GUIDANCE

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General scientific guidance for stakeholders on health claim applications (Revision 1)[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2]

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Abstract

The general guidance for stakeholders on the evaluation of Article 13(1), 13(5) and 14 health claims was first published in March 2011. Since then, the Panel on Dietetic Products Nutrition and Allergies (NDA) has completed the scientific assessment of Article 13(1) claims except for claims put on hold by the European Commission, and has assessed 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 scientific assessment 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 scientific assessment of health claims, and it may be further updated, as appropriate, when additional issues are addressed. The document also aims to inform applicants of new provisions in the pre-submission phase and in the application procedure set out in the General Food Law, as amended by the Transparency Regulation. These new provisions are applicable to all applications submitted as of 27 March 2021. The version of this guidance published in 2016 remains applicable for applications submitted before 27 March 2021.

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

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[1]The guidance was adopted on 10 December 2015 by the former Panel on Dietetic products, Nutrition and Allergies. The revision only aims to inform stakeholders of the new provisions set out in the General Food Law (Regulation (EC) No 178/2002, as amended by Regulation (EU) 2019/1381 on the transparency and sustainability of the EU risk assessment in the food chain), and to guide them through EFSA's Practical Arrangements implementing these new provisions. For this purpose, the revision concerns only the administrative part. The scientific content remains unchanged. The present guidance (revision 1) was endorsed on 21 January 2021 by the Panel on Nutrition, Novel Foods and Food Allergens (NDA): Dominique Turck, Jacqueline Castenmiller, Stefaan de Henauw, Karen-Ildico Hirsch-Ernst, John Kearney, Helle Katrine Knutsen, Alexandre Maciuk, Inge Mangelsdorf, Harry J McArdle, Androniki Naska, Carmen Pelaez, Kristina Pentieva, Alfonso Siani, Frank Thies, Sophia Tsabouri and Marco Vinceti.

[2] As of 1 July 2018, it has been renamed to Panel on Nutrition, Novel Foods and Food Allergens (NDA).

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Summary

The General guidance for stakeholders on the evaluation of Article 13(1), 13(5) and 14 health claims was first published in March 2011.

Since then, the Panel on Dietetic Products Nutrition and Allergies (NDA) has completed the scientific assessment of Article 13(1) claims (except for claims put on hold by the European Commission), and has assessed 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 scientific assessment of all health claims and outlines a series of steps for the compilation of applications.

The guidance also aims to inform stakeholders of the provisions set out in Regulation (EC) No 178/2002[3] (i.e. the General Food Law, hereinafter 'GFL Regulation'), as amended by Regulation (EU) 2019/1381[4] on the transparency and sustainability of the EU risk assessment in the food chain (hereinafter 'Transparency Regulation'). They concern provisions in the pre-submission phase and in the application procedure that are applicable to all applications submitted as of 27 March 2021: general pre-submission advice, notification of information related to studies commissioned or carried to support an application, public disclosure of non-confidential version of all information submitted in support of the application and related confidentiality decision-making process, public consultation on submitted applications. An overview of these provisions, as implemented by the Practical Arrangements[5] laid down by EFSA, is described in Figure 1 and in Annex A of the document.

This revised guidance applies to all applications submitted as of 27 March 2021 and should be consulted for the preparation of applications intended to be submitted from that date onwards. For applications submitted until 26 March 2021, the guidance adopted in 2015 (EFSA NDA Panel, 2016)[6] remains applicable.

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

[3] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January2002 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 amended by Regulation (EU) 2019/1381 of the European Parliament and of the Council of 20 June 2019 on the transparency and sustainability of the EU risk assessment in the food chain and amending Regulations (EC) No 178/2002, (EC) No 1829/2003, (EC) No 1831/2003, (EC) No 2065/2003, (EC) No 1935/2004, (EC) No 1331/2008, (EC) No 1107/2009, (EU) 2015/2283 and Directive 2001/18/EC, PE/41/2019/REV/1. OJ L 231, 6.9.2019, p. 1–28. https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=celex%3A32002R0178

[4] Regulation (EU) 2019/1381 of the European Parliament and of the Council of 20 June 2019 on the transparency and sustainability of the EU risk assessment in the food chain and amending Regulations (EC) No 178/2002, (EC) No 1829/2003, (EC) No 1831/2003, (EC) No 2065/2003, (EC) No 1935/2004, (EC) No 1331/2008, (EC) No 1107/2009, (EU) 2015/2283 and Directive 2001/18/EC, PE/41/2019/REV/1. OJ L 231, 6.9.2019, p. 1–28. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32019R1381

[5] https://www.efsa.europa.eu/en/corporate/pub/tr-practical-arrangements

[6] https://www.efsa.europa.eu/en/efsajournal/pub/4367

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Background and Terms of Reference as provided by EFSA in 2015

Background

Regulation (EC) No 1924/2006[7] 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 the European Food Safety Authority (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.[8]

Based on experience gained with the evaluation of health claims and taking into account outcomes of public consultation (EFSA NDA Panel, 2015), 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 (EFSA NDA Panel, 2011a).

Terms of reference in 2015

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.

Background and Terms of Reference as provided by EFSA in 2020

EFSA requested the Nutrition Unit to update the General scientific guidance for stakeholders on health claim applications[9] in order to align it to the provisions set out in the GFL Regulation, as amended by the Transparency Regulation, which apply as of 27 March 2021.

Thus, this guidance document needs to be updated as regards its administrative part. This request does not cover the scientific part of the document that has been left unchanged.

[7] 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. https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=celex%3A32006R1924

[8] https://www.efsa.europa.eu/en/applications/nutrition/regulationsandguidance

[9] https://www.efsa.europa.eu/en/efsajournal/pub/4367

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 (EFSA NDA Panel, 2011a), laid down the general principles applied by the European Food Safety Authority (EFSA) Panel on Dietetic products, Nutrition and Allergies (NDA Panel) for the scientific assessment of health claims and was based on the experience gained by the NDA Panel from earlier assessments.

Since then, the NDA Panel has completed the scientific assessment of Article 13(1) claims (except for claims put on hold by the European Commission) and has assessed 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 (EFSA NDA Panel, 2015), during stakeholder meetings, and by email through the EFSA Applications 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 scientific assessment of all health claims and outlines a series of steps for the compilation of applications.

The guidance document was subject to public consultation (from 17 July to 11 September 2015), and was adopted by the NDA Panel on 10 December 2015 and published on 18 January 2016.

Subsequently with Regulation (EC) No 178/2002[10] (i.e. the General Food Law, hereinafter 'GFL Regulation'), as amended by Regulation (EU) 2019/1381[11] on the transparency and sustainability of the EU risk assessment in the food chain (hereinafter 'Transparency Regulation') coming into force, this guidance has been updated to reflect the new provisions that are applicable for all applications submitted as of 27 March 2021. These provisions concern the pre-submission phase and the application procedure: general pre-submission advice, notification of information related to studies commissioned or carried out to support an application, proactive disclosure of non-confidential version of all information submitted in support of the application and related confidentiality decision-making process, public consultation on submitted applications.

An overview of these new provisions, as implemented by EFSA's Practical Arrangements[12],[13] is described in:

- Figure 1: on key steps in the process of authorisation of health claims,
- Annex A – - Administrative and procedural aspects governing the life cycle of a claim application from pre-submission phase to authorisation.

This revised guidance applies to applications submitted as of 27 March 2021. For applications submitted until 26 March 2021, the guidance adopted in 2015 (EFSA NDA Panel, 2016)[14] remains applicable.

[10] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January2002 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 amended by Regulation (EU) 2019/1381 of the European Parliament and of the Council of 20 June 2019 on the transparency and sustainability of the EU risk assessment in the food chain and amending Regulations (EC) No 178/2002, (EC) No 1829/2003, (EC) No 1831/2003, (EC) No 2065/2003, (EC) No 1935/2004, (EC) No 1331/2008, (EC) No 1107/2009, (EU) 2015/2283 and Directive 2001/18/EC, PE/41/2019/REV/1. OJ L 231, 6.9.2019, p. 1–28.

[11] Regulation (EU) 2019/1381 of the European Parliament and of the Council of 20 June 2019 on the transparency and sustainability of the EU risk assessment in the food chain and amending Regulations (EC) No 178/2002, (EC) No 1829/2003, (EC) No 1831/2003, (EC) No 2065/2003, (EC) No 1935/2004, (EC) No 1331/2008, (EC) No 1107/2009, (EU) 2015/2283 and Directive 2001/18/EC, PE/41/2019/REV/1. OJ L 231, 6.9.2019, p. 1–28.

[12] See Decision of the Executive Director of the European Food Safety Authority laying down the practical arrangements on pre-submission phase and public consultations

[13] See Decision of the Executive Director of the European Food Safety Authority laying down Practical Arrangements concerning Transparency and Confidentiality

[14] https://www.efsa.europa.eu/en/efsajournal/pub/4367

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 assessment of health claim applications;

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

Examples drawn from previous and ongoing assessments are used in this guidance to illustrate the approach of the Panel in the scientific assessment of health claims. A better understanding of this approach could help applicants in preparing health claim applications.

This document does not intend to cover health claims which have not been assessed by the Panel, or to provide detailed advice on claims made in specific areas. It is also not within the scope of this guidance to provide detailed instructions on the design of scientific studies or on the statistical analyses of the results, which rely on general scientific knowledge. It is the responsibility of the applicant to ensure that studies are designed and performed according to scientific standards that are generally accepted by experts in the relevant field, and that they are appropriately reported following, where applicable, EFSA guidelines on statistical reporting (EFSA NDA Panel, 2014a), or other consensus guidelines published by scientific bodies.[15] It is intended that the guidance will be kept under review and will be amended and updated as appropriate in the light of experiences gained from the assessment of additional health claim applications.

