PREQUALIFICATION TEAM - MEDICINES
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 (Ref. WHO technical Report Series 981, Annex 3, 2013). It is intended to complement the aforementioned guideline, by providing guidance to holders of an APIMF on the requirements for seeking changes to the details of their APIMF.

An APIMF holder may submit an APIMF to the Prequalification Team - Medicines (PQT - Medicines) in support of an application for a prequalified API (Ref. WHO technical Report Series 953, Annex 4, 2009) or in support of a FPP seeking prequalification (APIMF procedure - Ref. WHO technical Report Series 948, Annex 4, 2008) or both.

Necessarily over time, 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 WHO Prequalification Team - Medicines (PQT - Medicines) prior to implementation.

Technical requirements for the different types of amendments are set out in this guideline in order to facilitate the submission of appropriate documentation by APIMF holders and their assessment by PQT - Medicines 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 guideline. Advice on the procedure for submitting an amendment, associated application forms and review timelines are set out on the PQT - Medicines website that may be updated from time to time. APIMF holders are advised to consult information on the website whenever considering the submission of an amendment.

1.2. Objectives

This guideline is intended to:

- assist APIMF holders with the classification of changes made to their APIMF.
- provide guidance on the technical and other general data requirements to support changes to the active pharmaceutical ingredient (API) details.

1.3. Scope and Application

This guideline 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* as well as other related WHO guidelines.

This guidance document applies to APIMFs submitted either in support of a prequalified FPP or a prequalified API.

This guidance document is applicable only to APIs manufactured by chemical synthesis or semi-synthetic processes. APIs from fermentation, biological, biotechnological or herbal origin are treated as special cases. APIMF holders are requested to contact the PQT - Medicines 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. PQT - Medicines should be informed immediately if any problems with the stability appear during storage, e.g. if outside specification or potentially outside specification.

APIMF holders should be vigilant that some amendments may require the submission of additional consequential amendments. Therefore, for any given change, the APIMF holder should consider if one or more amendments may be required to be submitted.

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 then 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 in order that the FPP manufacturer can consider the implications of the changes for their own product and also determine whether a subsequent FPP variation is required.

Since the FPP manufacturer is best placed to determine the significance to their 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 then 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 in this guideline. However, it is to be noted that a change not cited in this guideline, should be considered as a major change by default. Whenever the APIMF holder is unclear about the classification of a particular change, PQT - Medicines should be contacted. It remains the responsibility of the APIMF holder to submit relevant documentation to justify that the change will not have a negative impact on the quality of the product.

The general principle for determining the specific amendment severity for a change is to start by determining if 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 then 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 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 PQT - Medicines prior to submission of the amendment application in order to obtain guidance in classifying such changes.

2.1.1. Notifications

Notifications are changes that could have minimal or no adverse effects on the overall quality of the API. Such notifications do not require prior acceptance, but must be notified to PQT - Medicines immediately (Immediate APIMF notification (AIN)), or within 12 months following implementation (Annual APIMF Notification (AAN)) of the change.

It should be highlighted that a notification (AIN or AAN) may be rejected in specific circumstances with the consequence that the APIMF holder must cease to apply the already implemented change.

Annual APIMF Notification (AAN)

APIMF holders must satisfy themselves that they meet all of the prescribed conditions for the change. The change should be summarized as part of the notification but the indicated documentation is not required to be submitted, with the exception of the provision of revised and authorized API specifications. The documentation indicated for AAN's should be available on request or at the time of inspection. AAN applications should be submitted to PQT - Medicines within 12 months of implementation of the changes. For convenience, APIMF holders may group several AAN changes as a single submission.

Immediate APIMF Notification (AIN)

APIMF holders must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the notification application. Such changes should be notified immediately upon implementation. Commencing from the date of confirmation of receipt, they can be considered accepted if no objection is raised within the period of time specified on the PQT - Medicines 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 all of the prescribed conditions for the change and submit all required documentation with the amendment application.

Such amendments can be implemented if no objection letter has been issued within a time period indicated on the PQT - Medicines website. Should questions arise during the specified period, the change can only be implemented on receipt of a letter of acceptance from PQT - Medicines.

