Annex 2 of the Guideline for Variation

Quality Changes, Active Pharmaceutical Ingredient

- CTD 3.2.S API (or Drug Substance)
- CTD 3.2.S.2 Manufacture

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
8	**Replacement or addition of a new manufacturing site or manufacturer of an API involving:**			
8 a 1)	API testing only	1-2, 4	1, 3-4	**IN**
8 a 2)		2, 4	1, 3-4	**Vmin**
8 b 1)	production of API starting material	3–4	No variation is required; such changes are handled as amendments to the APIMF by the APIMF holder	
8 b 2)		4–5	1–2, 12	**IN**
8 b 3)		None	1, 2, 5, 7–8, 12, 13	**Vmaj**
8 c 1)	production of API intermediate	3–4	No variation is required; such changes are handled as amendments to the APIMF by the APIMF holder	
8 c 2)		4, 6	1–2, 12	**IN**
8 c 3)		None	1–2, 5, 7–8, 12, 13	**Vmaj**
8 d 1)	production of API (APIMF procedure)	3, 7–9	1, 2, 6, 8	**IN**
8 d 2)		3, 7, 9	1, 2, 6–8	**Vmin**
8 e 1)	production of API (full dossier)	1, 9-11	1–2, 4, 8–9	**IN**
8 e 2)		None	1, 2, 4, 5, 7–8, 10–11, 13	**Vmaj**
	Conditions to be fulfilled 1 The API is non-sterile 2 The transfer of analytical methods has been successfully undertaken 3 The new site is supported by an APIMF that is currently accepted through the APIMF procedure and the FPP manufacturer holds a valid Letter of Access 4 No change in the FPP manufacturer's API specifications 5 The impurity profile of the API starting material is essentially the same as other accepted sources. The introduction of the new supplier does			

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
	not require the revision of the API manufacturer's API starting material specifications. The route of synthesis is verified as identical to that already accepted 6 Specifications (including in-process, methods of analysis of all materials), method of manufacture and detailed route of synthesis are verified as identical to those already accepted. The introduction of the new supplier does not require the revision of the API manufacturer's API intermediate specifications 7 No change in the FPP release and end-of-shelf-life specifications 8 No difference in impurity profile of the proposed API to be supplied, including organic, inorganic and genotoxic impurities and residual solvents. The proposed API manufacturer's specifications do not require the revision of the FPP manufacturer's API specifications 9 For low-solubility APIs the API polymorph is the same, and whenever particle size is critical (including low-solubility APIs) there is no significant difference in particle size distribution, compared to the API batch used in the preparation of the biobatch 10 Specifications (including in-process controls, methods of analysis of all materials), method of manufacture (including batch size) and detailed route of synthesis are verified as identical to those already accepted (such situations are generally limited to additional sites by the same manufacturer or a new contract manufacturing site with evidence of an acceptable and similar quality system to that of the main manufacturer) 11 Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment is required of viral safety or of 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 agents via human and veterinary medicinal products* (www.emea.europa.eu/ema) or equivalent guidelines of the ICH region and associated countries			
	Documentation required 1 (S.2.1) Name, address, and responsibility of the proposed site or facility involved in manufacture or testing (including block(s) and unit(s)). A valid testing authorisation or a certificate of GMP compliance, if applicable 2 (S.2.2) A side-by-side comparison of the manufacturing flowcharts for production of the API, intermediate, or API starting material (as applicable) at the parent and proposed sites and a tabulated summary of the differences 3 (S.4.3) Copies or summaries of validation reports or method transfer reports, which demonstrate equivalence of analytical procedures to be used at the proposed testing site 4 (S.4.4) Description of the batches, copies of certificates of analysis and batch analysis data (in a comparative tabular format) for at least			