This guidance should be read in conjunction with the scientific and technical guidance for the preparation and presentation of a health claim application (EFSA NDA Panel, 2021), the Administrative guidance for the processing of applications for regulated products (EFSA, 2021a), Regulation on Nutrition and Health Claims made on foods[16], Guidance on the implementation of Regulation (EC) No 1924/2006 (Standing Committee on the Food Chain and Animal Health, 2007), Commission Regulation (EC) No 353/2008[17], Commission Implementing Decision of 24 January 2013[18], and applicable guidelines and regulations.

For the new provisions introduced by the GFL Regulation, this guidance should be read in conjunction with Union legal acts, in particular with EFSA's Practical Arrangements on pre-submission phase and public consultations[19] (EFSA, 2021b) and EFSA's Practical Arrangements concerning Transparency and Confidentiality[20] (EFSA, 2021c), available on EFSA's website[21], which provide comprehensive information and instructions on that matter.

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).

[15] Equator network: http://www.equator-network.org/

[16] 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

[17] 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). http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2008R0353:20091221:EN:PDF

[18] 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

[19] See Decision of the Executive Director of the European Food Safety Authority laying down the practical arrangements on pre-submission phase and public consultations

[20] See Decision of the Executive Director of the European Food Safety Authority laying down practical arrangements concerning transparency and confidentiality

[21] https://www.efsa.europa.eu/en/corporate/pub/tr-practical-arrangements

- The term **essential nutrient** is used to denote a substance required for normal human body function(s) and which cannot be synthesised by the body, or cannot be synthesised in amounts which are adequate to maintain normal body function(s), and thus must be obtained from a dietary source. Essential nutrients include components of carbohydrate, protein and fat, as well as vitamins, minerals and water.
- A **disease/disorder** means a pathological process, acute or chronic, inherited or acquired, of known or unknown origin, having a characteristic set of signs and symptoms which are used for its diagnosis. The diagnosis of diseases/disorders relies on widely accepted, well-defined criteria (i.e. the criteria used for diagnosis are widely accepted by the medical community and can be verified by a physician). In this guidance document, the term disease is used to include diseases and disorders, which for the purpose of this guidance are considered as synonymous and have the same meaning.
- 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).
- **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 study from which scientific conclusions that are relevant to the substantiation of a claim (e.g. efficacy studies, bioavailability studies, studies on the mechanism(s) by which a food could exert the claimed effect) can be drawn.
- **Supportive evidence** refers to studies/data which, on their own, are not sufficient for the scientific substantiation of a claim and that may be part of the totality of the evidence only if pertinent human studies showing an effect of the food/constituent are available.
- The **target population** is the population group(s) for which health claims are intended (e.g. the general healthy population or specific subgroup(s) thereof).
- The **study group** denotes individuals recruited for human studies which are submitted for the scientific substantiation of a claim. A study group is considered as representative of the target population for a claim when the characteristic(s) of the study subjects may not limit the generalisation of the results 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 appropriate.

4. 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.[22] 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) 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

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

Panel 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, where applicable, by weighing the evidence (see Section 6). What constitutes generally accepted scientific evidence in the context of claims substantiation is a scientific judgement of the NDA Panel. It should be noted that a safety assessment is not foreseen under the framework of Regulation (EC) No 1924/2006. However, where relevant, the NDA Panel may recommend restrictions of use based on safety considerations.

Decisions regarding the authorisation of health claims, including the final wording and the conditions/restrictions of use, are taken by risk managers. In order to make such decisions, risk managers may take into account other legitimate factors, such as safety and nutrition policy 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 assessment.

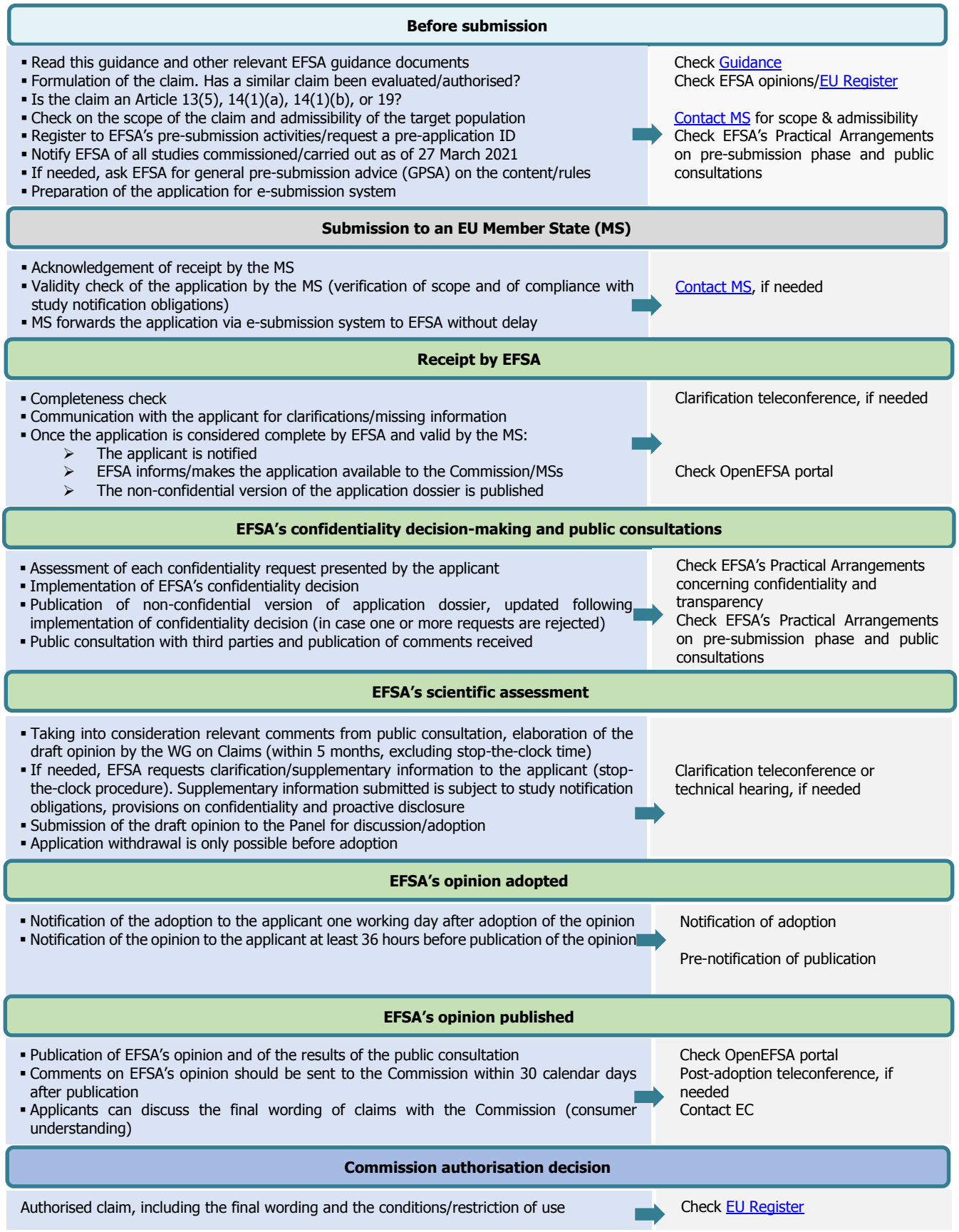

Figure 1: Key steps in the process of authorisation of health claims (see description in Annex A)

5. Scientific standards vs regulatory requirements

Article 7(3) of Regulation (EU) No 1169/2011[23] 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. Thus, in principle, the target population for health claims made on food should be the general (healthy) population or specific subgroups thereof;

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;[24]

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;[25]

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.[26]

In order to fill the gap between the above-mentioned scientific principles and regulatory requirements, the NDA Panel has worked with applicants during the assessment of applications on the formulation of health claims which could allow a scientific assessment 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[27] (see Section 7.6).

[23] Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/5/EC and Commission Regulation (EC) No 608/2004. J L 304, 22.11.2011, p. 18–63. http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32011R1169&from=EN

[24] 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).

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

[26] 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.

[27] For example, studies in obese subjects could be used to substantiate a claim on the reduction of body weight addressed to overweight adults https://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[28] 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.[29]

c) studies on the relationship between a food/constituent and the incidence[30] of disease in subjects free of disease at recruitment may also be used to substantiate disease risk reduction claims[31] (see Section 7.2.2).

6. 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 based on the essentiality of nutrients differ from those applied for the assessment of other claims. Such differences refer to the requirements for the definition of the claimed effect (Section 7.2), for the scientific substantiation of the claim (Section 6.1) and for establishing conditions of use (Section 7.9).

6.1. Claims based on the essentiality of nutrients

The essentiality of a nutrient is determined by knowledge of its unique ability to reverse clinical signs and symptoms of deficiency, and/or by knowledge of its essential mechanistic role in metabolic functions. The recognition by the scientific community of the essentiality of individual nutrients first took place in the early decades of the last century and is based on a large body of scientific evidence, which includes case reports of clinical signs and symptoms of deficiency (e.g. during long-term total parenteral nutrition), depletion–repletion studies in humans, invasive animal studies and meticulous *in vitro* studies, among other evidence.

