PROJECT DELIVERABLE

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7.6	Documents supporting the implementation of the European legislation framework on nutritional and health claims.	7	ILSI	R	PU	M60

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1. Background on the Regulation on nutrition and health claims made on foods

Until 2006 when the new European Regulation on nutrition and health claims made on foods was passed at the European Parliament, different systems where in place in European countries, such as the Swedish Code of Practice on health claims, the Joint Health Claims Initiative in the UK, etc.

Due to a need for harmonisation the European Commission Directorate General Research successively funded two projects to set up the scientific bases for the 2006 Regulation, before the Directorate General SANCO would finalise the Regulation:

1.1 Functional Food Science in Europe (FUFOSE) – 1995-1997

The goal of the European Union Concerted Action 'Functional Food Science in Europe' (FUFOSE) coordinated by ILSI Europe was to reach consensus on scientific concepts of functional foods in Europe by using the science base that supports evidence that specific nutrients positively affect physiological functions. The outcome proposed "a working definition" of functional foods: "foods can be regarded as functional if they can be satisfactorily demonstrated to affect beneficially one or more target functions in the body, beyond adequate nutritional effects, in a way relevant to an improved state of health and well-being and/or reduction of risk of disease". Functional foods must remain foods and they must achieve their effects in amounts normally consumed in a diet. Evidence from human studies, based on markers relating to biological response or on intermediate endpoint markers of disease, could provide a sound scientific basis for messages and claims about the functional food products.

Two types of claims were proposed that relate directly to these two categories of markers: Enhanced function claims (type A) and reduced risk of disease claims (type B) (see Fig. 1).

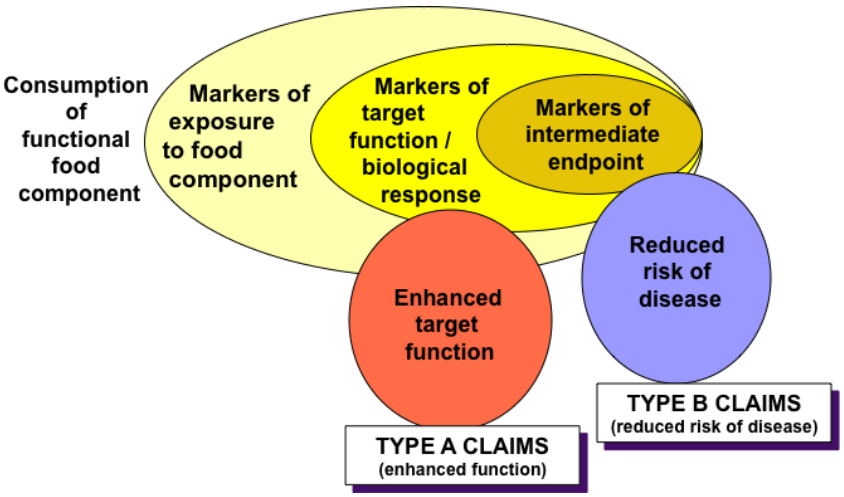

Figure 1 Types of claims as proposed by the FUFOSE project

Project funded under the Food, Agriculture and Fisheries, and Biotechnology theme (KBBE)

SEVENTH FRAMEWORK PROGRAMME

Relevant publications include:

A.T. Diplock et al. , Editors. Scientific Concepts of Functional Foods in Europe – Consensus Document. *British Journal of Nutrition*1999;81(1):1-27.

F. Bellisle et al., Editors. Functional Food Science in Europe – Theme Papers. *British Journal of Nutrition* 1998;80(1):1-193.

Another European Union Concerted Action followed, and built upon, the principles defined within FUFOSE.

1.2 Process for Assessment of Scientific Support for Claims on Food (PASSCLAIM)

The objectives of this other European Union Concerted Action coordinated by ILSI Europe were:

- To produce a generic tool with principles for assessing the scientific support for health-related claims for foods and food components which are eatable or drinkable;
- To evaluate critically the existing schemes which assess the scientific substantiation of claims;
- To select common criteria for how markers should be identified, validated and used in well-designed studies to explore the links between diet and health.

