SCIENTIFIC OPINION

EFSA Journal

ENDORSED FOR PUBLIC CONSULTATION: 30 June 2015 PUBLISHED: dd mmmm yyyy

doi:10.2903/j.efsa.20YY.NNNN

Draft general scientific guidance for stakeholders on health claim applications

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)

Abstract

The European Food Safety Authority asked the Panel on Dietetic Products Nutrition and Allergies to update the General guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims published in March 2011. Since then, the NDA Panel has completed the evaluation of Article 13.1 claims except for claims put on hold by the European Commission, and has evaluated additional health claim applications submitted pursuant to Articles 13.5, 14 and also 19. In addition, comments received from stakeholders indicate that general issues that are common to all health claims need to be further clarified and addressed. This guidance document aims to explain the general scientific principles applied by the NDA Panel for the evaluation of all health claims and outlines a series of steps for the compilation of applications. The general guidance document represents the views of the NDA Panel based on the experience gained to date with the evaluation of health claims, and it may be further updated, as appropriate, when additional issues are addressed.

Keywords: guidance, health claims, general principles, scientific aspects, applications

Requestor: EFSA

Question number: EFSA-Q-2015-00200

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Acknowledgements: The Panel wishes to thank the members of the Working Group on Claims: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Marina Heinonen, Ambroise Martin, Hildegard Przyrembel, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Sean (J.J.) Strain, Inge Tetens, Hendrik Van Loveren, Hans Verhagen and Peter Willatts for the preparatory work on this scientific output and EFSA staff members: Silvia Valtueña Martínez and Leng Heng for the support provided to this scientific output.

Suggested citation: EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2015. Draft general scientific guidance for stakeholders on health claim applications. EFSA Journal 20YY;volume(issue):NNNN, 29 pp. doi:10.2903/j.efsa.20YY.NNNN

ISSN: 1831-4732

The EFSA Journal is a publication of the European Food Safety Authority, an agency of the European Union.

Summary

The European Food Safety Authority (EFSA) asked the Panel on Dietetic Products Nutrition and Allergies (NDA) to update the General guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims published in March 2011.

Since then, the NDA Panel has completed the evaluation of Article 13.1 claims (except for claims put on hold by the European Commission), and has evaluated additional health claim applications submitted pursuant to Articles 13.5, 14 and also 19. In addition, comments received from stakeholders indicate that general issues that are common to all health claims need to be further clarified and addressed.

This guidance document aims to explain the general scientific principles applied by the NDA Panel for the evaluation of all health claims and outlines a series of steps for the compilation of applications.

Once it is adopted, it will supersede the General guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims and the pre-submission guidance on administrative and procedural questions for applicants intending to submit applications for authorisation of health claims made on foods.

The guidance document was subject to public consultation (17 July to 11 September 2015). The general guidance document represents the views of the NDA Panel based on the experience gained to date with the evaluation of health claims, and it may be further updated, as appropriate, when additional issues are addressed.

Table of contents

Background and Terms of Reference as provided by EFSA

Background

Regulation (EC) No 1924/2006[1] harmonises the provisions related to nutrition and health claims and establishes rules governing the Community authorisation of health claims made on foods. According to the Regulation, health claims should be only authorised for use in the Community after a scientific assessment of the highest possible standard to be carried out by EFSA.

Owing to the scientific and technical complexity of health claims, the EFSA Panel on Dietetic products, Nutrition and Allergies (NDA Panel) has placed considerable focus on developing scientific criteria for substantiation of health claims and has published guidance documents on the scientific substantiation of health claims since 2007[2].

Based on experience gained with the evaluation of health claims and taking into account outcomes of public consultation[3], it is noted that general issues that are common to all health claims (e.g. general principles, administrative and procedural aspects related to the health claim evaluation process) need to be further clarified and addressed in the general guidance document for stakeholders to assist applicants in preparing and submitting their applications for the scientific evaluation of health claims.

To this end, the NDA Panel is asked to update the General guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims[4].

Terms of reference

The NDA Panel is requested by EFSA to update the General guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims.

The guidance document shall clarify and address general issues that are common to all health claims (i.e. pursuant to Articles 13.1, 13.5, 14 and 19 of Regulation (EC) No 1924/2006), taking into account the experience gained with the evaluation of health claims by the NDA Panel including outcomes of public consultation.

The draft guidance shall be released for public consultation prior to finalisation.

Before the adoption of the guidance document by the NDA Panel, the draft guidance needs to be revised taking into account the comments received during the public consultation.

A technical report on the outcome of the public consultation on the guidance document shall be published.

[1] 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. OJ L 404, 30.12.2006, p. 9–25.
[2] http://www.efsa.europa.eu/en/nda/ndaclaims.htm
[3] http://www.efsa.europa.eu/en/supporting/pub/758e.htm
[4] http://www.efsa.europa.eu/en/efsajournal/pub/2135.htm

Assessment

1. Introduction

The general guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims, published in March 2011[5], laid down the general principles applied by the EFSA Panel on Dietetic products, Nutrition and Allergies (NDA Panel) for the evaluation of health claims and was based on the experience gained by the NDA Panel from earlier evaluations.

Since then, the NDA Panel has completed the evaluation of Article 13.1 claims (except for claims put on hold by the European Commission), and has evaluated additional health claim applications submitted pursuant to Articles 13.5, 14 and also 19. In addition, comments received from stakeholders during public consultations on guidance documents for health claims on specific areas[6], during stakeholder meetings, and by e-mail through the EFSA's Application Desk, indicate that an update on general issues that are common to all health claims is needed.

This guidance document aims to explain the general scientific principles applied by the NDA Panel for the evaluation of all health claims and outlines a series of steps for the compilation of applications.

The draft guidance was discussed and endorsed at the NDA Plenary meeting on 30 June 2015 for release for public consultation. Once adopted, it will supersede the guidance published in 2011[7], and the Pre-submission guidance for applicants published in 2007[8].

2. Objectives and scope

This guidance is intended to assist applicants in preparing applications for the authorisation of health claims (pursuant to articles 13.5, 14 and 19 of Regulation (EC) No 1924/2006) through an understanding of:

a) the general principles which have been applied by the NDA Panel for the scientific evaluation of health claim applications;

b) the elements which should be considered by applicants for the compilation of applications.

Examples drawn from previous evaluations are used in this guidance to illustrate these aspects. This document does not intend to cover potential future health claims which have not been evaluated by the Panel, or provide detailed advice on specific applications.

This guidance should be read in conjunction with the Scientific and technical guidance for the preparation and presentation of an application for authorisation of a health claim[9], Regulation on Nutrition and Health Claims made on foods[10], Guidance on the implementation of Regulation (EC) N° 1924/2006[11], Commission Regulation (EC) No 353/20908[12], Commission Implementing Decision of 24 January 2013[13], and future guidelines and regulations, as applicable.

[5] http://www.efsa.europa.eu/en/efsajournal/pub/2135.htm
[6] http://www.efsa.europa.eu/en/supporting/pub/758e.htm
[7] http://www.efsa.europa.eu/en/efsajournal/pub/2135.htm
[8] http://www.efsa.europa.eu/en/ndaguidance/docs/ndapresubmissionguidance.pdf
[9] http://www.efsa.europa.eu/en/efsajournal/pub/2170.htm
[10] 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. OJ L 404, 30.12.2006, p. 9–25. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2006R1924:20100302:EN:PDF
[11] Guidance on the implementation of Regulation (EC) No 1924/2006 on nutrition and health claims made on foods – Conclusions of the Standing Committee on the Food Chain and Animal Health, 14 December 2007. http://ec.europa.eu/food/food/labellingnutrition/claims/guidance_claim_14-12-07.pdf
[12] Commission Regulation (EC) No 353/2008 of 18 April 2008 establishing implementing rules for applications for authorisation of health claims as provided for in Article 15 of Regulation (EC) No 1924/2006 of the European Parliament and of the Council (Text with EEA relevance) (OJ L 109, 19.4.2008, p. 11): http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2008R0353:20091221:EN:PDF
[13] Commission Implementing Decision of 24 January 2013 adopting guidelines for the implementation of specific conditions for health claims laid down in Article 10 of Regulation (EC) No 1924/2006 of the European Parliament and of the Council. OJ L 22, 25.1.2013, p. 25–28. http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32013D0063

3. Definition of terms

In the context of this guidance document:

- **Food/constituent** means a food category, a food or a food constituent (e.g. a nutrient or other substance, or a fixed combination of nutrients/other substances).
- The term **essential nutrient** refers to a substance that must be obtained from the diet because the body cannot make it, or cannot make it in sufficient quantities for normal function(s).
- **Other substance** means any food/constituent which is **not** an essential nutrient.
- **Efficacy study** refers to an intervention study (in humans, in animals) which investigates the relationship between the food/constituent and the claimed effect.
- **Pertinent study** means a human study from which scientific conclusions can be drawn for the substantiation of a claim.
- The **totality of the evidence** describes all the studies (e.g. in humans, in animals, *in vitro*) which are taken into consideration to conclude on the substantiation of a claim (including studies in favour and not in favour of the claim).
- **Supportive evidence** refers to studies/data which, on their own, are not sufficient for the scientific substantiation of a claim, but may become part of the totality of the evidence if pertinent human (efficacy) studies are available.
- A **study group** is considered as **representative** of the target population for a claim (i.e. the general healthy population or subgroups thereof) when the study subjects have been randomly selected from the target population and not on the basis of a particular characteristic which may limit the generalisation of the results obtained to the target population for a claim.
- A **suitable study group** means a study group which is representative of the target population for the claim or a study group from which extrapolation of the results to the target population is biologically plausible.

