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**SCIENTIFIC AND TECHNICAL GUIDANCE FOR THE
PREPARATION AND PRESENTATION OF THE APPLICATION FOR
AUTHORISATION OF A HEALTH CLAIM**

Draft Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies

Agreed on 3 May for release for public consultation

(Request N° EFSA-Q-2007-066)

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69 **Draft**
70 **Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies**
71 **on a request from the Commission related to**
72 **scientific and technical guidance for the preparation and presentation of the**
73 **application for authorisation of a health claim**
74

75 **(Request N° EFSA-Q-2007-066)**

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77 **(Agreed on 3 May 2007 for release for public consultation)**
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81 **SUMMARY**

82 The European Commission has requested the European Food Safety Authority (EFSA) to
83 issue an opinion on scientific and technical guidance for the applications for authorisations of
84 health claims under Regulation (EC) No 1924/2006 on nutrition and health claims made on
85 foods. In this context, a 'food' may be a nutrient or other substance, or a combination of
86 nutrients/substances, or a food or a category of food.

87 The Scientific Panel on Dietetic Products, Nutrition and Allergies has prepared a draft
88 Opinion which is published for consultation and which will be adopted following amendment,
89 as considered appropriate, in the light of comments received.

90 The purpose of this guidance is to assist applicants in preparing and presenting their
91 applications for authorisation of health claims which fall under Article 14 of the Regulation,
92 i.e. reduction of disease risk claims and claims referring to children's development and health.
93 This guidance will be updated at a later stage to cover applications for authorisation of the
94 health claims which fall under Article 18 of the Regulation, i.e. applications for inclusion of
95 health claims in the Community list of permitted claims provided for in Article 13(3) which
96 are based on newly developed scientific evidence and/or which include a request for the
97 protection of proprietary data. It is intended that the guidance will be kept under review and
98 will be amended and updated as appropriate in the light of experience gained from evaluation
99 of health claim applications.

100 The guidance presents a common format to assist the applicant in the preparation of a well-
101 structured application. This will also help EFSA to deliver its scientific advice in an effective
102 and consistent way.

103 In accordance with the requirements of the Regulation, the application must contain:

104 (a) information on the characteristics of the food for which a health claim is made. This
105 information should contain aspects considered pertinent to the claim, such as, manufacturing
106 process, composition, physical and chemical characteristics, stability, and bioavailability.

107 (b) a proposal for the wording of the health claim, including, as appropriate, the specific
108 conditions of use. The following should be specified, with a rationale: the target population
109 for the intended health claim; where appropriate, a statement addressed to persons who should
110 avoid using the food for which the health claim is made; the quantity of the food and pattern

111 of consumption required to obtain the claimed beneficial effect, and whether this quantity
112 could reasonably be consumed as part of a balanced diet; a warning for foods that are likely to
113 present a health risk if consumed to excess; any other restrictions of use. The application
114 should also include examples of how the claim will be presented, where the claim will be
115 used, e.g. labelling, advertising, and a rationale (and data, if available) in support of consumer
116 understanding of the health claim.

117 The application must also contain all pertinent scientific data (published and unpublished,
118 including proprietary data) identified that form the basis for substantiation of the health claim.
119 Data from studies in humans will be required for substantiation of a health claim; because of
120 the scientific uncertainties in extrapolating non-human data to humans, data from studies in
121 animals or model systems may be included only as supporting evidence, e.g. to explain the
122 mechanism underlying the health effect of the food.

123 A comprehensive review of the data from human studies pertaining to the specific food-health
124 relationship is required. This review, and the identification of data considered pertinent to the
125 claim, should be performed in a systematic and transparent manner in order to demonstrate
126 that the application reflects adequately the balance of all the evidence available.

127 In cases where any of the required data does not apply for a particular application,
128 reasons/justification must be given for the absence of such data in the application.

129 Guidance is provided for the presentation of summaries of the data from intervention studies
130 and observational studies in humans according to a hierarchy of study designs, reflecting the
131 relative strength of evidence that may be obtained from different types of studies. Templates
132 are provided for presenting summaries of data from individual studies in humans so as to
133 highlight the relevant aspects related to the design, outcome and quality of the studies.

134 As specified in the Regulation, health claims should be substantiated by taking into account
135 the totality of the available scientific data and by weighing the evidence, subject to the
136 specific conditions of use. In particular, the evidence should demonstrate the extent to which:

137 (a) the claimed beneficial effect of the food is relevant for human health,

138 (b) a cause and effect relationship is established between the consumption of the food and the
139 health outcome in humans (including the strength, consistency, specificity, dose-response, and
140 biological plausibility of the relationship),

141 (c) the quantity of the food and pattern of consumption required to obtain the claimed
142 beneficial effect could reasonably be achieved as part of a balanced diet,

143 (d) the evidence obtained from the specific study group(s) can be generalised to the target
144 population for which the claim is intended.