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
	two (minimum pilot- scale) batches of the API from the currently accepted and proposed manufacturers and/or sites 5 Relevant sections of (S) documentation in fulfilment of requirements for full information provided in the dossier under section 3.2.S of the *WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme*: quality part.7 6 The open part of the new APIMF (with a Letter of Access provided in Module 1) and documentation in fulfilment of requirements for the APIMF option under section 3.2.S of the WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product* 7 (P.8.2) If the quality characteristics of the API are changed in such a way that it may impact the stability of the FPP, a commitment to put under stability one production-scale batch of the FPP and to continue the study throughout the currently accepted shelf-life and to immediately report any out of specification results to MCA 8 (S.4.1) A copy of the FPP manufacturer's API specifications 9 (S.2) A declaration from the supplier of the prequalified FPP that the route of synthesis, materials, quality control procedures and specifications of the API and key (ultimate) intermediate in the manufacturing process of the API (if applicable) are the same as those already accepted 10 A discussion of the impact of the new API on the safety, efficacy and/or quality of the FPP 11 For low solubility APIs where polymorphic form is different or whenever particle size is critical (including low-solubility APIs) where there is a significant difference in particle size distribution compared to the batch used in the biobatch, evidence that the differences do not impact the quality and bioavailability of the FPP 12 Certificates of analysis for at least one batch of API starting material or intermediate (as applicable) issued by the new supplier and by the API manufacturer. Comparative batch analysis of final API manufactured using API starting material or intermediate (as applicable) from the new source and from a previously accepted source. For an alternative source of plant-derived starting material, control of pesticide residues must be established. This can either be in the form of an attestation from the starting material supplier that no pesticides are used during the growth of the plant material, or by providing the results of pesticide screening from one batch of the starting material 13 An analysis of the impact of the change in supplier with respect to the need for API stability studies and a commitment to conduct such studies if necessary			
9	**Change or addition of a manufacturing block or unit at a currently accepted site of API manufacture**			
9 a		1–5	No variation is required; such changes are handled	

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
			as amendments to the APIMF by the APIMF holder	
9 b		1, 3–5	1–4	**IN**
	Conditions to be fulfilled 1 The API is non-sterile 2 The API manufacturing block or unit is currently accepted through the APIMF procedure 3 The same quality system covers currently accepted and proposed units or blocks 4 For low-solubility APIs, there is no change in the polymorphic form and whenever particle size is critical (including low solubility APIs) there is no significant change to the particle size distribution compared to the API batch used in the preparation of the biobatch 5 No change in the route of synthesis, quality control procedures and specifications of the API and key (ultimate) intermediate in the manufacturing process of the API (if applicable). Minor changes in the equipment are acceptable			
	Documentation required 1 (S.2) A declaration from the supplier of the FPP that the route of synthesis, quality control procedures and specifications of the API and key (ultimate) intermediate in the manufacturing process of the API (if applicable) are the same as those already accepted 2 (S.2.1) Name, address, and responsibility of the proposed production site or facility involved in manufacturing and/or testing (including block(s) and unit(s)). A valid manufacturing and/or testing authorisation and a certificate of GMP compliance, if available 3 (S.4.4) Description of the batches, copies of certificates of analysis and batch analysis data (in a comparative tabular format) for at least two (minimum pilot-scale) batches of the API from the currently accepted and proposed units or blocks 4 (S.2.2) A summary of differences between manufacture and control of the API at the currently accepted and proposed units or blocks, if applicable			
10	**Change in the manufacturing process of the API**			
10 a		1–3, 9	1–2, 8	**AN**
10 b 1)		1–2, 4, 6–9	3–4, 11–12	**IN**
10 b 2)		1–2, 4, 6–8, 10	3–4, 11–12	**Vmin**
10 c		1–2, 4-7	3–4, 11–12	**Vmin**
10 d		None	2–14	**Vmaj**
	Conditions to be fulfilled 1 No change in the physical state (e.g. crystalline, amorphous) of the API			