One of the main deliverables of PASSCLAIM was the PASSCLAIM Consensus Document that contains consensus criteria on a pan-European level to assess the scientific support for claims on foods, and was widely disseminated among scientists, industry, consumer groups and regulators. This document was considered as extremely helpful for those making and regulating claims. It was also acknowledged that PASSCLAIM provided consumers with the assurance that claims are well founded and justified.

In its comments on Codex Circular Letter 2005/46-FBT on Food Safety Assessment of Food Derived from Recombinant-DNA Plants Modified for Nutritional or Health Benefits, the European Commission referred to PASSCLAIM as follows: “As regards to the methods (…) it is essential that only those recognised by the whole of the international scientific community be used. In the case of the evaluation of health claims, those already being drawn up (PASSCLAIM, Codex) lay down that the quantity and availability of the nutrient about which the claim is made must be verified throughout the lifecycle of the product.”

EFSA referred to PASSCLAIM in its draft opinion on scientific and technical guidance for preparation and presentation of the application for authorisation of a health claim.

One of the key outcomes from the discussion with the large group of experts involved in PASSCLAIM is shown in Figure 2:

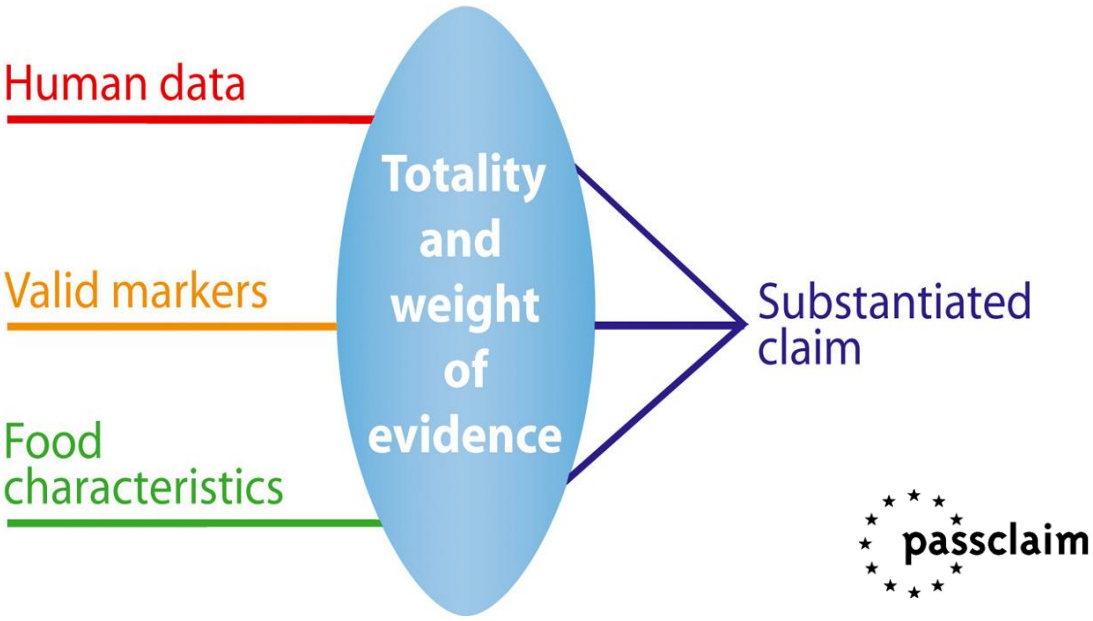

Figure 2: Process for the Assessment of Scientific Support for Claims on Foods (PASSCLAIM)

This figure is translated in the current Regulation (EC) No 1924/2006 in *Article 17* as follows: 'A claim should be scientifically substantiated by taking into account the totality of the available scientific data and by weighing the evidence'.

Relevant publications include:

Aggett, P. J., et al. "PASSCLAIM: Process for the assessment of scientific support for claims made on foods. Consensus on criteria." *European Journal of Nutrition* 44 (2005).

Cummings, John H., et al. "PASSCLAIM —gut health and immunity." *European Journal of Nutrition* 43.2 (2004): ii118-ii173.

Mensink, Ronald P., et al. "PASSCLAIM–Diet-related cardiovascular disease." *European Journal of Nutrition* 42.1 (2003): i6-i27.

