

GUIDANCE ON AMENDMENTS TO AN ACTIVE PHARMACEUTICAL INGREDIENT MASTER FILE (APIMF) SUBMITTED IN SUPPORT OF A PREQUALIFIED PHARMACEUTICAL PRODUCT (FPP) OR PREQUALIFIED ACTIVE PHARMACEUTICAL INGREDIENT (API)

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1. INTRODUCTION

1.1. Background

This guidance document is technically and structurally influenced by the WHO “Guidance on variations to a prequalified product” (see WHO Technical Report Series 981, Annex 3, 2013). It is intended to complement that document by providing guidance to holders of an APIMF on the requirements with respect to changes to the details of their active pharmaceutical ingredient master file (APIMF).

An APIMF holder may submit an APIMF to the Prequalification Team: medicines (PQTm) in support of an application for a prequalified API (see WHO technical Report Series 953, Annex 4, 2009) or in support of a FPP seeking prequalification (WHO Technical Report Series 948, Annex 4, 2008), or both.

APIMF holders are required to make changes to the details of their APIMF to reflect changes in API preparation and control. Such changes, whether administrative or substantive, are referred to as amendments and may be subject to acceptance by PQTm before implementation.

Technical requirements for the different types of amendments are set out in this guidance document in order to facilitate the submission of appropriate documentation by APIMF holders and their assessment by PQTm, and to ensure that ultimately such changes do not give rise to health concerns.

The procedure for submitting amendments is not within the scope of this guidance. Advice on the procedure for submitting an amendment, associated application forms and review timelines can be found on the PQTm website and may be updated from time to time. APIMF holders are advised to consult the website whenever considering the submission of an amendment.

1.2. Objectives

This guidance is intended to:

1. assist APIMF holders with the classification of changes made to their APIMF
2. provide guidance on the technical and other general data requirements to support changes to the details of the API.

1.3. Scope and application

This guidance applies to APIMF holders intending to make changes to the details of their APIMF. This guidance should be read in conjunction with the *WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part* (Technical Report Series 970, Annex 4, 2012) as well as other related WHO guidelines.

This guidance document applies to APIMFs submitted either in support of a prequalified finished pharmaceutical product (FPP) or a prequalified API.

This guidance document is applicable only to APIs manufactured by chemical synthesis or semi-synthetic processes. APIs produced from fermentation, or of biological, biotechnological or herbal origin are treated as special cases. APIMF holders are requested to contact PQTm when planning changes to such APIs.

For amendments that require generation of stability data, the stability studies required, including commitment batches, should always be continued to cover the currently-accepted retest or shelf-life period. PQTm should be informed immediately if any problems with stability become apparent during storage, e.g. outside specification or potentially outside specification.

Some amendments may require the submission of additional amendments. For any given change, the APIMF holder should consider whether multiple amendments may be required.

For APIMFs that support a prequalified API: where a revision to the Confirmation of Prequalification (CPQ) document is required as a result of a change, a revised CPQ will be sent to the applicant.

1.4. APIMF holder obligations

The obligation of APIMF holders to notify changes in API details does not end with the submission of an applicable amendment. Having complied with the amendment requirements, the APIMF holder should inform associated FPP manufacturers of relevant changes so that the FPP manufacturer can consider the implications of the changes for its own product and also determine whether a subsequent FPP variation is required.

Since the FPP manufacturer is best placed to determine the significance to its product of an API-related change, API manufacturers are encouraged to announce all changes to their recipient FPP manufacturers.

For manufacturers of a prequalified API: if the APIMF change results in the revision of the CPQ, the revised CPQ should also be forwarded to associated FPP manufacturers.

2. GUIDANCE FOR IMPLEMENTATION

2.1. Reporting types

The definitions outlined in the following reporting types are intended to provide guidance with respect to the classification of changes. Specific change examples are provided. However, any change that is not cited here should be considered as major. Whenever the APIMF holder is unclear about the classification of a particular change, PQTm should be contacted. It remains the responsibility of the APIMF holder to submit relevant documentation to confirm that the change will not have a negative impact on the quality of the product.

The general principle for determining the appropriate amendment for a change begins with determining whether the proposed change meets the conditions and documentation requirements of the lowest level of change category. If the proposed change does not comply with the requirements for this category, the applicant should proceed to check compliance with the next level of change category. These steps should be repeated until a specific change category is determined. Should the change not meet the requirements of any of the specified change categories, it should be considered to be a major amendment.

Several individual changes to a single APIMF can be grouped together, particularly if the change affects common sections of the APIMF common technical document (CTD) document. However, in doing so the amendment will be considered as the highest risk type, e.g. an amendment grouping both a minor change and a major change will be classified as a major change.

APIMF holders are also advised to exercise caution whenever several changes are envisaged. Although individual changes may be classified as a particular reporting type, classification at a higher risk category may be warranted as a result of the composite effect of these changes. In all such cases, APIMF holders are advised to contact PQTm before submitting the amendment application, in order to obtain guidance in classifying such changes.

2.1.1. Notifications

Notifications are changes that are likely to have no minimal or no adverse effects on the overall quality of the API. Such notifications do not require prior acceptance, but must be notified to PQTm immediately (immediate APIMF notification (AIN)), or within 12 months following implementation (annual APIMF notification (AAN)) of the change.