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. Prior acceptance by PQT - Medicines is 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 will have often 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, PQT/MED will contact APIMF holders to request the submission of a collated and revised APIMF version as needed. APIMF holders may of course submit a collated and revised version of their APIMF if they choose to do so.

In both situations, the updated APIMF should be submitted in line with Amendment 1 of the Guidance on amendments to an APIMF submitted in support of a prequalified FPP or API.

Since, this amendment is intended to be purely administrative, only editorial corrections to the existing APIMF details may be included in this type of amendment. Other changes should be notified using a separate application.

2.3. Conditions to be fulfilled

For each change, attempts have been made to identify particular circumstances where lower reporting requirements (AIN, AAN or Amin) are possible. A change that does not meet all of the conditions 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. This has been done to indicate to APIMF holders what documents should be considered to 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.

If the specific conditions or documentation requirements cannot be met for a given change, then this should be considered a major amendment by default and the applicant is advised to speak with PQT- Medicines before submission

2.4. Documentation requirements

Full details on the procedure and documentation requirements for amendments and APIMFs can be located in separate documents present on the PQT - Medicines website.

For each amendment, certain documents have been specifically identified in this document and organized according to CTD structure as supporting data. Regardless 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 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 provided in addition to the printed version.
2. A document describing, discussing and justifying the change.
3. Those documents specified in this guidance to be submitted to support the specific amendment category.
4. Replacement sections of the APIMF as per CTD format.
5. An updated API Quality Information Summary (API-QIS) (if applicable).

The API-QIS provides a summary of the key quality information of the API. For APIMF that have an agreed upon QIS, the QIS should be revised and submitted (in word format only) with every variation application. Any revised sections within the QIS should be highlighted in red. If there is no change to the QIS as a result of the amendment, the current QIS should be submitted and a statement made in the covering letter that there has been no change made to the QIS.

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

It is to be noted that PQT - Medicines reserves the right to request further information not explicitly described in this guideline.

3. GLOSSARY

The definitions provided below apply to this guidance. They may have different meanings in other 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 (ref. 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 (ref. 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 which has undergone all stages of manufacture including packaging in its final container and labeling (reference: 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 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 in order 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 in the PQT - Medicines (i.e. The International Pharmacopoeia (Ph.Int.), the European Pharmacopoeia (Ph.Eur.), the British Pharmacopoeia (BP), the Japanese Pharmacopoeia (JP) and the United States Pharmacopeia (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 (reference: WHO Technical Report Series, No. 953, Annex 3, 2009)

4. ADMINISTRATIVE CHANGES

1. New APIMF version

Description of Change		Conditions to be fulfilled	Documentation required	Reporting type
1a	New APIMF version (editorial changes only)	1	1	AIN
1b	New APIMF version (as requested by PQT)	2	1	AIN
1c	eCTD Baseline submission	1, 3	2	Amin

Conditions to be fulfilled

1. The proposed APIMF version differs from that currently accepted only by editorial changes or correction of typographical errors.
2. The proposed APIMF version differs from that previously accepted only in editorial changes, or changes specifically requested by PQT medicines.
3. The APIMF is already accepted by PQT and there are no on-going applications associated with this APIMF. No changes are made, whether editorial or otherwise, to the details of the currently accepted APIMF

Documentation required

1. An APIMF should be provided that reflects all currently accepted details and which meets all PQT - Medicines formatting and documentation requirements.
2. An eCTD version of the APIMF should be provided that reflects all currently accepted details and which meets all PQT - Medicines formatting and documentation requirements with respect to eCTD.

2. Change in manufacturing site address or APIMF holder name or address

Description of Change		Conditions to be fulfilled	Documentation required	Reporting type
2a.1	Change in the name or address of a manufacturer of an intermediate or active pharmaceutical ingredient (API)	1	1, 2	AIN
2a.2	Change in the name or address of a manufacturer of a starting material	1	2	
2b.1	Change in the name or corporate address of the APIMF Holder	2	1, 2	AIN
2.b.2	Change in the APIMF Holder	-	1	AIN

