Q&A: Submission of Applications for Prequalification of Magnesium Sulfate Injection

What dosage forms for magnesium sulfate are being sought for prequalification?

Magnesium sulfate injection 500 mg/ml in 2ml and 10ml ampoules are currently invited for prevention and treatment of eclampsia.

Is a bioequivalence study report required?

As the products in question are aqueous solutions for injection, a bioequivalence study comparing the proposed product to a comparator product is not required. A biowaiver will be granted based on the acceptable demonstration of pharmaceutical quality, as long as excipients that may affect the availability of the active pharmaceutical ingredient (API) are not employed i.e. only simple excipients such as water for injection should be employed. If excipients that may affect the availability of the API are present, clinical studies may be required to establish the safety and efficacy of the proposed product.

Is evidence of compliance with GMP required for the API manufacturer?

All manufacturers of APIs used in prequalified medicinal products are expected to comply with Good Manufacturing Practices (GMP). If available, a certificate of GMP compliance should be submitted. Since magnesium sulfate is an atypical API, the manufacturing process and controls are not typically designed to meet API GMPs. As an alternative, there should be a clear specification, the site should have been audited, changes should be controlled and appropriate checks should be made on incoming goods.

What information is required regarding the API?

Information on the API can be submitted to WHO using one of the following four options:

- as a confirmation of API prequalification document (see WHO Prequalification Team: medicines (PQTm) website under Key Resources, Procedures and Fees)
- as a valid European Certificate of Suitability (CEP) with all Annexes
- as an API Master File as described in WHO’s “Guidelines on active pharmaceutical ingredient master file procedure” (WHO TRS 948, Annex 4, 2008)
- full details provided in the product dossier.

In addition, data on the API is required for each of the above options as outlined in the WHO prequalification quality guideline (WHO Technical Report Series 970, Annex 4, 2012).

Are there any API specification requirements for magnesium sulfate?

API specifications should be in line with a pharmacopoeial monograph (International Pharamcopoeia (Ph. Int.), European Pharmacopoeia (Ph. Eur.)/British Pharmacopoeia (BP), Japanese Pharmacopoeia (JP) or United States Pharmacopeia (USP)) with additional tests/limits for arsenic if not included in that monograph as well as for bacterial endotoxins. Such additional tests may be based on another pharmacopoeial monograph (Ph. Int., Ph. Eur./BP, JP, or USP).
Is analytical validation information for the assay of the API required to be submitted with the dossier?

Information on validation is required if an in-house method is used. Such information is not required if the assay method is pharmacopoeial (Ph. Int., Ph. Eur./BP, JP or USP).

What are the minimum stability requirements for the API and the finished pharmaceutical product (FPP)?

The minimum data required at the time of submitting the dossier should be from three (3) months accelerated and three (3) months long-term stability studies conducted on at least two (2) batches of at least pilot scale.

Testing of the FPP should include all stability-indicating parameters including sterility at \( t_0 \) and \( t_{\text{shelf-life}} \), subvisible particulates, weight change over the shelf-life (plastic containers), and bacterial endotoxins at \( t_0 \). Data should be provided to support the in-use period/storage conditions (after opening/reconstitution/dilution).

What information is required regarding the FPP?

In general, data on the FPP is required as outlined in the WHO PQP quality guideline (WHO TRS 970, Annex 4, 2012). Further guidance follows for some sections.

Is evidence of Marketing Authorization required to demonstrate that the product is registered or approved for sale in accordance with national requirements?

No such evidence is required at the time of submission of the dossier to for WHO prequalification. However, any requirements for national registration will need to be considered after prequalification.

Is evidence of compliance with GMP required for the FPP manufacturer?

Yes, a copy of a valid Manufacturing License and/or GMP certificate for the FPP manufacturer is required. In case the FPP manufacturing site is not regularly inspected by a stringent regulatory authority\(^1\) (PIC/S\(^2\) or ICH\(^3\)), PQTm will arrange for its inspection before prequalification and regularly thereafter.

What level of development pharmaceutics data is required?

Considering the nature of the product, extensive documentation on formulation and manufacturing process development of the product may not be required. However, discussions on selection of sterilization processes and parameters, container closure system and its integrity as well as microbiological attributes and compatibility with diluents (as mentioned below) should be included.

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\(^1\) An SRA is the regulatory authority of a country officially participating in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The current ICH members are Canada, the European Union, Japan, Switzerland and the USA. Other countries associated with ICH (through legally binding mutual recognition agreements) include Australia, Norway, Iceland and Liechtenstein.


How much evidence is required as proof of validation of the manufacturing process of the FPP?

A manufacturing process validation protocol for the validation of the first three production scale batches should be submitted. In addition, completed process validation reports for the sterile processes for three cycles/runs should be submitted. In the case where the manufacturer is already manufacturing production scale batches, then full validation data for the production of at least three (3) consecutive production scale batches should be submitted.

Note that complete information on the primary batch manufacture as well as proposed manufacture is expected as part of the dossier submission, with due emphasis on sterile processes and procedures as per GMP requirements.

Are there any FPP specification requirements for magnesium sulfate injection?

FPP specifications should be in line with a pharmacopoeial monograph (Ph. Int., BP, JP or USP)

Is analytical validation information required for the assay of the API in the FPP?

If the assay is pharmacopoeial (Ph. Int., USP, JP or BP), only evidence of specificity (with respect to effects of placebo) and method precision should be submitted. Full validation data is required if an in-house method is used.

Are there any specific packaging and labelling requirements?

Suitability of containers should be demonstrated, including sterilization/depyrogenation of components, extractables/leachables, moisture/light testing, and pack integrity regarding microbial contamination. Compatibility of the FPP with diluents (such as 5% dextrose injection or 0.9% sodium chloride as per the label instruction), if relevant, over the proposed dilution range (label) in specified containers such as PVC may also need to be demonstrated.