Prentice, Ann, et al. "PASSCLAIM–Bone health and osteoporosis." *European Journal of Nutrition* 42.1 (2003): i28-i49.

Saris, Wim HM, et al. "PASSCLAIM–Physical performance and fitness." *European journal of nutrition* 42.1 (2003): i50-i95.

Richardson, David P., et al. "PASSCLAIM–Synthesis and review of existing processes." *European Journal of Nutrition* 42.1 (2003): i96-i111.

2. Current European Regulation – REGULATION (EC) No 1924/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 20 December 2006 on nutrition and health claims made on foods

In December 2006 EU decision makers adopted a Regulation on the use of nutrition and health claims for foods which lays down harmonised EU-wide rules for the use of health or nutritional claims on foodstuffs based on nutrient profiles. Nutrient profiles are nutritional requirements that foods must meet in order to bear nutrition and health claims. One of the key objectives of this Regulation is to ensure that any claim made on a food label in the EU is clear and substantiated by scientific evidence.

- Regulation 1924/2006 on nutrition and health claims made on foods
- Commission Regulation No 353/2008 establishing implementing rules for applications for authorisation of health claims
- Commission Regulation No 1169/2009 amending Regulation (EC) No 353/2008 establishing implementing rules for applications for authorisation of health claims

3. Importance of the selection of relevant 'valid' (bio)markers for health claim substantiation

It is important to note that the selection of relevant 'valid' (bio)markers is a key step when preparing a health claim dossier. Such biomarker should be validated to support the substantiation of the health claim.

Some recent publications have tried to bring more clarity on how to best identify or select the relevant (bio)-markers:

- Markers for Nutrition Studies: Review of Criteria for the Evaluation of Markers - de Vries J, Antoine JM, Burzykowski T, Chiodini A, Gibney M, Kuhnle G, Méheust A,

Pijls L, Rowland I. *European Journal of Nutrition*. October 2013, Volume 52, Issue 7, pp 1685–1699.

Markers are a well-known and useful tools used in nutrition sciences to estimate the effects of nutrition interventions on health. The ILSI Europe Functional Foods Task Force reviewed existing criteria for the evaluation of markers related to nutrition, health and disease and proposed generic criteria for evaluation.

- Improving selection of markers in nutrition research: evaluation of the criteria proposed by the ILSI Europe Marker Validation Initiative - Calder, P.C., Boobis, A., Braun, D., Champ, C.L., Dye, L., Einöther, S., Greyling, A., Matthys, C., Putz, P., Wopereis, S., Woodside, J.V. and Antoine, J.-M. *Nutrition Research Reviews* (2017), 30, 73–81.

Biomarkers are essential in nutrition research, however, their use is not standardised across the discipline. This publication tests criteria biomarkers should meet and provides a template to evaluate their utility in nutrition research.

- A Consideration of Biomarkers to be Used for Evaluation of Inflammation in Human Nutritional Studies - Calder PC, Ahluwalia N, Albers R, Bosco N, Bourdet-Sicard R, Haller D, Holgate ST, Jönsson LS, Latulippe ME, Marcos A, Moreines J. *British Journal of Nutrition*. 2013;109(Suppl 1):S1-S34.

To monitor inflammation in a meaningful way, the markers used must be valid: they must reflect the inflammatory process under study and they must be predictive of future health status. The overall aim of this article is to attempt to identify robust and predictive markers, or patterns or clusters of markers, which can be used to assess inflammation in human nutrition studies in the general population.

There are several other European and American initiatives on markers.

3.1 Other European initiatives on markers: Joint Action Biomarkers in Nutrition and Health (JPI HDHL)

3.1.1. MIRDINET project

The purpose of the miRDIET project was to identify and validate circulating microRNAs as quantitative dietary markers.

3.1.2. FOODBALL project

The Food Biomarkers Alliance (FOODBALL) is an initiative aimed at identifying and quantifying dietary biomarkers in order to improve the capabilities of nutritional assessment and research.

3.2. American initiatives on markers

Two mains initiatives were conducted in the last decade in the US to help bringing clarity on definition and use of biomarkers in translational science.