4. What is the legal framework for the authorisation of health claims in the EU? Who does what and when?

The process of authorisation of health claims made on food is governed by Regulation (EC) No 1924/2006[14]. **Figure 1** summarises the key steps of the process, as well as the main players at each step. **Annex A** explains the administrative and procedural aspects of applications, from claim formulation to authorisation.

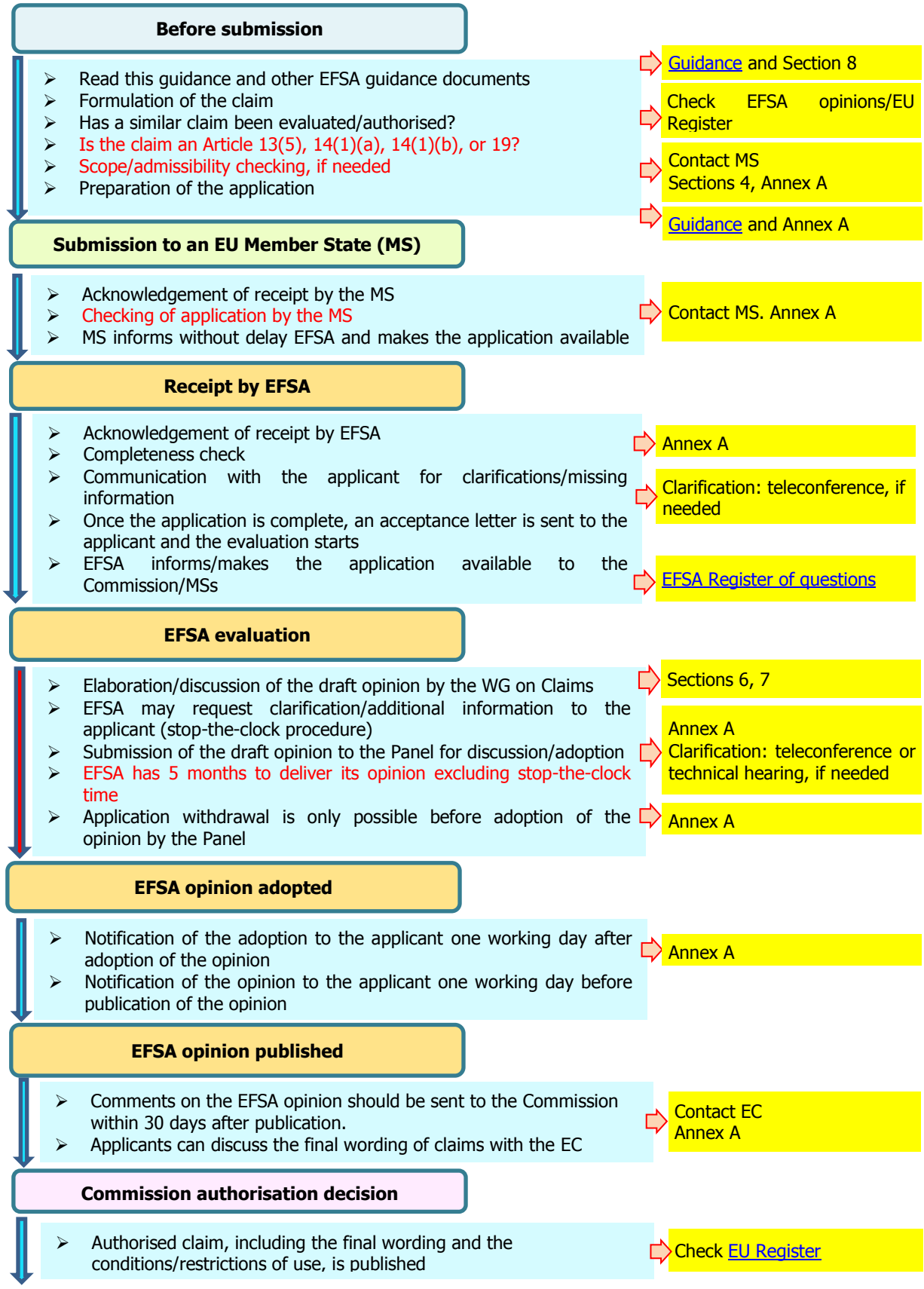
It is the responsibility of risk managers (i.e. the European Commission and the Member States), but **not** EFSA, to decide on whether or not a health claim falls under the scope of Regulation (EC) No 1924/2006, e.g. whether a health claim is/is not a medicinal claim. This responsibility includes decisions on the admissibility of the target population for a claim (e.g. whether or not subjects under medications can be the target population for health claims made on foods).

Regulation (EC) No 1924/2006 establishes that health claims should be scientifically substantiated by generally accepted scientific evidence (Article 6.1), by taking into account the totality of the available scientific data, and by weighing the evidence (Recital 17). Health claims should only be authorised for use in the Community after a scientific assessment of the highest possible standard (Recital 23). Regulation (EC) No 1924/2006 also establishes that, in order to ensure harmonised scientific assessment of these claims, EFSA should carry out such assessments (Recital 23). Within this framework, the NDA Panel applies similar criteria for all health claims and considers whether the beneficial effect of a food/constituent on a function or a risk factor for disease is substantiated by generally accepted scientific evidence, by taking into account the totality of the available scientific data, and by weighing the evidence (see section 6). It should be noted that a safety assessment is not foreseen under the framework of Regulation (EC) No 1924/2006.

[14] http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02006R1924-20121129&from=EN

Decisions regarding the authorisation of health claims, including the final wording and the conditions/restrictions of use, are taken by risk managers, and **not** EFSA. In order to make such decisions, risk managers may take into account other legitimate factors, such as safety aspects (e.g. to modify the conditions/restrictions of use) or consumer understanding (e.g. to modify the wording of the claim), in addition to EFSA's scientific evaluation.

Figure 1: Key steps in the process of authorisation of health claims made on food



5. Scientific standards *versus* regulatory requirements

Article 7(3) of Regulation (EU) No 1169/2011[15] states: food information to consumers shall not attribute to any food the property of preventing, treating or curing a human disease, nor refer to such properties. In addition, Article 2(6) of Regulation (EC) No 1924/2006 defines a 'reduction of disease risk claim' as any health claim that states, suggests or implies that the consumption of a food category, a food or one of its constituents significantly reduces a risk factor in the development of a human disease. The Regulation, therefore, indicates that, for the purpose of communicating the health properties of a food/constituent to consumers:

a) subjects with a disease cannot be the target population for health claims made on food;

b) function claims cannot refer to a disease;

c) disease risk reduction claims cannot refer to the reduction of the risk of a disease, but should refer to the reduction of a risk factor for disease[16].

However, stakeholders have noted that this regulatory framework may be in contradiction to some basic scientific principles which have governed the assessment of the relationship between food/constituents and health, such as:

a) several studies investigating whether or not, and how, a food/constituent exerts a beneficial effect on a function have been conducted in subjects meeting the diagnostic criteria for a disease which negatively affects such function. In addition, the first-line therapy for patients with diet-related chronic diseases (e.g. obesity, type 2 diabetes, hypertension) is often dietary advice, and thus they could benefit the most from health claims made on foods;

b) in some cases, the relationship between a food/constituent and a function can be best measured by using disease outcomes[17];

c) with respect to the likelihood that the consumption of a food/constituent would effectively modify the risk of the disease, disease outcomes provide stronger evidence than risk factors for disease. In addition, in some circumstances it may be easier to measure disease outcomes than risk factors for disease[18].

In order to fill the gap between the above-mentioned scientific principles and regulatory requirements, the NDA Panel has worked with applicants during the evaluation of applications on the formulation of health claims which could allow a scientific evaluation with the type of human studies provided but also comply with the requirements of Regulation (EU) No 1169/2011, as follows:

a) studies conducted in subjects with a disease may be used to substantiate function claims for the general population or subgroups thereof (without the disease) as long as the effect of the food/constituent on the body function which is named in the claim is expected to occur in subjects without the disease and a rationale is given for such expectations[19].

[15] http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32011R1169&from=EN

[16] For example, claims on the reduction of the risk for coronary heart disease (CHD) cannot be made, but they must refer to the reduction of a risk factor for CHD (e.g. LDL-cholesterol, blood pressure).

[17] For example, the effect of a food/constituent on cardiac function can be measured by its effects on CHD disease outcomes http://www.efsa.europa.eu/en/efsajournal/doc/1796.pdf

[18] For example, it may be easier to assess the incidence/severity/duration of lower urinary tract infections than the inhibition of bacterial adhesion to the bladder wall *in vivo* in humans.

[19] For example, studies in obese subjects could be used to substantiate a claim on the reduction of body weight addressed to overweight adults http://www.efsa.europa.eu/en/search/doc/1798.pdf, whereas studies on subjects with arthritis of various origins (rheumatoid arthritis, psoriatic arthritis, arthritis of infectious origin) and which relate to the treatment of symptoms of the disease cannot be considered for the scientific substantiation of health claims on joint function for the general population.

b) longitudinal (observational and intervention) studies on the relationship between a food/constituent and the incidence[20] of disease in subjects free of disease at recruitment may be used to substantiate claims on a function which affects the development of the disease[21].

c) studies on the relationship between a food/constituent and the incidence[22] of disease in subjects free of disease at recruitment may also be used to substantiate disease risk reduction claims[23] (see section 7.2.2).