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
	2 For low solubility APIs, there is no change in the polymorphic form and whenever particle size is critical (including low solubility APIs) there is no significant change in the particle size distribution compared to that of the API batch used in the preparation of the biobatch 3 The API manufacturing site is currently accepted through the APIMF procedure 4 Where materials of human or animal origin are used in the process, the manufacturer does not use any new process for which assessment of viral safety data or TSE risk assessment is required 5 No change in the route of synthesis (i.e. intermediates remain the same) and there are no new reagents, catalysts or solvents used in the process 6 No change in qualitative and quantitative impurity profile or in physi-cochemical properties of the API 7 The change does not affect the sterilization procedures of a sterile API 8 The change involves only steps before the final intermediate 9 The change does not require revision of the starting material, interme-diate or API specifications 10 The change does not require revision of the API specifications			
	Documentation required 1 A copy of the APIMF amendment acceptance letter 2 (P.8.2) If the quality characteristics of the API are changed in a way that may impact the stability of the FPP, a commitment to put under stability one production-scale batch of the FPP and to continue the study throughout the currently accepted shelf-life and to immediately report any out of specification results to MCA 3 (S.2.2) A side-by-side comparison of the current process and the new process 4 (S.2.2) A flow diagram of the proposed synthetic process(es) and a brief narrative description of the proposed manufacturing process(es) 5 (S.2.3) Information on the quality and controls of the materials (e.g., raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed API, where applicable 6 (S.2.3) Either a TSE CEP for any new source of material or, where ap-plicable, documented evidence that the specific source of the material that carries a risk of TSE has previously been assessed by the compe-tent authority and shown to comply 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 agents via human and veterinary medicinal products* (www.emea.europa.eu/ema) or equivalent guidelines of the ICH re-gion and associated countries 7 (S.2.4) Information on controls of critical steps and intermediates, where applicable 8 (S.2.5) Evidence of process validation and/or evaluation studies for			

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
	sterilization, if applicable 9 (S.3.1) Evidence for elucidation of structure, where applicable 10 (S.3.2) Information on impurities 11 (S.4.1) A copy of currently accepted specifications of API (and starting material and intermediate, if applicable) 12 (S.4.4) Description of the batches, certificates of analysis or batch analysis report, and summary of results, in a comparative tabular format, for at least two batches (minimum pilot-scale) manufactured according to the current and proposed processes 13 (S.7.1) Results of two batches of at least pilot-scale with a minimum of three months of accelerated (and intermediate as appropriate) and three months of long-term testing of the proposed API 14 For low-solubility APIs where the polymorphic form has changed or whenever particle size is critical (including low-solubility APIs) where there is dissimilar particle size distribution compared to the batch used in the biobatch, evidence that the differences do not impact the quality and bioavailability of the FPP			
11	**Change in the in-process tests or limits applied during the manufacture of the API:**			
11 a	any change in the manufacturing process controls	1	No variation is required; such changes are handled as amendments to the APIMF by the APIMF holder	
11 b	tightening of in process limits	2–4	1	**AN**
11 c	addition of a new in-process test and limit	2–5	1–5	**AN**
11 d	addition or replacement of an in–process test as a result of a safety or quality issue	None	1–5, 7, 8–10	**Vmin**
11 e 1)	deletion of an in–process test	2, 6–7	1–3, 6	**AN**
11 e 2)		None	1-3, 5, 7–10	**Vmaj**
11 f	relaxation of the in-process test limits	None	1–3, 5, 7–10	**Vmaj**
	Conditions to be fulfilled 1 API manufacturing site is currently accepted through the APIMF procedure 2 The change is not necessitated by unexpected events arising during manufacture e.g. a new unqualified impurity or a change in total impurity limits 3 The change is within the range of currently accepted limits 4 The analytical procedure remains the same, or changes to the analytical procedure are minor			