Conditions to be fulfilled

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

1. A formal document from a relevant official body (e.g. NMRA, 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 WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part namely: section 3.2.S.2.1. or section 3.2.S.2.3.
3. Documentation from the current APIMF holder detailing the transfer of ownership of the APIMF
4. Confirmation from the new APIMF holder confirming they:
    - Confirm that the sites of manufacture specified in the submitted APIMF are operating in compliance with ICHQ7 GMP.[1]
    - Confirm that the API manufacturer has undertaken review of their API intermediate suppliers to determine that they are operating in compliance with ICHQ7 GMP.[1]
    - Agree to permit WHO inspectors to undertake an on-site inspection at any time, either announced or unannounced, to confirm that the API manufacturing site; and or any associated intermediate, testing or contract manufacturing site, is manufacturing in compliance with WHO GMP.
    - Confirm that changes to the contact person for this application will be communicated to PQTm in a timely manner.
    - Confirm that any changes to the APIMF details and circumstances pertaining to this API will be notified to PQTm in a timely manner.

[1] The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. See: www.ich.org/.

3. Deletion of a manufacturing block, site or manufacturer

Description of Change		Conditions to be fulfilled	Documentation required	Reporting type
3a	production of the API starting material	1	1, 2	AAN
3b	production or testing of the API intermediate or API	1, 2	1, 2	AIN

Conditions to be fulfilled

1. At least one other site continues to perform the same function(s) as the site(s) intended to be deleted.
2. The deletion of site is not a result of critical deficiencies in manufacturing.

Documentation required

1. Identification of the manufacturing, packaging and/or testing site to be deleted, in the letter accompanying the application.
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* namely: section 3.2.S.2.1. or section 3.2.S.2.3

4. Change in the numbering system or format of product codes, reference numbers and other documentation

Description of Change		Conditions to be fulfilled	Documentation required	Reporting type
4a	The change in numbering and format is editorial only	1, 2	1, 2	AAN
4b	Affects the numbering of the API specifications	1	1, 2	AIN

Conditions to be fulfilled

1. The change in numbering and format is editorial only. There is no change to the detail of the documentation.
2. The changes do not affect the numbering of the API specifications.

Documentation required

1. Clear identification of the changes made and the documents affected.
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*, including section 3.2.S.4.1.

5. QUALITY CHANGES

3.2.S.2 Manufacture

5. Replacement or addition of a new manufacturing site or manufacturer of an API

Description of Change		Conditions to be fulfilled	Documentation required	Reporting type
5a.1	API testing only	1-3	1-3, 15	AIN
5a.2		2, 3	1-3, 15	Amin
5b.1	production of API starting material	3, 4, 6, 10	1, 3-6	AIN
5b.2		3, 4, 10	1, 3-6	Amin
5b.3		None	1, 3-7, 17	Amaj
5c.1	production of API intermediate	3, 5, 9, 10	3-5, 8, 9, 16	AIN
5c.2		None	3-5, 8-10, 17	Amaj
5d.1	production of API	1, 7-9, 10	3, 4, 7, 11-14, 16	AIN
5d.2		None	3, 4, 8, 9, 13, 14, 17	Amaj

Conditions to be fulfilled

1. The API is non-sterile.
2. The transfer of analytical methods has been successfully undertaken.
3. No change in the API specifications and analytical methods.
4. 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.
5. 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.
6. The API starting material is not obtained from a fermentation manufacturing process.
7. For APIs that are not BCS-highly-soluble the API polymorph is the same.
8. 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 sites currently accepted.
9. 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 EMA's *Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via*

Human and Veterinary Medicinal Products or an equivalent guideline of the ICH region and associated countries.

10. The change has been assessed for the impact this has on the risk of nitrosamine contamination and no increase to the risk of nitrosamine contamination was concluded.

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* 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. (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.
5. 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.
6. For an alternative source of plant-derived starting material pesticides residuals control must be provided. Evidence of this must be provide either in the form of an attestation from the SM supplier that no pesticides are used during the growth of the plant material, or by the providing the results of pesticide screening from one batch of the starting material from the proposed supplier.
7. (S.4.1) A copy of the API specifications.
8. (S.2.1) Evidence supporting the compliance of the site of manufacture with the principles of GMP practice (ICHQ7).
9. (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.
10. 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.
11. (S.2.1) A valid GMP Certificate issued by the WHO or a stringent Regulatory Authority, within the last three years pertaining to the manufacture of this API at the proposed site.
12. (S.2) A declaration from 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.
13. A commitment to initiate stability studies on the first three batches of API manufactured at the new site.
14. (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.
15. A declaration is provided that the testing sites are operating under GMP.
16. A declaration is provided attesting to that the new site proposed is part of the same pharmaceutical group as the sites currently accepted.
17. If applicable, a detailed risk assessment report regarding the potential of the contamination of nitrosamines is provided.