In some specific circumstances, a notification (AIN or AAN) may be rejected, with the result that the APIMF holder must cease applying the already implemented change.

Annual APIMF notification (AAN)

APIMF holders must satisfy themselves that their APIMF meets each of the criteria for the change. The change should be summarized as part of the notification. However, with the exception of revised and authorized API specifications, the documentation indicated does not have to be submitted. The documentation indicated for AANs should be available on request or at the time of inspection. AAN applications should be submitted to PQTm within 12 months of implementation of the changes. For convenience, APIMF holders may group several AAN changes as a single submission, or submit these together with a new APIMF version.

Immediate APIMF notification (AIN)

APIMF holders must satisfy themselves that they meet each of the criteria for the change and submit all required documentation with the notification application. Such changes should be notified immediately upon implementation. They can be considered to have been accepted from the date of confirmation of receipt, provided no objection was raised during the time period indicated on the PQTm website for such a change.

2.1.2. Minor amendment (Amin)

Minor amendments are changes that may have minor effects on the overall quality of the API. APIMF holders must satisfy themselves that they meet each of the criteria for the change and submit all required documentation with the amendment application.

Such amendments can be implemented provided no objection letter was issued during the time period indicated on the PQTm website. Should questions arise during this period, the change cannot be implemented until a letter of acceptance has been received from PQTm.

2.1.3. Major amendment (Amaj)

Major amendments are changes that could have major effects on the overall quality of the API. The documentation required for the changes included in this reporting type should be submitted. Acceptance by PQTm must be received required before the changes can be implemented. A letter of acceptance will be issued for all major amendments when the amendment is considered acceptable.

2.2. New APIMF versions

A unique feature of an APIMF is that it may be used at different times to support multiple FPP dossiers. The details of the APIMF submitted in support of the first FPP application are likely to have changed by the time it is used to support a further FPP application.

The availability of a complete and current APIMF outlining the accepted preparation, control and stability of the API is therefore an important resource for assessors and FPP manufacturers wishing to use the APIMF. For this reason APIMF holders are required to submit at regular intervals a complete and updated version of the APIMF that matches the approved details.

Revised versions of an APIMF should not include any AIN, Amin or Amaj changes that have not already been accepted, but may include new type AAN changes. Amendments should not be made after a revised APIMF has been submitted and awaits acceptance.

Conversely, revised versions of the APIMF should not be submitted as supporting documentation for amendments. Only the revised sections relating to the amendment are required.

A feature of the amendment procedure is that a new version of an APIMF is expected every 24 months. When no changes have been made to API details during this period, an amendment attesting to this should be submitted instead. The 24-month period should be calculated from the date of acceptance of the APIMF or date of acceptance of the latest APIMF version. A new version of an APIMF may be submitted at shorter intervals.

2.3 Criteria to be met

For each change, particular circumstances have been identified for which lesser reporting requirements (AIN, AAN or Amin) are possible. A change that does not meet each of the criteria stipulated for these specific circumstances is considered to be a major amendment.

In some circumstances, Amaj categories have been specifically stated for a given amendment in order to indicate to APIMF holders what documents should be provided. This is for informational purposes only. The list of documentation is not intended to be comprehensive and further documentation may be required. For all changes, it remains the responsibility of the APIMF holder to provide all necessary documents to demonstrate that the change does not have a negative effect on the quality of the API.

2.4. Documentation requirements

Full details on the procedure and documentation requirements for amendments and APIMFs are included in separate documents that are available on the PQTm website.

This document identifies a number of documents that relate to each amendment. They are organized according to the CTD structure as supporting data. Irrespective of the documents specified, APIMF holders should ensure that they have provided all relevant information to support the amendment. In general, an amendment application should include:

1. An amendment application form (a template can be downloaded from the PQTm website). All sections of this form should be completed and the document signed. Electronic versions of the application form, both as a Word Document and a scanned signed PDF file, should be submitted, in addition to the printed version.
2. A document describing, discussing and justifying the change.
3. The documents specified in this guidance to be submitted to support the specific amendment category.
4. Replacement sections of the APIMF in CTD format.
5. An updated API Quality Information Summary (API-QIS) (if applicable).
6. The API-QIS provides a summary of the key quality information of the API. For an APIMF that has an agreed QIS, the QIS should be revised and submitted (in Word format only) with each variation application. Any revised sections within the QIS should be highlighted in red. If no change has been made to the QIS following the amendment, the current QIS should be submitted and a statement made in the covering letter that no change has been made to the QIS.

For applicants without a API-QIS: an API-QIS will be provided by PQTm to the applicant at the conclusion of the assessment of the next major amendment or following the submission of the next periodically updated APIMF.

Please note that PQTm reserves the right to request further information not explicitly described in this guidance.

3. GLOSSARY

The definitions provided below apply to the terms used in this guidance. They may have different meanings in other contexts and documents.

Active pharmaceutical ingredient (API)

A substance used in the FPP intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings (see WHO Technical Report Series 961, Annex 10, 2011).

API starting material

A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house (see WHO Technical Report Series 957, Annex 2, 2010).

APIMF holder

The person or company responsible for the submission and maintenance of the APIMF. Typically, this is the API manufacturer but may, on occasion, be an agent representing the API manufacturer.