145

146 **KEY WORDS**

147 Health claims, Regulation, food(s), substantiation, human data, comprehensive review

148 **BACKGROUND**

149 The Regulation (EC) No 1924/2006 of the European Parliament and of the council of 20
150 December 2006 on nutrition and health claims made on foods (hereafter “**the Regulation**”)
151 entered into force on 19th January 2007¹. In relation to applications for authorisation of health
152 claims, Article 15, paragraph 4 of the Regulation provides the following provision:

153 “The Commission, having first consulted EFSA, shall establish in accordance with the
154 procedure referred to in Article 25(2) (comitology procedure) implementing rules for
155 application of this Article, including rules concerning the preparation and presentation of the
156 application.”

157 The Commission will make available administrative guidance for the preparation and the
158 presentation of the application. This guidance needs to be complemented with scientific and
159 technical guidelines regarding the content of the application for health claim authorisation.

160 Therefore the Commission requests EFSA to provide scientific guidance for the preparation
161 and the presentation of the application for health claim authorisation.

162

163 **TERMS OF REFERENCE**

164 In accordance with Article 31 of Regulation (EC) N° 178/2002, the European Commission
165 requests the European Food Safety Authority (EFSA) to issue an opinion on scientific and
166 technical guidance for the application for authorisations of health claims.

167

168 **OBJECTIVES**

169 This guidance is intended to assist applicants in preparing and presenting their applications
170 for authorisation of health claims. It presents a common format for the organisation of the
171 information to be presented to assist the applicant in the preparation of a well-structured
172 application.

173 This guidance outlines:

- 174
- 175 • the information and scientific data which must be included in the application,
 - 176 • the hierarchy of different types of data and of study designs, reflecting the
177 relative strength of evidence which may be obtained from different types of
studies,
 - 178 • templates for presenting summaries of data so as to highlight the relevant
179 aspects related to the design, outcome and quality of the studies, and
 - 180 • the key issues which should be addressed in the application to substantiate the
181 health claim

182

183

¹ European Parliament and Council (2006). 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. Official Journal of the European Union OJ L 404, 30.12.2006. Corrigendum OJ L 12, 18.1.2007, p. 3–18.

184 **I. SCOPE**

185 The guidance presented in this document is for preparing and presenting applications for
186 authorisation of the health claims which fall under Article 14 of the Regulation, i.e.:
187 Reduction of disease risk claims and claims referring to children’s development and health.

188 • “Reduction of disease risk claim” means any health claim that states, suggests
189 or implies that the consumption of a food category, a food or its constituents
190 significantly reduces a risk factor in the development of a human disease.

191 • “For children’s claims”, there is no definition given in the Regulation.
192 Therefore the proposed health claims referring to children’s development and
193 health will be considered on a case by case basis, and once a definition is
194 available the guidance will be updated as appropriate.

195 It is intended that the guidance will be kept under review and will be amended and updated as
196 appropriate in the light of experience gained from evaluation of health claims applications.

197 This guidance will also be updated as appropriate at a later stage to cover applications for
198 authorisation of the health claims which fall under Article 18 of the Regulation, i.e.
199 applications for inclusion of health claims to the Community list of permitted claims provided
200 for in Article 13(3) which are based on newly developed scientific evidence and/or which
201 include a request for the protection of proprietary data.

202

203

204 **II. GENERAL PRINCIPLES**

205 This document should be read in conjunction with the Regulation (EC) N° 1924/2006 of the
206 European Parliament and of the Council on nutrition and health claims made on foods, and all
207 other pertinent elements outlined in available administrative guidance² and current and future
208 community guidelines and regulations.

209 1. The term “**food**” hereafter means a nutrient or other substance, or a combination of
210 nutrients/substances, or a food or a category of food, for which a health claim is made.

211 2. The term “**application**” hereafter means a stand-alone dossier containing the information
212 and the scientific data submitted for authorisation of the health claim in question.

213 3. It is the duty of the applicant to provide all of the available scientific data (including data
214 in favour and not in favour) that are pertinent to the health claim in order to demonstrate
215 that the health claim is substantiated by the totality of the scientific data and by weighing
216 the evidence. Assessors should not be required to consider other data that are not part of
217 the application, to undertake any additional literature reviews, or assemble, or process data
218 to evaluate the application. As such, the application substantiating a proposed health claim
219 should be comprehensive and complete. Each application will be considered on a case by
220 case basis.

221 4. This guidance presents a common format for the organisation of the information to assist
222 the applicant in the preparation of a well-structured dossier for applications that will be

² EFSA Pre-submission guidance for applicants intending to submit applications for authorisation of health claims (http://www.efsa.europa.eu/en/science/nda/Pre_submission_guidance.html)

