution) involving:**			
48 a	reduction	1	1	**IN**
48 b	extension	None	1-2	**Vmin**
	Conditions to be fulfilled 1 The change is not necessitated by unexpected events arising during manufacture or because of stability concerns			
	Documentation required 1 (P 8) Proposed in-use period, test results and justification of change 2 (P.5.1) Copy of currently accepted end of shelf-life FPP specifications and, where applicable, specifications after dilution or reconstitution			
49	**Change in the labelled storage conditions of the FPP (as packaged for sale), the product during the in- use period or the product after reconstitution or dilution**			

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
49		1	1-2	**Vmin**
	Conditions to be fulfilled 1 The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns			
	Documentation required 1 (P.8.1) If applicable, stability and/or compatibility test results to support the change to the storage conditions 2 (P.8.2) Updated post-acceptance stability protocol and stability commitment and justification of change			