Biopharmaceutics Classification System (BCS) highly soluble

An API for which the highest dose recommended by WHO (if the API appears on the WHO Model List of Essential Medicines) or highest-dose strength available on the market as an oral solid dosage form (if the API does not appear on the WHO Model List of Essential Medicines) is soluble in 250 ml or less of aqueous media over the pH range of 1.2–6.8 at 37 °C.

Finished pharmaceutical product (FPP)

A finished dosage form of a pharmaceutical product that has undergone all stages of manufacture including packaging in its final container and labeling (see WHO Technical Report Series, No. 953, Annex 3, 2009).

Final intermediate

The reaction intermediate that undergoes synthetic transformation (formation or breaking of covalent bonds) to afford (produce) the API, or more typically the crude API. Purification, (de)-salification or acid-base conversion are not considered to be a synthetic transformation.

In-process control

Check performed during manufacture to monitor or to adjust the process to ensure that the final product conforms to its specifications.

Manufacturer

A company that carries out operations such as production, packaging, repackaging, labelling and relabelling of pharmaceuticals (WHO Technical Report Series 961, Annex 3, 2011).

Officially recognized pharmacopoeia (or compendium)

Those pharmacopoeias recognized by PQTm (i.e. The International Pharmacopoeia (Ph.Int.), the European Pharmacopoeia (Ph.Eur.), the British Pharmacopoeia (BP), the Japanese Pharmacopoeia (JP) and the United States Pharmacopoeia (USP)).

Pilot scale batch

A batch of an API or FPP manufactured, by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For example, for solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is the larger, unless otherwise adequately justified (reference: WHO Technical Report Series, No. 953, Annex 3, 2009).

Production batch

A batch of an API or FPP manufactured at production scale by using production equipment in a production facility as specified in the application (see WHO Technical Report Series, No. 953, Annex 3, 2009).

4. ADMINISTRATIVE CHANGES

Description of change		Conditions to be fulfilled	Documentation required	Reporting type
1	New APIMF version:			
1a	no changes to currently-accepted APIMF version	1	1	AIN (see note 1)
1b	new APIMF version (editorial changes only)	2	2, 3, 4	AIN (see note 1)
1c	new APIMF version	3	4, 5, 6	AIN (see note 1)
Conditions to be fulfilled				
<ol style="list-style-type: none"> The currently-accepted APIMF version remains valid, no change has been made to any detail of the currently-accepted APIMF document. The proposed APIMF version differs from that currently-accepted only by editorial changes or correction of typographical errors. With the exception of AAN type changes, all differences between the proposed and current APIMF have previously been submitted and accepted as amendments (or as additional data provided in response to deficiency letters) or are editorial/typographical changes. 				
Documentation required				
<ol style="list-style-type: none"> A formal declaration should be provided specifying the version number of the current APIMF and stating that no changes have been made to any aspect of the API that would require alteration of the current APIMF. A formal declaration should be provided specifying the version number of the current APIMF document and stating that the proposed APIMF differs from the current APIMF document only with respect to editorial changes or correction of typographical errors. A detailed summary of changes document should be provided specifying the changes made to each section of the current APIMF and the reason for the change. A revised APIMF should be provided that describes all currently-accepted details, and meets all PQTm formatting and documentation requirements. A formal declaration should be provided specifying the version number of the current APIMF document and stating that all differences between the proposed and current APIMF versions have previously been submitted and accepted as amendments, or as additional data provided in response to deficiency letter, or are editorial/typographical changes, or are ANN-type changes. A detailed summary of changes document should be provided specifying the changes made to each section of the current APIMF; the reason for the change; and reference to the specific WHO amendment number supporting the change, or to the date of the cover letter of the response to deficiency letter. In addition a summary of all amendments submitted against the current APIMF should be provided. 				

Note:

1. Due to its unique nature, Amendment 1 should be submitted using the specific application form for this purpose. The amendment can be considered accepted only if an objection letter was not issued by PQTm during the time period indicated on the PQTm website. Although not required for an AIN, amendment acceptance letters and a copy of the current API-QIS will be issued on a routine basis for this specific amendment.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
2	Change in manufacturing site address or APIMF holder name or address:			
2a	change in the name or address of a manufacturer of an intermediate, starting material, or active pharmaceutical ingredient (API)	1	1–3	AIN
2b	change in the name or corporate address of the APIMF Holder	2	1, 3	AIN
Conditions to be fulfilled				
<ol style="list-style-type: none"> 1. No change in the location of the manufacturing site in the manufacturing operations. 2. Confirmation that the APIMF Holder remains the same legal entity 				
Documentation required				
<ol style="list-style-type: none"> 1. A formal document from a relevant official body (e.g. national medicines regulatory authority, companies registrar) in which the new name and/or address is mentioned. 2. Replacement sections for the APIMF resulting from the change in fulfillment of requirements under section 3.2.S of the <i>WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part</i> namely: section 3.2.S.2.1. or section 3.2.S.2.3 (Technical Report Series 970, Annex 4, 2012). 3. A declaration is provided that a new APIMF version will be submitted, in accordance with Amendment 1c, within 24 months of acknowledgement of receipt (or acceptance in the case of an Amaj change) of this amendment. 				

