

APIMF Amendments FAQ

Why is the time period of review for immediate notifications (AINs) and minor amendments (Amin) not specified in the amendment guidance document. Where can these times be found?

The timelines for the various amendment types can be located in the webpage *Procedural Guidance on submitting amendments to an accepted APIMF*, which is located on the PQT - Medicines website. The times are specified here since it is a simpler and faster process to update this document rather than the Amendment guidance itself.

What are the timelines for review of AAN, AIN and Amin amendments?

The timelines for review of AAN, AIN and Amin amendments are specified in the *Procedural Guidance on submitting amendments to an accepted APIMF*. The timelines are subject to change and will be updated once greater experience is gained with the workload and the rate at which PQT - Medicines can complete amendment applications.

How should APIMF version numbers be applied to revised sections of an APIMF submitted as part of a response to a request for information?

If an updated subsection is requested during the amendment assessment, then it should be assigned a further amendment number to differentiate this subsection from the subsection originally submitted.

Will revised APIMFs submitted under Amendment #1 be reassessed?

The procedure and conditions for the submission of a revised APIMF are specifically designed to avoid reassessment. This is why they have been assigned an AIN change type. Although AIN submissions are subject to an audit process it is intended that the review of revised APIMF is effectively an administrative task. Of course, this relies upon the correct submission of a revised APIMF.

Can I submit a revised APIMF with other amendments?

No. To avoid prolonging the amendment assessment, only the specific subsections that have changed as a result of the amendment should be submitted

How do I know when to submit an updated APIMF version (Amendment 1)?

APIMF holders will be contacted if PQT/MED considers a collated and revised version of the submitted APIMF needs to be provided. Otherwise, submission of APIMF updates on a routine basis is not required anymore. In the future, with the use of eCTD applications, the need to submit such applications is not expected to continue.

There is no amendment category for an existing approved equipment used for the manufacture, what should I do?

Unless the change in equipment has resulted in a change to the manufacturing process then no amendment is required.

Artemisinin is a common starting material for several APIs - artemether, artesunate and dihydroartemisinin. If an API manufacturer introduces a new source of artemisinin for use in all three APIs do they need approval for all three APIMFs?

Yes, the change must be notified for all three APIMFs; however, since the change is common to all three they may be grouped together in one amendment application.

How to handle the introduction of recovered solvents under the new amendment guidance?

The use of recovered solvents is covered by amendment 7, change in the manufacturing process of the API. If the recovery of a solvent is used in the steps prior to the final intermediate, then it is covered by amendment #7a (AIN). The use of recovered solvents in the final steps of purification and/or crystallization is not recommended.

If the recovery of a solvent is used in the steps after the final intermediate, then it is covered by amendment #7c (Amin).

The following data should be provided in support of the introduction of a recovered solvent.

- Certificates of analysis or batch analysis reports for three batches of recovered solvent.
- Certificates of analysis or batch analysis for three batches of the resulting intermediate or API batches.
- Solvent batches should be chosen with impurity content near the limits proposed for the recovered solvent.

What amendment change category should be used for the adoption of skip testing?

A skip test is a quality parameter that has been determined during assessment to present a sufficiently low chance of non-compliance that it does not need to be conducted routinely, with the understanding that those batches not being tested still must meet all acceptance criteria established. This contrasts with reduced testing, which is the practise whereby a manufacturer may omit a test during the testing of a specific batch. Reduced testing is not the subject of this discussion.

To change an existing test in the API specifications from a routine test to a skip test an amendment should be submitted. Such a change should be submitted as an amendment #11f. In addition to the replacement CTD subsections, the data package for such a change should consist of the justification for the revision and data to support this justification.

Tests within specifications that are skip tests should be indicated as such within the specification itself. This can be done either by including the comment skip test in brackets or as a footnote. In contrast the frequency of skip testing is considered a GMP matter for the manufacturer to decide and is not evaluated during APIMF assessment; however, documentation explaining and justifying the frequency of testing should be developed and be available for inspectors. Finally, even after the frequency of skip testing has been set internally by the manufacturer, this frequency should not be applied blindly. The decision to skip test a parameter for any given batch should always be decided by the manufacturer on a batch to batch basis taking into account the specific circumstances relating to the manufacture of the batch in question. Therefore, no indication of testing frequency should be included within the specifications.

Will local GMP Certificate issued by Drug control Authorities as per Schedule M will be accepted for Intermediate /Key intermediate /final intermediate manufacturing at a new site?

All intermediate manufacturers are expected to manufacture in compliance with ICH Q7, since intermediate manufacture forms part of the API manufacturing process. PQT - Medicines recognizes the difficulties intermediate manufacturers may have to obtain GMP evidence from stringent regulatory authorities. Therefore, the provision of specific GMP evidence for intermediate manufacturers (as per amendment 5c) is deliberately non-specific. Any evidence of GMP should be provided in order that the inspectorate team can make a judgment over acceptability. Such evidence could include: certificates issued by state and national authorities, previous WHO inspection or evidence of auditing by recipient API manufacturers.

What do I need to do regarding nitrosamine contamination with respect to an amendment?

Since changes to the preparation or storage of an API may affect the potential for the presence of nitrosamines, PQT/MED expects that manufacturers have considered what effect the changes proposed have had on the potential for nitrosamine contamination.

For this reason, all amendment applications include a declaration that a risk assessment for the proposed change has been undertaken. Should the risk profile change, then the applicant is advised to speak with PQT/MED before submission.