6. Change or addition of a manufacturing block/unit at a currently accepted site of API manufacture

Description of Change		Conditions to be fulfilled	Documentation required	Reporting type
6a	Evidence of GMP is available	1-6	1-5	AIN
6b	Evidence of GMP is unavailable	1, 2, 4, 5, 6	1-5	Amin

Conditions to be fulfilled

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 PQT - Medicines or another Stringent Regulatory Authority, supporting the compliance of the block with the principles of 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.
6. The change has been assessed for the impact this has on the risk of nitrosamine contamination and no increase to the risk of nitrosamine contamination was concluded.

Documentation required

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 PQT - Medicines or another Stringent Regulatory Authority.
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 WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part* 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.

7. Change in the manufacturing process of the API

Description of Change		Conditions to be Fulfilled	Documentation to be supplied	Reporting Type
7a	Change in the manufacturing process of the API	1-7, 10	1-6	AIN

7b	*Note: The API manufacturing process encompasses all manufacturing steps commencing from the API starting material until the final packaged API*	1-6, 8, 10	1-6	Amin
7c		1-5, 9, 10	1-6	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.
10. The change has been assessed for the impact this has on the risk of nitrosamine contamination and no increase to the risk of nitrosamine contamination was concluded.

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 *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part* 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. (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.
7. (S.2.3) Either a TSE CEP 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 guideline of the ICH region and associated countries.
8. (S.2.4) Information on controls of critical steps and intermediates, where applicable.
9. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization, if applicable.
10. (S.3.1) Evidence for elucidation of structure, where applicable.
11. (S.3.2) Information on impurities.
12. (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.
13. If applicable, a detailed risk assessment report regarding the potential of the contamination of nitrosamines is provided.

8. Change in the in-process tests or limits applied during the manufacture of the API

Description of Change		Conditions to be Fulfilled	Documentation to be supplied	Reporting Type
	Note: The API manufacturing process encompasses all manufacturing steps commencing from the API starting material until the final packaged API			
8a	tightening of in-process limits	1-3	1-3	AAN
8b	addition of a new in-process test and limit	1, 4	1-6	AAN
8c	addition or replacement of an in-process test as a result of safety or quality issue	None	1-10, 12	Amin
8d.1	deletion of an in-process test	1, 5, 6, 8	1-4, 11	AAN
8d.2		None	1-4, 8-10, 12	Amaj
8e	relaxation of the in-process test limits	None	1-4, 6-10, 12	Amaj
8f	Change in analytical method	1, 4, 6, 7, 8	1, 5	AAN

Conditions to be fulfilled

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.
8. The change has been assessed for the impact this has on the risk of nitrosamine contamination and no increase to the risk of nitrosamine contamination was concluded.

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* 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. (S.2.2) Flow diagram of the proposed synthetic process(es) and a brief narrative description of the proposed manufacturing process(es). 4. (S.2.4) Information on the controls performed at critical steps of the manufacturing process and on intermediates of the proposed API. 5. Details of any new non-pharmacopoeial analytical method and validation data where relevant. 6. Justification for the new in-process test and/or limits. 7. (S.2.5) Evidence of process validation and/or evaluation studies for sterilization, 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. 11. Justification/risk-assessment showing that the parameter is non-significant. 12. If applicable, a detailed risk assessment report regarding the potential of the contamination of nitrosamines is provided.

9. Change in batch size of the API or intermediate

Description of Change		Conditions to be fulfilled	Documentation required	Reporting type
9a	up to 10-fold compared to the currently accepted batch size	1-4, 6	1-4	AAN
9b	more than 10-fold increase compared to the currently accepted batch size	1-4, 6	1-4	Amin
9c.1	downscaling	1-3, 5, 6	1-4	AAN
9c.2		1-2, 5, 6	1-5	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. 6. The change has been assessed for the impact this has on the risk of nitrosamine contamination and no increase to the risk of nitrosamine contamination was concluded.
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* that may include, but is not limited to, sections 3.2.S.2 and 3.2.S.4.4. 5. (S.2.5) Where applicable, evidence of process validation and/or evaluation studies for sterilization.

