(1) Does the application adequately address the issue of the public health need for the medicine?

✓ Yes No □

Please provide brief details: It has addressed anaemia especially iron deficiency type which is among main public health problems particularly in children and in LMIC. Zinc deficiency was addressed and to less extent vitamin A deficiency.

(2) Have all important studies/evidence of which you are aware been included in the application?

✓ Yes No □

Please provide brief comments on any relevant studies that have not been included: The application included Cochrane meta-analysis, WHO guideline and UNICEF document on the effect of micronutrient powder (MNP) on anaemia and it’s iron deficiency which is a main public health problem at global level, however, there are other new publications that were not cited because it was published later than this application. We considered some at the end of this form.

(3) Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed use?

✓ Yes No □

(a) Briefly summarise the reported benefits (e.g. clinical versus surrogate) and comment, where possible, on the actual magnitude of benefit associated with use of the medicine:

According to the Cochrane reviews, MNP iron content of 12.5mg was significantly effective in reducing anemia (RR 0.69 CI [0.60, 0.78]), iron deficiency (RR 0.49 CI[0.35, 0.67]), and improving hemoglobin concentrations (MD 5.87 g/L CI[3.25, 8.49 d/L]) among young children aged 6-23 months. MNP zinc content of 5mg or more was also significantly effective at improving anemia (RR0.69 CI[0.60, 0.78]) and iron deficiency (RR 0.51 CI[0.38, 0.67]. The above evidence suggested that inclusion of 5mg of elemental zinc was effective in reducing diarrhea (RR 1.33 CI[1.00, 1.78]). Therefore, in general, the use of MNP was well accepted by participants across the studies included in the review. Adherence to the intervention was varied and high adherence was more likely when the product was provided on an intermittent basis.
In addition, MNP iron content of 12.5mg was significantly effective in reducing anemia (RR 0.66 CI [0.49, 0.88]), and improving hemoglobin concentrations (MD 3.37 g/L CI[0.94, 5.80 g/L]) over a duration period between 2-12 months. Also, children who received MNP were significantly less likely to have iron deficiency at follow-up (PR 0.35 CI [0.27, 0.47]). Children receiving MNP were not at increased risk of diarrhea (3 liquid stools or more per day) at follow up (RR 0.97 CI [0.53, 1.78]). Based on the body of evidence in this application, the author/s concluded that the use of iron-containing MNP for point of-use fortification of foods can help to control anemia and iron deficiency in pre-school and school age children (i.e. 2-12 years of age).
Our literature review, however, didn't show such good results as some found no significant difference between MNP use and placebo or a positive effect in short duration but not longer duration use..etc(1-6)

(b) Is there evidence of efficacy in diverse settings and/or populations? Please provide brief details:

Some new multicentric RCTs and pragmatic RCT which were included in the above mentioned systematic reviews and meta-analysis on the effect of MNP on nutrition deficiency particularly iron deficiency in various countries, mostly LMIC, two age groups (infants and children) and in malaria endemic settings (1-7).

(4) Has the application adequately considered the safety and adverse effects of the medicine? Are there any adverse effects of concern, or that may require special monitoring?

Yes □ √ No

Please provide brief details: Safety or efficacy was not addressed well in the application. None of international agencies including FDA, Australian Therapeutics Goods Administration (TGA), and the UK’s Medicines and Healthcare Products Regulatory Agency (MHRA) included this product in their lists, however, the US pharmacopoeia included it in it's list. One systematic review of our literature review that was not considered in the application, showed a range of adverse effects of 3 to32% including diarrhea, vomiting and constipation(6)

(5) Please comment on the overall benefit to risk ratio of the medicine (e.g., favourable, uncertain etc).

According to risk ratio in Cochrane reviews, the MNP is generally beneficial, it’s risk of bias was acceptable, but recent reports we listed below were not included, and relevant letters to the application were not supportive. Therefore, we suggest that MNP be studied by other expert group who are familiar with the formulation and standards of nutrition products like the proposed new WHO Model List of Essential Nutritious Products.
**ADDITIONAL CONSIDERATIONS:**

(6) Are there special requirements or training needed for the safe, effective and/or appropriate use of the medicine?

- [✓] Yes
- [ ] No

Please provide brief details: As this supplement should be used in food, to increase bioavailability and efficacy of the micronutrients, it is necessary to train individuals on food preparation and the process of fortifying, hygienic preparation, preservation, cooking and eating manners and feeding of complementary foods for children older than 6 months and a healthy diet for children older than 2 years.

(7) Are there any issues regarding the registration of the medicine by regulatory authorities? (e.g., recent registration, new indications, off-label use)

- [✓] Yes
- [ ] No

Please provide brief details:

It is registered only as food supplement. MNP held to good manufacturing practices for purities only. None of FDA, Australian TGA, or the UK Medicines and healthcare Agency reviewed or approved MNP. At individual country level especially when MNP is on the essential medicines list of that country, it was classified as pharmaceutical or food related with different implication, sometimes lead to it’s exemption from taxes. Regulatory only classified it for how it is imported, packaged, distributed and/or promoted. It is available in US pharmacopoeial standards (USP).

(8) Is the medicine recommended for use in a current WHO GRC-approved Guideline (i.e., post 2008)?

- [ ] Yes
- [✓] No

Please provide brief details: Although it has been suggested in WHO guideline 2016, however there is no referral to it in previous Essential List of Medicine for Children documents.

(9) Please comment briefly on issues regarding cost and affordability of this medicine.

The cost of MNP is reasonable (about 0.02/ 1g sachet) and affordable even in LMIC, and this might be one of the reasons to include it in national EML of some countries

(10) Any additional comments?

Well written application but missing recent studies with no supportive relevant letters and no approval by international regulatory agencies. Besides, this is a nutritional product and not a medicine to be included in the EMLc.
Please frame the decisions and recommendations that the Expert Committee could make.

I suggest that the EMLc expert committee asks for developing a separate WHO Model List of Essential Nutritious Products and to discuss MNP and any other future nutrition product. It’s because the formulation and standards of nutritious products are different from Medicines and should follow international food quality standards (Codex Alimentarius) and not the regulatory standards for medicines.

References (if required)

REFERENCES: