

# Workshop on probiotics

24 March 2010, Renaissance Hotel, Brussels



A debate among the scientific community on the data required to establish a probiotic health benefit claim is currently taking place, the objective being to provide a “practical guide” for those involved in the scientific substantiation of probiotic health claims used in the EU. For this reason, EFFCA (the European Food & Feed Cultures Association) and LABIP (the Lactic Acid Industrial Platform) joined forces to organise a workshop for the purpose of facilitating an open discussion among scientists with a core expertise in the field of Probiotics. The goal is to provide more clarity on the scientific documentation required to approve gut and immune health related claims in the EU.

Short overviews of the current scientific state of play were given by the 4 keynote speakers: Prof. Ger Rijkers, Prof. Lorenzo Morelli, Prof. Robert-Jan Brummer and Prof. Eric Claassen and the discussion with the workshop participants was moderated by Dr. Jan Sikkema. The keynote speakers gave their opinions on some of the success factors for substantiating a specific gut or immune health claim. The workshop was attended by over 50 scientists from academia as well as from industry.

## Current state of play on what can be found in the literature today

It was concluded that an extensive body of literature on probiotic functionality and potential mechanisms is available. However, all these studies use different (combinations) of strains and, although significant beneficial effects are reported, the use of different biomarkers and clinical endpoints make it difficult to establish cause-effect relationships based on generally accepted evidence.

As the substantiation of probiotics benefits is based on emerging sciences, more clarity is needed on the EFSA NDA panel requirements regarding, for example, which clinical endpoints are considered beneficial to human health, usability of biomarkers as surrogate endpoints, study population versus target population, required number of clinical studies for each claim, as well as guidance on statistical methodology and reporting. The guidelines should also address how to take into account in the assessment the “totality of evidence”, as in vivo and in vitro studies are able to provide information on the mode of action of the probiotic strain.

### “Health” vs “functionality”

In regards to claims it is more useful to study ‘optimal functionality’ than to study ‘health’, which is rather poorly defined and thereby useless. According to the resilience model the gastrointestinal and immune systems have a large resilience capacity, and as long as clinical studies are conducted in subjects who are within their limits of normal functionality, no effect on their ‘health’ is seen. A dynamic study design, where measures are how the system reacts to a challenge, is useful to study functionality. Whether the system is pushed outside the limits of normal functionality would be a combination of how strong the challenge is, and how large the resilience capacity of the system is.

There is a clear need to identify areas of functionality which are relevant to the consumer, and to investigate these areas of functionality in clinical studies. As an example, a patient would not see his doctor to complain about 'problems with his transit time', but would rather complain about 'having abdominal discomfort'. Abdominal comfort would therefore be a relevant area of functionality to study within gastrointestinal health.

## **Specific gut health benefits**

In the gastrointestinal system, relevant areas of functionality to study are abdominal comfort, constipation, diarrhea and the microbiota. For each area of functionality, valid makers and/or clinical end point relevant to health should be assessed in a challenge model that mimics real-life in the target population.

For instance, diarrhea could be seen as a disturbed situation, a bad functionality, of the intestinal system that is only transient (not for all kinds of diarrhea, but AAD or traveler's diarrhea are examples whereby the gut health of a healthy person has been altered temporarily). This challenge model could be used to investigate the functionality of probiotics in the intestinal tract.

## **Specific immune health benefits**

A wealth of experimental data concerning the immune modulator role of probiotics has been published. Data are obtained from in-vitro, animal and human studies and pertain to such areas as; improved response of antibodies to influenza vaccination in the elderly, reduction of eczema in infants, reduction of risk of infections in children or common cold episodes in adults.

For Art 14 claims (reduction of risk of disease) it was highlighted that apart from influenza infections, it is difficult to find markers for infection since pathogens are not identified in most infections.

For Art 13.5 claims, the challenge is to substantiate that a biomarker correlates with protection. Clinical studies investigating the benefit of probiotics in relation to immune health report a stimulating effect of probiotics on components of the immune system (like natural killer cell activity for instance). One suggested solution was to incorporate both clinical outcomes and measurements of biomarkers in the same clinical trial.

## **How to demonstrate beneficial effects in healthy populations?**

One of the main difficulties in substantiating the health benefits of probiotics is to demonstrate significant physiological effects in healthy populations. The two key questions are:

(1) How to select the study population?

Probiotics will have a significant effect on those individuals who are in a suboptimal health condition, meaning those who are healthy but at risk of decreased function of the body or of developing a risk factor to a disease. Individuals in an optimal health condition, for instance, with a very strong immune system, will not be significantly impacted by a daily intake of probiotics. By studying a cohort composed of both individuals in a suboptimal health condition and in an optimal health condition, the effect is diluted and becomes less significant. The question is how to define the study population of healthy individuals so that significant effect on those individuals who will be impacted by probiotics will be easier to demonstrate.

(2) Length of the study vs long term physiological effect of a probiotic.

Probiotics have an impact on health by being part of the regular diet which means that their intake has to be daily and long-term. The strongest clinical trial for demonstrating health benefits of probiotics would need to study the targeted population for life, which is, totally unrealistic.

Consequently, the requirements for demonstrating the long-term health benefits of probiotics in foods cannot be similar to the requirements for demonstrating the acute health benefits of drugs, whose goal is prevention or cure of a compromised population in the short term.

## **General conclusions**

This workshop has confirmed that, even though there is not always consensus on the relation of immune parameters to general health or how to maintain the normal situation in the intestinal tract, there is a large number of excellent human studies that warrant substantiating specific gut or immune health claims for probiotics. Therefore, we must secure that these scientific findings are acknowledged in the EU regulations.

EFFCA and LABIP want to enter into a constructive dialogue with EFSA and DG SANCO and urge EFSA to explicate their view in a technical guidance addressing the design of the efficacy studies to be reported in an immune or gut health claim dossier to be submitted under Regulation (EC) No. 1924/2006. We hope that DG SANCO will support this initiative, which will provide the industry with a valuable tool to compile successful dossiers.

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