- 223 submitted to EFSA for evaluation, so that EFSA can deliver scientific advice (i.e.
224 scientific Opinion) in an effective and consistent way.
- 225 5. To facilitate easy access to information and scientific data in applications and to help the
226 evaluator become quickly oriented to the application contents, information and data
227 should be presented in conformity with the format and requirements given in this
228 guidance document.
- 229 6. Not all the points included in this guidance document may apply to every case. In cases
230 where some of the data that are required as described in this guidance document do not
231 apply to a particular application, reasons/justification must be given for the absence of
232 such data in the application.
- 233 7. The application must contain information on the characteristics of the food for which a
234 claim is made. This information should contain aspects such as the manufacturing process,
235 composition, physical and chemical characteristics, stability, and bioavailability.
- 236 8. The application must contain a proposal for the wording of the health claim, including, as
237 appropriate, the specific conditions of use. The following should be specified, with a
238 rationale: the target population for the intended health claim; where appropriate, a
239 statement addressed to persons who should avoid using the food for which the health
240 claim is made; the quantity of the food and pattern of consumption required to obtain the
241 claimed beneficial effect, and whether this quantity could reasonably be consumed as part
242 of a balanced diet; a warning for foods that are likely to present a health risk if consumed
243 to excess; any other restrictions of use. The application should include examples of how
244 the claim will be presented, where the claim will be used, e.g. labelling, advertising, and a
245 rationale (and data if available) in support of consumer understanding of the health claim.
- 246 9. The application must contain all pertinent scientific data (published and unpublished,
247 including proprietary data) which form the basis for substantiation of the health claim.
248 Data from studies in humans will be required for substantiation of a health claim; because
249 of the scientific uncertainties in extrapolating non-human data to humans, data from
250 studies in animals or other model systems alone cannot substitute for human data to
251 substantiate the health claim but may be included only as supporting evidence, e.g. to
252 explain the mechanism underlying the health effect of the food.
- 253 10. A comprehensive review of the data from human studies pertaining to the specific food-
254 health relationship is required. This review, and the identification of data considered
255 pertinent to the claim, should be performed in a systematic and transparent manner in
256 order to demonstrate that the application reflects adequately the balance of all the
257 evidence available.
- 258 11. The data from intervention studies and observational studies in humans should be
259 organised according to a hierarchy of study designs, reflecting the relative strength of
260 evidence which may be obtained from different types of studies.
- 261 12. Data provided to substantiate a health claim should be of the quality expected from a peer-
262 reviewed journal.
- 263 13. As specified in the Regulation, health claims should be substantiated by taking into
264 account the totality of the available scientific data and by weighing the evidence, subject
265 to the specific conditions of use. In particular, the evidence should demonstrate the extent
266 to which:
- 267 (a) the claimed beneficial effect of the food is relevant for human health,

268 (b) a cause and effect relationship is established between the consumption of the food and
269 the health outcome in humans (including the strength, consistency, specificity, dose-
270 response, and biological plausibility of the relationship),

271 (c) the quantity of the food and pattern of consumption required to obtain the claimed
272 beneficial effect could reasonably be achieved as part of a balanced diet,

273 (d) the evidence obtained from the specific study group(s) can be generalised to the target
274 population for which the claim is intended.

275 14. The application in itself cannot be confidential. Sections considered as confidential by the
276 applicant should be kept to a minimum. As defined in the Regulation, EFSA will make
277 public the summary of the application upon its receipt. EFSA will also make public, once
278 adopted, its scientific Opinion on the data and information included in the application,
279 excluding those considered as confidential by the applicant.

280 15. One application should be prepared for each individual health claim; this means that only
281 a relationship between a food and **a single health outcome can be the object of each**
282 **application**. However, multiple formulations of a food can be proposed by the applicant
283 as candidates to bear the health claim in the same application, provided the scientific
284 evidence is valid for all proposed formulations of a food bearing that same health claim.

285

286 III. ORGANISATION AND CONTENT OF THE APPLICATION

287 The following information should be provided in the application and the structure should
288 follow a common format, i.e. **order and numbering system (particularly for the Parts,**
289 **their main heading and first and second sub-heading)**. Data provided in the application
290 should be organised into **five Parts** (see **Diagram 1**).

291 - **Part 1** contains the specific requirements for the administrative and technical data,
292 such as the application form, information related to the applicant(s) and the nature of
293 the application including its national and international status, health claim particulars,
294 the summary of the application, model health claim, and aspects related to consumer
295 understanding.

296 - **Part 2** contains information specific to the food and its characteristics (such as the
297 manufacturing process, composition, physical and chemical characteristics, stability,
298 and bioavailability data).

299 - **Part 3** contains summaries (the overall summary of pertinent human data and the
300 overall summary of pertinent non-human data) and overall conclusions, which follow
301 the scope and the outline of the body of scientific data identified under Part 4.

302 - **Part 4** contains all pertinent scientific data (published and unpublished including
303 proprietary data) identified that form the basis for substantiation of the health claim.

304 - **Part 5** comprises the glossary or abbreviations of terms quoted throughout different
305 Parts, including copy of reprints of those pertinent references identified, and study
306 reports.

307 Where requested information is not applicable or is not submitted on any of the points set out
308 below, justification should be given for any omission.