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
3	Deletion of a manufacturing block, site or manufacturer involving:			
3a	production of the API starting material	1	1–3	AAN
3b	production or testing of the API intermediate or API	1, 2	1–3	AIN
Conditions to be fulfilled				
<ol style="list-style-type: none"> At least one other site continues to perform the same function(s) as the site(s) intended to be deleted. The deletion of site is not a result of critical deficiencies in manufacturing. 				
Documentation required				
<ol style="list-style-type: none"> Identification of the manufacturing, packaging and/or testing site to be deleted, in the letter accompanying the application. Replacement sections for the APIMF resulting from the change in fulfillment of requirements under section 3.2.S of the <i>WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part</i> (Technical Report Series 970, Annex 4, 2012), namely: section 3.2.S.2.1. or section 3.2.S.2.3. A declaration is provided that a new APIMF version will be submitted, in accordance with Amendment 1c, within 24 months of acknowledgement of receipt (or acceptance in the case of an Amaj change) of this amendment. 				

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
4a	Change in the numbering system or format of product codes, reference numbers and other documentation.	1, 2	1–3	AAN
4b		1	1–3	AIN
Conditions to be fulfilled				
<ol style="list-style-type: none"> The change in numbering and format is editorial only. There is no change to the detail of the documentation. The changes do not affect the numbering of the API specifications. 				
Documentation required				
<ol style="list-style-type: none"> Clear identification of the changes made and the documents affected. Replacement sections for the APIMF resulting from the change in fulfillment of requirements under section 3.2.S of the <i>WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part</i>, including section 3.2.S.4.1 (Technical Report Series 970, Annex 4, 2012). A declaration is provided that a revised APIMF will be submitted, in accordance with Amendment 1c, within 24 months of acknowledgement of receipt (or acceptance in the case of an Amaj change) of this amendment. 				

5. QUALITY CHANGES

3.2. S.2 Manufacture

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
5	Replacement or addition of a new manufacturing site or manufacturer of an API involving:			
5a.1	API testing only	1–3	1–4, 16	AIN
5a.2		2, 3	1–4, 16	Amin
5b.1	production of API starting material	3, 4, 6	1, 3–7	AIN
5b.2		3, 4	1, 3–7	Amin
5b.3		None	1, 3–8	Amaj
5c.1	production of API intermediate	3, 5, 9	3–6, 9, 10, 17	AIN
5c.2		None	3–6, 9–11	Amaj
5d.1	production of API	1, 7–9	3–5, 8, 12–15, 17	AIN
5d.2		None	3–5, 9, 10, 14, 15	Amaj
Conditions to be fulfilled				
<ol style="list-style-type: none"> The API is non-sterile. The transfer of analytical methods has been successfully undertaken. No change in the API specifications and analytical methods. The impurity profile of the API starting material is essentially the same as other accepted sources. The introduction of the new supplier does 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. Specifications (including in-process controls, 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. The API starting material is not obtained from a fermentation manufacturing process. For APIs that are not BCS-highly-soluble, the API polymorph is the same. (BCS = Biopharmaceutics Classification System.) 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. The new site proposed is part of the same pharmaceutical group as the currently-accepted sites. 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 or the <i>Note</i> 				

for *Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products* of the European Medicines Agency (EMA) or an equivalent ICH guideline.

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)).
2. (S.4.3) Copies or summaries of validation reports or method transfer reports, which demonstrate equivalency of analytical procedures to be used at the proposed testing site.
3. Replacement sections for the APIMF resulting from the change in fulfillment of requirements 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* (Technical Report Series 970, Annex 4, 2012) that may include, but is not limited to, sections 3.2.S.2, 3.2.S.4.3, 3.2.S.4.4 and 3.2.S.7.
4. A declaration that a new APIMF version will be submitted, in accordance with Amendment 1c, within 24 months of acknowledgement of receipt (or acceptance in the case of an Amaj change) of this amendment.
5. (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.
6. Certificates of analysis for at least one batch of API starting material/intermediate (as applicable) issued by the new supplier and by the API manufacturer. Comparative batch analysis (at least one batch) of final API manufactured/intermediate (as applicable) using API starting material/intermediate (as applicable) from the new source and from a previously accepted source.
7. For an alternative source of plant-derived starting material, pesticides residuals control must be provided. Evidence of this must be provided either in the form of an attestation from the supplier of the starting material 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 from the proposed supplier.
8. (S.4.1) A copy of the API specifications.
9. (S.2.1) Evidence supporting the compliance of the site of manufacture with GMP principles (ICHQ7).
10. (S.2.2) A side-by-side tabularized summary of the differences between production of the intermediate or API at the accepted and new site of manufacture.
11. An analysis of the impact of the change in supplier with respect to the need for stability studies and a commitment to conduct such studies if necessary.
12. (S.2.1) A valid GMP certificate issued by an SRA, or reference to a previous successful inspection conducted by the WHO. Evidence should refer to inspections performed within the last three years and pertain to the manufacture of this API at the proposed site.
13. (S.2) A declaration from the API manufacturer that the route of synthesis, materials, quality control procedures and specifications of the API and final intermediate in the manufacturing process of the API (if applicable) are the same as those already accepted.
14. A commitment to initiate stability studies on the first three batches of API manufactured at the new site.
15. (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 manufacturers/sites.
16. A declaration is provided that the testing sites are operating under GMP.
17. A declaration is provided attesting that the new site proposed is part of the same pharmaceutical group as the currently-accepted sites.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
6	Change or addition of a manufacturing block/unit at a currently-accepted site of API manufacture	1–5	1–6	AIN
6a		1, 2, 4, 5	1–6	Amin
Conditions to be fulfilled				
<ol style="list-style-type: none"> 1. The API is non-sterile. 2. The same quality system covers the currently-accepted and proposed units/blocks. 3. Evidence is available, issued by PQTm or a stringent regulatory authority (SRA), supporting the compliance of the block with the principles of Good Manufacturing Practice (GMP) practice (ICHQ7). 4. For APIs that are not BCS-highly-soluble, there is no change in the polymorphic form. 5. No change in the route of synthesis, quality control procedures and specifications of the API and final intermediate in the manufacturing process of the API (if applicable). Minor changes due to different equipment are permitted. 				
Documentation required				
<ol style="list-style-type: none"> 1. (S.2) A declaration from the API manufacturer that the route of synthesis, quality control procedures and specifications of the API and final 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)). Evidence supporting the compliance of the block with the principles of GMP practice (ICHQ7) issued by PQTm or an SRA. 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/blocks. 4. (S.2.2) If applicable, a summary of differences between manufacture and control of the API at the currently-accepted and proposed units/blocks. 5. Replacement sections for the APIMF resulting from the change in fulfillment of requirements under section 3.2.S of the <i>WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part</i> (Technical Report Series 970, Annex 4, 2012) that may include, but is not limited to, sections 3.2.S.2.1, 3.2.S.2.2 and 3.2.S.4.4. 6. A declaration is provided that a new APIMF version will be submitted, in accordance with Amendment 1c, within 24 months of acknowledgement of receipt (or acceptance in the case of an Amaj change) of this amendment. 				