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
	5 Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way 6 The affected parameter is non-significant 7 The change does not affect the sterilisation procedures of a sterile API			
	Documentation required 1 A comparison of the currently accepted and the proposed in-process tests 2 (S.2.2) Flow diagram of the proposed synthetic process(es) and a brief narrative description of the proposed manufacturing process(es) 3 (S.2.4) Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed API 4 Details of any new non-pharmacopoeia analytical method and validation data where relevant 5 Justification for the new in-process test and/or limits 6 Justification and/or risk-assessment showing that the parameter is non-significant 7 (S.2.5) Evidence of process validation and/or evaluation studies for sterilisation, where applicable 8 (S.3.2) Information on impurities, if applicable 9 (S.4.1) Copy of currently accepted specifications of API (and intermediates, if applicable) 10 (S.4.4) Description of the batches, certificates of analysis or batch analysis report and summary of results, in a comparative tabular format, for at least two batches (minimum pilot-scale) for all specification parameters			
12	**Change in batch size of the API or intermediate involving:**			
12 a	up to 10-fold compared to the currently accepted batch size	1–2, 4, 6	1, 3–4	**AN**
12 b 1)	downscaling	1–4	1, 3–4	**AN**
12 b 2)		1–3	1 –4	**IN**
12 c	any change in scale (APIMF procedure)	5	1–2, 4–5	**AN**
12 d	more than 10-fold increase compared to the currently accepted batch size	1–2, 4, 6	1, 3–4	**Vmin**
	Conditions to be fulfilled 1 No changes to the manufacturing process other than those necessitated by changes in scale (e.g. use of a different size of equipment) 2 The change does not affect the reproducibility of the process 3 The change is not necessitated by unexpected events arising during manufacture or due to stability concerns 4 The change does not concern a sterile API			

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
	5 The API manufacturing site and batch size is currently accepted through the APIMF procedure 6 The proposed batch size increase is relative to either the originally accepted batch size, or the batch size accepted through a subsequent major or minor variation			
	Documentation required 1 (S.2.5) Where applicable, evidence of process validation and/or evaluation studies for sterilisation 2 (S.4.1) Copy of the currently accepted specifications of the API (and of the intermediate, if applicable) 3 (S.4.4) Batch analysis data (in tabular format) issued by the FPP manufacturer for a minimum of two batches each of the currently accepted batch size and the proposed batch size 4 A copy of the APIMF amendment acceptance letter			
13	**Change or addition of a manufacturing block or unit at a currently accepted site of API manufacture involving:**			
13 a	any change	1	No variation is required; such changes are handled as amendments to the APIMF by the APIMF holder	
13 b	tightening of the specification limits	2–4	1–3	**AN**
13 c	minor change to an analytical procedure	5–7	2–3	**AN**
13 d	addition of a new specification parameter and a corresponding analytical procedure where necessary	2, 7–9	1-3	**AN**
13 e	deletion of a specification parameter or deletion of an analytical procedure	2, 10	1–4	**AN**
13 f	addition or replacement of a specification parameter as a result of a safety or quality issue	None	1–3, 5	**Vmin**
13 g	relaxation of the currently accepted specification limits for solvents, reagents, catalysts and raw Materials	4, 7, 9–10	1, 3–4	**IN**
13 h	relaxation of the currently accepted specification limits for API starting materials and Intermediates	None	1–3, 5	**Vmaj**

