

FAQ: Variations to prequalified pharmaceutical products

This questions and answers (Q&A) document addresses the questions most frequently asked by the applicants on matters related to variations to finished pharmaceutical product (FPP) subsequent to prequalification.

This Q&A document aims to provide clarification, and additional information, as needed, and should be read in conjunction with the [WHO guidelines on variations to a prequalified product](#) and other [guidance documents](#).

This document will be updated regularly to reflect new developments.

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1. What is the timeline for implementation and review of a variation? Where can these timelines be found?

The implementation and assessment timelines for the various change categories are provided in the section for [Variations to FPP](#) on the Prequalification of Medicines website. Each type of variation has its own approval mechanism and timeline, as summarized in the [Variations Approval Mechanism and Timelines \(PDF\)](#) table.

For changes to an Innovator or Multisource (Generic) FPP Prequalified on the basis of SRA approval, please refer to [SRA-approved Multisource \(generic\) or Innovator FPPs](#).

The timelines are subject to change and will be updated, as and when appropriate. Whenever there is conflict, the timeline published on Prequalification of Medicines website prevails over the timeline included in the [variation guideline](#).

2. Should data to support the annual notification be submitted?

An annual notification should be submitted with a completed [variation application form](#) including a summary of the change(s) and the date(s) of implementation. The summary should be sufficiently detailed to enable the assessor to quickly determine whether the appropriate reporting category has been used.

When an annual notification involves a change in specifications or standard test procedures (STP) for an API or FPP, the signed and dated version of the revised specification and STP including the change history should be attached to the application form.

For FPPs that have an agreed-upon [Quality of Information Summary \(QIS\)](#), the QIS should be revised and submitted with the revised sections highlighted. See more discussion on the QIS under (3) below.

Additional associated documentation is not required to be submitted. However, the information used to support the change must be generated prior to distributing the product manufactured with the change, and should be available on request, or to WHO inspectors during an inspection. A summary of studies performed to assess the impact of each change on product quality should be provided in the application form, if applicable.

3. Do I need to update the quality information summary (QIS) for each variation application? (Rev. Nov 2019)

The QIS provides a summary of the key quality information from the product dossier which has been accepted by WHO PQ. It is a useful tool for post-prequalification activities, e.g. GMP inspections, variations and requalification of the product. The final QIS also facilitates the information exchange between WHO and national regulatory authorities participating in the WHO collaborative registration procedure.

The QIS is a living document which needs to be revised each time a particular section is affected by a proposed change. A revised QIS with track changes and clean version should be submitted as part of the variation package and the change history updated.

The applicant is required to update the "Applicant's date of preparation or revision of the QIS" section (under Introduction (b)) whenever a revision is made to the QIS for tracking purposes.

After a change is accepted, the QIS represents the approved quality data in the product dossier, which should be used as the basis for any future application submissions.

If there is no change to the QIS as a result of the variation, a statement should be made in the variation application form to this effect.

Please note that if no agreed QIS was made available at the time of prequalification of the FPP concerned, a QIS is not required for submission of a variation. However, if a QIS was made available through requalification of the FPP concerned, a revised QIS should be submitted with the variation, if applicable.

Commitments section in the QIS:

At time of prequalification, the final QIS is revised by WHO to include the commitments made by the applicant during the assessment process (greyed out, as per the current QIS template). These commitments should be retained for the variation applications.

Commitments made during variation assessments are not included in the QIS. The commitments are mostly made in line with the GMP principles. The applicant must fulfil the commitments and make the information available to the inspectors or whenever requested by WHO.

4. For a grouped variation, should I file an application form for each change separately? (Rev. Dec 2022)

Grouping of variations is acceptable only under the following circumstances.

- the variations are consequential to each other, e.g. introduction of a new impurity specification that requires a new test method
- the same change affects multiple FPPs from the same applicant e.g. addition of a new API manufacturing site for multiple FPPs
- each of the changes is of the AN type. It is strongly recommended to group ANs and submit annually (around the anniversary of prequalification of the product).