6. What are the general principles applied by the Panel to decide whether a health claim is substantiated?

The general principles applied by the NDA Panel for the assessment of claims on established functions of essential nutrients differ from those applied for the assessment of claims on non-established functions of essential nutrients, and of claims on other substances. Such differences refer to the requirements for the definition of the claimed effect, for the scientific substantiation of the claim, and for establishing conditions of use (see also sections 6.1, 6.2, 7.2.1, and 7.8).

6.1. Claims on essential nutrients

Essential nutrients have unique roles in physiological processes based on a large body of scientific evidence including deficiency symptoms in humans. The scientific substantiation of these claims is based on the well-established biochemical role of such nutrients and/or on deficiency symptoms, and in such cases the NDA Panel does not review the primary scientific studies submitted on the relationship between the food/constituent and the claimed effect and it does not weigh the evidence. These claims will not be discussed further in this guidance, except in sections 7.2 (characterisation of the claimed effect) and 7.8 (conditions of use).

Claims related to non-established functions of essential nutrients[24] are assessed by the NDA Panel following the same general principles applied to claims on other substances (see section 6.2).

6.2. Claims on other substances

In assessing each specific food/health relationship which forms the basis of a claim, the NDA Panel makes a scientific judgement on the extent to which a cause and effect is established between the consumption of the food/constituent and the claimed effect (i.e. for the target group under the proposed conditions of use) by considering the strength, consistency, specificity, dose-response, and biological plausibility of the relationship, and by weighing the totality of the evidence. A grade is not assigned to the evidence.

Pertinent human (intervention and observational) studies are central for health claim substantiation and pertinent human intervention studies are at the top of the hierarchy that informs decisions on substantiation[25]. The reason is that it is most important to show that the food/constituent can influence the claimed effect in humans and that the effect is specific for the food/constituent. Since the impact of introducing or replacing a single food/constituent in the whole diet on the claimed effect is expected to modest, it is only possible to provide such evidence from human intervention studies. Intervention (and observational) studies can also provide evidence for a dose response relationship and for consistency of the effect (or the association) across studies. Efficacy studies in animals and

[20] Severity and duration of the disease can also be considered for acute disease states which generally resolve, such as acute infections or allergic reactions.

[21] For example, studies on the incidence of dental caries can be used to substantiate claims on the maintenance of normal tooth mineralisation.

[22] Severity and duration of the disease can also be considered for acute disease states which generally resolve, such as acute infections or allergic reactions.

[23] For example, evidence that a food/constituent decreases the risk of lower urinary tract infections could be used for the substantiation of disease risk reduction claim. In this context, evidence that the food/constituent decreases bacterial adhesion *in vitro* could be used as a risk factor in the wording of the claims (as required by Regulation (EU) No 1169/2011) because it may be plausibly involved in the pathogenesis of the disease, and in this case evidence that the modification of *in vitro* bacterial adhesion also modifies the incidence of the disease is not required.

[24] E.g. vitamin C and function of the immune system assessed as a reduction in the incidence of common cold during and after extreme physical exercise; http://www.efsa.europa.eu/en/efsajournal/doc/1226.pdf

[25] Guidance for the preparation and presentation of health claim applications: http://www.efsa.europa.eu/en/efsajournal/doc/2170.pdf

non-efficacy studies in humans, animals and/or *in vitro* (e.g. evidence for a mechanism by which a food could exert the claimed effect) may be part of the totality of the evidence only if pertinent human studies showing an effect of the food/constituent are available.

The outcome of each assessment is one of three possible conclusions:

(i) A cause and effect relationship has been established between the consumption of the food/constituent and the claimed effect.

The NDA Panel considers that the evidence provided is convincing and sufficient for a positive outcome.

(ii) The evidence provided is insufficient to establish a cause and effect relationship between the consumption of the food/constituent and the claimed effect.

The Panel considers that, although there is some evidence in favour of the claim, such evidence is neither convincing nor sufficient for a positive outcome.

(iii) A cause and effect relationship has not been established between the consumption of the food/constituent and the claimed effect.

The NDA Panel considers that there is no, or at most very limited, scientific evidence in favour of the claim.

7. What are the main issues addressed by the NDA Panel for the evaluation of health claims?

In assessing each specific food/health relationship which forms the basis of a health claim the NDA Panel considers the following key questions:

(i) the food/constituent is defined and characterised;

(ii) the claimed effect is a well-established function of an essential nutrient; OR

the claimed effect is defined and is a beneficial physiological effect for the target population, and can be measured *in vivo* in humans;

(iii) a cause and effect relationship is established between the consumption of the food/constituent and the claimed effect (for the target group under the proposed conditions of use).

Each of these three questions needs to be assessed by the NDA Panel with a favourable outcome for a claim to be substantiated. In addition, an unfavourable outcome of the assessment of questions (i) and/or (ii) precludes the scientific assessment of question (iii).

If a cause and effect relationship is considered to be established, the NDA Panel considers whether:

- the quantity of food/pattern of consumption required to obtain the claimed effect can reasonably be consumed within a balanced diet;
- the proposed wording reflects the scientific evidence;
- the proposed wording complies with the criteria for the use of claims specified in the Regulation;
- the proposed conditions/restrictions of use are appropriate;
- the data claimed as proprietary by the applicant were needed to reach the conclusion.

7.1. Characterisation of the food/constituent

7.1.1. To what extent should a food/constituent be characterised?

The NDA Panel considers whether the information provided in relation to the food/constituent includes those characteristics which may influence the specific physiological effect that is the basis of the claim. Such characteristics may depend on the nature of the food constituent, but also on the specific claimed effect.

- If the claim is for an individual constituent, the source and specifications (e.g. physical and chemical properties) should be provided. Characterisation of essential nutrients would relate mainly to the chemical form of the nutrient naturally present in foods and forms that are approved for addition to foods[26].
- If the claim is for a specific formulation or a fixed combination of constituents, then studies are needed on the specific formulation or combination, whereas studies on the individual constituents or combinations of constituents other than the combination for which the claim is proposed are not required. However, if individual constituent(s) in the specific formulation have an established role on the claimed effect (e.g. evidence for their role on the claimed effect has been already evaluated by the Panel with a positive outcome), the NDA Panel also considers whether: i) the effect could be explained by the individual constituent(s), regardless of the source; ii) other constituent(s) in the specific formulation are required for/contribute to the claimed effect (i.e. whether the specific formulation has an effect beyond what could be expected from the presence of the individual constituent(s) with an established role on the claimed effect[27]).
- For a food category (e.g. "dairy products"[28]), the NDA Panel considers whether the information provided sufficiently addresses the variability between individual foods regarding those characteristics which may influence the specific claimed effect.
- For plant products[29], the NDA Panel considers whether the information provided includes the scientific (latin) name (full systematic species, name incl. botanical family, genus, species, variety, subspecies, author's name, and chemotype, where relevant; e.g. *Punica granatum* L, Lythraceae (Punicaceae)), the part used (e.g. fruit, root, leaf, seed), complete specifications of the manufacturing process (e.g. dried, hydroalcoholic extraction, plant extract ratio), and how the product is standardised (e.g. by its content of one or more specific constituents).
- For microorganisms (e.g. bacteria and yeast), the NDA Panel considers whether, in addition to species identification, sufficient information is provided for characterisation (genetic typing) at strain level by internationally accepted molecular methods, and regarding the naming of strains according to the International Code of Nomenclature[30]. In the case of a combination of two or more microorganisms, the Panel considers that if one of the microorganisms used in the combination is not sufficiently characterised, the combination proposed is also not sufficiently characterised[31].
- For comparative claims, both the food/constituent that is the subject of the claim and the comparator, or the food/constituent it should replace in foods in order to obtain the claimed effect, should be sufficiently characterised for a scientific evaluation with respect to the factors which may have an impact on the claimed effect. Applicants should take into account the Commission guidance on the implementation of Regulation (EC) No 1924/2006, of December 2007 for the use of comparative claims[32].

The NDA Panel also considers whether the specific food/constituent is sufficiently characterised in order to:

[26] Regulation (EC) No 1925/2006 of the European Parliament and of the Council on the addition of vitamins and minerals and of certain other substances to foods, as amended. OJ L 183, 12.7.2002, p. 51

[27] E.g. whether the consumption of soy lecithin preparations (in which phosphatidyl cholines are the most abundant phospholipid) has an effect on blood cholesterol concentrations beyond what could be expected from their content of linoleic acid http://www.efsa.europa.eu/en/scdocs/doc/1741.pdf

[28] http://www.efsa.europa.eu/en/efsajournal/doc/2243.pdf

[29] EFSA Scientific Committee; Guidance on safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements, on request of EFSA. EFSA Journal 2009; 7(9):1249. [19 pp.]. doi:10.2093/j.efsa.2009.1249. http://www.efsa.europa.eu/en/efsajournal/doc/1249.pdf

[30] See International Committee on Systematics of Prokaryotes: http://icsp.org/

[31] See also the Guidance on the scientific requirements for health claims related to the gastro-intestinal tract, the immune system, and defence against pathogenic microorganisms http://www.efsa.europa.eu/en/calls/docs/150209.pdf

[32] Guidance on the implementation of Regulation (EC) No 1924/2006 on nutrition and health claims made on foods – Conclusions of the Standing Committee on the Food Chain and Animal Health, 14 December 2007. http://ec.europa.eu/food/food/labellingnutrition/claims/index_en.htm

(i) establish that the studies submitted for the substantiation of the claim were performed with a food/constituent which complies with the specifications given for the food/constituent for which the claim is proposed (e.g. the microbial strain(s) used).