3.2.1. BOND - The Biomarkers of Nutrition for Development (BOND) program

The ability to assess the health impacts of nutritional status depends on the availability of accurate and reliable biomarkers that reflect nutrient exposure, status, and effect.] Biomarkers are essential in this regard; yet, confusion remains surrounding their use and application. What might be a useful index of nutrient exposure may not necessarily reflect nutrient status, which, in turn, may not necessarily reflect the impact or function of that nutrient. Systematic reviews of a range of nutritional biomarkers have emphasized the lack of clarity in the definition of biomarkers and their application and purpose. The usefulness of even the well-documented biomarkers has been limited by gaps in the understanding of their physiologic significance.

The BOND program was created to address this need; it is supported by a consortium that includes the Bill and Melinda Gates Foundation (BMGF), PepsiCo, the NIH Office of Dietary Supplements, and the NIH Division of Nutrition Research Coordination, and includes memberships with organizations and agencies representing the breadth of the global food and nutrition community. BOND is managed by the NICHD and aims to harmonize the process of making decisions about the best uses of biomarkers in individual situations.

BOND has targeted four primary user communities for its translational activities:

1. Research (including basic research examining the role of nutrition in biological systems, clinical research, and operations research);
2. Clinical care;
3. Programs (surveillance to identify populations at risk, and monitoring and evaluation of public health programs); and,
4. Policy (evaluation of the evidence base to make national or global policy about diet and health, and funding agencies that make decisions about priorities in food and nutrition).

Related relevant publications include:

- Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease (2010)
- Executive summary--Biomarkers of Nutrition for Development: Building a Consensus (2011)
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3.2.2. BEST (Biomarkers, EndpointS, and other Tools) Resource (2015-2017)

In the spring of 2015 the FDA-NIH Joint Leadership Council identified the harmonization of terms used in translational science and medical product development as a priority need, with a focus on terms related to study endpoints and biomarkers. Working together with the goals of improving communication, aligning expectations, and improving scientific understanding, the two agencies developed the BEST (Biomarkers, EndpointS, and other Tools) Resource. The first phase of BEST comprises a glossary that clarifies important definitions and describes some of the hierarchical relationships, connections, and dependencies among the terms it contains.

The BEST glossary aims to capture distinctions between biomarkers and clinical assessments and to describe their distinct roles in biomedical research, clinical practice, and medical product development. Because the glossary is intended to be broadly applicable to multiple communities of users and stakeholders, its definitions address nuances of usage and interpretation for a wide variety of terms currently in use. Further, based on differing stakeholder needs, it has built in flexibility, when possible and appropriate, to accommodate those interests. NIH and FDA intend to use the definitions included in this glossary when communicating on topics related to its contents (e.g., biomarkers) to ensure a consistent use of the terms and therefore, a common understanding of the issues.

4. Pivotal Assessment of the Effects of Bioactives on the Health and Wellbeing, from Human Genome to Food Industry (PATHWAY-27)

PATHWAY-27 (1 Feb 2013 – 31 Jan 2018) was a research project carried out by a pan-European interdisciplinary team of 16 public and private research institutes and 9 high tech/food processing SMEs. It uniquely addressed the role and mechanisms of action of three bioactives: docosahexaenoic acid, oat β-glucan and anthocyanins. These have been chosen for their known/claimed effectiveness in reducing specific risk factors of metabolic syndrome (MetS), enriching three different widely-consumed food matrices (dairy, bakery and egg products).

One of the main objectives of PATHWAY-27 was to produce two set of guidelines:

- Guidelines for the European scientific community;
- Guidelines for the food industry & small and medium enterprises.

4.1. PATHWAY-27 Scientific Guidelines

The Guidelines for the European scientific community were developed within the framework of the EU-funded project PATHWAY-27 and are addressed to scientists from both academia

and the food industry. The guidance helps to understand and apply the relevant steps of the health claim substantiation process. These steps include:

1. Thoroughly reviewing the published evidence concerning any putative beneficial physiological effect(s) of the food or food constituent of interest (e.g. a bioactive compound); and

2. Correctly designing, conducting, interpreting, and reporting any necessary human dietary interventions.

The guidance focuses on randomised controlled trials as they are the most rigorous type of interventions to investigate the claimed health effect of a specific food. In this regard, the critical aspects of randomisation, blinding and control are discussed, with hands-on examples from the PATHWAY-27 project of issues that can be encountered when dealing with bioactive compounds and how to solve them. Furthermore, it addresses sample size and data analysis, emphasising the need to involve an experienced (bio)statistician from the outset. Study duration and (non-)compliance are also discussed. As recruitment of study participants can often be a major bottleneck, various recruitment strategies are described. This guidance document also refers to successfully submitted dossiers as well as failed applications and other publically available relevant resources which will help with the appropriate scientific substantiation of health claims.