A grouped variation should be filed in one application form, and will be reviewed as one application. For the purpose of classification, an application involving two or more types of variations will be considered to be of the highest risk type. For example, additional manufacturing site for an FPP for all the manufacturing processes (the new site has been satisfactorily inspected by WHO) with scale up of batch size at the new site (up to 10 times to the biobatch) should be submitted as a grouped variation of variation no.28c (Vmin) and variation no. 30a(IN). The overall variation type is a minor variation, and the implementation and assessment timelines will therefore be those for a minor variation. The conditions and documentation for both changes should be considered and submitted in the application. The supportive documentation for all variations concerned should be submitted as one integrated package covering all changes resulting from the variations (there is no need to submit a separate documentation package for each variation). However, the relevant CTD sections in support of each variation should be clearly identified under the supporting documentation section.

5. For an additional FPP manufacturing site, a minor variation may be submitted if the proposed site has been inspected and found GMP compliant by WHO or an SRA in the last three years (variation no.28). Should a major variation be used if the GMP inspection for the proposed site was conducted more than 3 years ago?

It is recommended that the applicant consults WHO PQ in advance when planning the submission (address enquiry to: prequalvariation@who.int).

6. May a batch size that has been accepted for one of the approved manufacturing sites of the product be implemented at the other approved FPP site? What change category should be applied for?

If a batch size has been accepted for one of the FPP sites, it may be implemented at other approved FPP sites, and be notified to WHO as an Annual notification. The following conditions should be fulfilled:

- 1) The change pertains only to immediate-release oral pharmaceutical forms and to non-sterile liquid forms.
- 2) Manufacturing equipment used at these sites is similar, except capacity differences.
- 3) Formulation, controls on starting materials, manufacturing process, in-process controls, specifications and packaging materials remain the same at both sites.
- 4) The necessary validations/qualifications at the other (proposed) site must be carried out as per cGMP prior to distributing the product and the data generated should be made available for verification by the WHO inspection team or for evaluation by assessors when requested.

7. What is the variation requirement when the heavy metals test is removed from API and/or excipient specifications?

The change can be implemented and be notified to WHO as annual notification or when submitting a related variation application for the affected product. The revised specifications of API and/or excipient (with version history) should be submitted with the notification. Information about the elemental impurities in API or excipients should be available to the FPP manufacturer. The FPP manufacturer should conduct associated risk assessment on elemental impurities which should be available in case requested by assessors or for verification by the WHO inspection team.

8. There is no change category in the variation guideline for a proposed change, what should I do? (Rev. Nov 2019)

A change that is not addressed in the [WHO guidelines on variations to a prequalified product](#) (variation guideline) should be considered as a major change by default as per the guideline. This is to give WHO enough time to review the unclassified change. However, if the applicant believes that the change is unlikely to have major effects on the overall safety, efficacy and quality of the product (refer to the Appendix I: Examples of changes that should be submitted as major variations), the applicant may choose to use one of the following options.

Option 1: Submit an unclassified minor variation, with the following information;

- [An application form](#)
- Justification of why the change is considered unclassified in the variation guideline;
- Justification of why the change is not considered as a major variation
- Supportive documents. Please note that it remains the responsibility of the applicant to submit relevant documentation to justify that the change will not have a negative impact on the quality, safety and efficacy of the product.
- An updated [quality information summary \(QIS\)](#), if applicable.

The application will be handled as per minor variation procedure. If WHO is of the opinion that the proposed variation may have a significant impact on the quality, safety or efficacy of the product, the applicant will be notified that the change will have to be reclassified as a major variation. As a consequence, the applicant may be requested to submit additional information. The major variation procedure will be used after receipt of the additional information.

Option 2: WHO PQTm may be consulted for classification of the particular change, by email addressed to prequalvariation@who.int. The subject of the email should use the following standardized wording: WHO reference number (e.g. HA800)– variation classification request. It is important that the email contains sufficient details of the proposed change to enable WHO to provide advice, which should include the

following information:

- Details of the proposed change;
- Why the applicant considers the change to be unclassified in the variation guideline;
- Classification proposed by the applicant;
- Justification for the classification proposed by the applicant.