(ii) define appropriate conditions of use for the claim.

(iii) allow control authorities to verify that the food/constituent which bears a claim is the same as that which was the subject of a Community authorisation, although this aspect is not required for the substantiation of a claim (e.g. it is strongly recommended that microbial strains are deposited in an internationally recognised culture collection[33] with access number for control purposes).

It is the responsibility of the applicant to provide this information along with information regarding the manufacturing process and stability of the food/constituent, where applicable, in order to show consistency in the final product for those characteristics considered to influence the specific claimed effect.

7.1.2. In what context can food/constituents be characterised in relation to the claimed effect?

In principle, food/constituents cannot be characterised on the basis of the claimed effect (e.g. non-cariogenic carbohydrates, antioxidant foods, microorganisms which contribute to the defence against pathogens in the respiratory tract).

However, in specific circumstances, the food/constituent(s) could be characterised on the basis of a property which could explain their contribution to the claimed effect (i.e. when the mechanism by which the claimed effect is achieved is known)[34].

7.2. Characterisation of the claimed effect

According to Regulation (EC) No 1924/2006, the use of health claims shall only be permitted if the food/constituent, for which the claim is made, has been shown to have a beneficial physiological effect.

In assessing each claim, the NDA Panel makes a scientific judgement on whether the claimed effect is considered to be a beneficial physiological effect, as described in the information provided by the applicant and by taking into account the target population for which the claim is intended. In principle, the target population of claims made on food is the general population or subgroups thereof defined on the basis of age, sex, physiological conditions and/or lifestyle (e.g. children, men, post-menopausal women, adults performing endurance exercise). Decisions on the admissibility of a different target population for a claim (e.g. subjects with a disease) are taken by the risk managers (see section 4) and are out of the scope of this guidance.

7.2.1. Characterisation of the claimed effect for function claims

For function claims, the beneficial physiological effect relates to the maintenance, reduced loss or improvement of a body function.

For claims which are based on the well-established biochemical role of essential nutrients, and/or on deficiency symptoms, the claimed effect can refer to general functions of organs, tissues or systems (i.e. does not need to be a specific function which is testable and measurable *in vivo* in humans by generally accepted methods) because symptoms of deficiency of a nutrient can result from broad effects on one or more organs and/systems and it is sometimes not possible or appropriate to single out a precise function that is affected by deficiency of that nutrient.

[33] http://www.wfcc.info/collections/

[34] For example, non-digestible carbohydrates have been defined on the basis of a property (non-digestibility in the small intestine) which explains their contribution to the reduction of post-prandial blood glucose responses when replacing digestible carbohydrates in foods http://www.efsa.europa.eu/en/search/doc/3513.pdf; some food/constituents have been characterised on the basis of their α-amylase inhibitory activity, which was considered to explain their potential effect on body weight changes http://www.efsa.europa.eu/it/search/doc/2999.pdf; http://www.efsa.europa.eu/en/efsajournal/doc/3754.pdf

For function claims on other substances, and for function claims on non-established functions of essential nutrients, the NDA Panel considers whether the claimed effect:

i) refers to a specific body function (i.e. it is not general and non-specific), as required by Regulation (EC) No 1924/2006, and whether it is sufficiently defined for a scientific evaluation. Claims referring to general wellbeing or unspecified functions of organs, tissues and systems are not considered by the NDA Panel as sufficiently defined for a scientific evaluation[35];

ii) is a beneficial physiological effect for the target population for which the claim is intended[36];

iii) can be assessed *in vivo*[37] in humans by generally accepted methods. To this end, the Panel considers the appropriateness of the outcome variable(s) and of the methods of measurement proposed to assess the claimed effect in human studies.

In this context, it should be noted that:

a) some claimed effects, which are considered as beneficial physiological effects, cannot be evaluated by the Panel if no generally accepted methods for the assessment of the outcome variable(s) of interest *in vivo* in humans have been provided[38].

b) changes in outcome variable(s), which can be measured *in vivo* in humans by generally accepted methods, may not be considered beneficial physiological effects *per se*, and thus cannot be the claimed effect (i.e. constitute the only basis for the scientific substantiation of a health claim)[39]. Changes in such outcome variable(s) should be accompanied by evidence of a beneficial physiological effect or clinical outcome. Alternatively, they could be proposed as part of the mechanisms by which a food may exert the claimed effect, i.e. induce a beneficial change on a function. In certain circumstances, however, changes in outcome variable(s) measured *in vivo* in humans, and which do not refer to a function directly, may be the claimed effect if evidence is provided that changes in such variable(s) generally induce a beneficial change in a function[40].

In principle, if a body function which is the subject of the claim (e.g. maintenance of normal defecation) is best described by a number of outcome variables which are interrelated (e.g. stool frequency, faecal bulk, stool consistency and transit time), and which in combination could provide information about the function and eventually about the underlying mechanism of action, the Panel will consider the information provided on all these variables to evaluate the claim. However, the selection of the outcome variable(s) to be tested in a study and the decision to treat such variable(s) as primary or as secondary outcomes would depend, among other considerations, on the study objectives (e.g. exploratory, confirmatory), the study population, and the information which is already available (in the literature, or to the applicant) regarding the relationship between the consumption of the food/constituent and the claimed effect (e.g. whether a mechanism of action by which the food/constituent could exert the claimed effect is already known).

[35] For example, "gut health", "natural defences", "immune function" or "skin health".

[36] For example, "a reduction of gastric acid levels" or "a reduction of inflammation" could represent therapeutic objectives for the management or treatment of some disease conditions, but they are not considered by the NDA Panel as beneficial physiological effects for the target population (i.e. the general population or subgroups thereof).

[37] It includes the measurement of functional outcome variables in vivo and the measurement (ex vivo) of outcome variables in biological samples following an intervention in vivo.

[38] An example is the lack of generally accepted methods for the measurement of the inhibition of adhesion of P-fimbriated E. coli to uroepithelial cells *in vivo* in humans, even though this particular effect was considered a beneficial physiological effect in a particular application for a claim on the reduction of bacterial colonisation of the urinary tract by inhibition of the adhesion of P-fimbriated E.coli to uroepithelial cells. The reasons for the Panel's conclusions can be found in the published opinion: http://www.efsa.europa.eu/en/efsajournal/doc/3082.pdf

[39] Examples of outcome variable(s) which can be measured in vivo in humans by generally accepted methods but do not refer to a benefit on specific functions and thus cannot constitute the only basis for the scientific substantiation of a health claim include, but are not limited to, changes in macular pigment optical density, changes in stool pH and short-chain fatty acid production in the gut, and changes in the composition of the gut microbiota.

[40] For example, changes in skeletal muscle glycogen stores, which can be measured *in vivo* in humans by generally accepted methods but do not refer to a benefit on a function directly, can be used as an appropriate outcome variable for claims on the recovery of normal muscle function after strenuous exercise because evidence has been provided that changes in skeletal muscle glycogen stores lead to the recovery of normal skeletal muscle function after exercise: http://www.efsa.europa.eu/en/efsajournal/doc/3409.pdf

7.2.2. Characterisation of the claimed effect for reduction of disease risk claims

For reduction of disease risk claims, the beneficial physiological effect is the reduction (or beneficial alteration) of a risk factor for the development of a human disease (not the reduction of the risk of disease).

Whether or not the alteration of a factor is considered by the NDA Panel to be beneficial in the context of a reduction of a disease risk claim depends on the extent to which it is established that:

i) the factor is an independent predictor of the risk of disease (such a predictor may be established from intervention and/or observational studies);

ii) the relationship between the factor and the development of the disease is biologically plausible.

If there is evidence from intervention (drug or dietary) studies that a reduction of the risk factor generally reduces the risk of disease and the involvement of the risk factor in the development of the disease is biologically plausible, a reduction of the risk factor is considered beneficial in the context of a reduction of disease risk claim. In this case, evidence that the dietary intervention with the specific food/constituent induces a reduction (or beneficial alteration) of the risk factor would be sufficient for the scientific substantiation of the claim[41].

If there is no such evidence from intervention studies, but there is evidence for an independent association between the proposed risk factor and the incidence of the disease from observational studies and the involvement of the risk factor in the development of the disease is biologically plausible, a reduction of the risk factor may be considered a beneficial physiological effect in the context of a reduction of disease risk claim. In this case, however, evidence that the dietary intervention with the specific food/constituent induces a reduction (or beneficial alteration) of the risk factor and also a reduction of the risk of disease needs to be provided[42].

7.3. What is the evidence required for the scientific substantiation of health claims?

Each relationship between a food/constituent and a claimed effect is assessed by the NDA Panel separately on a case by case basis for specific claim applications. Pertinent human studies are an absolute requirement for the scientific substantiation of health claims, and pertinent human efficacy studies are at the top of the hierarchy that informs decisions on substantiation. However, there is no pre-established formula as to how many or which types of studies are needed for substantiation. The reproducibility of the effect of the food/constituent as indicated by the consistency of the findings (within and across studies) and the biological plausibility of the effect needs to be considered.

