

FAQ: Active Pharmaceutical Ingredient (API) Micronization

Q1. 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 in 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. Separate Confirmation of Prequalification Documents (CPQ) will be issued for each grade.

Q2. We would like to introduce a micronized grade of API for an already accepted APIMF. What supporting information would be required by PQT Medicines?

This type of change falls under amendment category #7d and is treated as a major amendment. In addition to the required information mentioned in the amendment guidance for category #7d, supporting information is required as outlined in the question 6.

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Q3. 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 commences from the date of production of the non-micronized API.

Q4. How do I set particle size distribution (PSD) limits for the micronized grade of API in the APIMF?

The methodology and options outlined below apply only to control of particle size for the release of batches of API in a general situation. The primary concern is the stability of micronized API. Please note that when an API manufacturer has demonstrated stability of API batches micronized at or below 10 µm, then no specific limits are needed in the API specifications.

The control of API particle size distribution (PSD) for API batches used in a specific Finished Pharmaceutical Products (FPP), to ensure consistent dissolution, are determined differently and are specific to each FPP.

There are two options that can be followed to set particle size limits for API batches within an APIMF.

Option 1: Limits for PSD (D_{90} or $D_{10}/D_{50}/D_{90}$), where D_{90} or D_{50} is expressed as a range.

The lower limit of the D_{50} or D_{90} range should be set with respect to the lowest obtained batch value from three micronized API batches, less an optional margin of up to 10 μm .

The upper limit of the range is up to the manufacturer to decide.

For example:

The three provided micronized batches have D_{90} values of: 25 μm , 30 μm and 32 μm .

The lowest D_{90} value is 25 μm , so the lower limit can not be smaller than 15 μm (being 25 μm minus 10 μm).

The upper D_{90} limit is for the manufacturer to decide, for instance 50 μm .

The D_{90} limit would therefore be 15 μm to 50 μm .

Option 2: General D_{90} limit

Option 2 is recommended when product-specific API particle size limits by different FPP manufacturers are anticipated.

To be expressed as: “As per manufacturer's requirements, but of a grade with D_{90} NLT [X]”.

[X] should be set based on the lowest D_{90} obtained from three micronized API batches, less an optional margin of up to 10 μm .

For example,

The three provided micronized batches have D_{90} values of: 25 μm , 30 μm and 32 μm .

The lowest D_{90} value is 25 μm , so the lower limit can not be smaller than 15 μm (being 25 μm minus 10 μm).

The general D_{90} limit would therefore be “As per manufacturer's requirements, but of a grade with D_{90} NLT 15 μm ”.

Q5. What if the FPP manufacturer requires specific limits for a particular FPP?

The API manufacturer is free to define product-specific API particle size limits for supply to a specific FPP manufacturer (i.e. as submitted in the FPP dossier), so long as the API batch continues to also conform to the limits agreed in the APIMF.

The API particle size limits determined in an APIMF are set to control particle fineness. The limits should be set generally enough to cater to FPP client requirements.

Q6. What information is required to support a micronized grade of material?

If a micronized grade is claimed, the following information should be provided.

3.2.S.1.3: the claimed API grades (e.g. “micronized” or “non-micronized and micronized”) should be stated.

3.2.S.2.1: it should be confirmed if micronization takes place at the proposed API manufacturing site. In case another site is involved, the name and address of the micronization site and block should be stated.

3.2.S.2.2: the micronization equipment and process should be described.

3.2.S.3.1: diffractograms of the micronized API should be provided along with a discussion on whether micronization impacts the polymorphic form of the API. If micronization does impact the polymorphic form, it should be submitted as a separate APIMF.

3.2.S.4.1: The specification of the micronized grade should include a test for particle size distribution. WHO prefers that separate API specifications, clearly labelled, are provided for non-micronized and micronized grades.

3.2.S.4.2: The analytical procedure for particle size distribution should be described.

3.2.S.4.4: Certificates of analysis of three micronized batches of the API should be provided.

3.2.S.7: Stability data of three micronized batches should be provided. Whilst the primary interest is the chemical stability of the micronized API, the inclusion of routine monitoring for PSD is strongly encouraged to understand better any tendency towards agglomeration/coalescence.