In this context, information about the essentiality of nutrients cannot be obtained from randomised controlled trials (RCTs), which are at the top of the hierarchy of evidence for the scientific substantiation of health claims for two reasons: i) RCTs in most nutrient-deficient subjects are unethical, and ii) RCTs in nutrient-replete subjects are unsuitable because the body functions for which the nutrient is required will not be modified by higher intakes (EFSA NDA Panel, 2009a).[32]

For the scientific substantiation of claims based on the essentiality of nutrients, the Panel considers the following well-established scientific principles:

i. the nutrient is required for normal human body function(s), i.e. it has an essential mechanistic role in a metabolic function and/or it has the ability to reverse clinical signs and symptoms of its deficiency;

ii. the nutrient cannot be synthesised by the body, or cannot be synthesised in amounts which are adequate to maintain normal body function(s);

iii. the nutrient must be obtained from a dietary source.

Only claims which meet the above-mentioned requirements on the relationship between the consumption of a nutrient and human body function(s) have been considered by the Panel as claims based on the essentiality of nutrients. The scientific substantiation of these claims has been based on a large body of scientific evidence which led to the recognition of the essentiality of a particular nutrient

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

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

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

[31] 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.

[32] A claim on vitamin C and function of the immune system intended for the general population (ID134) was based on the essentiality of vitamin C for the function, whereas a claim in vitamin C and function of the immune system during and after extreme physical exercise (ID 144) was substantiated on the basis of RCTs showing a reduction in the severity/duration of common cold in the target population, and thus was not based on the essentiality of vitamin C for the function: https://www.efsa.europa.eu/en/efsajournal/pub/1226

with respect to one or more body functions. For these claims, the NDA Panel did not review the primary scientific studies submitted and did 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 7.9 (conditions of use).

6.2. Claims other than those based on the essentiality of nutrients

For the scientific substantiation of a claim, the NDA Panel considers the totality of the available scientific evidence. It is the responsibility of the applicant to provide these data. In its assessment, the NDA Panel may use data which are not included in the application if such data are considered pertinent to the claim.

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, 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. Pertinent human intervention studies are at the top of the hierarchy that informs decisions on substantiation because it is of utmost importance to show that the food/constituent can exert the claimed effect in humans and that the effect is specific for the food/constituent, an information which can only be obtained from human intervention studies (EFSA NDA Panel, 2011b). Human 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 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.[33]

The outcome of each scientific 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.

[33] For example, in an application related to monacolin K from red yeast rice and maintenance of normal blood LDL-cholesterol concentrations (https://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/2304.pdf), the Panel took into consideration the results of an *in vitro* study showing that a fermented red yeast rice preparation (Cholestin) had an inhibitory effect on HMG-CoA reductase activity in human hepatic cells to support the mechanism by which monacolin K from red yeast rice could exert the claimed effect. Another example on how animal and *in vitro* studies can support the effect and mechanism of action of the food/constituent in humans comes from an application related to water-soluble tomato concentrate (WSTC I and II) and platelet aggregation (https://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/1101.pdf). In that case, the Panel considered the results of four *in vitro* studies and of one animal study for the biological plausibility of the effect observed in human studies.

7. Main issues addressed by the NDA Panel for the scientific assessment 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 (Section 7.1);

(ii) the claimed effect is based on the essentiality of a 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 (Section 7.2);

(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) (Sections 7.3 and 7.4).

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 proposed wording reflects the scientific evidence (Section 7.8);
- the proposed wording complies with the criteria for the use of claims specified in the Regulation (Section 7.8);
- the quantity of food/pattern of consumption required to obtain the claimed effect can reasonably be consumed within a balanced diet (Section 7.9);
- the proposed conditions/restrictions of use are appropriate (Section 7.9);
- the data claimed as proprietary by the applicant were needed to reach the conclusion (Annex A.4).

7.1. Characterisation of the food/constituent

7.1.1. Extent to which a food/constituent should 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.

It may be necessary to distinguish between a specific constituent, a combination of constituents, or a specific formulation. The following cases have been identified by the Panel:

- 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.[34]
- 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 assessed by the Panel with a positive outcome), the NDA Panel also considers

[34] Commission Regulation (EC) No 1170/2009 of 30 November 2009 amending Directive 2002/46/EC of the European Parliament and of Council and Regulation (EC) No 1925/2006 of the European Parliament and of the Council as regards the lists of vitamin and minerals and their forms that can be added to foods, including food supplements. OJ L 314, 1.12.2009, p. 36–42. https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A32009R1170

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[35]).

- For a food category (e.g. 'dairy products' (EFSA NDA Panel, 2011c)), 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 (EFSA Scientific Committee, 2009), the NDA Panel considers whether the information provided includes the scientific (latin) name (full systematic species, name including 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 the naming of strains according to the International Code of Nomenclature.[36] 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 (see Annex B – for characterisation of microorganisms at strain level).
- 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 assessment 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 (Standing Committee on the Food Chain and Animal Health, 2007).

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

(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). Sufficient characterisation would 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;

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

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.

[35] 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: https://www.efsa.europa.eu/en/scdocs/doc/1741.pdf

[36] The approved nomenclature for bacteria is kept at the International Committee on Systematics of Prokaryotes for (http://icsp.org/), and the International Code of Nomenclature of fungi is kept by the International Commission on the Taxonomy of Fungi (ICTF) (www.fungaltaxonomy.org) and the approved nomenclature for fungi can also be found on the MycoBank (http://www.mycobank.org).

7.1.2. Contexts in which a food/constituent could 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). 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 postprandial blood glucose responses when replacing digestible carbohydrates in foods (EFSA NDA Panel, 2014b); 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 (EFSA NDA Panel, 2012a, 2014c).

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, postmenopausal women, adults performing endurance exercise). Decisions on the admissibility of a different target population for a claim (e.g. whether or not subjects under medications can be the target population for health claims made on foods) 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 essentiality of nutrients, 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.

For claims other than those based on the essentiality of 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 assessment. 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 assessment;[37]

ii) is a beneficial physiological effect for the target population for which the claim is intended;[38]

iii) can be assessed *in vivo*[39] 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.

[37] For example, 'gut health', 'natural defences', 'immune function' or 'skin health'.

[38] 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).

[39] 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*.

In this context, it should be noted that:

a) some claimed effects, which are considered as beneficial physiological effects, cannot be assessed 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.[40]

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).[41] Changes in such outcome variable(s) should be accompanied by evidence of a beneficial physiological effect or clinical outcome, and 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.[42]

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, stool consistency, faecal bulk 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 assess 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 outcome variable(s) on which the power calculation was based, the study group, 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).

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 in the incidence 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 incidence 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

[40] 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: https://www.efsa.europa.eu/en/efsajournal/pub/3082

[41] 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.

[42] 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: https://www.efsa.europa.eu/en/efsajournal/pub/3409

the scientific substantiation of the claim.[43] The general principles applied by the Panel to decide whether there is a causal relationship between a beneficial modification of the risk factor and a reduction of the risk of the disease (i.e. whether the risk factor for disease is well established) are the same (i.e. hierarchy of studies, weighing of the evidence) as the principles applied by the Panel to decide whether a causal relationship between the consumption of a food/constituent and the claimed effect is established (i.e. whether a health claim is substantiated) (see Section 6.2).

If there is no such evidence from intervention studies that a reduction of the risk factor generally reduces the incidence of disease, 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.[44]

7.3. 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 rule 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 also need to be considered.

The scientific opinions on health claim applications assessed 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.[45]

For example, a claim on arabinoxylan and a reduction on postprandial 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, iii) strong evidence for a plausible mechanism of action (EFSA NDA Panel, 2011d). 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,

[43] 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 (https://www.efsa.europa.eu/en/efsajournal/pub/2474). 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 (https://www.efsa.europa.eu/en/efsajournal/pub/2382).

[44] For example, there is some evidence that low blood HDL-cholesterol concentration, elevated blood concentration of triglycerides, or elevated blood homocysteine concentration are 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 nutrition intervention. https://www.efsa.europa.eu/en/efsajournal/pub/2474

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

even though no evidence for a mechanism by which the food/constituent may have exerted the claimed effect was provided (EFSA NDA Panel, 2013). A health claim on eicosapentaenoic acid (EPA) and docosahexaenoic acid (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 (EFSA NDA Panel, 2010a).

7.4. Identification of 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 assesses:

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;[46]

iv) whether the study group is representative of the target population for the claim, or whether extrapolation of the results from the study group 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 (EFSA NDA Panel, 2011b). 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.[47]

For human studies which assess outcome variables subject to seasonal variations (e.g. respiratory tract infections, blood pressure), the design of the study should be such that seasonal bias is avoided (e.g. bias introduced by differences between the intervention and control groups regarding the number of subjects investigated in different seasons of the year). The period of enrolment should be defined accordingly. For self-reported outcome variables (i.e. symptoms), which are subjective in nature, adequate blinding of subjects and investigators to the intervention is particularly important. Specific tools, in the form of questionnaires, have been used to measure self-reported outcome variables(s) in human intervention studies. Considerations on the validation of questionnaires and their use as outcome variables for the scientific substantiation of claims are in Annex C –.

7.5. Use of meta-analyses to inform decisions on substantiation

If a meta-analysis of human (observational and/or intervention) studies is provided for the scientific substantiation of a claim, the Panel reviews the primary data to ensure that all the individual studies included in the meta-analysis are pertinent to the claim.