[41] For example, it is well established that elevated blood LDL-cholesterol concentration is independently associated with an increased risk of coronary heart disease (CHD), and that reducing blood LDL-cholesterol concentration (by dietary modification or drugs) would generally reduce the risk of development of CHD. It is also well established that elevated (systolic) blood pressure is independently associated with an increased risk of CHD and stroke, and that reducing (systolic) blood pressure (by dietary modification and drugs) would generally reduce the risk of development of CHD and stroke. Reduction in blood LDL-cholesterol concentration, therefore, is considered beneficial in the context of a reduction of disease risk claim for CHD, and reduction in (systolic) blood pressure is considered beneficial in the context of a reduction of disease risk claim for CHD and stroke. http://www.efsa.europa.eu/en/search/doc/2474.pdf. It is also well established that falling is a risk factor for bone fractures in the elderly, and that reducing the risk of falling (e.g. by dietary modification, by drugs, by modification of architectonical barriers) reduces the risk of bone fractures. http://www.efsa.europa.eu/en/efsajournal/doc/2382.pdf.

[42] For example, there is some evidence that low blood HDL-cholesterol concentration, elevated blood concentration of triglycerides, or elevated blood homocysteine concentration is associated with an increased risk of coronary heart disease (CHD). Reduction in blood concentration of triglycerides, reduction in blood homocysteine concentration, or an increase in blood HDL-cholesterol concentration, have been associated with a decreased incidence of CHD following certain dietary interventions in some human intervention studies. However, changes in any of these factors (by dietary modification or drugs) have not generally been shown to reduce the risk of CHD. Therefore, human studies on the risk of CHD are required for the substantiation of these disease risk reduction claims in order to validate the association between these variables and the risk of disease in the context of a particular nutritional intervention. http://www.efsa.europa.eu/en/efsajournal/doc/2474.pdf

The scientific opinions on health claim applications evaluated by the NDA Panel with a positive outcome provide examples as to the number, type and quality of the studies which may be needed for the scientific substantiation of health claims in the context of specific applications[43].

For example, a claim on arabinoxylan and a reduction on post-prandial blood glucose responses was substantiated on the basis of: i) a single well-designed and scientifically sound human intervention study showing a dose-response effect of the food/constituent in a study group which is representative of the target population, ii) a human study showing an effect of the food/constituent on an outcome variable which was only indirectly related to the claimed effect, and iii) strong evidence for a plausible mechanism of action[44]. In contrast, three well-designed and scientifically sound human intervention studies showing a consistent effect of the food/constituent across study groups which are representative of the target population or from which the results could be extrapolated to the general population were sufficient to substantiate a claim on Limicol® and reduction of blood LDL-cholesterol concentrations, even if no evidence for a mechanism by which the food/constituent may have exerted the claimed effect was provided[45]. A health claim on EPA and DHA and maintenance of normal cardiac function was substantiated on the basis of a wealth of human observational studies showing a consistent association between the consumption of the food/constituent and coronary heart disease outcomes in the target population plus human intervention studies showing an effect of the food in diseased subjects under medication[46].

7.4. How does the NDA Panel identify pertinent human studies?

As mentioned in the previous section, pertinent human studies are central for the scientific substantiation of health claims. In order to identify such studies among those submitted in an application, the NDA Panel evaluates:

i) whether the food/constituent investigated in the study complies with the specifications of the food/constituent for which the claim is proposed;

ii) whether the outcome variable(s) are well-defined and appropriate to assess the claimed effect, and whether they have been measured using valid methods;

iii) the design and quality of the study in relation to the risk of bias;

iv) whether the study population is representative of the target population for the claim, or whether extrapolation of the results from the study population to the target population is scientifically plausible;

v) how the conditions under which the study has been conducted relate to the conditions of use (e.g. quantity and pattern of consumption of the food/constituent) proposed for the claim.

Well-designed and conducted randomised controlled trials (i.e. at low risk of bias) investigating the effect of a food/constituent which complies with the specifications of the food/constituent for which the claim is proposed on appropriate outcome variables for the claimed effect, in a suitable study group, and under the conditions of use proposed for the claim are at the top of the hierarchy which informs decisions on substantiation[47]. In principle, the study duration should be adequate in order to exclude: i) adaptation to the continuous consumption of the food/constituent through compensatory mechanisms; ii) chance findings (e.g. for fluctuating outcome measures). The quality of reporting, although not inherently linked to the quality of the study, will have an impact on the outcome of the NDA Panel's assessment[48].

[43] Examples of health claims substantiated using different types and amount of studies include, but are not limited to: http://www.efsa.europa.eu/en/efsajournal/pub/2809.htm; http://www.efsa.europa.eu/it/efsajournal/doc/1101.pdf; http://www.efsa.europa.eu/en/efsajournal/pub/2382.htm;http://www.efsa.europa.eu/en/scdocs/doc/1776.pdf; http://www.efsa.europa.eu/en/efsajournal/doc/1885.pdf.

[44] http://www.efsa.europa.eu/en/efsajournal/doc/2205.pdf

[45] http://www.efsa.europa.eu/en/efsajournal/pub/3327.htm

[46] http://www.efsa.europa.eu/en/efsajournal/doc/1796.pdf

[47] Scientific and technical guidance for the preparation and presentation of health claim applications: http://www.efsa.europa.eu/en/efsajournal/doc/2170.pdf

[48] Guidelines for adequate reporting of research studies can be found at http://www.equator-network.org and EFSA Guidance on Statistical Reporting: http://www.efsa.europa.eu/en/efsajournal/doc/3908.pdf

7.5. How meta-analyses can be used to inform decisions on substantiation?

The NDA Panel considers the results of meta-analyses of (observational and/or intervention) human studies as part of the body of evidence if the meta-analyses specifically evaluate the relationship between the particular food/constituent and the claimed effect by including all the human studies from which conclusions can be drawn for the substantiation of the claim[49]. Information derived from meta-analyses has been used by the Panel in published opinions to summarise the overall evidence provided by individual studies and to establish conditions of use for the claim (e.g. to define the effective dose) when a cause and effect relationship between the consumption of the food/constituent and the claimed effect has been established on the basis of the primary data provided in the application (e.g. the individual studies included in the meta-analyses from which conclusions can be drawn plus the supporting evidence)[50].

7.6. Extrapolation of the results from the study group to the target population

The study group refers to subjects recruited for human studies that are submitted for the scientific substantiation of the claim. When a particular study has been conducted in a study group (e.g. subjects with a disease) which is different from the target population for a claim (e.g. the general population or subgroups thereof), the NDA Panel considers whether the results from that study can be extrapolated to the target population for the claim. In principle:

(i) results from studies performed in *non-diseased subjects*, including *subjects at high risk* for disease[51] (e.g. women with high frequency of lower urinary tract infections (LUTI) in the previous year but free of LUTI at recruitment) in whom the function targeted by the claim (e.g. defence against pathogens in the lower urinary tract) may be affected, could be extrapolated to the target population (e.g. adult women in the general population). However, as this decision is made by the Panel on a case-by-case basis, accurate information on the selection criteria used in these studies to identify and recruit *subjects at high risk for disease* should be provided to allow the Panel to decide whether extrapolation of the results from the study population to the target population is biologically plausible.

(ii) results from studies performed in *subjects with a disease* (i.e. type 2 diabetic patients) that affects the function mentioned (e.g. reduction of post-prandial blood glucose responses) in the claim can be extrapolated to the target population for a claim (e.g. the general population) as long as the effect of the food/constituent on the beneficial physiological effect which is mentioned in the claim is also reasonably expected to occur in subjects without the disease. If subjects with a disease are under pharmacological treatment, the Panel considers whether the effect of the food/constituent is also reasonably expected to occur in subjects without medication.

(iii) results from studies performed *exclusively* in healthy subjects selected on the basis of a genetic (e.g. sex), demographic (e.g. age[52]), physiological (e.g. pregnancy, menopause) or lifestyle (e.g. level of physical activity[53], diet[54]) characteristic, or on the basis of ethnicity, may be pertinent to the scientific substantiation of health claims addressed to a different target population (e.g. the general population) only if the effect of the food/constituent is also observed in subjects who are representative of the target population (e.g. in other studies submitted in the application) or if extrapolation of the results from the study group to the target population is biologically plausible. Biological plausibility will be considered by the NDA Panel on a case-by-case basis.

[49] http://www.efsa.europa.eu/en/supporting/doc/569e.pdf
[50] Examples can be found in published opinions: http://www.efsa.europa.eu/en/search/doc/2053.pdf; http://www.efsa.europa.eu/en/scdocs/doc/781.pdf
[51] Subjects at high risk for disease means individuals with one or more risk factors for a disease who do not meet the diagnostic criteria for such disease.
[52] E.g. children, adults, elderly.
[53] E.g. athletes.
[54] E.g. vegetarians, vegans.

If an application includes one or more human studies showing a relationship between the consumption of the food/constituent on the claimed effect in the target group under the proposed conditions of use (see section 7.4), the Panel may also consider studies conducted in study groups from which the results could not be extrapolated to the target population as part of the evidence for the claim[55].

7.7. How are comparative claims evaluated by the NDA Panel?

Claims for a beneficial effect of the absence (or reduced content) of a food/constituent in a food or category of foods are evaluated as comparative claims. Substantiation may be based on evidence for an independent role of the food/constituent in an adverse effect. For example, for claims related to a reduced content of saturated fatty acids (SFAs) in relation to blood LDL-cholesterol concentrations, SFAs have been shown to increase blood LDL-cholesterol concentrations when compared to carbohydrates, which have no effect on LDL-cholesterol concentrations, and therefore SFAs have an independent role in the adverse effect.