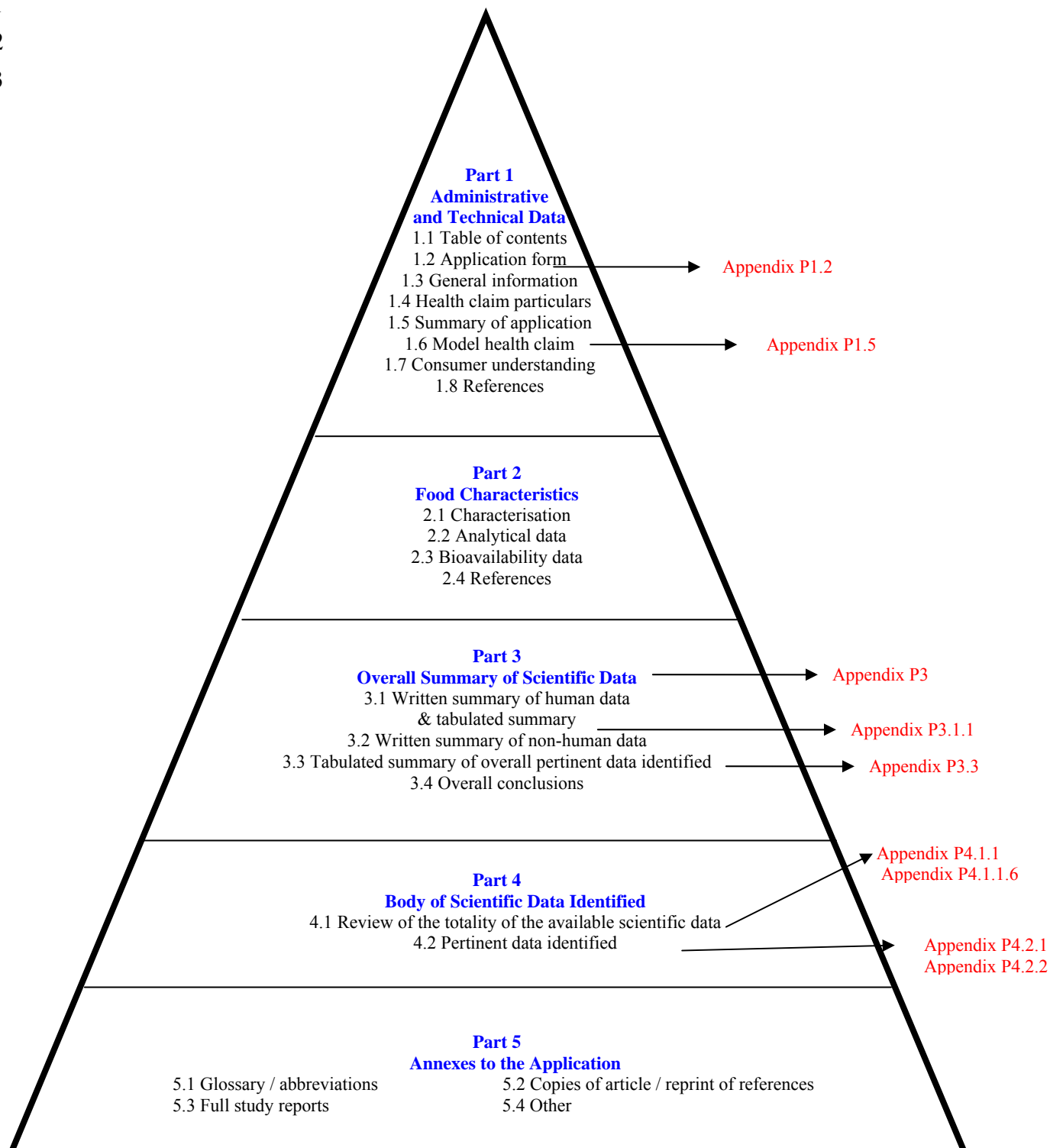
309 If a study appears under different Parts, cross-references should be given.

- 310 Acronyms and abbreviations should be defined the first time they are used, and should also be
311 listed in **Part 5.1**.
- 312 Any reference to published information, considered pertinent by the applicant after
313 performing the review of the data, should be accompanied in **Part 5.2** by full reprints, or
314 easily readable copies of such information.
- 315 Study reports of pertinent data (including proprietary data) should be enclosed in **Part 5.3**.
- 316 If available, scientific Opinions of national/international authorising body and relevant data
317 related to consumer understanding should be enclosed in **Part 5.4**.
- 318 Suggested steps for the preparation of the application are given below (**Diagram 2**).

319 **Diagram 1: Representation of the organisation of the application***

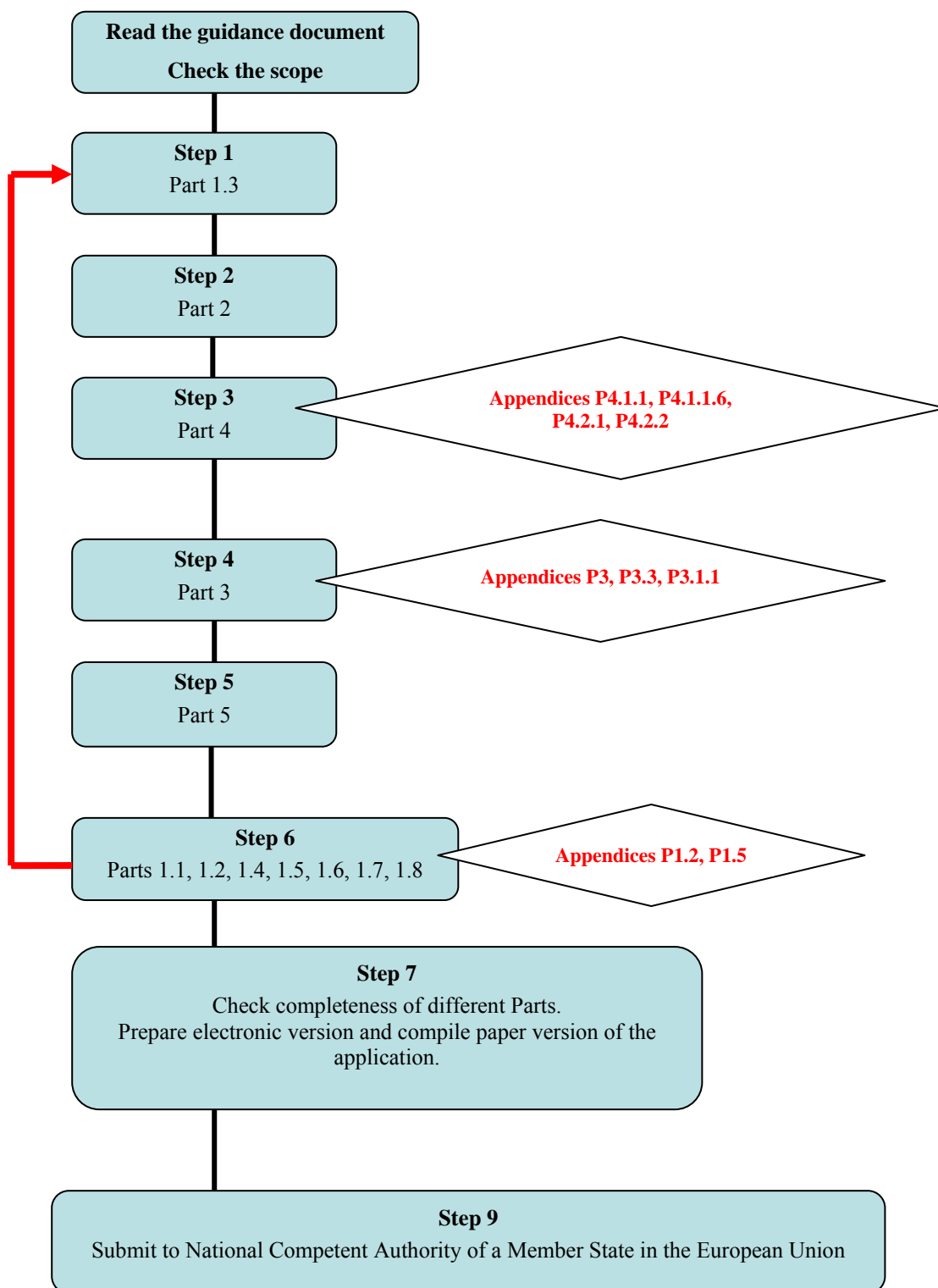
320 * The numbering of each Appendix corresponds to the related Part/Section of the guidance document.

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322
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Diagram 2: Suggested steps for the preparation of the application



327
328

329 **PART 1: ADMINISTRATIVE AND TECHNICAL DATA**

330 **1.1 Comprehensive table of contents of the application**

331 **1.2 Application form**

332 Please use the **Template provided in Appendix P1.2.**

333 **1.3 General information**

334 **1.3.1 Applicant**

335 1.3.1.1 Provide the name and address of the company or organisation:

336 1.3.1.2 Indicate the contact person authorised to communicate with
337 EFSA on behalf of the applicant:

338 To facilitate communication purposes, EFSA requires having
339 **only one contact person per application.**

340 **1.3.2 Nature of the application**

341 1.3.2.1 Application for authorisation of a health claim pursuant to Article 14 of the
342 Regulation

343 Indicate whether it is a disease risk reduction claim

344 If yes, please specify the health claim

345 Indicate whether it is referring to children's development and health

346 If yes, please specify the health claim

347 State whether it includes proprietary data

348 If yes, please specify & locate the related Part in the application,
349 section and page number:

350 Please provide verifiable justification/declaration

351 State whether it includes confidential data

352 If yes, please specify & locate the related Part in the application,
353 section and page number:

354 Please provide verifiable justification/declaration

355 **1.3.3 National and international status**

356 State whether approval for the health claim in this application has been already
357 sought through any regulatory body, either in or outside the European Union.
358 If so, please indicate the status of **each** application for the proposed health
359 claim (in case of submission to more than one regulatory body) as appropriate:

360 Under consideration

361 Provide the wording of the claim submitted, the date of
362 submission, the formulation and nutrient content of the food(s)
363 for which the claim has been submitted. Indicate the regulatory
364 body dealing with the application for authorisation.

365 Approved

366 Provide the wording of the claim approved, the date of
367 approval, the formulation and nutrient content of the food(s) for
368 which the claim has been approved. Indicate the regulatory
369 body authorising the health claim.

370 If possible, provide the scientific Opinion of the regulatory
371 body authorising the health claim (in Part 5.4).

372 Rejected

373 Provide the wording of the claim which was rejected, the date
374 of rejection and the reasons for rejection. Indicate the regulatory
375 body which rejected the health claim.

376 If possible, provide the scientific Opinion of the regulatory
377 body rejecting the health claim (in Part 5.4).

378 Withdrawn

379 Provide the wording of the claim that was withdrawn, the date
380 of submission, date of withdrawal and the reason for
381 withdrawal. Indicate the regulatory body evaluating the health
382 claim at the time of withdrawal.

383

384 **1.4 Health claim particulars**

385 *1.4.1 Specify the food (as defined in the General Principles) for which a health claim is*
386 *made*

387 *1.4.2 Describe the relationship between the food and the health claim*

388 *1.4.3 Provide a proposal for the wording of the health claim for which authorisation is*
389 *sought*

390 The proposed wording should be in English (For language requirement, please
391 refer to EFSA Pre-submission guidance for applicants intending to submit
392 applications for authorisation of health claims).

393 *1.4.4 Specify the target population for the intended health claim and provide a rationale*

394 Cross-referencing should be given for the scientific data provided in Parts 3
395 and 4 (i.e. study groups are representative of target group).

396 *1.4.5 Specific conditions of use:*

397 1.4.5.1 Provide, where appropriate, a statement addressed to the category(ies) of
398 population who should avoid using the food for which the health claim is
399 made, and include the rationale.

400 1.4.5.2 Indicate the quantity of the food and pattern of consumption required to obtain
401 the claimed beneficial effect, and whether this quantity could reasonable be
402 consumed as part of a balanced diet.

403 Provide a rationale, with cross-referencing to the scientific data provided in
404 Parts 3 and 4 (i.e. claimed effect observed with the amount of food and pattern
405 of consumption proposed).

406 1.4.5.3 Specify, where applicable, warning for foods that are likely to present a health
407 risk if consumed to excess, and provide a rationale.

408 1.4.5.4 Specify, where applicable, other restrictions of use, and provide a rationale.
409

410 **1.5 Summary of the application**

411 Please use the **Template provided in Appendix P1.5.**
412

413 **1.6 Model health claim**

414 *1.6.1 Provide a model health claim (mock-up), if available, that may be used for a food*

415 *1.6.2 Indicate where the health claim is intended to be used, as appropriate:*

- 416 Labelling
- 417 Brochure
- 418 Internet marketing directed at consumers
- 419 Expert documentation
- 420 Advertisements
- 421 Other forms of marketing, specify
422

423 **1.7 Consumer understanding**

424 *1.7.1 Rationale to support consumer understanding*

425 Provide here a supporting rationale.

426 *1.7.2 Indicate whether surveys on consumer understanding of the health claim have been*
427 *carried out*

428 Provide relevant data if available [in Part 5.4.](#)
429

430 **1.8 References**

431 References quoted under Part 1 should be given here (alphabetical order of
432 first authors).
433

434 **PART 2: FOOD CHARACTERISTICS**

435 **2.1 Characterisation**

436 *2.1.1 Characterise the nutrient or combination of nutrients and/or other substance for*
437 *which the health claim is made:*

438 This section is only applicable to the nutrient(s)/other substance intentionally
439 added to foods. Otherwise, go directly to Part 2.1.2.

440 *2.1.1.1 Name and general properties (i.e. physicochemical characterisation and other*
441 *relevant properties)*

- 442 2.1.1.2 Manufacturing process
443 Provide a brief overview and indicate whether the production is in compliance
444 with good manufacturing practice (GMP).
445 Provide specifications.
- 446 2.1.1.3 Stability information
447 Provide a brief summary of the studies undertaken (e.g. conditions, batches,
448 analytical procedures) and a brief summary of the results and conclusions of
449 the stability studies. Conclusions with respect to storage conditions and shelf-
450 life should be given.
451
- 452 2.1.2 *Characterise the food or category of food (i.e. the final product(s)) for which the*
453 *health claim is made:*
- 454 2.1.2.1 Composition and specifications of final product(s)
455 A description of the final product(s) and its composition, including
456 characterisation of the food matrix, should be provided.
- 457 2.1.2.2 Manufacturing process of the final product(s)
458 Provide a brief overview and indicate whether the production is in compliance
459 with good manufacturing practice (GMP).
- 460 2.1.2.3 Stability information
461 Provide a brief summary of the studies undertaken (e.g. conditions, batches,
462 analytical procedures) and a brief summary of the results and conclusions of
463 the stability studies. Conclusions with respect to storage conditions and shelf-
464 life should be given.
465
466
- 467 **2.2 *Analytical data***
468 Provide analytical data for the final product(s) for which the health claim is
469 made.
470 Using relevant analytical methods, investigations should focus especially on:
471 the determination of the content and the amount of the nutrient(s) (macro- and
472 micronutrients)/other substance(s), including the nutrient/combination of
473 nutrients/other substance for which the health claim is made, that are contained
474 in the final products determined in a representative number of samples of food
475 and covering the period up to the end of its shelf-life;
476 the variability of the nutrient(s) content from batch to batch (or from different
477 foods).
478 Analytical methods applied have to be valid/scientifically sound to ensure
479 quality and consistency of the data. The results of the validation studies must
480 be provided. Indicate whether the analytical study has been conducted in
481 compliance with relevant International Standards (e.g.: ISO 17025).
482

483 2.3 *Bioavailability data*

484 If available, provide the relevant data and/or a supporting rationale that the
485 food for which the health claim is made is in a form that is available to be used
486 by the human body (e.g.: absorption studies).

487 In the case where the food is not absorbed (e.g.: plant sterols, fibres, lactic acid
488 bacteria), provide if available the relevant data and/or a supporting rationale
489 that the food reaches the target site.

490 Any factors (e.g.: formulation, processing, other ingredients of the product)
491 that could impair the absorption or utilisation in the body of the food on which
492 a health claim is based should be provided, if available (e.g.: interaction
493 studies).

494

495 2.4 *References*

496 References quoted under [Part 2](#) should be given here (alphabetical order of
497 first authors).

498

499 **PART 3: OVERALL SUMMARY OF PERTINENT SCIENTIFIC DATA**

500 The overall summary is a summary that follows the scope and the outline of
501 the body of scientific data identified in Part 4. Provide the information in the
502 following order. See [Appendix P3](#) for guidance.

503

504 3.1 *Written summary of human data* [resulting from 4.2.1]

505 The written summary is intended to provide a factual summary of the human
506 data presented under Part 4.2.1 and which are deemed pertinent to the health
507 claim in the intended population. See [Appendix P3](#) for guidance.

508 3.1.1 *Tabulated summary of human data*

509 Use the **Templates provided under [Appendix P3.1.1](#)**.

510

511 3.2 *Written summary of non-human data* [resulting from 4.2.2]

512 This section should present an integrated summary of the pertinent non-human
513 studies identified or performed that support the claimed effect.

514

515 3.3 *Tabulated summary of overall pertinent data identified* [resulting from 4.2.1 516 and 4.2.2]

517 Use the **Templates provided under [Appendix P3.3](#)**.

518

519 3.4 *Overall conclusions*

520 The overall conclusions should clearly define the health effects of the food as
521 demonstrated by the totality of the data (including evidence in favour and not
522 in favour) and by weighing the evidence to arrive at logical, well-argued

523 conclusions substantiating the relationship between the food and the health
524 effect. In particular, the evidence should demonstrate the extent to which:

- 525 (a) the claimed beneficial effect of the food is relevant for human health,
526 (b) a cause and effect relationship is established between the consumption
527 of the food and the health outcome in humans (including the strength,
528 consistency, specificity, dose-response, and biological plausibility of
529 the relationship),
530 (c) the quantity of the food and pattern of consumption required to obtain
531 the claimed beneficial effect, and whether this quantity could
532 reasonably be consumed as part of a balanced diet,
533 (d) the evidence obtained from the specific study group(s) can be
534 generalised to the target population for which the claim is intended.

535

536 **PART 4: BODY OF PERTINENT SCIENTIFIC DATA IDENTIFIED**

537 Part 4 contains all pertinent scientific data (published and unpublished,
538 including proprietary data) which form the basis for substantiation of the
539 health claim.

540 Unpublished or proprietary data must be clearly indicated (see also **Part 1**, i.e.
541 1.3.2.1).

542 Studies with inconclusive or negative results must also be considered and
543 included.

544

545 **4.1 *Review of the totality of available scientific data***

546 All references identified and considered as pertinent after review should be
547 compiled and listed alphabetically under **Part 4.1.1.5**, and accompanied by
548 copies of article/reprint of references under **Part 5.2**. Full study reports for
549 unpublished studies should be annexed under **Part 5.3** and cross-reference
550 should be given.

551 In addition, these references should be presented as follow:

- 552 - They should be clustered and listed under **Part 4.2.1.4** if they are
553 related to human data
554 - They should be clustered and listed under **Part 4.2.2.1** if they are
555 related to non-human data

556 If a study appears under different Parts, cross-references should be given.

557

558 **4.1.1 *Processing a comprehensive review of human data***

559 For assistance in completing the required information below, please refer to the
560 guidance given under **Appendix P4.1.1 on Comprehensive Review of**
561 **Human Data**.

562 Please provide the following information:

- 563 4.1.1.1 Authorship
- 564 4.1.1.2 Background
- 565 4.1.1.3 Food-health relationship
- 566 4.1.1.4 Literature search
- 567 4.1.1.5 Identification of pertinent literature
- 568 List here all references identified (excluded and included) following the
569 comprehensive review. The list comprises those references selected, **which are**
570 **excluded** (by exclusion criteria) and **which are included** (by inclusion
571 criteria) and considered as pertinent for the food-health relationship (see also
572 **sections (ii) 5.1-5.2 of Appendix P4.1.1**).
- 573 4.1.1.6 Results of the comprehensive review
- 574 Please use the **Template provided in Appendix P4.1.1.6**.
- 575 In addition, go to Part 4.2 to organise the data which have been identified as
576 pertinent following the comprehensive review.
- 577
- 578 4.1.2 *Other pertinent data, including proprietary data*
- 579 Data not considered in the comprehensive review (i.e. unpublished data not
580 identified under 4.1.1.6) and considered as pertinent (including proprietary
581 data), should be mentioned here.
- 582 In addition, go to Part 4.2 to organise the data which have been identified
583 under Part 4.1.2.
- 584
- 585 **4.2** *Pertinent data identified*
- 586 Organise the data identified as pertinent (i.e. resulting from **4.1.1 and 4.1.2**) in
587 the following recommended order: human data, followed by non-human data if
588 appropriate.
- 589 For presentation of human data, please refer to **Appendix P4.2.1** for guidance.
- 590 For presentation of non-human data, please refer to **Appendix P4.2.2** for
591 guidance.
- 592 4.2.1 *Human data*
- 593 Classify human data in accordance with hierarchy of study design.
- 594 Individual studies should be presented using the **Templates provided in**
595 **Appendix P4.2.1 - Synopsis of individual human studies**.
- 596 4.2.1.1 Human intervention studies
- 597 Present each study by using the **Template provided in Appendix P4.2.1.1**.
- 598 4.2.1.1.1 Randomised controlled studies
- 599 4.2.1.1.2 Other randomised studies (non-controlled)
- 600 4.2.1.1.3 Controlled, non-randomised studies