WHO PQTm will provide recommendation within 30 calendar days following the receipt of the request. The recommendation will include the change category, (e.g. #31u -immediate notification as agreed with PQT) and the conditions applicable for the recommended classification of the variation but not the required documentation.

The recommendation should be included in the future variation application. It should be noted that such recommendation of PQTm relates to the situation described in the specific request only.

Any request which is considered inadequately justified or which is already classified in the guideline shall be rejected.

How to categorize a change which is not addressed in the Variation guideline

For an unclassified change, the variation can be categorized with suffix “u” within the most relevant classification as laid down in the Variation Guideline.

For example, change in manufacturing process of the FPP is described in the variation guideline No. 31, which includes two change categories, i.e. #31a-Annual notification and #31b-Minor variation. If a proposed change in the manufacturing process does not meet one or more conditions of #31a and #31b, it may be submitted as #31u- Major change by default, or #31u -unclassified minor variation (if the applicant believes the change will not significantly affect the safety, efficacy and quality of the product), or #31u- immediate notification as agreed with PQT (if an agreement has been reached with PQT pre-submission).

Examples of changes which are not described in the Variation guideline that should be submitted as major, or be reclassified as minor or notification, are given in appendix I and appendix II. Examples of changes that do not need to be filed as variation applications but should be handled as per GMP change control are given in appendix III. The appendices will be updated regularly to reflect new developments.

9. Additional guidance to API-related changes (Rev. Dec 2022)

Regarding the changes to the information of active pharmaceutical ingredients (APIs), relevant to the following variation categories described in the [variation guideline](#):

- #5- Submission of a new or updated CEP for an API or starting material or intermediate used in the manufacturing process of the API
- #6- Submission of a new or updated confirmation of API-prequalification document
- #8- Replacement or addition of a new manufacturing site or manufacturer for production of an API (except #8a)
- #9- Change or addition of a manufacturing block or unit at a currently accepted site of API manufacture
- #10- Change in the manufacturing process of the API
- #12- Change in batch size of the API or intermediate

When there is a change/addition of API manufacturer, or in case of an API-related change where equivalency in impurity profiles* and/or physical properties** is not demonstrated, in addition to the conditions and requirements for each category outlined in the variation guideline, the following information should be considered and provided in the variation submission:

- 1) A commitment to validate FPP batch(es) made with the post-change API before distributing the FPP.

Process validation should be carried out in accordance with GMP guidelines. A risk based approach should be followed to determine the extent of process validation. In order to determine the number of batches to be validated, consideration should also be given to the extent of the API-related changes, the complexity of the dosage form and the validation strategy (i.e. traditional process validation vs. continuous process verification).

Process validation should include evaluation of critical quality attributes. For example, for solid dosage forms, a comparative study of granules properties (e.g. flow, density, PSD, etc) to the pre-change API batches (including biobatch), as well as blend uniformity, in-process data during tablet compression, release testing results, and comparative dissolution profiles against the biobatch results should be evaluated.

The FPP batches can only be released if the manufacturing process by using the post-change API is successfully validated. E.g. critical quality attributes are equivalent to the pre-change API batches and within the accepted specification, similarity is demonstrated for dissolution profile compared to the biobatch dissolution profile.

The process validation report should be made available whenever requested by assessors or inspectors. Failure of the process validation should be reported to WHO immediately.