[46] Different tools to appraise the design and quality of human studies (of different designs) with respect to the risk of bias have been developed by different bodies and are publicly available. Although these tools are different from each other, they cover a common core of concepts for assessing study quality. As an indication of aspects that the Panel considers when appraising the quality of RCTs, see also Appendix B at: https://www.efsa.europa.eu/en/supporting/pub/836e

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

Meta-analysis can provide information about the reproducibility and consistency of the effect across studies and study groups, about the dose–response relationship, and about the minimum effective dose of the food/constituent which is required to obtain the claimed effect (i.e. to establish conditions of use).

Information derived from meta-analyses has been used by the Panel in published opinions to summarise the overall evidence provided by individual human studies and to establish conditions of use (e.g. to define the effective dose), for example EFSA (2008) and EFSA NDA Panel (2011e). The NDA Panel, however, did not rely on the results of meta-analyses to make a scientific judgement on whether a cause and effect relationship between the consumption of the food/constituent and the claimed effect has been established.

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

When a particular study submitted for the scientific substantiation of the claim 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[48] (e.g. women with high frequency of lower urinary tract infections (LUTI) in the previous year but free of LUTI at recruitment) and 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 of the disease* should be provided to ascertain that the subjects recruited are free from disease and to allow the Panel to decide whether extrapolation of the results from the study group to the target population is biologically appropriate.

(ii) results from studies performed in *subjects with a disease* (i.e. type 2 diabetic patients) that affects the function mentioned in the claim (e.g. reduction of postprandial blood glucose responses) 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 (e.g. if it can be established that the mechanism by which the food/constituent exerts a beneficial effect on the disease is the same by which it could reduce the risk of a disease in the target population). 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, ethnicity), demographic (e.g. age[49]), physiological (e.g. pregnancy, menopause) or lifestyle (e.g. level of physical activity,[50] diet[51]) characteristic may be pertinent to the scientific substantiation of health claims addressed to a different target population (e.g. the general population) when: i) 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 ii) if extrapolation of the results from the study group to the target population is biologically plausible (i.e. if there are no known scientific reasons which could prevent the extrapolation of results from the study group to the target population). Biological plausibility will be considered by the NDA Panel on a case-by-case basis.

[48] 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.
[49] E.g. children, adults, elderly.
[50] E.g. athletes.
[51] E.g. vegetarians, vegans.

If it is unclear whether the results from a study group (e.g. diseased patients) could be extrapolated to the target population (e.g. if the mechanism of action is unknown), the results from those studies could be used as supportive evidence for substantiation only if pertinent efficacy studies in the target population are available (see Section 7.4) (EFSA NDA Panel, 2012b).

The Panel acknowledges that an effect of the food/constituent observed in diseased subjects or in subjects at risk of disease may not be necessarily beneficial for, or may not be measurable in, some subgroups of the target population (e.g. a decrease in blood cholesterol, blood pressure, postprandial blood glucose responses, long-term blood glucose control, endothelial dysfunction). However, the Panel considers that certain functions of the body are expected to deteriorate over time as part of the ageing process, even in apparently healthy individuals (e.g. blood cholesterol, blood pressure, postprandial blood glucose responses, long-term blood glucose control, endothelial function). Thus, regular consumption of food/constituent by the target population may contribute to the maintenance of such functions for longer periods of time.

7.7. Scientific assessment of comparative claims

Claims for a beneficial effect of the absence (or reduced content) of a food/constituent in a food or category of foods are assessed 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 assessed 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 postprandial 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 assessment 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 (Standing Committee on the Food Chain and Animal Health, 2007) for the use of comparative claims, including characterisation of the appropriate reference or comparator (see also Section 7.1.1).

7.8. Wordings for health claims assessed 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 Panel, although scientifically correct, do not take into account consumer understanding and may not be appropriate for consumer communication.[52] As explained in Section 4 and Annex A –, applicants can negotiate with risk managers for alternative wordings during the authorisation process.

[52] 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

7.9. Conditions of use for health claims assessed with a favourable outcome

For claims based on the essentiality of 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 claims other than those based on the essentiality of 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 balanced 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).

7.10. Extension or modification of the conditions of use for an authorised claim

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 formulation 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 assess 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 (EFSA NDA Panel, 2010b, 2014d, 2014e).

Applications for the modification of an existing authorisation pursuant to Article 19 of Regulation (EC) No 1924/2006 should follow the Scientific and technical guidance for the preparation and presentation of an application for authorisation of a health claim (EFSA NDA Panel, 2011b).

8. Scientific aspects to be considered for preparing a health claim application

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

The **first** step is to consider whether the claim is based on the essentiality of a nutrient. In this context, it is important to reflect on whether the nutrient:

i. is required for normal human body function(s), i.e. it has an essential mechanistic role in a metabolic function and/or it has a unique ability to reverse clinical signs and symptoms of its deficiency;

ii. cannot be synthesized by the body, or cannot be synthesised in amounts which are adequate to maintain normal body function(s) in the target population;

iii. must be obtained from a dietary source.

If all 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 claim is not based on the essentiality of nutrients, 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 Sections 6.2 and 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.[53] 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, 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 be strong. Applicants are then advised to reflect on whether the outcome(s) investigated[54] may describe a beneficial physiological effect[55] (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)[56] used in the studies are direct measures of the claimed effect, and whether the methods of assessment[57] 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.[58]

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. 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[59] 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[60] 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 assess the quality of each individual human study in relation to:

[53] Commission Regulation (EC) No 1170/2009 of 30 November 2009 amending Directive 2002/46/EC of the European Parliament and of Council and Regulation (EC) No 1925/2006 of the European Parliament and of the Council as regards the lists of vitamin and minerals and their forms that can be added to foods, including food supplements. OJ L 314, 1.12.2009, p. 36–42. https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A32009R1170

[54] E.g. coronary heart disease.

[55] E.g. cardiac function.

[56] E.g. fatal myocardial infarction, non-fatal myocardial infarction, sudden death, angina, hear failure.

[57] E.g. self-reported, clinical records, death certificates.

[58] 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.

[59] 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.

[60] 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.

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;[61]

ii) the risk of bias.[62]

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

As a **seventh** step, applicants are advised to review all the evidence available to them (pertinent human studies plus other studies) and make a scientific judgement on whether or not such evidence may be appropriate/sufficient for the scientific substantiation of the claim[63]. If the answer is yes, applicants should proceed to the next step. If the answer is no, a careful analysis of the gaps in the data available to the applicant can provide an idea of the type and amount of ad hoc research which may be needed to fill those gaps, and which may vary widely from application to application (see Section 7.3).

The **eighth** step is to refine the claimed effect on the basis of the scientific evidence available.

The **ninth** step is to define the wording and the conditions of use for the claim, i.e. the dose and pattern of consumption of the food/constituent which is required to achieve the claimed effect. The wording should reflect the scientific evidence as much as possible, as consumer understanding is not a requirement for the scientific assessment. The conditions of use should be defined on the basis of the individual human studies used for substantiation and/or meta-analysis of such studies (see Sections 7.5 and 7.9).

The **tenth** and final step is to compile the application, having regard to the scientific and technical guidance for the preparation and presentation of a health claim application (Revision 3) (EFSA NDA Panel, 2020).

Annex A explains in detail the administrative and procedural requirements for applications, from pre-submission phase to authorisation.

[61] Applicants are encouraged to consult experts in the particular research field.

[62] Including study design (e.g. randomisation, blinding, control for confounders), statistical analyses, completeness of reporting, etc. Different tools to appraise the design and quality of human studies (of different designs) with respect to the risk of bias have been developed by different bodies and are publicly available. Although these tools are different from each other, they cover a common core of concepts for assessing study quality. As an indication of aspects that the Panel considers when appraising the quality of RCTs, see also Appendix B at: https://www.efsa.europa.eu/en/supporting/pub/836e. Applicants are also encouraged to consult epidemiologists/biostatisticians for that purpose.

[63] 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.

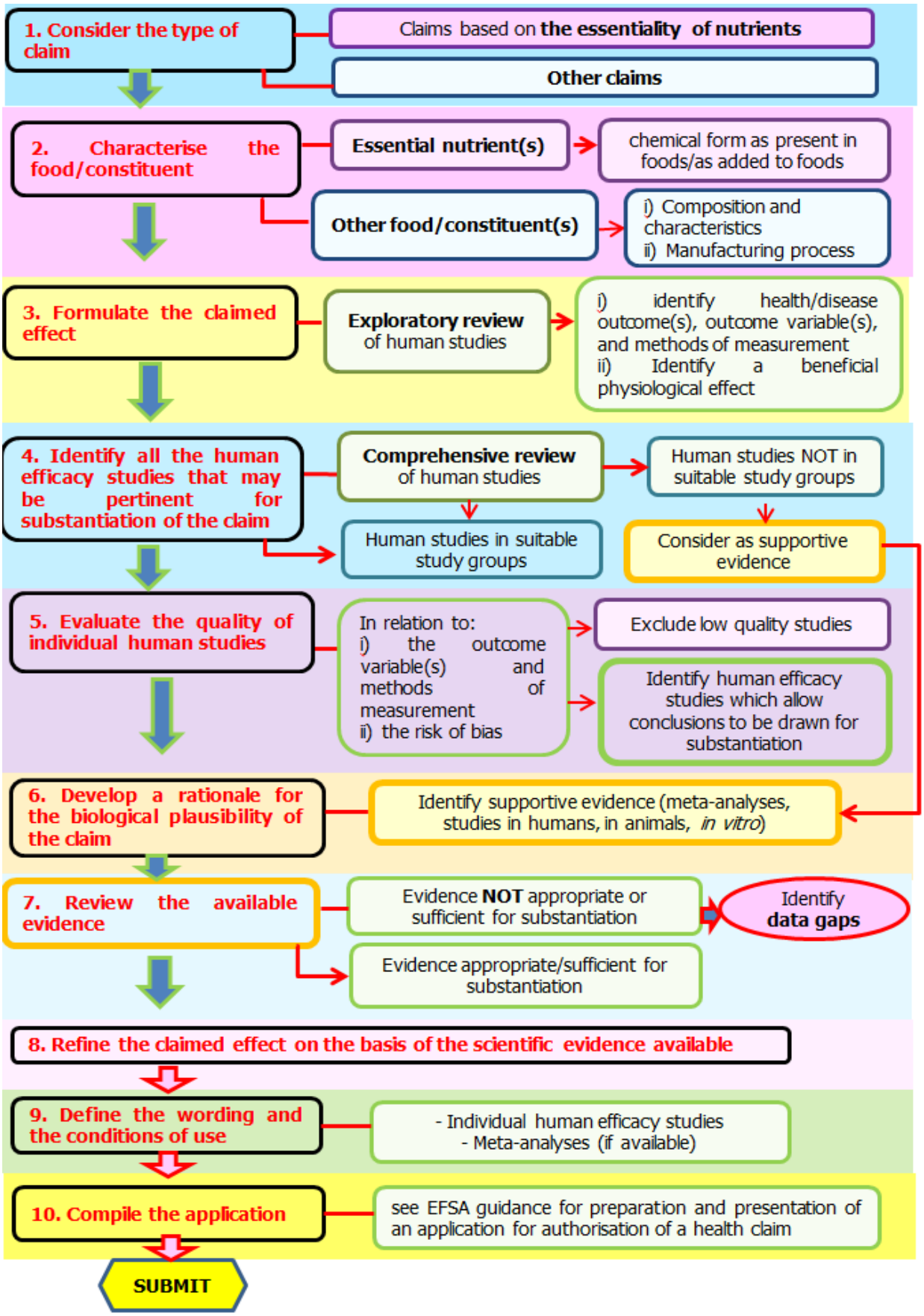

Figure 2: Key scientific aspects to consider for preparing a health claim application

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contribution to the normal function of the immune system by decreasing the levels of eicosanoids, arachidonic acid-derived mediators and pro-inflammatory cytokines (ID 520, 2914), and "immunomodulating agent" (4690) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal 2010;8(10):1796, 32 pp. doi:10.2903/j.efsa.2010.1796 Available at http://www.efsa.europa.eu/en/efsajournal/pub/1796

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Glossary and Abbreviations

AFLP	amplified fragment length polymorphism
Construct validity	The extent to which scores on a particular instrument relate to other measures in a manner that is consistent with theoretically derived hypotheses concerning the concepts that are being measured
Content validity	The extent to which the concepts of interest are comprehensively represented by the items in the questionnaire
CoU	conditions of use
Criterion validity	The extent to which scores on a particular instrument relate to a gold standard
Disease/disorder	A pathological process, acute or chronic, inherited or acquired, of known or unknown origin, having a characteristic set of signs and symptoms which are used for its diagnosis
Efficacy study	An intervention study (in humans, in animals) which investigates the relationship between the food/constituent and the claimed effect
Essential nutrient	A substance required for normal human body function(s) and which cannot be synthesized by the body, or cannot be synthesized in amounts which are adequate to maintain normal body function(s), and thus must be obtained from a dietary source
Floor and ceiling effects	Lowest or highest possible scores
Food/constituent	A food category, a food or a food constituent (e.g. a nutrient or other substance, or a fixed combination of nutrients/other substances)
GFL	General Food Law
Internal consistency	A measure of the extent to which items in a questionnaire (sub)scale are correlated (homogeneous), thus measuring the same concept
Interpretability	The degree to which one can assign qualitative meaning to a quantitative scores
ITS	internal transcribed spacer
LUTI	lower urinary tract infections
MLST	multilocus sequence typing
MS	Member State
NDA	EFSA Panel on Dietetic Products Nutrition and Allergies. As of 1 July 2018, it has been renamed to Panel on Nutrition, Novel Foods and Food Allergens.
Pertinent study	A study from which scientific conclusions that are relevant to the substantiation of a claim (e.g. efficacy studies, bioavailability studies, studies on the mechanism(s) by which a food could exert the claimed effect) can be drawn
PFGE	pulsed-field gel electrophoresis
RAPD	randomly amplified polymorphic DNA
Reproducibility	The degree to which repeated measurements in stable persons (test-retest) provide similar answers
Responsiveness	The ability of a questionnaire to detect clinically important changes over time, even if these changes are small
RFLP	restriction fragment length polymorphism analysis
rRNA	ribosomal RNA

Study group	Individuals recruited for human studies which are submitted for the scientific substantiation of a claim
Suitable study group	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 appropriate
Supportive evidence	Studies/data which, on their own, are not sufficient for the scientific substantiation of a claim and that may be part of the totality of the evidence only if pertinent human studies showing an effect of the food/constituent are available
Target population	The population group(s) for which health claims are intended (e.g. the general healthy population or specific subgroup(s) thereof)
Totality of the evidence	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)
UTI	urinary tract infection
WGM	whole genome mapping

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

A.1 Before submitting an application

A.1.1 Checking scientific guidance

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:[64]

- ***Scientific and technical guidance for the preparation and presentation of a health claim application***, 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:
  - the immune system, the gastrointestinal tract and defence against pathogenic microorganisms;
  - antioxidants, oxidative damage and cardiovascular health;
  - muscle function and physical performance;
  - appetite ratings, weight management and blood glucose concentrations;
  - bone, joints, skin and oral health;
  - functions of the nervous system, including psychological functions.

These guidance documents present examples drawn from past assessments to illustrate the approach of the NDA Panel in the assessment 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 Checking the provisions set out in the GFL Regulation in the pre-submission phase and in the application procedure

The sections below aim at giving an overview to applicants on the procedure governing pre-submission phase that is applicable to all applications submitted as of 27 March 2021. They are to be read in conjunction with Union legal acts, in particular with the GFL Regulation and EFSA's Practical Arrangements on pre-submission phase and public consultations[65], which provide comprehensive information and instructions on that matter.

Applicants are also invited to consult the Administrative guidance for the processing of applications for regulated products (EFSA, 2021a) for the general workflow of applications, the key steps of the scientific assessment process to the publication of the scientific opinion.

[64] https://www.efsa.europa.eu/en/applications/nutrition/regulationsandguidance

[65] See Decision of the Executive Director of the European Food Safety Authority laying down the practical arrangements on pre-submission phase and public consultations.

Before submitting an application, the potential applicant should first register in EFSA's portal supporting pre-submission activities available on EFSA's website.[66] The registration is needed only if at least one of the pre-submission activities is carried out.

The potential applicant is given a reference i.e. pre-application identification 'ID' (EFSA_ID_YYYY_NNNNNN[67]), valid for a specific regulated product in a given regulated product area, to be used for any activity related to the pre-submission phase, as set out in the GFL Regulation and outlined below.

The pre-application ID is to be provided when submitting the application.

- ***General pre-submission advice (optional)***

In accordance with Article 32a(1) of the GFL Regulation, potential applicants may request general pre-submission advice (GPSA) from EFSA at any time before submitting the corresponding envisaged application (*applicable to both application types i.e. application for a new health claim or modification of an existing health claim authorisation*). The GPSA is optional for the potential applicant.

Within the framework of GPSA, EFSA provides advice on the rules applicable to, and the content required for, an application prior to its submission.

In particular, the following items are considered outside of the scope of the GPSA:

- design of the studies to be submitted and questions related to hypotheses to be tested;
- risk management questions;
- any aspects going beyond the information available in the rules and guidance documents or guidelines applicable to applications.

For questions outside the scope of the GPSA, applicants should contact the European Commission.

EFSA recommends submitting the request for GPSA at least six months before the envisaged submission date of the application.

Requests for general pre-submission advice must be submitted to EFSA by filling in the dedicated general pre-submission advice online form ('GPSA form') available on the EFSA website.[68]

For accepted requests, the advice is notified to the potential applicant. A summary of the advice is drawn up and stored by EFSA. It is sent to the potential applicant for information purposes. For a comprehensive description of applicable procedures and provisions, please refer to the Practical Arrangements on pre-submission phase and public consultations.[69] For an overview of the support initiatives provided by EFSA to applicants, please consult EFSA's Catalogue of support initiatives (EFSA, 2021d).

The summary of the advice is made public together with the non-confidential version of the application dossier, as soon as the application is declared valid. On applicable transparency and confidentiality requirements, please see Section A.3 below.

- ***Notification of studies (mandatory)***

In accordance with Article 32b of the GFL Regulation, potential applicants commissioning or carrying out studies as of 27 March 2021 to support an health claim application have the obligation to notify EFSA without delay of the following information[70] related to those studies:

- title and scope of the study;
- laboratory or testing facility carrying out the study;
- starting and planned completion dates of the study.

[66] https://www.efsa.europa.eu/en/applications/toolkit
[67] YYYY corresponds to the year and NNNNNN is a progressive number.
[68] https://www.efsa.europa.eu/en/applications/toolkit
[69] See Decision of the Executive Director of the European Food Safety Authority laying down the practical arrangements on pre-submission phase and public consultations
[70] The full list of information to be notified for each study is provided in Annex II to Decision of the Executive Director of the European Food Safety Authority laying down the practical arrangements on pre-submission phase and public consultations

The same obligation applies to the laboratories and other testing facilities located in the EU[71] for studies commissioned by potential applicants and carried out by such laboratories and other testing facilities. Therefore, both potential applicant and laboratories/testing facilities have the obligation to notify information about all studies commissioned/carried out to support an application (*applicable to both application types i.e. application for a new health claim or modification of an existing health claim authorisation*). Study notifications are to be submitted in the database of study notifications available on the EFSA website[72] without delay before the starting date of the study. The database will assign a unique study identification 'ID' to each study notification (i.e. EFSA-YYYY-NNNNNNNN[73]).

