FAQ: ACTIVE PHARMACEUTICAL INGREDIENT MASTER FILE (APIMF) AMENDMENTS

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 are given in the section *Amendments to APIMFs* on the Prequalification Team: medicines (PQTm) website. The timelines are subject to change and will be updated once greater experience has been gained of the rate at which PQTm can complete the 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, 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.

Can I submit a revised APIMF with other amendments?

No, revised APIMFs may not include changes of type AIN, Amin or Amaj and therefore cannot be submitted as a supporting document. Only amended sections relevant to the changes are acceptable.

If the change is of type AAN, only then can the change and the revised APIMF be submitted as per amendment 1.

How do I know when to submit the first revised APIMF version?

APIMF holders will be contacted in due course and informed of the initial anniversary date.

If an applicant is unclear they should contact fakea@who.int, cc: stahlm@who.int.

If there has been no change in APIMF details since the acceptance of the APIMF, then a declaration attesting to this fact can be provided in lieu of a new APIMF document, as per amendment #1a.

Can I submit a revised APIMF sooner than the 24-month anniversary date?

Yes, there are many reasons why a new version of an APIMF may be required, However, the new APIMF version may not include any AIN, Amin or Amaj changes that have not been previously submitted and deemed acceptable.

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

No amendment is required unless the change in equipment has resulted in a change to the manufacturing process.

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 should the introduction of recovered solvents under the new amendment guidance be handled?

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, 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 practice whereby a manufacturer may omit a test during the testing of a specific batch.

To change an existing test in the API specifications from a routine test to a skip test, an amendment #11f should be submitted. 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 Good Manufacturing Practices issue 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.. Therefore, no indication of testing frequency should be included within the specifications.

Will a local good manufacturing practice (GMP) Certificate issued by national drug control authorities as per Schedule M 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. PQTm recognizes the difficulties intermediate manufacturers may face in obtaining GMP evidence from stringent regulatory authorities. The provision of specific GMP evidence for intermediate manufacturers (as per amendment 5c) is deliberately non-specific. Any evidence of GMP should be provided, so that the inspectorate team can make a judgment on acceptability. Such evidence could include: certificates issued by state and national authorities, previous WHO inspection or evidence of auditing by recipient API manufacturers.