	Description of change	Conditions to be fulfilled	Documentation to be supplied	Reporting type
7a	Change in the manufacturing process of the API <i>Note: The API manufacturing process encompasses all manufacturing steps commencing from the API starting material until the final packaged API</i>	1–7	1–7	AIN
7b		1–6, 8	1–7	Amin
7c		1–5, 9	1–7	Amin
7d		None	1–13	Amaj

Conditions to be fulfilled

1. No change in the physical state (e.g. crystalline, amorphous) of the API.
2. For APIs that are not BCS-highly-soluble, there is no change in the polymorphic form.
3. 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.
4. No change in qualitative and quantitative impurity profile or in physicochemical properties of the API.
5. The change does not affect the sterilization procedures of a sterile API.
6. The change involves only steps before the final intermediate.
7. The change does not require revision of the starting material, intermediate or API specifications.
8. The change does not require revision of the API specifications.
9. 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.

Documentation to be supplied

1. (S.2.2) A side-by-side comparison of the current process and the new process.
2. (S.2.2) A flow diagram of the proposed synthetic process(es) and a brief narrative description of the proposed manufacturing process(es).
3. (S.4.1) A copy of currently-accepted specifications of API (and starting material and intermediate, if applicable).
4. (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. For the introduction of the use of a recovered solvent, certificates of analysis or batch analysis reports for the batches of recovered solvent used to produce the intermediate or API batches and a declaration of the ratio (or range of mixtures) of fresh and recovered solvents that were used declared.
5. Replacement sections for the APIMF resulting from the change in fulfillment of requirements under section 3.2.S of the WHO *WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part* (Technical Report Series 970, Annex 4, 2012) that may include, but is not limited to, sections 3.2.S.2, 3.2.S.3.1, 3.2.S.4.4 and 3.2.S.7.
6. A declaration is provided that a new APIMF version will be submitted, in accordance with Amendment 1c, within 24 months of acknowledgement of receipt (or acceptance in the case of an Amaj change) of this amendment.
7. (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.
8. (S.2.3) Either a transmissible spongiform encephalopathy (TSE) Certificate of suitability of Monographs of the European Pharmacopoeia for any new source of material or, where applicable, documented evidence that the specific source of the material that carries a risk of TSE has previously been assessed by the competent authority

and shown to comply with the current [WHO guideline on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical Products](#) or EMA's "Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products" or an equivalent ICH guideline.

9. (S.2.4) Information on controls of critical steps and intermediates, where applicable.
10. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization, if applicable.
11. (S.3.1) Evidence for elucidation of structure, where applicable.
12. (S.3.2) Information on impurities.
13. (S.7.1) Results of two batches of at least pilot scale, with a minimum of three (3) months of accelerated (and intermediate as appropriate) and three (3) months of long-term testing of the proposed API.