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
	Conditions to be fulfilled 1 API manufacturing site is currently accepted through the APIMF procedure 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 change is within the range of currently accepted limits 4 The analytical procedure remains the same 5 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) 6 Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated analytical procedure is at least equivalent to the former analytical procedure 7 No change to the total impurity limits; no new impurities are detected 8 Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way 9 The change does not concern a genotoxic impurity 10 The affected parameter is non-significant or the alternative analytical procedure has been previously accepted			
	Documentation required 1 Comparative table of currently accepted and proposed specifications 2 (S.2.3) Information on the quality and controls of the materials (e.g. raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the proposed API, where applicable 3 (S.2.4) Information on intermediates, where applicable 4 Justification and/or risk assessment showing that the parameter is non-significant 5 (S.3.2) Information on impurities, where applicable			
3.2.S.4 Control of the API by the API manufacturer				
14	**Changes to the test parameters, acceptance criteria, or analytical procedures of the API manufacturer that do not require a change to the FPP manufacturer's API specifications involving:**			
14 a	API supported through the APIMF procedure	1–2	No variation is required; such changes are handled as amendments to the associated APIMF.	
14 b	API not supported through the APIMF procedure	2	1–4	**IN**
	Conditions to be fulfilled 1 The revised test parameters, acceptance criteria, or analytical procedures have been submitted as amendments to the associated APIMF			

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
	and accepted 2 The API manufacturer has provided the relevant documentation to the FPP manufacturer. The FPP manufacturer has considered the API manufacturer's revisions and determined that no consequential revisions to the FPP manufacturer's API test parameters, acceptance criteria, or analytical procedures are required to ensure that adequate control of the API is maintained			
	Documentation required 1 (S.4.1) Copy of the current and proposed API specifications dated and signed by the API manufacturer 2 (S.4.2) Copies or summaries of analytical procedures, if new analytical procedures are used 3 (S.4.3) Copies or summaries of validation reports for new or revised analytical procedures, if applicable 4 Justification as to why the change does not affect the FPP manufacturer's specifications			
3.2.S.4 Control of the API by the FPP manufacturer				
15	**Change to the test parameters or acceptance criteria of the API specifications of the FPP manufacturer involving:**			
15 a	updating a test parameter or acceptance criterion controlled in compliance with an officially recognised pharmacopoeial monograph as a result of an update to this monograph to which the API is controlled.	11	1–5	**AN**
15 b 1)	deletion of a test parameter	1–2	1, 6	**AN**
15 b 2)		10	1, 6, 8	**IN**
15 b 3)		10	1, 6, 8	**Vmaj**
15 c 1)	addition of a test parameter	1, 4–8	1–6	**AN**
15 c 2)		1, 5–6, 10	1–6, 8	**IN**
15 c 3)		1, 5–6	1–6	**Vmin**
15 c 4)		None	1–7	**Vmaj**
15 d 1)	replacement of a test parameter	1, 5–8	1–6	**IN**
15 d 2)		5, 7, 10	1–6, 8	**Vmin**
15 d 3)		None	1–7	**Vmaj**
15 e	tightening of an acceptance criterion	1, 3, 9	1, 6	**AN**
15 f 1)	relaxation of an acceptance criterion	1, 5–9	1, 6	**IN**
15 f 2)		5, 7, 10	1, 6, 8	**Vmin**

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
15 f 3)		None	1, 6-7	**Vmaj**
	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 2 The deleted test has been demonstrated to be redundant with respect to the remaining tests 3 The change is within the range of currently accepted acceptance criteria 4 Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way 5 For insoluble APIs there is no change in the polymorphic form and whenever particle size is critical (including low-solubility APIs) there is no change in particle size distribution acceptance criteria 6 No additional impurity found over the ICH identification threshold 7 The change does not concern sterility testing 8 The change does not involve the control of a genotoxic impurity 9 The associated analytical procedure remains the same 10 The change has resulted from a revision of the API manufacturer's specifications and is accepted as part of an APIMF amendment 11 No change is required in FPP release and shelf-life specifications			
	Documentation required 1 (S.4.1) A copy of the proposed API specifications (of the FPP manufacturer) dated and signed by authorised personnel and a comparative table of currently accepted and proposed specifications. In addition, if the change has resulted from a revision to the API manufacturer's specifications, a copy of the API specifications (of the API manufacturer) dated and signed by authorised personnel and a comparative table of currently accepted and proposed specifications 2 (S.4.2) Copies or summaries of analytical procedures, if new analytical procedures are used 3 (S.4.3) Copies or summaries of validation or verification reports issued by the FPP manufacturer, if new analytical procedures are used 4 (S.4.3) 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 (S.4.4) Description of the batches, certificates of analysis or batch analysis report, and summary of results in tabular format, for at least one batch if new tests and/or analytical methods are implemented 6 (S.4.5) Justification of the proposed API specifications (e.g. test parameters, acceptance criteria, or analytical procedures) 7 (P.2) Where changes have occurred to the particle size criteria of an insoluble API or wherever particle size is critical, evidence is provided that the changes do not affect the in vitro release properties and bioavailability of the FPP. In general, it is sufficient to provide multipoint			