Claims for a beneficial effect of a food/constituent used to replace a food/constituent with an independent role in an adverse effect are also evaluated as comparative claims. Substantiation may be based on evidence for an independent role on an adverse effect of the food/constituent which is being replaced, together with evidence for the lack of an effect or a reduced effect of the food/constituent which is used for replacement. Examples include claims for unsaturated fats and reduced blood LDL-cholesterol concentrations when replacing saturated fats, for low-fermentable carbohydrates and maintenance of tooth mineralisation ('non-cariogenic') when replacing fermentable sugars, and for low-digestible carbohydrates and reduced post-prandial blood glucose when replacing digestible carbohydrates.

Claims related to a comparison between a "test" food and a "control" food (e.g. for changes in appetite ratings after food consumption) are also comparative claims. Both the test and the control food should be sufficiently characterised for a scientific evaluation with respect to the factors (e.g. energy, volume, appearance and taste) which may have an impact on the claimed effect.

In presenting such claims, applicants should take into account the Commission guidance on the implementation of Regulation (EC) No 1924/2006, of December 2007[56] for the use of comparative claims, including characterisation of the appropriate reference or comparator food/constituent (see also 7.1.1).

7.8. On what basis does the NDA Panel propose conditions of use for health claims evaluated with a favourable outcome?

For claims on established functions of essential nutrients conditions of use are set on the basis that any significant amount of the essential nutrient in the diet will contribute to the claimed effect (e.g. conditions of use can be linked to nutrition claims).

For all other claims, including claims on other substances and claims on non-established function of essential nutrients, conditions of use are set on the basis of the human studies submitted for substantiation by considering the minimum amount of the food/constituent (and pattern of consumption, where appropriate), which consistently exerts an effect on the function that is mentioned in the claim. In this case, the NDA Panel also considers whether such an amount can be reasonably consumed in the context of a balance diet (e.g. whether the consumption of the food/constituent in the amounts required to achieve the claimed effect is realistic and unlikely to induce a nutritional imbalance).

7.9. On what basis does the NDA Panel propose wordings for health claims evaluated with a favourable outcome?

The NDA considers whether the wording of the claim proposed by the applicant reflects the scientific evidence. If not, the NDA Panel proposes a different wording. However, wordings proposed by the

[55] http://www.efsa.europa.eu/it/search/doc/2809.pdf
[56] http://ec.europa.eu/food/food/labellingnutrition/claims/index_en.htm

Panel, although scientifically correct, do not take into account consumer understanding and may not be appropriate for consumer communication. As explained in section 4 and Annex A, the applicants can negotiate with risk managers for alternative wordings during the authorisation process.

7.10. Can the conditions of use for an authorised claim be extended or modified?

For the modification or extension of the conditions of use (CoU) of an authorised claim, applications can be submitted pursuant to Article 19 of Regulation (EC) No 1924/2006. The request may refer to the extension or modification of the authorised CoU with respect to e.g. the (chemical) form of the food constituent, the food matrix, the effective dose, the pattern of consumption, the target population, or the restrictions of use. In order to evaluate whether the CoU for an already authorised health claim could be modified, the NDA Panel needs to be assured that the claimed effect assessed in the original opinion can also be achieved by the consumption of the food/constituent under the "new" conditions proposed by the applicant. The nature and amount of information needed for that purpose may depend on the food/constituent, the matrix, the claimed effect, the target population, and the proposed mechanisms by which the claimed effect may be achieved (short-and long-term efficacy). Examples of Article 19 applications can be found in EFSA published opinions[57].

8. What are the key scientific aspects to consider for preparing a health claim application?

Before submitting a health claim application, applicants are advised to consider, step-wise, a series of elements which are needed for the compilation of applications (**Figure 2**).

The **first** step is to consider whether or not the food/constituent is an essential nutrient, and whether or not the claimed effect refers to a well-established function of the nutrient. In this context, it is important to reflect on whether the nutrient:

i) plays a unique (biochemical or structural) role in a function (e.g. as known from *in vitro* studies, from animal studies, from symptoms of deficiency in humans) and

ii) cannot be synthesised by the human body, or not in sufficient amounts to cover the needs for the function in the target population for the claim.

If both of the above-mentioned conditions are met, the relationship between the consumption of the food/constituent and the maintenance of the function (claimed effect) is likely to be established (see section 6.1). However, if the claimed effect refers to a function of the essential nutrient that is not well-established, human studies on the relationship between the consumption of the food/constituent and the claimed effect are required for the scientific substantiation of the claim (see section 7.4). The remainder of this section focuses on how to prepare applications for this type of claims.

The **second** step is the characterisation of the food/constituent. The characterisation of essential nutrients relates mainly to the chemical form of the nutrient naturally present in foods and forms that are approved for addition to foods[58]. For the characterisation of other substances, it is important to consider: i) its composition and characteristics, and particularly those characteristics which may contribute to or be responsible for the claimed effect. To this end, it is important that applicants have good information about the digestion, absorption, metabolism, excretion and/or bioavailability of the food/constituent, its metabolic fate, and an hypothesis/data regarding the mechanism by which the food/constituent could exert the claimed effect; ii) the manufacturing process (if applicable), e.g. that the food/constituent can be manufactured consistently to the stated specifications and it is stable during processing, storage, and preparation for consumption (e.g. cooking).

The **third** step is the formulation of the claimed effect. To this end, applicants are advised to conduct an exploratory review of the human studies available to identify the health/disease outcome(s) which have been investigated in relation to the food/constituent and for which the available evidence may

[57] http://www.efsa.europa.eu/en/efsajournal/doc/1689.pdf; http://www.efsa.europa.eu/en/efsajournal/doc/3654.pdf http://www.efsa.europa.eu/en/efsajournal/doc/3577.pdf

[58] Regulation (EC) No 1925/2006 of the European Parliament and of the Council on the addition of vitamins and minerals and of certain other substances to foods, as amended. OJ L 183, 12.7.2002, p. 51

be strong. Applicants are then advised to reflect on whether the outcome(s) investigated[59] may describe a beneficial physiological effect[60] (claimed effect) in the context of function and/or reduction of disease risk claims (see section 7.2), the extent to which the outcome variable(s)[61] used in the studies are direct measures of the claimed effect, and whether the methods of assessment[62] are appropriate.

The **fourth** step is to conduct a comprehensive review of (published and unpublished) human studies on the relationship between the food/constituent and the health/disease outcome(s) which best describe the claimed effect in order to identify all human studies that may be pertinent for substantiation.

It is important to ensure that the studies have investigated food/constituents which comply with the specifications provided in the application. If not, applicants should consider changing the specifications of the food/constituent for which the claim is requested[63].

If human studies on the relationship between the consumption of the food/constituent and health/disease outcome(s) are available, then it is important to consider, for each study, whether or not it has been conducted in a suitable study group i.e. a study group which is representative of the target population for the claim or a study group from which extrapolation of the results to the target population is biologically plausible.

If all or some of the studies have been conducted in suitable study groups, then proceed to the next step. In this context, studies not conducted in suitable groups may be used as supportive evidence for the claim. If extrapolation of the results from the study group to the target population is not biologically plausible because the study subjects have a certain disease[64] and only studies in patients with this disease are available, such studies will not be pertinent to the claim. If extrapolation of the results is not biologically plausible because the study subjects belong to a different subgroup of the general population[65] and no studies in the target subgroup are available, these studies could be pertinent for a claim on a different target subgroup.

The **fifth** step is to evaluate the quality of each individual human study in relation to:

i) whether the outcome variable(s) are well-defined and appropriate to assess the claimed effect, and whether they have been measured using valid methods[66];

ii) the risk of bias[67]

Studies of low quality may not allow conclusions to be drawn for the scientific substantiation of the claim, and thus may not be pertinent to the claim (i.e. may not be part of the totality of the evidence).

The **sixth** step is to identify studies (in humans, in animals, *in vitro*) which may be used to develop a rationale for the biological plausibility of the claim (e.g. in the context of all that is known about the food/constituent and about the claimed effect). These include efficacy studies in humans the results of

[59] E.g. coronary heart disease
[60] E.g. cardiac function
[61] E.g. fatal myocardial infarction, non-fatal myocardial infarction, sudden death, angina, hear failure
[62] E.g. self-reported, clinical records, death certificates
[63] For example, if a claim is requested for a fixed combination of ingredients but all human studies available have investigated one of them only and not the fixed combination, applicants should consider to request the claim for the single ingredient only; the claim could then be used in a product with the fixed combination of ingredients if it complies with the conditions of use for the single ingredient.
[64] Please note that extrapolation of the results obtained in diseased subjects to the target population of the claim may or may not be biologically plausible depending on the disease and/or the medications taken by the subjects. A decision on whether extrapolation of the results from diseased to non-diseased subjects is biologically plausible is taken by the NDA on a case-by-case basis upon consideration of the evidence/data/rationale provided by applicants in specific applications to support such extrapolation. Providing a complete list of cases in which such extrapolation is/is not biologically plausible is beyond the scope of this general scientific guidance.
[65] Please note that extrapolation of the results obtained in subjects from a particular subgroup of the general healthy population to another may depend on the claimed effect. Providing a complete list of cases in which such extrapolation is/is not biologically plausible is beyond the scope of this general scientific guidance.
[66] Applicants are encouraged to consult experts in the particular research field.
[67] Including study design (e.g. randomisation, blinding, control for confounders), statistical analyses, completeness of reporting, etc. Several tools to assess the risk of bias of human studies are available in the literature; applicants are also encouraged to consult epidemiologists/biostatisticians for that purpose.

734 which could not be extrapolated to the target population, efficacy studies in animals, and studies on
735 bioavailability and plausible mechanisms of action.

736 As a **seventh** step, applicants are advised to review all the evidence available to them (pertinent
737 human studies plus other studies) and make a scientific judgement on whether or not such evidence
738 may be appropriate/sufficient for the scientific substantiation of the claim[68]. If the answer is yes,
739 applicants should proceed to the next step. If the answer is no, a careful analysis of the gaps in the
740 data available to the applicant can provide an idea of the type and amount of *ad-hoc* research which
741 may be needed to fill those gaps, and which may vary widely from application to application (see
742 section 7.3).

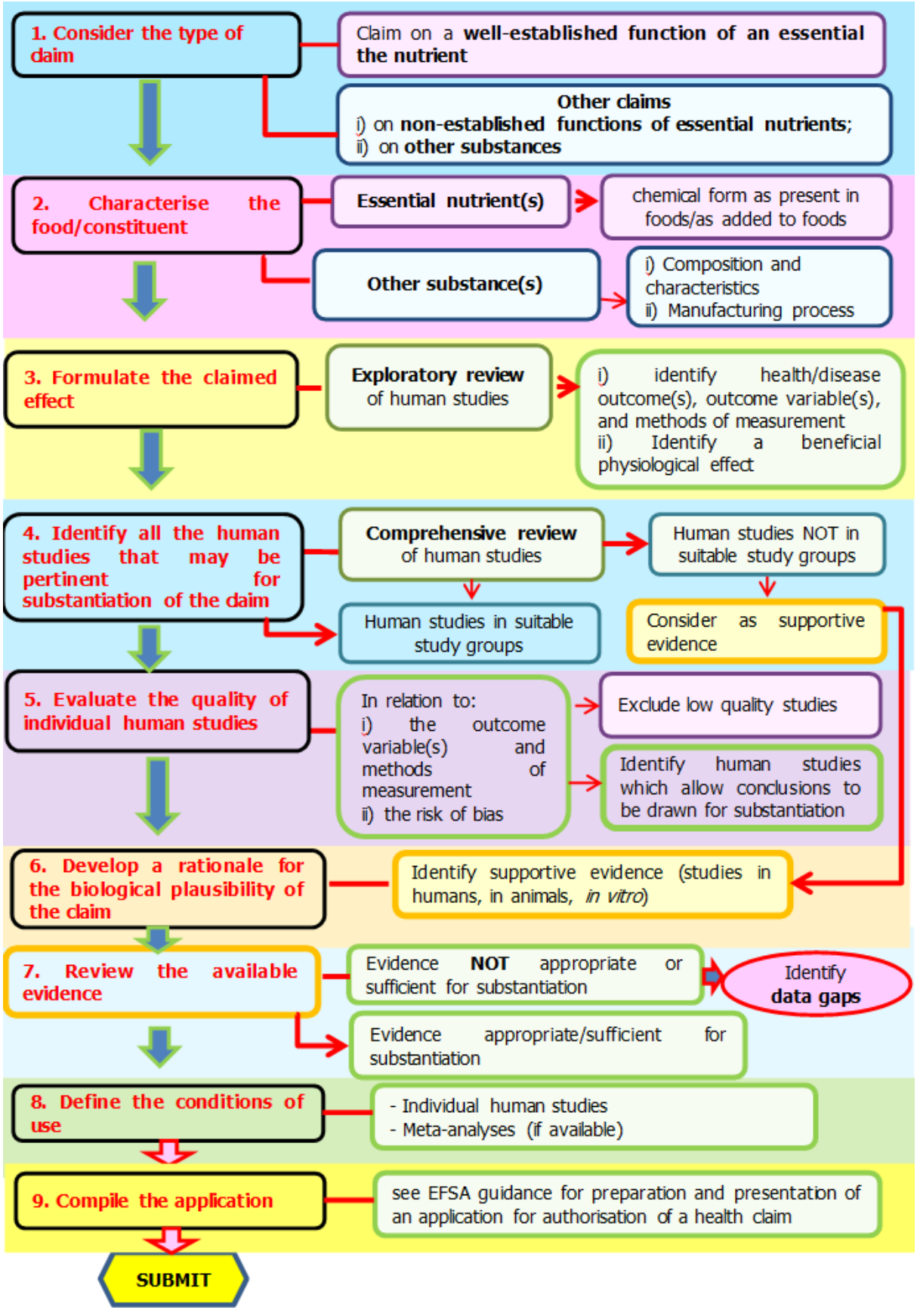
743 The **eighth** step is to define the conditions of use for the claim, i.e. the dose and pattern of
744 consumption of the food/constituent which is required to achieve the claimed effect. The conditions of
745 use should be defined on the basis of the individual human studies used for substantiation and/or
746 meta-analysis of such studies (see sections 7.5 and 7.8).

747 The **ninth** and final step is to compile the application, having regard of the Scientific and technical
748 guidance for the preparation and presentation of an application for authorisation of a health claim
749 (revision 1)[69].

750 **Annex A** explains in detail the administrative and procedural aspects of applications, from claim
751 formulation to authorisation.

[68] Relevant EFSA guidance documents as well as published opinions on evaluations performed by the NDA Panel on previous applications, and particularly those evaluated with a positive outcome, may help applicants to make such judgement.
[69] http://www.efsa.europa.eu/en/efsajournal/pub/2170.htm

752 **Figure 2: key scientific aspects for preparing a health claim application**



753

754 # 9. Conclusions

755 The general guidance document represents the views of the NDA Panel based on the experience
756 gained to date with the evaluation of health claims, and it may be further updated, as appropriate,
757 when additional issues are addressed.

758

Annex A – Administrative and procedural aspects governing the life cycle of a claim application from claim formulation to authorisation

A.1 Before submitting an application

A.1.1 Guideline checking

Applicants who wish to submit an application for authorisation of a health claim under Article 13.5 or 14 of Regulation (EC) No 1924/2006 or for modification of an existing authorisation pursuant to Article 19 should read carefully the NDA Panel guidance documents which are published on EFSA's website [70]:

- ***Scientific and technical guidance for the preparation and presentation of an application for authorisation of a health claim (revision 1)***[71], which presents a common format for the organisation of the information to assist the applicants for the preparation of a well-structured application (i.e. technical dossier) for authorisation of health claims. This guidance outlines:
  - the information and scientific data which must be included in the application;
  - the hierarchy of different types of data and study designs (reflecting the relative strength of evidence which may be obtained from different types of studies) and the key issues which should be addressed in the application to substantiate the health claim;
  - the number of claims allowed in an application.
- ***Specific guidance on the scientific requirements for health claims,*** which are intended to assist applicants in preparing their applications for the authorisation of health claims in specific areas, such as those related to:
  - gastrointestinal tract, the immune system, and defence against pathogenic microorganisms (currently under revision)[72];
  - antioxidants, oxidative damage and cardiovascular health[73];
  - appetite ratings, weight management and blood glucose concentrations[74];
  - bone, joints, skin and oral health[75];
  - physical performance[76];
  - functions of the nervous system, including psychological functions[77].

  These guidance documents present examples drawn from past evaluations to illustrate the approach of the NDA Panel in the evaluation of health relationships and outcome variables which may be acceptable in these areas, as well as the conditions under which they may be acceptable. A better understanding of such an approach could help applicants in preparing applications on health relationships and related outcome variables.

A.1.2 The language and the format required for a claim application

In order to facilitate the processing of the application (i.e. technical dossier) and make the assessment more efficient, applications should preferably be submitted in **English**. Should the applicant not submit the application in English, EFSA will proceed with the English translation. However, it should be noted that the responsibility for validating the English translation of the application provided by EFSA rests with the applicant.

[70] http://www.efsa.europa.eu/en/nda/ndaguidelines.htm
[71] http://www.efsa.europa.eu/en/efsajournal/pub/2170.htm
[72] http://www.efsa.europa.eu/en/supporting/pub/758e.htm; http://www.efsa.europa.eu/en/consultationsclosed/call/150209.htm
[73] http://www.efsa.europa.eu/en/efsajournal/pub/2474.htm
[74] http://www.efsa.europa.eu/en/efsajournal/pub/2604.htm
[75] http://www.efsa.europa.eu/en/efsajournal/pub/2702.htm
[76] http://www.efsa.europa.eu/en/efsajournal/pub/2817.htm
[77] http://www.efsa.europa.eu/en/efsajournal/pub/2816.htm

Claims applications which adhere to the format of the Scientific and technical guidance for the preparation and presentation of an application for authorisation of a health claim (see section A.1.1) must be submitted on a standard electronic medium such as a CD ROM, DVD or USB key. All applications submitted via a Member State to EFSA for evaluation should include the original of a signed cover letter with the table of contents and the mandate[78].

A.1.3 Where to submit a claim application?

Applications for authorisation of health claims pursuant to Articles 14, 13(5) and 19 of the Regulation (EC) No 1924/2006 shall be submitted to the National Competent Authority of a Member State in the European Union in accordance with Articles 15 and 18, respectively.

Applicants are invited to check the scope and admissibility of the claim with the recipient Member State **at the earliest possible stage** before submitting the application (see also section 4). The National Competent Authority will check admissibility before making the application and any supplementary information supplied by the applicant available to EFSA.

The list of competent authorities of the Member States within the framework of Regulation (EC) No 1924/2006 is published on EFSA's website[79].

A.2 What happens to a claim application upon receipt by EFSA?

Upon receipt of a claim application via a Member State, EFSA checks the completeness of the application[80].

The completeness check includes administrative compliance, clear identification of the food/constituent for which the claim is made (consistency throughout the application), clear definition of the claimed effect (a defined claimed effect including identification of outcome variable(s) and methods of measurement, identification of (a) risk factor(s) for disease risk reduction claims), and definition of the conditions of use.

In the event that EFSA requires additional data, information or clarification in order to consider an application complete, the applicant will be asked to supply these data, information or clarifications within a notified time limit. EFSA may also communicate with applicants regarding studies which are claimed as confidential (see also section A.4 on EFSA's handling of confidential and proprietary data). Applicants can request a teleconference to clarify a request from EFSA for missing information.

During the completeness check, EFSA may consult the Commission Services on points of interpretation of EU legislation particularly in relation to the scope.

Once EFSA considers that the application is complete for a scientific evaluation, EFSA sends an acceptance letter to the applicant. EFSA makes the application and any supplementary information supplied by the applicant available to Member States and the Commission. EFSA publishes relevant information for the identification of the application in the Register of Questions, and assigns it an official question number. Applicants and stakeholders can follow the status of each application via EFSA's Register of Questions.

The applicant will also be notified of the name of the scientific officer in the Nutrition Unit in charge of the application and related communications with the applicant. All communication between EFSA and the applicant during the life-cycle of an application is through the assigned scientific officer (not the NDA Panel experts).

A.3 What happens during the evaluation process?

Once the application is considered complete, the scientific evaluation starts. EFSA shall ensure that the Opinion of the NDA Panel is given **within 5 months** (excluding the stop-the-clock time for the applicant to provide answers to questions from EFSA, if needed).

[78] http://www.efsa.europa.eu/en/press/news/140924.htm
[79] http://www.efsa.europa.eu/en/ndaguidance/docs/ndacompetentauthorities.pdf
[80] http://www.efsa.europa.eu/en/apdeskapplworkflow/docs/apdeskapplworkflownutrihealthclaims.pdf

A.3.1 When does the stop-the-clock procedure apply?

During the evaluation, EFSA may request the applicant to provide supplementary information on the application ('stop-the-clock' procedure). Requests from EFSA to applicants for supplementary information are made on the basis of a case-by-case judgement by the NDA Panel or its Working Group on Claims in the context of specific applications.

Based on an analysis of the stop-the-clock letters sent to applicants[81], the issues identified by the NDA Panel which have triggered in the stop-the-clocks are: clarifications on the studies submitted for substantiation (75%); clarifications on the claimed effect and/or the target population (13%); and clarifications on the characterisation of the food/constituent for which the claim was proposed (12%).

Issues related to, for example, the definition of the food/constituent, of the claimed effect, of risk factors for disease, or of the conditions of use may only become apparent during the scientific assessment of the application by the NDA Panel and not necessarily during the completeness check. The NDA Panel may work with the applicants on the re-formulation of health claims based on the human studies provided for substantiation, if needed.

Therefore, communication between EFSA and the applicant during this phase is critical for both the applicants and the NDA Panel. To this end, upon receipt of EFSA's letter requesting supplementary information, applicants can request a teleconference to clarify a request from EFSA for additional information. After submitting additional or supplementary information, applicants may be invited by EFSA to attend a meeting of an EFSA working group or scientific panel to clarify issues related to the newly submitted material (i.e. *Applicants technical hearing).*

The applicant should respond to requests for missing or additional information using electronic formats (CD-ROMs, DVDs or USB keys). If the applicant fails to provide the supplementary information within the time limit specified by EFSA, the NDA Panel will issue an opinion based on the data available to the Panel.

EFSA applies stop-the-clock timelines in accordance to Regulation (EC) No 1924/2006 and EFSA guidance on 'Indicative timelines for submitting additional or supplementary information to EFSA during the risk assessment process of regulated products'[82].

A.3.2 Can a claim application be withdrawn?

Article 7b of Regulation (EC) No 353/2008[83] specifies the rules for the withdrawal of applications i.e.:

(1) An application submitted under Article 15 or 18 of Regulation (EC) No 1924/2006 may be withdrawn by the applicant up to the moment the Authority adopts its opinion pursuant to Article 16(1) or Article 18(3) of Regulation No 1924/2006.

(2) A request for withdrawal of an application must be submitted to the national competent authority of a Member State, to which the application was submitted in accordance with Article 15(2) or Article 18(2) of Regulation (EC) No 1924/2006.

A.4 How confidential and proprietary data are handled by EFSA?

Many studies submitted for scientific substantiation of health claims have been claimed as confidential by applicants. In this respect, EFSA would like to clarify that, in order to comply with its requirements for transparency as outlined in Article 38 of Regulation (EC) No 178/2002[84] and Article 16 of Regulation (EC) No 1924/2006[85], key data from key studies which are considered essential for the scientific assessment of a health claim may need to be disclosed in the final scientific opinion

[81] http://www.efsa.europa.eu/en/events/documents/131120-p03.pdf
[82] http://www.efsa.europa.eu/en/press/news/140414a.htm
[83] Commission Regulation (EC) No 353/2008 of 18 April 2008 establishing implementing rules for applications for authorisation of health claims as provided for in Article 15 of Regulation (EC) No 1924/2006 of the European Parliament and of the Council. OJ L 109, 19.4.2008, p. 11.
[84] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety, as last amended.
[85] Corrigendum to 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 (OJ L 404, 30.12.2006), as last amended.

published by EFSA. Confidentiality can only be given to specific parts of a study if duly justified, and not to an entire study.

In practice, when applicants submit studies for the scientific substantiation of a health claim that are claimed as confidential, EFSA requests applicants to identify and justify which elements of the studies are claimed as confidential during the completeness check. If the request for confidential treatment for those elements identified by the applicant is accompanied by verifiable justification and this is accepted by EFSA, those elements will be kept confidential. Should the applicant disagree with EFSA's conclusions on their request, they may withdraw their application before a scientific opinion is adopted, file a request addressed to EFSA to review this decision, or avail themselves of the ordinary means of legal redress (i.e. challenging the legality of EFSA's decision under the conditions set out in Article 263 of the Treaty on the Functioning of the European Union, or bringing a complaint for alleged maladministration before the European Ombudsman).

Once a scientific opinion for a health claim is adopted by the NDA Panel, and before its publication on the EFSA website, the scientific opinion is sent to the applicant in order to check whether the scientific opinion discloses any data that EFSA had accepted to keep confidential.

It should be noted that, in principle and without prejudice to Regulation (EC) No 1049/2001 on public access to documents, if a study has not yet been published and its disclosure would undermine the commercial interests and rights of the applicant, EFSA will not make such a study available to third parties.

With respect to the handling, use and protection of proprietary data (e.g. requirements needed for data exclusivity), it should also be noted that where evidence for substantiation includes a request for the protection of proprietary data, the NDA Panel considers only whether the claim could have been substantiated with or without the data claimed as proprietary by the applicant. The decision on granting the protection of proprietary data falls under the responsibility of the European Commission when authorising the claims.

A.5 Adoption and publication of EFSA opinion on claims

EFSA informs the applicant that EFSA's NDA Panel has adopted a scientific opinion on its application one working day after adoption (i.e. *Notification email on adoption of scientific output*).

The applicant receives the adopted scientific opinion under embargo one working day before publication of the opinion on EFSA's website (i.e. *Pre-notification of publication*).

Following the publication of an adopted scientific opinion, a teleconference with EFSA can be requested by the applicant to clarify the rationale for the decision of the NDA Panel and explain the evidence and other factors that influenced the outcome (i.e. *Teleconference post-adoption*).

A.5.1 Can stakeholders and the public comment on EFSA opinions?

According to Article 16 of Regulation (EC) No 1924/2006, the applicant or members of the public may make comments on EFSA-published scientific opinions. Comments should be sent to the Commission within 30 days of publication of the EFSA opinion in question. If considered appropriate, the Commission may decide to ask EFSA to address the comments relating to scientific issues. Comments are made public by the Commission on its webpage[86].

EFSA responses to the requests received from the Commission are also published on EFSA's website[87].

A.6 Process for health claim authorisation

Upon publication of EFSA opinions that have a favourable outcome, any issues related to the final wording of health claims including consumer understanding aspects should be addressed to the Commission (see section 4).

The Commission prepares a draft decision and submits it to the Standing Committee on the Food Chain and Animal Health after EFSA publishes its opinion.

[86] http://ec.europa.eu/nuhclaims/?event=claimsBeingProcessed
[87] http://www.efsa.europa.eu/en/publications/supporting.htm

928 After a favourable opinion of the Standing Committee on the Food Chain and Animal Health, the
929 European Parliament and the Council have the right of scrutiny on the Commission's draft decision.

930 If there is no objection, the Commission adopts the draft decision.

931 Authorised health claims, their conditions of use and applicable restrictions, if any, are published in
932 the EU Register of claims[88].

[88] http://ec.europa.eu/nuhclaims/