10. Change to the specifications or analytical procedures applied to materials used in the manufacture of the API

	Description of Change	Conditions to be Fulfilled	Documentation required	Reporting Type
	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	1-4	AAN
10b	minor change to an analytical procedure	4-6	2-4	AAN
10c	addition of a new specification parameter and a corresponding analytical procedure where necessary.	1, 6-8	1-4	AAN
10d	deletion of a specification parameter or deletion of an analytical procedure	1, 9, 10	1-5	AAN
10e	addition or replacement of a specification parameter as a result of a safety or quality issue	None	1-4, 6, 7	Amin
10f	relaxation of the currently accepted specification limits for solvents, reagents, catalysts and raw materials	3, 6, 8, 9, 10	1, 3-5	AIN

10g	relaxation of the currently accepted specification limits for API starting materials and intermediates	None	1-4, 6, 7	Amaj

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.
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.
10. The change has been assessed for the impact this has on the risk of nitrosamine contamination and no increase to the risk of nitrosamine contamination was concluded.

Documentation to be supplied

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 WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part* that may include, but is not limited to, section 3.2.S.2.3.
5. Justification/risk-assessment showing that the parameter is non-significant.
6. (S.3.2) Information on impurities, where applicable.
7. If applicable, a detailed risk assessment report regarding the potential of the contamination of nitrosamines is provided.

3.2.S.4 Control of the API

11. Change to the test parameters or acceptance criteria of the API specifications

Description of Change		Conditions to be Fulfilled	Documentation required	Reporting Type
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	1-4, 7	AAN
11b.1	deletion of a test parameter	2-3, 11	1, 4, 6	AAN
11b.2		None	1, 3-4, 10	Amaj
11c.1	addition of a test parameter	2, 4-8	1-6	AAN
11c.2		2, 5, 6	1-6	Amin
11c.3		None	1-6	Amaj
11d.1	replacement of a test parameter	2, 5-8, 11	1-6	AIN
11d.2		5, 7, 11	1-6	Amin
11d.3		None	1-6, 10	Amaj
11e.	tightening of an acceptance criterion	2, 9, 10	1, 4, 6	AAN
11f.1	relaxation of an acceptance criterion	2, 5-8, 10, 11	1, 4, 6	AIN
11f.2		None	1, 4, 6, 10	Amaj
11g	Submission of a risk management summary (RMS) for elemental impurities based on ICHQ3D guideline.	None	8,9	AIN
11h	Submission of a risk management summary for nitrosamine impurities.	None	10	AIN

Conditions to be fulfilled
1. No change is required in API specifications. 2. The change is not necessitated by unexpected events, resulting in failure to meet specifications, arising during manufacture or because of stability concerns. 3. The deleted test has been demonstrated to be redundant with respect to the remaining tests. 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. 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. The change does not concern sterility testing. 8. The change does not involve the control of a genotoxic impurity. 9. The change is within the range of currently accepted acceptance criteria. 10. The associated analytical procedure remains the same. 11. The change has been assessed for the impact this has on the risk of nitrosamine contamination and no increase to the risk of nitrosamine contamination was concluded.
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* 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. (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. 6. (S.4.5) Justification of the proposed API specifications (e.g., test parameters, acceptance criteria, or analytical procedures). 7. Discussion of the change(s) in terms of the suitability of the monograph to control the API. 8. Detailed discussion about all the potential sources of elemental impurities. 9. A table summarizing the conclusion of the risk assessment of elemental impurities. 10. Risk assessment report on the nitrosamine impurities and revised 3.2.S.3.2 summary on the conclusion of the risk assessment on nitrosamine impurities.

