FAQ: Active pharmaceutical ingredient (API) micronization

1. Our API is manufactured in two grades — non-micronized and micronized. Do we need to submit a separate APIMF document for each grade?

No. A single APIMF document may be used for both non-micronized and micronized API. However, the inclusion of different grade(s) of the API should be clearly described by the APIMF.

Where information within the APIMF pertains to a specific grade then it should be clearly distinguishable, e.g., the specifications for non-micronized API and the specifications for micronized API.

If the APIMF supports a prequalified API, then separate entries will be made on the WHO List of Prequalified APIs for each grade and will be distinguished by an additional letter suffix, e.g. WHOAPI- 999a.

2. What additional information would be required in an APIMF for a micronized APIs?

Since the micronization process yields very fine particles, WHO is primarily interested in whether this process alters the polymorphic form of the API, and the long-term physical and chemical stability of the micronized API.

For a prequalified API, if a micronized grade of API is proposed, then the API specifications must include limits for particle size distribution.[1] If the APIMF is only being used in the APIMF procedure, specific particle size distribution limits are not mandatory.

Information expected to be provided is indicated under the CTD subheadings below.

1. **3.2.S.1.3**

   The API grade(s) (e.g. “micronized” or “non-micronized and micronized”) should be unambiguously stated.

2. **3.2.S.2.1**

   The site(s) and block(s) conducting micronization should be listed.

3. **3.2.S.2.2**

   The micronization process should be stated, e.g., jet milling, bead milling, etc. If micronization does not occur by jet milling, a description should be provided including the type of equipment used and the process parameters.

4. **3.2.S.3**

   It should be demonstrated that no change occurs to the polymorphic form due to micronization. The need to control for polymorphism in the API specifications should be discussed.

5. **3.2.S.4.1**

   If the APIMF is used to support a prequalified API, specific particle size distribution limits should be included in the API specifications.[2]

   If the APIMF is used only in the APIMF procedure, the API manufacturer may choose to include particle size distribution limits in the API specifications or not.

   WHO prefers that separate API specifications, clearly labelled, are provided for non-micronized and micronized grades.

[1] The manufacturer may either include limits for a specific particle size distribution or include a general statement that specific particle size limits will vary according to customer requirements but will be no finer than… [specifying a particle size distribution]. These general limits should of course have been justified in the APIMF provided.

[2] The manufacturer may either include limits for a specific particle size distribution or include a general statement that specific particle size limits will vary according to customer requirements but will be no finer than… [specifying a particle size distribution]. These general limits should of course have been justified in the APIMF provided.

6. **3.2.S.4.2**

The analytical method for particle size distribution and polymorphism should be provided (if applicable).

7. **3.2.S.4.3**

The analytical method validation for particle size distribution and polymorphism should be provided (if applicable).

8. **3.2.S.4.4**

Batch analytical data should include results for particle size distribution and polymorphism and polymorphic identity (if applicable).

9. **3.2.S.4.5**

The limits proposed for particle size should be discussed and justified.

10. **3.2.S.7**

Stability trials on micronized API should include particle size distribution among the parameters being monitored. The particle size distribution of the batches used in the stability trials should reflect those proposed in the API specifications, if limits are included. If limits are not included in the API specifications, the particle size distribution of the stability batches should reflect a worst-case scenario (finest grade).

Stability trials on micronized API should include a test for polymorphic identity if the API is not highly soluble across the physiological pH range. The inclusion of a test for polymorphic form in on-going stability trial protocols is generally considered unnecessary if the stability has been confirmed in primary batches.

3. When assigning a retest date for a micronized API, what date should be considered as the date of retest period commencement?

The retest period of the micronized API starts from the date of production of the non-micronized API.

4. We would like to introduce a micronized grade of API for an already accepted APIMF. What supporting information would be required by WHO?

This type of change falls under amendment category no. 7 and is treated as a major amendment. The required supporting information is as outlined in the document above.