4.2. PATHWAY-27 Industry Guidelines

The Guidelines for the food industry & small and medium enterprises follow step-by-step the complex tasks of the product development process focusing on all aspects that users should consider when designing products with health claims in Europe. The content of the guidelines is based on the results and experiences from the PATHWAY-27 project as well as relevant publications, guides and experience collected from industry practice. The specific challenges, good practices and the typical pitfalls for developing and placing products with health claims onto the market are highlighted.

4.3. Other relevant PATHWAY-27 outputs

4.3.1. Guidelines for designing, conducting and reporting a dietary intervention trial using bioactive-enriched food (Deliverable 5.5)

These guidelines provide an update to, and are intended to complement, previously published guidance documents. They are unique in providing practical information for intervention studies using bioactive-enriched foods, based on the PATHWAY-27 project.

4.2.3. Relevant PATHWAY-27 publications on in vitro and in vivo work

In vitro and *in vivo* work, although it cannot constitute the primary evidence in a health claim dossier, can provide insights in the possible mechanisms of action by which a food/food component might exert a physiological beneficial effect.

A number of peer-reviewed articles have been published during the course of the PATHWAY-27 project, on in vitro and in vivo effects of bioactive-enriched foods:

- Carlos Pineda-Vadillo et al., In vitro digestion of dairy and egg products enriched with grape extracts: Effect of the food matrix on polyphenol bioaccessibility and antioxidant activity. *Food Research International* (2016).
- Christel Björk, et al. Effects of selected bioactive food compounds on human white adipocyte function. *Nutrition & metabolism* (2016).
- PUFA and Oxidative Stress. Differential Modulation of the Cell Response by DHA
- The food matrix affects the anthocyanin profile of fortified egg and dairy matrices during processing and in vitro digestion.

5. Additional resources

5.1. EU Register of 'Nutrition and Health Claims Made on Foods'

The EU Register is for information only, showing:

- Permitted nutrition claims and their conditions of use
- Authorised health claims, their conditions of use and applicable restrictions, if any;
- Non-authorised health claims and the reasons for their non-authorisation;
- EU legal acts for the specific health claims;
- National measures mentioned in Art. 23(3) of Regulation EC 1924/2006 (115 Kb)

The Commission will update the EU Register when required, namely upon adoption of EU decisions on applications for claims or on changes to conditions of use and restrictions.

5.2. Guidance from EFSA & thematic workshops:

EFSA carried out a series of public consultations to receive input from the scientific community and all interested parties, first on discussion papers on guidance on the scientific requirements for health claims related to specific health functions and subsequently on an updated version of the draft guidance on the scientific requirements for health claims related

to these specific health functions prepared by the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA Panel).

The different guidance papers are listed below:

- Guidance for the scientific requirements for health claims related to antioxidants, oxidative damage and cardiovascular health (19 January 2018);
- Guidance for claims on the immune system, GI, and defence against pathogens (18 January 2016);
- Guidance on the scientific requirements for health claims related to physical performance (17 July 2012);
- Guidance on the scientific requirements for health claims related to functions of the nervous system, including psychological functions (17 July 2012);
- Guidance on the scientific requirements for health claims related to bone, joints, skin, and oral health (16 May 2012);
- Guidance on the scientific requirements for health claims related to appetite ratings, weight management, and blood glucose concentrations (21 March 2012).

6. Conclusion

This deliverable outlined important documents supporting the implementation of the European legislation framework on health claims. A flowchart – with hyperlinks to most relevant documents – was developed which illustrates this framework and the different steps to follow when considering submitting a health claim dossier in Europe (see Figure 3).

