COMMITTEE PAPER FOR DISCUSSION **ACNFP/150/02**

ADVISORY COMMITTEE FOR NOVEL FOODS AND PROCESSES

CALCIDIOL ADDITIONAL INFORMATION – RP35

Issue

The Committee reviewed this application for the first time at the June 2021 meeting, and requested further information so as to proceed with their assessment. Members are invited to consider the response from the applicant and assess whether it addresses the requests for information satisfactorily or if further information is required.

Background

1. On the 12th of January 2021, the FSA (Food Standards Agency) received the submission for "Calcidiol" from DSM Nutritional Products Ltd (Switzerland). Calcidiol is a new form of Vitamin D for use as a food supplement targeted at a generally healthy population including pregnant and lactating women, except children under 3 years. It is a vitamer of vitamin D3 (cholecalciferol) and is directly absorbed by the human body.

2. During the review in the June meeting, the Committee raised several areas where further information was required to assess the safety of the novel food and its proposed use. Information was requested in the following areas:

    - **Identity/Composition**
    - **Production process**
    - **Specification**
    - **History of use**
    - **Proposed use and intake**
    - **ADME/Nutritional information**
    - **Toxicology**

    The Secretariat requested further information in **Annex A** which is included with the applicant's response in **Annex B** and associated appendices **Annex C(contains confidential information).**

EFSA consideration of the novel food

3. In parallel to submitting the application to the UK for assessment the applicant has also submitted an application to EFSA. EFSA have completed their consideration and the EFSA opinion (**Annex D**) is provided to the Committee as further data to inform their assessment.

Applicants' response to request for further information
Identity/Composition

4. Further information was sought on the identity of the novel food and how this was confirmed experimentally. The applicant responded by clarifying that Calcifediol is a synonym for Calcidiol, and the monograph in Ph.Eur for Calcifediol was provided. They suggest that they ensure in line with the supplements regulations that their product and any impurities is produced in line with the monograph.

5. The Committee requested further information on the particle size distribution of the novel ingredient in order to understand if part of the product is in the form of nanoparticles. The applicant states that this question was partially answered in information provided previously and that the file has been made available for Members to consider.

6. To understand the impact on the absorption of the novel ingredient the applicant was requested to provide the exact formulation of the final product explaining for example whether the Calcidiol will be incorporated into tablets or capsule. This information was sought to inform interpretation of the toxicology data. The applicant explained they were an ingredient manufacturer and so would not be responsible for the final formulation. They indicated that the ingredient is sold in a formulation that supports its stability when used in a range of food supplements.

7. The applicant was requested to provide information on the standards/reference samples used for the infrared spectroscopy and UV spectroscopy so as to help give clarity on how standardisation between batches was carried out. The applicant provided this information and made a note that they are using 'Calcifediol USP RS' as the standard of reference for the basis of comparison.

Production Process

8. The Committee advised the applicant to provide a comprehensive HACCP plan including detail on microbiological safety from start of the production process with the yeast strain, to the end. This information would help inform on the risks the applicant considers need managing and how they are controlled. The applicant provided a document on their HACCP and food safety management system.

Specifications

9. The Committee had requested a specification for the final chemical synthesis of the product as well as for the final commercial preparation was needed. The applicant disagrees that a further specification is needed and provides justification of their view.

History of Use

10. The Committee noted that information on Calcidiol for use in animal feed had been provided and that this was considered by the applicant as not relevant to

human use. The Committee felt that further explanation should have been provided within the dossier on why this would be the case. The applicant responded explaining that they intended to indicate that the history of use of the ingredients for the synthesis were not relevant and sought to address the confusion.

11. The Committee had suggested that the applicant take account of experience of clinical use of Calcidiol in considering the risks associated with this novel ingredient, in particular the information on pharmacopoeia uses and potential side effects. The applicant sought further clarification from the Secretariat which will be provided to inform a further response on this to the Committee in due course.

12. The applicant was requested to consider how the experience of vitamin D being presented to consumers can be used to inform strategies to prevent foreseeable misuse of the product. The applicant made some proposals on how they can assist in customers avoiding misuse within their response as well as making reference to the legal requirements for food supplements in the UK.

Proposed use and intake

13. The Committee requested for further explanation of the evidence for the mechanisms of the conversion into the 25D form as well as the mechanisms of any negative effects. The applicant sought clarification on the question posed from the Secretariat which will be provided to support a further response for the Committee.

14. The applicant had been requested to provide a further view on the how given the greater bioavailability of their product compared to other comparable products consumers would be informed to ensure they were not exceeding recommended or safety doses for Vitamin D in the UK. The applicant discussed how this potential problem would be mitigated within their response, especially through clear information and concise labelling.

15. The Committee noted that there was no advice provided to stop manufacturers and/or consumers overusing this supplement if used as a replacement for vitamin D. The applicant was asked to consider the potential of foreseeable misuse and how this could be managed. The applicant stated that the information to the consumers is not within their control as they are an ingredients manufacturer, but they would ensure they provide adequate information to their customers especially reiterating that Calcidiol is more efficiently absorbed hence less is needed in comparison to cholecalciferol.

ADME/Nutritional information

16. It was raised that the applicant didn’t consider whether the use of a metabolite of vitamin D had an impact on the downstream metabolism and the homeostatic regulation of the product. They were requested to provide the evidence to support the assumption that the downstream metabolism remained unchanged. The applicant responded with an explanation of the basis of their view.

The Committee questioned whether the use of a metabolite might alter interactions with the cytochrome metabolism, and the potential for drug interactions which would also affect bioavailability. The applicant was asked to explain whether the evidence considered this risk. The applicant responded that as they mentioned previously, they had no reason to believe that Calcidiol would be metabolized any differently than any other form. As such they do not expect any implications for the cytochrome metabolism.

Toxicology

17. The applicant was asked to confirm the formulation used for toxicological testing was the same as the one intended to be marketed by the applicant. The applicant has provided information in their application to support the Committee's consideration of the study.

18. The Committee observed that the potential for effects during pregnancy and lactation as data gaps from the evidence provided and sought the applicants view on the potential risks for these groups. The applicant responded to the query that there was no expectation that metabolism of vitamin D would be different in these groups and so it was not expected that there would be additional risks for these groups in using the novel ingredient.

19. The applicant was asked to consider whether the vitamin D status of consumers may have implications in using the novel food safely. Additionally, whether there would be implications in using the product for populations of people that are susceptible to vitamin D toxicity. The applicant gave their thoughts on this and explained that within the UK and EU populations most individuals would not be exceeding the recommended level. Their focus had been on the safe level of vitamin D from the populations diet and that their calculations suggest this would not be exceeded. Existing mitigations against over supplementation were thought to reduce the risk of over consumption of the product.

Committee Action Required

- The Committee is asked whether the response from the applicant is sufficient to complete the risk assessment.

- If not, the Committee is asked to indicate what additional information would be required.

ACNFP Secretariat
October 2021

Annexes

Annex A– Request for further information

Annex B – The applicants response

Annex C – Response Annexes

Annex D – EFSA opinion