- 2) A tabulated comparison of impurity profiles between the proposed and current API sources should be provided, with indication of the origin of additional impurities from the proposed API source, if applicable. A discussion on the necessity for control of the additional impurities in the FPP specifications should be provided.
 - In case additional impurities resulting from the proposed API source need to be controlled in the FPP, a consequential variation to the FPP specification and test methods should be submitted alongside the API-related change.
 - If the additional impurities need not be controlled in the FPP specifications (e.g. process-related), the applicant should validate the FPP test procedure for impurities to ensure absence of co-elution of chromatographic peaks for API impurities, where applicable.
- 3) If it is a change/addition of API manufacturer or if the change in API may impact the stability of the FPP, a commitment is required to initiate stability studies (at accelerated and long-term conditions) for at least one batch of at least pilot-scale batch-size of the FPP, and to continue the study throughout the accepted shelf-life. Any out of specification results should be report to WHO-PQT without delay.
- 4) When the variation relates to a new manufacturing site, copies of the Manufacturer's License or equivalent issued by the National and/or State Regulatory Authority as well as GMP certificate issued by the National and State Drug Regulatory authority (where applicable), or a WHO recognized regulatory authority should be provided, including copies of the inspection report, CAPAs and close out communication of the inspection, if available.

* Impurity profiles includes organic impurities (specified identified impurities, specified unidentified impurities, unspecified impurities and total impurities), residual solvents and inorganic substances.

The impurity profile will be considered equivalent if the post-change batches of the API are tested and demonstrated that:

- There is no new impurity observed above the identification threshold of impurities as described in ICHQ3A and the results for specified and total impurities are within the stated limits.
- There is no new residual solvent observed above the limit described in ICHQ3C.

** physical properties of the API include solid state form (e.g. hydrate, solvate, polymorphic form), particle size, solubility, bulk/tapped density.

The equivalency should generally be assessed by comparing three consecutive pilot or commercial-scale, post-modification batches with the historical data from three or more consecutive, representative, pre-modification batches.

10. Additional guidance on variation applications regarding nitrosamine impurities

(New, Dec 2022)

10.1 Nitrosamines-related changes in Finished Pharmaceutical Products (FPPs) as part of the risk evaluation step 3 mitigation strategies

In April 2020, the WHO Prequalification Unit - Medicines Assessment Team (PQT/MED) contacted all FPP applicants requesting that risk evaluations for the possible presence of nitrosamine impurities be conducted for their products. If risks are identified and a nitrosamine impurity is detected in a medicine, the manufacturer should notify PQT/MED immediately, investigate the root cause, and apply mitigation measures to avoid or minimize the exposure. These measures may include routine testing of the API or FPP for the nitrosamine impurity, changes in formulation, manufacturing processes, and packaging, etc.

Any necessary changes to the control specifications, manufacturing process, product formulation, raw materials and packaging resulting from the nitrosamine risk assessment should be submitted through variation procedures.

Changes in the specification and test methods to include new impurities are normally classified as minor variations in the PQT/MED [variation guideline](#). However, for nitrosamine impurities, the applicant is requested to implement control strategies immediately. Therefore, any change to include control of nitrosamine impurities should be submitted as an immediate notification (IN).

Changes in the API specification and standard test procedure of the FPP manufacturer to include control of nitrosamine impurities, as a result of a risk assessment, should be submitted as follows:

- For CEP option, variation category #5u-IN: Submission of an updated CEP for an API from a currently accepted manufacturer
- For CPQ option, variation category #6u-IN: Submission of an updated confirmation of API-prequalification document (CPQ) for an API from a currently accepted manufacturer
- For APIMF procedure option and option 4 (i.e. full details of API in the product dossier), variation category #15u-IN: Change to the test parameters or acceptance criteria of the API specifications of the FPP manufacturer involving: addition of a test parameter, and variation category #16u-IN: Change to the analytical procedures used to control the API by the FPP manufacturer involving: addition of a test parameter

Changes in FPP specification and standard test procedure to include control of nitrosamine impurities should be submitted as follows:

- Variation category #37u-IN: Change in the specification of the FPP involving addition of a test for nitrosamine impurities
- Variation category #38u-IN: Change in the analytical procedure of the FPP involving addition of an analytical procedure for nitrosamine impurities

To submit the above immediate notifications, the following conditions should be fulfilled.

- The limits of nitrosamine impurities should be within the acceptable intake limits of the FPP, or as agreed with PQT/MED during risk assessment.
- The analytical methods should have been appropriately validated and shown to be sufficiently sensitive to detect trace levels of the nitrosamine impurities. Reference may be made to relevant guidance issued by major regulators (e.g. USFDA and EMA) during development of the analytical methods.

Relevant documentation as outlined under the corresponding variation category (#5, #6, #15, #16, #37, #38) in PQT/MED variation guideline should be considered and provided including revised specifications, test procedures, validation data of the methods, certificates of analysis of a representative number of batches, etc.

Any other changes related to mitigation strategies of nitrosamine impurities such as changes in product formulation, manufacturing process, raw materials and packaging should be submitted in accordance with the PQT/MED variation guideline, unless advised otherwise by PQT/MED.

10.2 Additional consideration on the potential for nitrosamine contamination for variation applications for FPPs

Since changes to the manufacturing site, manufacturing process, raw materials, packaging, and storage may affect the potential for the presence of nitrosamines in the product, it is expected that manufacturers verify, prior to submission, that there is no increase to the risk of nitrosamines contamination as a result of the change(s). In this respect, the variation application form for FPPs has been revised to include the necessary declaration, i.e. the change has been assessed for the impact on the risk of nitrosamine contamination and no increase to the risk of nitrosamine contamination was concluded. The risk assessments themselves do not need to be submitted. Risk assessment reports should be made available upon request.

If a proposed change may increase the risk of nitrosamine contamination, the applicant should contact PQT/MED before submission of the variation application. Justification of the change (benefit/risk assessment) should be provided, with detailed risk assessment report regarding the potential of the contamination of nitrosamines and proposed mitigation strategy. Such changes will be considered on a case-by-case basis.

Appendix I: Examples of changes that should be submitted as major variations

(It remains the responsibility of the applicant to submit relevant documentation to justify that the change will not have a negative impact on the quality, safety and efficacy of the product)

1. Addition of new API source with a new APIMF.
2. Qualitative or quantitative changes in composition of the product that may have a significant effect on the quality, safety, or efficacy of the product (required to be supported by a bioequivalence study).
3. Addition of a new manufacturing site and/or new production block which has not been satisfactorily inspected by WHO or by an SRA.
4. Major change in the manufacturing process of product that requires a new bioequivalence study, e.g. from dry to wet granulation, from one type of drying process to another for products containing insoluble APIs.
5. Change in manufacturing process that may affect the sterility assurance of a sterile product (e.g. change from aseptic processing to terminal sterilization or vice versa), including changes in the sterilization method for packaging materials (e.g. gas, dry heat, irradiation).
6. Change in the limit of an impurity exceeding the ICH qualification threshold which requires supportive toxicological data.
7. Change in the qualitative/quantitative composition of primary packaging of a sterile product.

Appendix II: Examples of changes which are not described in the Variation guideline and can be classified as minor change or notification (Rev. Dec 2022)

(The category and required conditions, if applicable, are given for each specified change. It remains the responsibility of the applicant to submit relevant documentation to justify that the change will not have a negative impact on the quality, safety and efficacy of the product)

1. Change in the manufacturing process of the FPP - Change in the holding time of an intermediate - #31u-Vmin

Conditions: Supportive hold time study data are available.

2. Change in in-process limits (relaxation) for immediate release products based on trend data for a minimum of 10 consecutive commercial batches, e.g. hardness, blend fines, bulk density - #32u-IN

Conditions:

- i. No change in the manufacturing process and specifications of the final product (except hardness, if applicable);
- ii. Similarity of dissolution profile to the biobatch dissolution profile is demonstrated under routine dissolution condition (in the case of change in hardness)

3. Change in FPP specification - introduction of skip testing of microbial limit for non-sterile dosage forms - #37u- AN (Rev, Dec 2022)

Conditions: Results for at least 5 commercial batches showing compliance with the acceptance criteria. At least one batch should be fully tested at regular intervals (one batch for every 10 batches or one batch in a year, whichever is sooner). Full testing must be reinstated as soon as any batch failure is observed or conditions under which skip testing was approved are no longer met.

