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IPA Europe response to EFSA guidance documents

On the 18th of January, the European Food Safety Authority (EFSA) published the long awaited revised guidance for health claims related to the immune system, the gastrointestinal tract and defence against pathogenic microorganisms (1) and also the general scientific guidance for stakeholders on health claim applications (2). These publications were long overdue; the International Probiotics Association (IPA) Europe has therefore read the documents with interest. Considering the challenges that the probiotic industry faces in Europe in relation to health claims and, in particular, engaging in dialogue with EFSA and the Dietetic Products, Nutrition and Allergies (NDA) panel, IPA Europe is happy to see that the documents clarify some questions and that the consultation procedure has therefore been productive. Unfortunately, there are also still a number of points that IPA Europe believes have not been adequately considered.

General scientific guidance for stakeholders on health claim applications (2).
In particular, the general guidance on health claim applications has a number of issues that have still not been addressed. For example, despite repeated requests for pre-submission consultation to make the evaluation process more efficient for both sides; this point has not been addressed.

Furthermore, from the "general principles" in the supporting publication (3) we understand that a number of procedural aspects are now considered by EFSA as not being under the NDA panel's responsibility but instead should be addressed to the risks managers. Nevertheless, a series of questions that arose during this consultation were on the evaluation of the generally accepted science for all types of substances, the scientific evaluation used by other systems and the admissibility of some study populations. These issues are about science, thus we are a confused by this apparent dilution of the scientific evaluation during the process.

The general guidance document also continues to stress that dossiers are evaluated according to the highest possible scientific standards, based on studies that are generally accepted by experts in the field. While systematic reviews and meta-analyses, even from reputable institutions such as Cochrane, conclude that probiotics have health benefits, this view does not appear to be shared by the NDA panel. IPA Europe considers there is a discrepancy in what is stated in the guidance and what is practiced by the panel, in particular relating to how meta-analyses are treated. Instead of accepting meta-analyses and their conclusions, the panel insists on reviewing the primary data. This is unfortunate as a meta-analysis is aimed at taking into account the quality of a study, giving more weight to higher quality studies.

Guidance on the scientific requirements for health claims related to the immune system, the gastrointestinal tract and defence against pathogenic microorganisms (1)
The guidance for health claims related to the immune system, the gastrointestinal tract and defence against pathogenic microorganisms has changed substantially from its draft version. One example of this is the content explaining why particular dossiers had previously received unfavourable opinions. In our opinion, it is not realistic to assume that all of the critical issues needing to be addressed could have been reflected in dossiers already submitted.

We also expected that the new guidance would have taken into account scientific developments since the publication of their 2011 guidance, and that the new guidance would have proposed new beneficial effects and/or outcome measures that would be acceptable above and beyond those already evaluated by EFSA or stipulated in their 2011 guidance (4).

Fortunately, the guidelines also contain many constructive comments and provide a better insight into what the NDA panel expects.

The comments concerning bacterial vaginosis are particularly interesting as the panel indicates that a claim approval could be based solely on a beneficial change to the microbiota composition. The basis for this is that 70% of women have at least 50% lactobacilli in their vaginal microbiota and increasing the proportion of lactobacilli is one of the parameters that can be considered beneficial (based on oral use). This is a particularly important point as it indicates that modulating the composition of a microbiota can, in some instances, be considered a benefit. We hope this is a first step towards EFSA considering the support or maintenance of microbial resilience as a potential health benefit, and for this to be the case for the intestinal microbiota. This would be in line with the increased understanding of the role the human microbiota plays in maintaining health.

There is a clear list of biomarkers that can be measured *in vivo* from humans but which are, in the opinion of the NDA panel, not strong enough to provide a basis for a health claim. We are pleased to see that the panel has followed the recommendations of an International Life Sciences Institute (ILSI) expert group on this topic (5). Regarding immune function, for example, the ILSI expert group indicated that vaccination is one of the best models to challenge the immune system under controlled conditions. IPA Europe is pleased to see that this has been adopted by EFSA and that there is guidance on how to interpret and use this (by determining an increase in the number of subjects that pass the minimal antibody response titre).

Since there is an obvious lack of strong immune biomarkers, it is also encouraging to see that the NDA panel has opened the door for the use of clinical endpoints such as incidence, severity and duration of symptoms associated with infection. EFSA has also stated that diagnosis should be done by a physician or a primary care worker; while this may be difficult, at least it is now clear what the NDA panel expects in this regard.

On the topic of intestinal discomfort, the NDA panel states that validated questionnaires should be used and that it is not acceptable to focus on individual symptoms in the questionnaires. It is regrettable, however, that the topic of questionnaires was not further discussed. A concern is that such questionnaires are usually designed for patients and thus may not be appropriate for otherwise healthy volunteers. The questionnaires are also meant for diagnosis and treatment and not for placebo-controlled studies comparing interventions.

EFSA's draft guidance document had indicated that colic could not be regarded as a gastrointestinal disorder. We are pleased to see that this was changed in the final document, and the panel has adopted the Rome III criteria, which indicate otherwise.

We agree with the panel that excessive intestinal gas may not be a health condition but that it causes substantial discomfort and is therefore an appropriate target. It is also good to see that suggestions are made for how to measure this.

A number of non-probiotic products have received positive opinions from EFSA regarding maintenance of bowel function. We welcome the acknowledgement that maintenance of normal bowel function can be assessed by a number of outcome variables, including intestinal transit time. It is good to see that the panel has reverted from its original suggestion that intestinal transit time can only be considered as supportive evidence; this was a substantial change from the earlier (2011) guidance document (4). The panel also indicated that studies should be of sufficient duration, suggesting 4-8 weeks. We question whether this duration period is always necessary since positive opinions on bowel function have been given for other products, based on data from shorter interventions. Some health effects may require longer interventions, while shorter interventions may suffice for other health effects.

In the current guidance, maintenance of normal bowel function focusses on constipation. Although diarrhoea is mentioned elsewhere in the document, it would have been appropriate to mention it in this section as well, in particular concerning diarrhoea of unknown aetiology (functional diarrhoea).

Thus, while IPA Europe welcomes the many clarifications that have been provided by EFSA in these new guidance documents, particularly with regard to study design and endpoints, there are still some areas that we would like to see amended and improved in the application process. IPA Europe will continue to work on promoting what it sees as constructive changes in the application process.

References

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