For any study notification submitted after the starting date of the study, at application submission phase, the applicant must provide justifications for the delay.

The obligations of notification of studies apply to any additional studies provided after the submission of the application, following a request for additional information during the validity check by Member State/completeness check by EFSA and/or scientific assessment, or provided as part of spontaneous submission of information, if such studies are commissioned or carried out as of 27 March 2021.

Applicants should be aware that the non-compliance with the notification of study obligations may result in the non-validity of the application or in delays in the scientific assessment process.

For a comprehensive description of applicable procedures and provisions, please refer to the Practical Arrangements on pre-submission phase and public consultations.[74]

A.1.3 The language and the format required for a claim application

In submitting an application under this guidance, please note that EFSA operates in accordance with its Decision on the Linguistic Regime[75], which recognises English as its working language. In order to facilitate the evaluation of the applications, scientific and technical documentation should be submitted in English. EFSA may ask the applicant to translate the parts of the dossier that are not submitted in English.

Claims applications should adhere to the format of the Scientific and technical guidance for the preparation and presentation of a health claim application (see Section A.1.1).[76]

EFSA strongly recommends that each document, including annexes (i.e. study reports, raw data, published studies and any other document in the technical dossier) be electronically **searchable** and accessible to allow downloading and printing of the file. This applies to **all documents or information** uploaded as part of the initial submission, or later during completeness/validity check or in the scientific assessment process.

The applicant must ensure that terms and conditions asserted by any rightsholder of studies, information or data submitted to EFSA are fully satisfied. The applicant may consult with copyright licensing authorities (i.e. at national level) for guidance on purchasing the appropriate licenses to provide studies, information or data to EFSA, taking into account the proactive disclosure requirements as detailed above. For publications already available to the public upon payment of fees (e.g. studies published in scientific journals) for which the applicant does not have or cannot obtain intellectual property rights for the purposes of the proactive public disclosure requirements, the applicant must provide (a) a copy of the relevant publications along with the relevant bibliographic references/citations for scientific assessment purposes only, in the confidential version of its application and (b) these relevant bibliographic references/citations where these publications are available to the public in the non-confidential version of its application for public dissemination on the OpenEFSA portal.[77]

Any information claimed to be confidential in the application (i.e. technical dossier) should be boxed or earmarked. When submitting confidentiality requests, applicants should also provide: a non-confidential

[71] The same obligation applies to laboratories and testing facilities located in third countries insofar as set out in relevant agreements and arrangements with those third countries, including as referred to in Article 49 of the GFL Regulation.
[72] https://www.efsa.europa.eu/en/applications/toolkit
[73] YYYY corresponds to the year and NNNNNNNN is a progressive number.
[74] See Decision of the Executive Director of the European Food Safety Authority laying down the practical arrangements on pre-submission phase and public consultations
[75] See Decision of the Executive Director on the Linguistic Regime of EFSA, 20 April 2015, REF. EFSA/LRA/DEC/14046420/2015.
[76] https://www.efsa.europa.eu/en/efsajournal/pub/2170
[77] https://open.efsa.europa.eu

(i.e. public) version of documents (with the elements claimed to be confidential blackened), for any document for which a confidentiality request is presented in accordance with Section A.3.

Regarding the study notification obligations of Article 32b(2) and (3) of GFL Regulation (Section A.1.2), when submitting an application, the applicant must provide the following information:

- **pre-application IDs** related to the health claim which is the subject matter of the submitted application given to the applicant at pre-submission phase, in case pre-submission advice was requested and/or or new studies have been notified;
- **study ID** generated by EFSA's database of study notifications for each study submitted in the application;
- if necessary, **justifications** explaining the divergences between the information notified in accordance to Section A.1.2. and the studies included in the application, linked, where applicable, to the study ID.

A.1.4 How to submit a claim application?

Applicants are invited to check with the recipient Member State on whether the claim falls under the scope of Regulation (EC) No 1924/2006 and on the admissibility of the target population for the claim at the earliest possible stage before submitting the application (see also Section 4).

Applications for authorisation of health claims pursuant to Articles 14, 13(5) and 19 of the Regulation (EC) No 1924/2006 must be submitted to the national competent authority of a Member State in accordance with Articles 15 and 18, respectively. The list of competent authorities of the Member States within the framework of Regulation (EC) No 1924/2006 is published on EFSA's website[78] and retrievable in the e-submission system when submitting the application.

Applications must be submitted using the e-submission system accessible through EC's website or EFSA's website.[79] The system allows the applicant to submit and follow-up on applications through an online web interface from the start to the end of the authorisation process. Detailed instructions for accessing and using the e-submission system are provided in the dedicated user guide.[80]

Applicants are reminded that notified studies and the justifications provided to prove compliance with notification of studies obligations (see Sections A.1.2 and A.1.3) are subject to validity check by the recipient Member State.

The application is declared as non-valid[81], if during the validity check it is concluded that:

- a submitted study was not previously notified in EFSA's database of study notifications or was notified after the starting date of the study (i.e. non-notification regulated upon by Article 32b(4) of the GFL Regulation) and the applicant has provided no valid justification; and/or
- a study previously notified in EFSA's database was not included in the application) and the applicant has provided no valid justification (i.e. non-inclusion of a study regulated upon by Article 32b(5) of the GFL Regulation); and/or
- a notification of a study was withdrawn and the applicant has provided no valid justification (Article 23(2)(c) of EFSA's Practical Arrangements on pre-submission phase and public consultations (EFSA, 2021b)).

The applicant may resubmit the application, provided that:

- it notifies in the database the studies that were not previously notified; and/or
- it submits all the studies which were previously notified in the database or, in case of unjustified withdrawal of a notification of a study, the data delivered by the relevant laboratory or testing facility even without the study having been completed.

To this end, the applicant should insert in the e-submission system a complete new application. When re-submitting the application, the applicant is also required to contextually provide the unique number

[78] https://www.efsa.europa.eu/sites/default/files/efsa_rep/blobserver_assets/ndacompetentauthorities.pdf
[79] https://www.efsa.europa.eu/en/applications/toolkit
[80] https://www.efsa.europa.eu/en/applications/toolkit
[81] In accordance with Articles 32b(4) and (5) of GFL Regulation.

of the application (i.e. EFSA's question number: EFSA-Q-YYYY-xxxxx) which was previously not considered valid. The validity check by the recipient Member State of the new application will commence six months after the re-submission of the application.

For a comprehensive description of applicable procedures and provisions, please consult the Practical Arrangements on pre-submission phase and public consultations[82] available on EFSA's website.

The national competent Authority will make the valid application and any supplementary information supplied by the applicant available to EFSA using the e-submission system.

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. EFSA aims at providing applicants with its first feedback on the completeness check within 30 working days of receipt of the application, depending on the size and quality of the application.[83]

The completeness check includes a verification of the administrative compliance as well as the elements which are essential to allow a scientific assessment by the Panel, including 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. If one or more of these elements is missing, the Panel may not be able to start the scientific assessment. In this context, a thorough check of the application by EFSA before starting the scientific assessment is essential for minimising the number of clock-stops applied during the assessment process. During the completeness check, EFSA may consult the Commission Services on points of interpretation of EU legislation particularly in relation to the scope.

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. Applicants can request a teleconference to clarify a request from EFSA for missing information.[84]

Applicants should note that if new studies are submitted to EFSA following a request during the completeness check, these studies are subject to the obligations on study notifications, if commissioned or carried out as of 27 March 2021 (see Sections A.1.2 and A.1.3). In this case, the relevant information must be notified in the database of study notifications in accordance with EFSA's Practical Arrangements on pre-submission phase and public consultations.

Once the application is considered **complete/valid**, the applicant is notified of the status (via the e-submission system)

EFSA makes the application and any supplementary information supplied by the applicant available via e-submission system to Member States and the Commission.

A.3 Transparency and confidentiality requirements

This section aims at giving an overview to applicants on the procedure governing transparency and confidentiality requests, in accordance with relevant provisions of the GFL Regulation, as amended by the Transparency Regulation, and EFSA's Practical Arrangements concerning transparency and confidentiality. It is to be read in conjunction with Union law[85] and case law, as well as with EFSA's Practical Arrangements[86], which provide a comprehensive description of applicable procedures and provisions.

[82] See Decision of the Executive Director of the European Food Safety Authority laying down the practical arrangements on pre-submission phase and public consultations
[83] See Administrative guidance for the processing of applications for regulated products (EFSA, 2021a).
[84] See EFSA's Catalogue of support initiatives during the life-cycle of applications for regulated products (EFSA, 2021d).
[85] Relevant provisions of GFL Regulation.
[86] See Decision of the Executive Director of the European Food Safety Authority laying down practical arrangements concerning transparency and confidentiality

A.3.1 Transparency requirements applicable to information shared by applicants with EFSA

The GFL Regulation as amended by the Transparency Regulation introduced a general principle of proactive disclosure and transparency of information and data submitted to EFSA for scientific assessment. In the light of this principle, and of the related provisions, EFSA must proactively disseminate all information shared by applicants for the purposes of EFSA's scientific assessment of regulated products, including the information submitted during the assessment process. Specifically, EFSA is to make publicly available[87] *inter alia* the following information[88]:

- all its scientific outputs;
- scientific data, studies and other information supporting applications, including supplementary information, as well as other scientific data and information supporting requests from the Commission and the Member States for a scientific output;
- the information on which its scientific outputs are based;
- a summary of the advice provided to potential applicants at pre-submission phase, if applicable.