Description of change		Conditions to be fulfilled	Documentation to be supplied	Reporting type
8	Change in the in-process tests or limits applied during the manufacture of the API: <i>Note: The API manufacturing process encompasses all manufacturing steps: from the API starting material until the final packaged API</i>			
8a	tightening of in-process limits	1–3	1–3	AAN
8b	addition of a new in-process test and limit	1, 4	1–7	AAN
8c	addition or replacement of an in-process test as a result of safety or quality issue	None	1–11	Amin
8d.1	deletion of an in-process test	1, 5, 6	1–5, 12	AAN
8d.2		None	1–5, 9–11	Amaj
8e	relaxation of the in-process test limits	None	1–5, 7–11	Amaj
8f	change in analytical method	1, 4, 6, 7	1, 6	AAN
Conditions to be fulfilled				
<ol style="list-style-type: none"> 1. The change is not necessitated by unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits. 2. The change is within the range of currently-accepted limits. 3. The analytical procedure remains the same, or changes to the analytical procedure are minor. 4. Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way. 5. The affected parameter is non-significant. 6. The change does not affect the sterilization procedures of a sterile API. 7. There is no change to the in-process limits applied to manufacture of the API. 				

Documentation to be supplied

1. A comparison of the currently-accepted and the proposed in-process tests.
2. Replacement sections for the APIMF resulting from the change in fulfillment of requirements 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* (Technical Report Series 970, Annex 4, 2012) that may include, but is not limited to, sections 3.2.S.2.2, 3.2.S.2.4, 3.2.S.3.2 and 3.2.S.4.4.
3. A declaration is provided that a new APIMF version will be submitted, in accordance with Amendment 1c, within 24 months of acknowledgement of receipt (or acceptance in the case of an Amaj change) of this amendment.
4. (S.2.2) Flow diagram of the proposed synthetic process(es) and a brief narrative description of the proposed manufacturing process(es).
5. (S.2.4) Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed API.
6. Details of any new non-pharmacopoeial analytical method and validation data where relevant.
7. Justification for the new in-process test and/or limits.
8. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization, where applicable.
9. (S.3.2) Information on impurities, if applicable.
10. (S.4.1) Copy of currently-accepted specifications of API (and intermediates, if applicable).
11. (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. Justification/risk-assessment showing that the parameter is non-significant.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
9	Change in batch size of the API or intermediate involving:			
9a	up to 10-fold compared to the currently-accepted batch size	1–4	1–5	AAN
9b	more than 10-fold increase compared to the currently-accepted batch size	1–4	1–5	Amin
9c.1	downscaling	1–3, 5	1–5	AAN
9c.2		1–2, 5	1–6	AIN

Conditions to be fulfilled

1. No changes to the manufacturing process other than those necessitated by changes in scale (e.g. use of different size of equipment).
2. The change does not affect the reproducibility of the process.
3. The change does not concern a sterile API.
4. 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 amendment.
5. The change is not necessitated by unexpected events arising during manufacture or due to stability concerns.

Documentation required

1. (S2.2) A brief narrative description of the manufacturing process.
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) for a minimum of two batches each of the currently-accepted batch size and the proposed batch size.
4. Replacement sections for the APIMF resulting from the change in fulfillment of requirements 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* (Technical Report Series 970, Annex 4, 2012) that may include, but is not limited to, sections 3.2.S.2 and 3.2.S.4.4.
5. A declaration is provided that a new APIMF version will be submitted, in accordance with Amendment 1c, within 24 months of acknowledgement of receipt (or acceptance in the case of an Amaj change) of this amendment.
6. (S.2.5) Where applicable, evidence of process validation and/or evaluation studies for sterilization.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
10	Change to the specifications or analytical procedures applied to materials used in the manufacture of the API (e.g. API starting materials, intermediates raw materials, solvents, reagents, catalysts) involving:			
10a	tightening of the specification limits	1–3	1–5	AAN
10b	minor change to an analytical procedure	4–6	2–5	AAN
10c	addition of a new specification parameter and a corresponding analytical procedure where necessary.	1, 6–8	1–5	AAN
10d	deletion of a specification parameter or deletion of an analytical procedure	1, 9	1–6	AAN
10e	addition or replacement of a specification parameter as a result of a safety or quality issue	None	1–5,7	Amin
10f	relaxation of the currently-accepted specification limits for solvents, reagents, catalysts and raw materials	3, 6, 8, 9	1, 3–6	AIN

10g	relaxation of the currently-accepted specification limits for API starting materials and intermediates	None	1–5, 7	Amaj
Conditions to be fulfilled				
<ol style="list-style-type: none"> 1. The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns. 2. Any change is within the range of currently-accepted limits. 3. The analytical procedure remains the same. 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, etc., but do not include variations beyond the acceptable ranges or a different type of column and method). 5. 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. 6. No additional impurity found over the ICH identification threshold. No widening of an existing impurity limit beyond the qualified limit. Assay limits remain unchanged. 7. Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way. 8. The change does not concern a genotoxic impurity. 9. The affected parameter is non-significant or the alternative analytical procedure has been previously accepted. 				
Documentation to be supplied				
<ol style="list-style-type: none"> 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. Replacement sections for the APIMF resulting from the change in fulfillment of requirements under section 3.2.S of the <i>WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part</i> (Technical Report Series 970, Annex 4, 2012) that may include, but is not limited to, section 3.2.S.2.3. 5. A declaration is provided that a revised APIMF will be submitted, in accordance with Amendment 1c, within 24 months of acknowledgement of receipt (or acceptance in the case of an Amaj change) of this amendment. 6. Justification/risk-assessment showing that the parameter is non-significant. 7. (S.3.2) Information on impurities, where applicable. 				