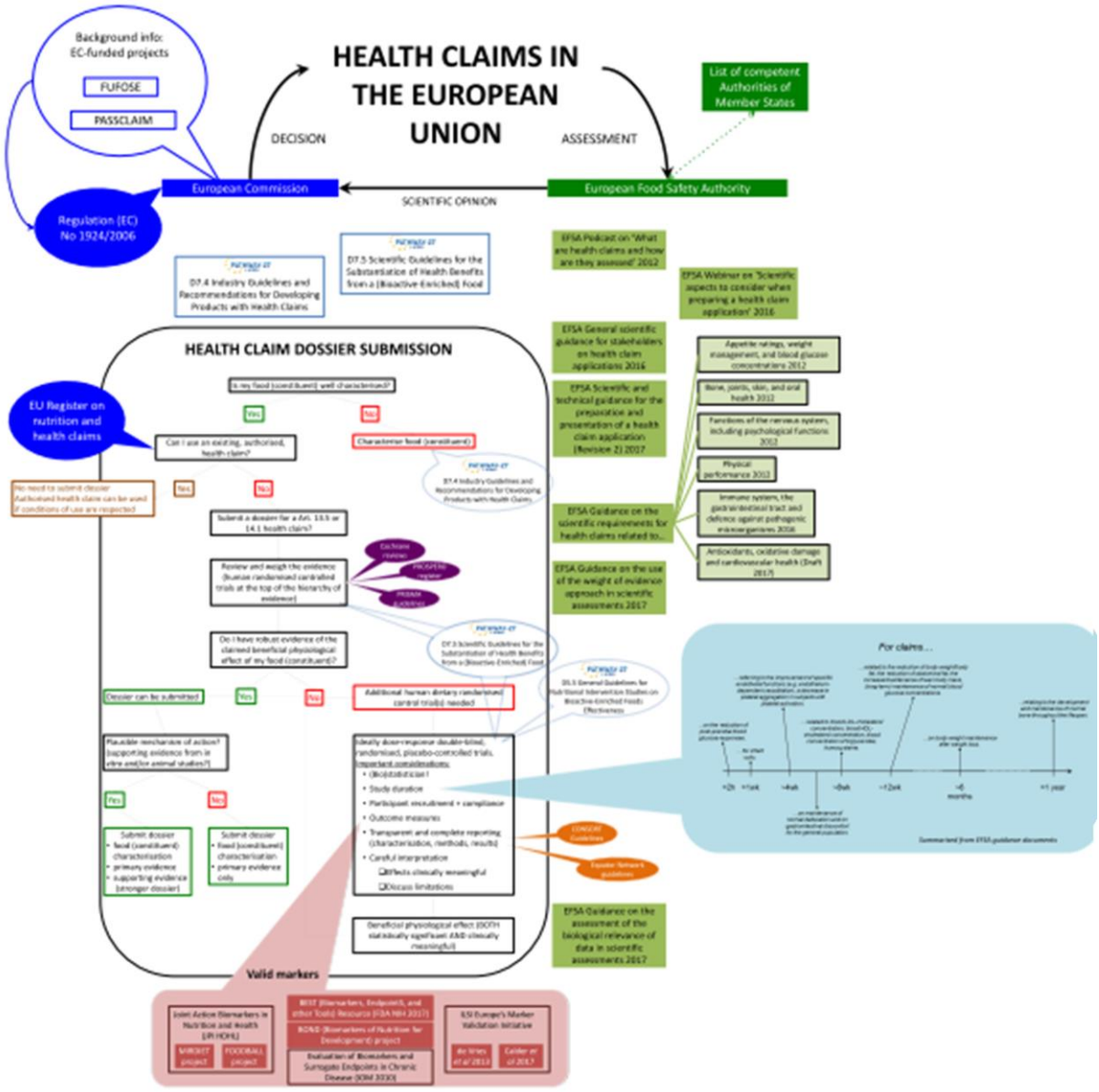

Figure 3 Summary flowchart: health claims in the European Union

The full-size flowchart with hyperlinks can be accessed here: [INSERT LINK ATFER IT HAS BEEN UPLOADED ON PATHWAY-27 WEBSITE]