By derogation from the general principle of proactive disclosure and transparency, EFSA, when required to issue an opinion, may grant confidential status to certain elements of application dossiers, provided applicants submit a verifiable justification, and EFSA accepts the confidentiality request.

For this purpose, and for each document for which confidentiality is requested, applicants are required to upload to the e-submission system:

- **a request to treat certain item(s) as confidential**, specifying: the confidentiality ground(s) and conditions, justification, excerpt of the text, location in the file. These requests should be inserted in the e-submission system at the time of submission of the information. Multiple requests can be submitted per file, but only with regard to specific items as indicated in the relevant Union law;
- **a version of the concerned document with all information visible and no blackening applied**. In this version, all information claimed to be confidential by the applicant should be boxed or earmarked (confidential version, not for public disclosure);
- **a non-confidential version with all elements claimed to be confidential blackened** (public version). This version will be made publicly available in the OpenEFSA portal as soon as the application is declared valid. This non-confidential version provided by the applicant and made available on the OpenEFSA portal will be replaced by the one sanitised by EFSA pursuant to its confidentiality decision, in case one or more confidentiality requests are rejected. Applicants should note that the public version should have all the names and addresses of individuals involved in testing on vertebrate animals or in obtaining toxicological information blackened as these elements must not be disclosed. Furthermore, the public version should also have all the personal data the applicants consider should not be disclosed pursuant to its confidentiality requests, equally blackened. For more information, see EFSA's Practical Arrangements concerning transparency and confidentiality (EFSA, 2021c).

A.3.2 Confidentiality requests and confidentiality decision-making process

Applicants are required to submit confidentiality requests via the e-submission system by providing reasoning supporting each request and addressing the requirements set out in Article 10 of EFSA's Practical Arrangement concerning transparency and confidentiality.

It is fundamental that applicants submit all relevant confidentiality requests at the time of submission of the related piece of information (e.g. technical dossier, information submitted following a request for missing or additional/supplementary information, etc.). After submission, applicants may not modify

[87] The proactive disclosure of the above information does not imply permission or licence for their re-use, reproduction, or exploitation in breach of the relevant existing rules concerning intellectual property rights or data exclusivity. EFSA cannot be held liable or responsible for any use of the disclosed data by third parties in breach of any existing intellectual property rights.

[88] For an exhaustive list of the types of information, documents or data which is made proactively available, please refer to Articles 5 and 6 of Decision of the Executive Director of the European Food Safety Authority laying down practical arrangements concerning transparency and confidentiality.

confidentiality requests anymore, unless requested to do so by EFSA. If EFSA requests the applicant to provide clarifications on the information initially provided to justify a confidentiality request, and the applicant does not react by the given timeline, EFSA will reject the confidentiality request.

For the procedure governing confidentiality requests and EFSA confidentiality decision-making process, please refer to EFSA's Practical Arrangements concerning transparency and confidentiality[89], which provide comprehensive information and instructions on that matter, in particular:

- How to submit a confidentiality request;
- Processing of confidentiality request;
- Possibility of commenting on, or changing, a negative decision on a confidentiality request;
- Implementation of EFSA's confidentiality decision;
- Implications of the award of confidential status to certain information.

A.4 Public consultation on information contained in the application

In accordance with Article 32c(2) of the GFL Regulation, in order to ensure that EFSA can have access to all relevant scientific data and studies available on a subject matter of an application, EFSA consults stakeholders and the public ('consultation of third parties') on the scientific data, studies and other information part of, or supporting, the submitted application to identify whether other relevant scientific data or studies are available.

Following the implementation of EFSA's confidentiality decision-making (see Section A.3) and upon publication by EFSA of the non-confidential version of the application dossier, and, EFSA launches a public consultation on its website.

All comments received from third parties will be made public by EFSA immediately upon the closure of the consultation of third parties. Relevant comments will be considered during the scientific assessment phase.[90] EFSA's scientific opinion will address the relevant comments received from the third parties.[91]

For a comprehensive description of applicable procedures and provisions, please refer to the Practical Arrangements on pre-submission phase and public consultations.[92]

A.5 What happens during the scientific assessment process?

Once the application is considered complete and valid, the scientific assessment starts. EFSA must 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).

A.5.1 When does the stop-the-clock procedure apply?

During the assessment, 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,[93] the issues identified by the NDA Panel which have triggered 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%).

[89] See Decision of the Executive Director of the European Food Safety Authority laying down practical arrangements concerning transparency and confidentiality

[90] In accordance with Article 32c(2) of the GFL Regulation, EFSA may extend the timeline to conclude the assessment for a maximum of seven weeks in case the results of the public consultation cannot be given proper consideration within the regulatory time limit allotted for delivering the opinion.

[91] The public disclosure of the results of the public consultation, as well as of the comments received, is done pursuant to Article 6(1), letter (d) and Article 5(2) letter (g) of the Decision of the Executive Director of EFSA laying down practical arrangements concerning transparency and confidentiality, respectively.

[92] See Decision of the Executive Director of the European Food Safety Authority laying down the practical arrangements on pre-submission phase and public consultations

[93] http://www.efsa.europa.eu/en/events/documents/131120-p03.pdf

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 reformulation 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 Panel. To this end, upon receipt of EFSA's request for supplementary information, applicants can ask for a teleconference to clarify EFSA's request, [94] if needed.

Applicants are reminded of the specific obligations on the notification of studies commissioned/carried out to support the application (see Sections A.1.2 and A.1.3).

f, following a more extensive verification of the data submitted by the applicant, it is detected that the studies previously notified in accordance with Article 32b(2) and (3) of GFL Regulation are not included in full in the submitted application, EFSA requests the applicant to provide justifications regarding any missing data.

The applicant is informed that the time-limit within which EFSA is required to deliver its scientific opinion is suspended, pending the provision of valid justifications for the absence of certain data of studies previously notified.

EFSA assesses the justifications provided by the applicant. If the justifications are considered valid, the scientific assessment process re-starts and the applicant is informed accordingly. If the justifications provided by the applicant are not considered valid, the applicant is requested to submit the missing data of the notified study/ies. The applicant is also informed that the scientific assessment process will remain suspended for six months after the submission of any missing data relating to any supporting studies.[95] For details on implications and duration of the suspension, please consult EFSA's Practical Arrangements on pre-submission phase and public consultations[96]

Moreover, if new studies are submitted when addressing a request for supplementary information during the scientific assessment, these studies are subject to the obligations on study notifications if commissioned or carried out as of 27 March 2021. In this case, the relevant information must be notified in the database of study notifications in accordance with EFSA's Practical Arrangements on pre-submission phase and public consultations.[97]

The provisions on confidentiality and proactive disclosure of the information, as detailed in Section A.3, fully apply to the assessment phase, as a result of submission of supplementary information or data.

The applicant should respond to requests for supplementary information using e-submission system. After submitting 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 application (i.e. *Applicants technical hearing).*[98]

In case the applicant does not provide the requested supplementary information within the specified time limit or responds by providing inadequate information, the Panel does not reiterate already formulated requests or does not ask for the same information a second time. In these cases, the Panel reserves the right to complete the assessment and issue an opinion based on the data available.

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'.[99]

[94] See EFSA's Catalogue of support initiatives during the life-cycle of applications for regulated products (EFSA, 2021d).
[95] In accordance with Article 32b(6) of the GFL Regulation.
[96] See Decision of the Executive Director of the European Food Safety Authority laying down the practical arrangements on pre-submission phase and public consultations
[97] See Decision of the Executive Director of the European Food Safety Authority laying down the practical arrangements on pre-submission phase and public consultations
[98] See EFSA's Catalogue of support initiatives during the life-cycle of applications for regulated products (EFSA, 2021d).
[99] In line with the 'Indicative timelines for submitting additional or supplementary information to EFSA during the risk assessment process of regulated products' included in the Administrative guidance for the processing of applications for regulated products (EFSA, 2021a)

A.5.2 Can a claim application be withdrawn?

Article 7b of Regulation (EC) No 353/2008[100] specifies the rules for the withdrawal of applications:

(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 through the e-submission system.

When an applicant withdraws its application prior to the adoption of a confidentiality decision (see Section A.3 and EFSA's Practical Arrangements concerning transparency and confidentiality[101]), EFSA, the European Commission and the Member States must not make public the information for which the confidential status had been requested.

In case an applicant withdraws its application after the adoption of a confidentiality decision, all actors having access to the relevant dataset must comply with the confidentiality decision.

For the effects of the withdrawal on information made publicly available on the OpenEFSA portal, please refer to EFSA's Practical Arrangements concerning transparency and confidentiality which give a comprehensive overview of the applicable procedure.

A.5.3 How proprietary data are handled by EFSA?

The decision on granting the protection of proprietary data (e.g. linked to requirements for data exclusivity) under Article 21 of Regulation 1924/2006 falls under the responsibility of the European Commission when authorising the claims. With respect to the handling, use and protection of proprietary data by EFSA, it should be noted that where evidence for substantiation includes a request for the protection of proprietary data, the NDA Panel considers in its opinion only whether the claim could have been substantiated without the data claimed as proprietary by the applicant or not.

A.6 Adoption and publication of EFSA's opinion on claims

One working day after the adoption of the scientific opinion by the NDA Panel, EFSA notifies the applicant that a scientific opinion on its application is adopted.[102]

Following the adoption of the scientific opinion by the Panel, the process of publication starts, and the opinion is checked for editorial review.

The applicant is pre-notified[103] at least 36 hours prior to publication. The scientific opinion is then published in the EFSA Journal,[104] implementing the decision of EFSA on the confidentiality (see Section A.3), as outlined in EFSA's Practical arrangements Concerning transparency and confidentiality.[105]

It should be noted that, at this stage, a reopening of the scientific assessment is not possible, and that the applicant is consulted only regarding data disclosed in the opinion that EFSA has previously accepted as being confidential.

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*).[106]

[100] 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. https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A32008R0353

[101] See Decision of the Executive Director of the European Food Safety Authority laying down practical arrangements concerning transparency and confidentiality

[102] See EFSA's Catalogue of support initiatives during the life-cycle of applications for regulated products (EFSA, 2021d).

[103] See EFSA's Catalogue of support initiatives during the life-cycle of applications for regulated products (EFSA, 2021d).

[104] EFSA Journal: https://www.efsa.europa.eu/en/publications

[105] See Decision of the Executive Director of the European Food Safety Authority laying down practical arrangements concerning transparency and confidentiality

[106] See EFSA's Catalogue of support initiatives during the life-cycle of applications for regulated products (EFSA, 2021d).

A.7 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.[107]

EFSA responses to the requests received from the Commission are also published on EFSA's website.[108]

A.8 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.

After a favourable opinion of the Standing Committee on the Food Chain and Animal Health, the European Parliament and the Council have the right of scrutiny on the Commission's draft decision. If there is no objection, the Commission adopts the draft decision.

In the case of Article 13(5) health claims which have received a favourable EFSA opinion, the Standing Committee on the Food Chain and Animal Health is consulted on the Commission's draft decision before the Commission adopts it. In this situation, there is no opinion (vote) of the Standing Committee and no scrutiny by the European Parliament and the Council.

Authorised health claims, their conditions of use and applicable restrictions of use, if any, are published in the EU Register of claims.[109]

[107] http://ec.europa.eu/nuhclaims/?event=claimsBeingProcessed

[108] http://www.efsa.europa.eu/en/search/site/%22Response%20to%20comments%22?f[0]=sm_canonical_subject%3AEFSA%20Panel%20on%20Dietetic%20Products%2C%20Nutrition%20and%20Allergies

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

Annex B – Characterisation of microorganisms at strain level

Health claims have been made on microorganisms (e.g. bacteria and yeast). Correct identification of the bacterial's and yeast's species and strain is of critical importance, as the observed effects in the host are species and strain specific, unless the contrary is demonstrated.

Species identification and sufficient characterisation (genetic typing) at strain level, by using internationally accepted molecular methods are needed. In addition, strains should be named according to the International Code of Nomenclature.[110] It is strongly recommended that strains are deposited in an internationally recognised culture collection[111] with access number for control purposes.

The Panel's recommendations have been updated, taking into consideration the current state-of-art techniques for identification and molecular characterisation of microorganisms. The Panel also indicates that several methods are often needed to be used in combination to obtain the required resolution (discriminatory power, reproducibility, etc.) depending on the microorganism in question. It should be noted that techniques listed below constitute examples of well-established molecular methods for microbial characterisation but these do not constitute an exhaustive list of all existing possibilities and that others may result from future advances in the understanding of microbial genetics linked to technical developments (see also EFSA BIOHAZ Panel (2013)).

Characterisation of bacteria (EFSA NDA Panel, 2009b, 2010c) – the Panel suggests the following techniques and criteria for characterisation of bacteria which are the subject of health claims:

- Species identification by sequence analysis of robust taxonomic markers including at least two of them if needed (e.g. 16S rRNA gene) (Kim et al., 2014) or fully assembled and validated whole-genome sequence analysis (Goris et al., 2007; Chun and Rainey, 2014) or other internationally accepted molecular methods.

- Strain identification by DNA macrorestriction followed by pulsed-field gel electrophoresis (PFGE), multilocus sequence typing (MLST), randomly amplified polymorphic DNA analysis (RAPD), amplified fragment length polymorphism (AFLP), whole genome mapping (WGM) or optical mapping analysis, fully assembled and validated whole-genome sequence analysis, or other internationally accepted genetic typing molecular methods.

The bacterium is considered to be sufficiently characterised only when these two criteria are fulfilled.

Characterisation of yeasts (EFSA NDA Panel, 2010c) – The Panel uses the following criteria for the characterisation of yeasts which are the subject of health claims:

- Species identification by sequencing analysis of DNA taxonomic markers (e.g. the D1 and D2 domains of 26S rDNA or internal transcribed spacer [ITS] regions between the rRNA gene subunits, including the 5.8S rRNA gene), restriction fragment length polymorphism analysis (RFLP) (e.g. RFLP of the 5.8S rDNA ITS region, RFLP of mitochondrial DNA), fully assembled and validated whole-genome sequence analysis or other internationally accepted genetic typing molecular methods.
- Strain identification by chromosome length polymorphism analysis by PFGE, RAPDs, microsatellite DNA polymorphism analysis, fully assembled and validated whole-genome sequence analysis or other internationally accepted genetic typing molecular techniques.

Only when these two criteria are fulfilled is the yeast considered to be sufficiently characterised.

In the case of combination of several bacteria and/or yeasts, the Panel considers that if one microorganism used in the combination is not sufficiently characterised, the combination proposed is not sufficiently characterised.

The NDA Panel recommends that applicants provide sufficient information complying with the above-mentioned criteria for the characterisation of microorganisms.

[110] The approved nomenclature for bacteria is kept at the International Committee on Systematics of Prokaryotes for (http://icsp.org/), and the International Code of Nomenclature of fungi is kept by the International Commission on the Taxonomy of Fungi (ICTF) (www.fungaltaxonomy.org) and the approved nomenclature for fungi can also be found on the MycoBank (http://www.mycobank.org).

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

Annex C – Considerations on the validation of questionnaires and their use as outcome variables for the scientific substantiation of health claims.

Questionnaires are used to assess subject-reported outcomes, which are subjective in nature. They may assess an outcome at a single time point or longitudinally over time, e.g. changes from baseline. They can be designed to investigate a single concept (e.g. a single symptom) or a combination of concepts (e.g. a combination of symptoms relevant for a specific outcome). Whenever objective measures are available for an outcome they are generally preferred over the use of subjective measures, such as questionnaires. A subjective measurement tool, such as a questionnaire, should have been shown to measure reliably the concept or the combination of concepts it intends to measure. This approach is not different from any new measurement instruments or novel laboratory methods, which have to be validated prior to routine use.

Questionnaires should have been validated (i.e. should actually measure what they are supposed to measure and be suitable for purpose), and should have been shown to be reliable (i.e. are able to yield consistent results). For a questionnaire to serve as an acceptable outcome variable for the scientific substantiation of a health claim, validation and reliability should ideally have been previously and independently established for the study group in the particular study setting. Validating a questionnaire in the same study in which the questionnaire is used to measure the outcome variable is not appropriate for the purpose of obtaining confirmatory results.

Several criteria have been developed to assess the measurement properties of questionnaires (Aaronson et al., 2002; Terwee et al., 2007), and guidelines on the use of subject-reported outcomes are available (FDA (Food and Drug Administration Center for Drug Evaluation and Research (CDER)), 2009) and provide guidance on how questionnaires could potentially be validated and on how the most applicable tool for a certain outcome could be selected.

Items which have been recommended to be considered when assessing the validity and reliability of a given questionnaire in a specific context are (Terwee et al., 2007): (1) content validity, (2) internal consistency, (3) criterion validity, (4) construct validity, (5) reproducibility (including agreement and reliability), (6) responsiveness, (7) floor and ceiling effects and (8) interpretability (see Glossary). These items could be considered by an applicant when determining if a specific questionnaire could be considered appropriate in a given context. The NDA Panel notes that, in some cases, it will not be possible to assess criterion validity in the absence of a gold standard for measuring the intended outcome. However, in cases where such a method is available, criterion validity is an important aspect to consider.

The Panel would like to highlight that particular attention should be paid to the following issues:

- A questionnaire can only be considered to be appropriate if the population in which the questionnaire has been validated is representative of the study population, and if the setting in which the questionnaire has been validated is representative of the setting of the study in which it is to be used.
- Any changes made (e.g. modifications of items) to a previously validated questionnaire require a revalidation of the questionnaire.
- Validation is language specific and translating a previously validated questionnaire into another language requires further validation steps.
- A questionnaire which has been validated for a composite score is not necessarily validated for the individual constructs which make up the composite score and vice versa.
- A questionnaire which has been validated to assess an outcome at a single time point may not necessarily be validated to assess changes of an outcome over time (responsiveness).
- A questionnaire which has been validated as an interviewer-administered questionnaire may not necessarily be validated in a self-administered setting and vice versa.
- A questionnaire which has been validated to assess the severity of a condition may not necessarily be validated to assess the incidence and vice versa.

The Panel wishes to highlight that there is no single correct way to demonstrate the validity of a questionnaire. It is a scientific judgement as to the extent to which the information available on

validation is sufficient to provide confidence in the validity of the results obtained with the questionnaire for the particular outcome variable(s) under the study conditions. Also, as the appropriateness of a tool will depend on the outcome variable(s) to be measured, the study group, the study design and the study setting, no exhaustive list of acceptable questionnaires can be given.