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
	comparative dissolution profiles (in three media covering the physiological range (pH 1.2 or (0.1N HCl), 4.5 and 6.8) without surfactant) for one batch of FPP manufactured using API that meets the proposed criteria; one batch of FPP manufactured using API that meets the currently accepted criteria; and data on the FPP batch used in the marketing authorisation (registration) bioequivalence study. However, if the routine dissolution medium contains a surfactant, the MAH should contact MCA for advice. For changes to the polymorph of an insoluble API the MAH should contact MCA for advice before embarking upon any investigation 8 Copy of the APIMF amendment acceptance letter			
16	**Change to the analytical procedures used to control the API by the FPP manufacturer involving:**			
16 a	change in an analytical procedure as a result of a revision to the officially recognised pharmacopeial monograph to which the API is controlled	None	1–3	**AN**
16 b	change from a currently accepted in-house analytical procedure to an analytical procedure in an officially recognised pharmacopoeia or from the analytical procedure in one officially recognised pharmacopoeia to an analytical procedure in another official recognised Pharmacopoeia	None	1–4	**IN**
16 c 1)	addition of an analytical procedure	1–3	1–3	**AN**
16 c 2)		3, 8	1–3, 5	**AN**
16 c 3)		8	1–3, 5	**Vmin**
16 c 4)		None	1–3	**Vmaj**
16 d 1)	modification or replacement of an analytical procedure	1–6	1–4	**AN**
16 d 2)		2–3, 5–6, 8	1–5	**AN**
16 d 3)		1–3, 5–6	1–4	**Vmin**
16 d 4)		5–6, 8	1–5	**Vmin**
16 d 5)		None	1–4	**Vmaj**
16 e 1)	deletion of an analytical procedure	6–7	1, 6	**AN**
16 e 2)		6, 8	1, 5, 6	**IN**
16 e 3)		None	1, 6	**Vmaj**

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
	Conditions to be fulfilled 1 Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way 2 The change is not necessitated by failure to meet specifications resulting from unexpected events arising during manufacture, or because of stability concerns 3 No new impurities have been detected as a result of the use of the new analytical method 4 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 5 Comparative studies are available demonstrating that the proposed analytical procedure is at least equivalent to the currently accepted analytical procedure 6 The change does not concern sterility testing 7 The deleted analytical procedure is an alternative method and is equivalent to a currently accepted method 8 The new or modified analytical method is identical to that used by the API manufacturer and has been accepted as part of an amendment to the associated APIMF			
	Documentation required 1 (S.4.1) Copy of the proposed API specifications dated and signed by authorized personnel and a comparative table of currently accepted and proposed specifications 2 (S.4.2) Copies or summaries of analytical procedures if new or significantly modified analytical procedures are used 3 (S.4.3) Copies or summaries of validation or verification reports issued by the FPP manufacturer if new or significantly modified analytical procedures are used 4 (S.4.4) Comparative analytical results demonstrating that the proposed analytical procedures are at least equivalent to the accepted analytical procedures 5 A copy of the APIMF acceptance letter 6 (S.4.5) Justification for the deletion of the analytical procedure, with supporting data			
3.2.S.6 Container Closure System				
17	**Change or addition of a manufacturing block or unit at a currently accepted site of API manufacture**			
17 a	change in the immediate packaging (primary and components) for storage	3, 4	1–2, 4	**AN**
17 b		1-2, 4	2-3	**IN**
17 c		4	1-3	**Vmin**