12. Change to the analytical procedures used to control the API

Description of Change		Conditions to be Fulfilled	Documentation required	Reporting Type
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	1-4	AAN
12b	change from a currently accepted house analytical procedure to an analytical procedure in an officially recognized pharmacopoeia or from the analytical procedure in one officially recognized pharmacopoeia to an analytical procedure in another officially recognized pharmacopoeia	2, 5	1-5	AIN
12c.1	addition of an analytical procedure	1-3	1-4	AAN
12c.2		None	1-4	Amaj
12d.1	modification or replacement of an analytical procedure	1-6	1-5	AAN
12d.2		1-3, 5, 6, 8	1-5	Amin
12d.3		None	1-5, 7	Amaj
12e.1	deletion of an analytical procedure	6-8	1, 4, 6	AAN
12e.2		None	1, 4, 6, 7	Amaj

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 unexpected events, resulting in failure to meet specifications, 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, etc., 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 alternate method and is equivalent to a currently accepted method.
8. The change has been assessed for the impact this has on the risk of nitrosamine contamination and no increase to the risk of nitrosamine contamination was concluded.

Documentation to be supplied
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 verification reports or validation reports as appropriate for the change or modification in analytical procedure. 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* 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. 5. (S.4.4) Comparative analytical results demonstrating that the proposed analytical procedures are at least equivalent to the accepted analytical procedures. 6. (S.4.5) Justification for the deletion of the analytical procedure, with supporting data. 7. If applicable, a detailed risk assessment report regarding the potential of the contamination of nitrosamines is provided.

3.2.S.6 Container Closure System

13. Change in the immediate packaging

	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	1-4	1-3	AIN
13b		3, 4	1-4	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. 4. The change has been assessed for the impact this has on the risk of nitrosamine contamination and no increase to the risk of nitrosamine contamination was concluded.

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 3 months of accelerated (and intermediate, as appropriate) and 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* 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. (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.

14. Change in the specifications of the immediate packaging for the storage and shipment of the API

Description of Change		Conditions to be fulfilled	Documentation required	Reporting type
14a	tightening of specification limits	1, 2	1-2	AAN
14b	addition of a test parameter	2, 3	1-4	AAN
14c	deletion of a non-critical parameter	2, 4	1-2, 5	AAN

Conditions to be fulfilled
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. 4. The change has been assessed for the impact this has on the risk of nitrosamine contamination and no increase to the risk of nitrosamine contamination was concluded.

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* that may include, but is not limited to, section 3.2.S.6. 3. Details of method and summary of validation of new analytical procedure. 4. (S.6) Certificate of analysis for one batch. 5. Justification to demonstrate that the parameter is not critical.

15. Change to an analytical procedure on the immediate packaging of the API

	Description of Change	**Conditions to be fulfilled**	**Documentation required**	**Reporting type**
15a	minor change to an analytical procedure	1-3	1-2	AAN
15b	other changes to an analytical procedure including addition or replacement of an analytical procedure	2-4	1-2	AAN
15c	deletion of an analytical procedure	5, 6	2, 3	AAN

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, 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. 6. The change has been assessed for the impact this has on the risk of nitrosamine contamination and no increase to the risk of nitrosamine contamination was concluded.

Documentation required
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 WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part* that may include, but is not limited to, section 3.2.S.6 3. Justification for deletion of the analytical procedure.

3.2.S.7 Stability

16. Change in the retest period/shelf-life of the API

Description of Change		Conditions to be fulfilled	Documentation required	Reporting type
16a	Reduction	1	1-3	AIN
16b	Extension	2, 3, 4	1-3	Amin

Conditions to be fulfilled

1. The change is not necessitated by unexpected events arising during manufacture or because of stability concerns.
2. No change to the primary packaging in direct contact with the API or to the recommended condition of storage.
3. Stability data was generated in accordance with the currently accepted stability protocol.
4. The change has been assessed for the impact this has on the risk of nitrosamine contamination and no increase to the risk of nitrosamine contamination was concluded.

Documentation required

1. (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.
2. (S.7.2) Updated post-acceptance stability protocol and stability commitment and justification of change, when applicable.
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* that may include, but is not limited to, section 3.2.S.7.1, 7.3 and 7.2 as necessary

17. Change in the labelled storage conditions of the API

Description of Change		Conditions to be fulfilled	Documentation required	Reporting type
17	Change in the labelled storage conditions of the API	1, 2	1, 2	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.
2. The change has been assessed for the impact this has on the risk of nitrosamine contamination and no increase to the risk of nitrosamine contamination was concluded.

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 WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part* that may include, but is not limited to, section 3.2.S.7.1, 7.3 and 7.2 as necessary