3.2. S.4 Control of the API

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
11	Change to the test parameters or acceptance criteria of the API specifications involving:			
11a	updating a test parameter or acceptance criterion controlled in compliance with an officially recognized pharmacopoeial monograph as a result of an update to this monograph to which the API is controlled	None	1–5, 8	AAN
11b.1	deletion of a test parameter	2–3	1, 4, 5, 7	AAN
11b.2		None	1, 3–5	Amaj
11c.1	addition of a test parameter	2, 4–8	1–7	AAN
11c.2		2, 5, 6	1–7	Amin
11c.3		None	1–7	Amaj
11d.1	replacement of a test parameter	2, 5–8	1–7	AIN
11d.2		5, 7	1–7	Amin
11d.3		None	1–7	Amaj
11e.	tightening of an acceptance criterion	2, 9, 10	1, 4, 5, 7	AAN
11f.1	relaxation of an acceptance criterion	2, 5–8, 10	1, 4, 5, 7	AIN
11f.2		None	1, 4, 5, 7	Amaj
Conditions to be fulfilled				
<ol style="list-style-type: none"> No change is required in API specifications. The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns. The deleted test has been demonstrated to be redundant with respect to the remaining tests. Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way. For insoluble APIs there is no change in the polymorphic form. No additional impurity found over the ICH identification threshold. No widening of an existing impurity limit beyond the qualified limit. Assay limits remain unchanged. The change does not concern sterility testing. The change does not involve the control of a genotoxic impurity. The change is within the range of currently-accepted acceptance criteria. 				

10. The associated analytical procedure remains the same.

Documentation to be supplied

1. (S.4.1) A 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 analytical procedures are used.
3. (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.
4. Replacement sections for the APIMF resulting from the change in fulfillment of requirements 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* (Technical Report Series 970, Annex 4,2012) that may include, but is not limited to, section 3.2.S.3.2, 3.2.S.4.1, and 3.2.S.4.5.
5. A declaration is provided that a new APIMF version will be submitted, in accordance with Amendment 1c, within 24 months of acknowledgement of receipt (or acceptance in the case of an Amaj change) of this amendment.
6. (S.4.3) Where an in-house analytical procedure is used and a pharmacopoeial standard is claimed, results of an equivalency study between the in-house and pharmacopoeial methods.
7. (S.4.5) Justification of the proposed API specifications (e.g. test parameters, acceptance criteria, or analytical procedures).
8. Discussion of the change(s) in terms of the suitability of the monograph to control the API.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting tType
12	Change to the analytical procedures used to control the API involving:			
12a	change in an analytical procedure as a result of a revision to the officially recognized pharmacopoeial monograph to which the API is controlled.	None	1–5	AAN
12b	change from a currently-accepted house analytical procedure to an analytical procedure in a officially recognized pharmacopoeia or from the analytical procedure in one officially recognized pharmacopoeia to an analytical procedure in another officially recognized pharmacopoeia	2, 5	1–6	AIN
12c.1	addition of an analytical procedure	1–3	1–5	AAN
12c.2		None	1–5	Amaj
12d.1	modification or replacement of an analytical procedure	1–6	1–6	AAN
12d.2		1–3, 5, 6	1–6	Amin
12d.3		None	1–6	Amaj
12e.1	deletion of an analytical procedure	6–7	1, 4, 5, 7	AAN

12e.2		None	1, 4, 5, 7	Amaj
Conditions to be fulfilled				
<ol style="list-style-type: none"> Any new analytical procedure does not concern a novel, non-standard technique or a standard technique used in a novel way. The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns. No new impurities have been detected as a result of the use of the new analytical method. 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, etc., but do not include variations beyond the acceptable ranges or a different type of column and method), and no new impurities are detected. Comparative studies are available demonstrating that the proposed analytical procedure is at least equivalent to the currently-accepted analytical procedure. The change does not concern sterility testing. The deleted analytical procedure is an alternate method and is equivalent to a currently accepted method. 				
Documentation to be supplied				
<ol style="list-style-type: none"> (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. (S.4.2) Copies or summaries of analytical procedures, if new or significantly modified analytical procedures are used. (S.4.3) Copies or summaries of verification reports or validation reports as appropriate for the change or modification in analytical procedure. Replacement sections for the APIMF resulting from the change in fulfillment of requirements under section 3.2.S of the <i>WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part</i> (Technical Report Series 970, Annex 4, 2012) that may include, but is not limited to, section 3.2.S.4.1, 3.2.S.4.2 and 3.2.S.4.3. A declaration is provided that a new APIMF version will be submitted, in accordance with Amendment 1c, within 24 months of acknowledgement of receipt (or acceptance in the case of an Amaj change) of this amendment. (S.4.4) Comparative analytical results demonstrating that the proposed analytical procedures are at least equivalent to the accepted analytical procedures. (S.4.5) Justification for the deletion of the analytical procedure, with supporting data. 				

3.2. S.6 Container closure system

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
13a	Change in the immediate packaging (primary and functional secondary components) for the storage and shipment of the API	1–3	1–4	AIN
13b		3	1–5	Amin

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, moisture permeability etc.).
2. The change does not concern a sterile API.
3. The change is not the result of stability issues.