4. Elimination or reduction of an overage from the batch formula which was previously used to compensate for presumed manufacturing losses - #31u- AN (Rev, Dec 2022)

Conditions: The change is solely made for elimination or reduction of an overage, there is no change to the manufacturing process.

5. Change in location of manufacturing (including terminal sterilization of finished product) within the accepted facility or site with no changes to currently accepted formulation, batch size(s), manufacturing process, equipment, in-process controls, finished product specifications, and packaging materials. The Quality systems, standard operating procedures, and manufacturing batch records will remain the same except for administrative information - #28u- AN

Conditions: The accepted facility or site, including the proposed location, has a satisfactory GMP status confirmed by WHO or by an SRA. Please note that such changes should follow proper change control procedures which should include but not be limited to risk assessment, qualification of new facility, equipment and process validation.

Appendix III: Examples of changes that do not need to be filed as variation applications but should be managed and documented within the pharmaceutical quality system (PQS) as per GMP change control (Rev. Dec 2022)

1. Reduced testing frequency of API, excipients, packaging material etc. by the finished product manufacturer on receipt of batches, whether the finished product manufacturer performs all of the tests listed in the approved specifications or accepts some of the results (except Identification) based on the certificate of analysis provided by the suppliers. The specifications should remain unchanged (a complete specification must be maintained for full periodic retesting). The reduced testing scheme should be documented and will be subject to review during a GMP inspection. Normally periodic or skip testing should only be implemented for the testing of regular commercial batches.
2. Reduced testing frequency of in-process controls of intermediates (e.g. final blend, core tablets) based on trend data of a sufficient number of commercial batches (e.g. more than 10 batches), except for low dose product manufactured by direct compression. The specifications of intermediates should remain unchanged. The reduced testing scheme should be documented and will be subject to review during a GMP inspection.

The manufacturer needs to perform continued process verification to demonstrate that process is well controlled. Full testing must be reinstated as soon as any batch failure is observed or if there is a change in the validated manufacturing process which might have a possible impact on the quality of product.

3. Editorial revisions or changes to add clarity to documents such as Batch manufacturing records, Validation protocols, Analytical Procedures, and SOPs. Such changes need not be submitted as separate variations, but they can be included in a variation concerning that part of the dossier. In such case, a declaration should be provided that the contents of the associated sections of the dossier have not been changed by the editorial changes beyond the aspects of the variation submitted. (Rev. Dec 2022)
4. Change in the in-process controls performed at non-critical manufacturing steps (e.g. a process/step that has no impact upon purity and impurity profile or requires no specific facility considerations, such as, buffer and media preparation, storage of intermediates, and packaging)
5. Replacement of equipment with that of the same design and operating principle, when there is no change in the approved process methodology or in-process control limits. An equivalency study is recommended.
However, for terminal sterilization of product, change from a qualified sterilization chamber to another, the new chamber and load configurations are required to be validated to operate within the previously validated parameters. This will be verified during a GMP inspection.
6. Addition of a new GMP compliant storage warehouse for raw materials, and drug substance, packaging materials.
7. Change in supplier of excipients without a risk of TSE contamination and without change in the technical grade and specification. Process validation/verification using excipients from the new supplier should be carried out in accordance with GMP requirements. (Rev. Dec 2022)
8. Change in dimensions of secondary packaging.
9. Change in tertiary packaging components (including tertiary pack size) of drug substance or drug product that do not affect stability.
10. Change in the color, design of label art work without change in the contents
11. Change to the specification of an excipient in order to comply with an update of the referenced monograph of the officially recognized pharmacopoeia (Ph. Int., Ph. Eur., BP, USP, JP), where the change is made exclusively to comply with the pharmacopoeia and the specifications for product specific properties (e.g. particle size distribution) are unchanged. (New, Dec 2022)