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
	Conditions to be fulfilled 1 Results demonstrate that the proposed primary packaging type is at least equivalent to the currently accepted primary packaging type with respect to its relevant properties (e.g. including results of transportation or interaction studies, and moisture permeability among others) 2 The change does not concern a sterile API 3 The change has previously been accepted through the APIMF procedure 4 The change is not the result of stability issues			
	Documentation required 1 (S.2.5) Evidence of process validation and/or evaluation studies for sterilisation if different from the current process 2 (S.6) Information on the proposed primary packaging (e.g., description and specifications) and data in fulfilment of condition 1. 3 (S.7.1) Results of (or a commitment to study in the case of demonstrated equivalent or more protective packaging) a minimum of 3 months of accelerated (and intermediate, as appropriate) and 3 months of long-term testing of the API in the proposed primary packaging type 4 A copy of the APIMF amendment acceptance letter			
18	**Change in the specifications of the immediate packaging for the storage and shipment of the API involving:**			
18 a	tightening of specification limits	1–2	1	**AN**
18 b	addition of a test parameter	2–3	1–3	**AN**
18 c	deletion of a non-critical parameter	2	1, 4	**AN**
18 d	any change (APIMF procedure)	4	No variation is required; such changes are handled as amendments to the associated APIMF	
	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 The change has previously been accepted through the APIMF procedure			
	Documentation required 1 (S.4.5) Comparative table of currently accepted and proposed specifications, justification of the proposed specifications 2 (S.4.2) Details of method and summary of validation of new analytical procedure			

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
	3 (S.6) Certificate of analysis for one batch 4 Justification to demonstrate that the parameter is not critical			
19	**Change to an analytical procedure on the immediate packaging of the API involving:**			
19 a	minor change to an analytical procedure	1–3	1.	**AN**
19 b	other changes to an analytical procedure including addition or replacement of an analytical procedure	2-4	1	**AN**
19 c	deletion of an analytical procedure	5	2	**AN**
19 d	any change (APIMF procedure)	6	No variation is required; such changes are handled as amendments to the associated APIMF	
	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 currently accepted procedure 4 Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way 5 The deleted analytical procedure is an alternative method and is equivalent to a currently accepted method 6 The change has previously been accepted through the APIMF procedure			
	Documentation required 1 (S.6) Comparative validation results demonstrating that the currently accepted and proposed procedures are at least equivalent 2 Justification for deletion of the analytical procedure			
3.2.S.7 Stability				
20	**Change in the retest period or shelf-life of the API involving:**			
20 a	any change (APIMF procedure)	4	4	**IN**
20 b	reduction	3	1–2	**IN**
20 c	extension	1–2	1–3	**Vmin**

	Description of Change	Conditions to be fulfilled	Documentation required	Reporting Type
	Conditions to be fulfilled 1 No change to the primary packaging in direct contact with the API or to the recommended condition 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 4 The revised retest period has previously been accepted through the APIMF procedure			
	Documentation required 1 (S.7.1) Proposed retest period or shelf-life, summary of stability testing according to currently accepted protocol and test results 2 (S.7.2) Updated post-acceptance stability protocol and stability commitment and justification of change, when applicable 3 (S.7.3) Stability data to support the change 4 A copy of the APIMF acceptance letter			
21	**Change in the retest period or shelf-life of the API involving:**			
21 a	any change in storage conditions (APIMF procedure)	1	1	**IN**
21 b	any change in storage conditions	2	2	**Vmin**
	Conditions to be fulfilled 1 The revised storage conditions have previously been accepted through the APIMF procedure 2 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 A copy of the APIMF acceptance letter 2 (S.7.1) Stability and/or compatibility test results to support the change to the storage conditions			