Documentation required

1. (S.6) Information on the proposed primary packaging (e.g. description, specifications etc.) and data in fulfillment of condition 1.
2. (S.7.1) Results of (or a commitment to study in the case of demonstrated equivalent or more protective packaging) a minimum of three (3) months of accelerated (and intermediate, as appropriate) and three (3) months of long-term testing of the API in the proposed primary packaging type.
3. Replacement sections for the APIMF resulting from the change in fulfillment of requirements 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* (Technical Report Series 970, Annex 4, 2012) that may include, but is not limited to, section 3.2.S.6, 3.2.S.7.1, 3.2.S.7.2 and 3.2.S.7.3.
4. A declaration is provided that a new APIMF version will be submitted, in accordance with Amendment 1c, within 24 months of acknowledgement of receipt (or acceptance in the case of an Amaj change) of this amendment.
5. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization if different from the current process.

Functional secondary components — For the purposes of this amendment it means packaging that provides additional protection to the API.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
14	Change in the specifications of the immediate packaging for the storage and shipment of the API involving:			
14a	tightening of specification limits	1, 2	1–3	AAN
14b	addition of a test parameter	2, 3	1–5	AAN
14c	deletion of a non-critical parameter	2	1–3, 6	AAN
Conditions to be fulfilled				
<ol style="list-style-type: none"> 1. The change is within the range of currently-accepted limits. 2. The change is not necessitated by unexpected events, resulting in failure to meet specifications, 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. (S.6) Comparative table of currently-accepted and proposed specifications, justification of the proposed specifications.
2. Replacement sections for the APIMF resulting from the change in fulfillment of requirements 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* (Technical Report Series 970, Annex 4, 2012) that may include, but is not limited to, section 3.2.S.6.
3. A declaration is provided that a new APIMF version will be submitted, in accordance with Amendment 1c, within 24 months of acknowledgement of receipt (or acceptance in the case of an Amaj change) of this amendment.
4. Details of method and summary of validation of new analytical procedure.
5. (S.6) Certificate of analysis for one batch.
6. Justification to demonstrate that the parameter is not critical.

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
15	Change to an analytical procedure on the immediate packaging of the API involving:			
15a	minor change to an analytical procedure	1–3	1–3	AAN
15b	other changes to an analytical procedure including addition or replacement of an analytical procedure	2–4	1–3	AAN
15c	deletion of an analytical procedure	5	2–4	AAN
Conditions to be fulfilled				
<ol style="list-style-type: none"> 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, etc., 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, non-standard technique or a standard technique used in a novel way. 5. The deleted analytical procedure is an alternate method and is equivalent to a currently-accepted method. 				
Documentation required				
<ol style="list-style-type: none"> 1. (S.6) Comparative validation results demonstrating that the currently-accepted and proposed procedures are at least equivalent. 2. Replacement sections for the APIMF resulting from the change in fulfillment of requirements under section 3.2.S of the <i>WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part</i> that may include, but is not limited to, section 3.2.S.6. 3. A declaration is provided that a revised APIMF will be submitted, in accordance with Amendment 1c, within 24 months of acknowledgement of receipt (or acceptance in the case of an Amaj change) of this amendment. 				

4. Justification for deletion of the analytical procedure.

3.2. S.7 Stability

Description of Change	Conditions to be fulfilled	Documentation required	Reporting type	
16	Change in the retest period/shelf-life of the API involving:			
16a	Reduction	1	1–4	AIN
16b	Extension	2, 3	1–4	Amin
Conditions to be fulfilled				
<ol style="list-style-type: none"> The change is not necessitated by unexpected events arising during manufacture or because of stability concerns. No change to the primary packaging in direct contact with the API or to the recommended condition of storage. Stability data was generated in accordance with the currently-accepted stability protocol. 				
Documentation required				
<ol style="list-style-type: none"> (S.7.1) Summary of stability testing conducted according to the currently-accepted protocol from a minimum of two pilot-scale or production-scale batches for a sufficient period to cover the proposed retest period or shelf life. (S.7.2) Updated post-acceptance stability protocol and stability commitment and justification of change, when applicable. Replacement sections for the APIMF resulting from the change in fulfillment of requirements under section 3.2.S of the <i>WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part</i> (Technical Report Series 970, Annex 4, 2012) that may include, but is not limited to, section 3.2.S.7.1, 7.3 and 7.2 as necessary. A declaration is provided that a new APIMF version will be submitted, in accordance with Amendment 1c, within 24 months of acknowledgement of receipt (or acceptance in the case of an Amaj change) of this amendment. 				

	Description of change	Conditions to be fulfilled	Documentation required	Reporting type
17	Change in the labelled storage conditions of the API	1	1–3	Amin
Conditions to be fulfilled				
1. The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns.				
Documentation required				
1. (S.7.1) Summary of stability testing from a minimum of two pilot-scale or production-scale batches for a sufficient period to support the proposed storage condition.				
2. Replacement sections for the APIMF resulting from the change in fulfillment of requirements under section 3.2.S of the <i>WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part</i> (Technical Report Series 970, Annex 4, 2012) that may include, but is not limited to, section 3.2.S.7.1, 7.3 and 7.2 as necessary				
3. A declaration is provided that a new APIMF version will be submitted, in accordance with Amendment 1c, within 24 months of acknowledgement of receipt (or acceptance in the case of an Amaj change) of this amendment.				