- 601 4.2.1.1.4 Other intervention studies
- 602 4.2.1.2 Human observational studies
- 603 Present each study by using the **Template provided in Appendix P4.2.1.2.**
- 604 4.2.1.2.1 Cohort studies
- 605 4.2.1.2.2 Case-controlled studies
- 606 4.2.1.2.3 Cross-sectional studies
- 607 4.2.1.2.4 Other observational studies (e.g.: case reports)
- 608 4.2.1.3 Other
- 609 E.g.: Human studies dealing with the mechanisms by which the food could be
- 610 responsible for the health outcome. These studies also include those on
- 611 bioavailability (cross-reference should be given to Part 2.3, if appropriate).
- 612 4.2.1.4 List of references of the pertinent human data should be given (alphabetical
- 613 order of first authors)
- 614 Copies of article/reprint of references should be given under **Part 5.2.** Full
- 615 study reports for unpublished studies should be annexed under **Part 5.3** and
- 616 cross-reference should be given.
- 617
- 618 4.2.2 *Non-human data*
- 619 A brief and concise overview of individual studies should be provided. Please
- 620 refer to **Appendix P4.2.2** for guidance.
- 621 4.2.2.1 List of references related to pertinent non-human data should be given
- 622 (alphabetical order of first authors)
- 623 Copies of article/reprint of references should be under **Part 5.2.** Full study
- 624 reports for unpublished studies should be annexed under **Part 5.3** and cross-
- 625 reference should be given.
- 626
- 627 **PART 5: ANNEXES TO THE APPLICATION**
- 628 **5.1 Glossary / Abbreviations**
- 629 Used throughout different Parts. To be presented alphabetically.
- 630 **5.2 Copies of article/reprint of references**
- 631 • those considered as pertinent after the comprehensive review conducted
- 632 under Part 4.1.1
- 633 • those identified under Part 4.2.2.
- 634 **5.3 Full study reports**
- 635 Include here the full study reports identified under Part 4.1.2
- 636 **5.4 Other**
- 637 If available, include here e.g.:

- 638 • Scientific opinions of national/international authorising body if
639 available as referred to in Part 1.3.4.
- 640 • Relevant data following surveys of consumer understanding as referred
641 to in Part 1.5.2.

642

643

644 **REFERENCES**

645 Aggett PJ, Antoine JM, Asp NG, Bellisle F, Contor L, Cummings JH, Howlett J, Müller
646 DJG, Persin C, Pijls LTJ, Rechkemmer G, Tuijtelaars S, Verhagen H (2005). Process for the
647 Assessment of Scientific Support for Claims on Foods (PASSCLAIM): Consensus on criteria.
648 Eur J Nutr 44 (supplement 1): 5-30.

649 Food Standards Australia and New Zealand:

650 <http://www.foodstandards.gov.au/foodmatters/healthnutritionandrelatedclaims/index.cfm>

651 Health Canada:

652 http://www.hc-sc.gc.ca/fn-an/label-etiquet/nutrition/claims-reclam/index_e.html

653 SCF (Scientific Committee for Food) (2000). Guidelines of the Scientific Committee on Food
654 for the development of tolerable upper intake levels for vitamins and minerals. Opinion
655 expressed on 19 October 2000. http://ec.europa.eu/food/fs/sc/scf/out80_en.html

656 U.S. Food and Drug Administration:

657 <http://www.cfsan.fda.gov/~dms/lab-hlth.html>

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659

660 **PANEL MEMBERS**

661 Jean-Louis Bresson, Albert Flynn, Marina Heinonen, Karin Hulshof, Hannu Korhonen,
662 Pagona Lagiou, Martinus Løvik, Rosangela Marchelli, Ambroise Martin, Bevan Moseley,
663 Andreu Palou, Hildegard Przyrembel, Seppo Salminen, J (Sean) J Strain, Stephan Strobel,
664 Inge Tetens, Henk van den Berg, Hendrik van Loveren, and Hans Verhagen.

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668 **GLOSSARY AND ABBREVIATION USED IN THE GUIDANCE DOCUMENT**

669

Notes: The definitions given in this glossary are valid only for the purpose of this guidance document

Application	Means a stand-alone dossier containing the information and the scientific data submitted for authorisation of the health claim in question.
Bioavailability	Bioavailability of a nutrient relates to its absorption and may be defined as its accessibility to metabolic and physiological processes (SCF, 2000).
Food	Means a nutrient or other substance, or a combination of nutrients/substances, or a food or a category of food, for which a health claim is made.
Health claim	Any claim which states, suggests or implies that a relationship exists between a food category, a food or one of its constituents and health.
Nutrient	Means protein, carbohydrate, fat, fibre, sodium, vitamins and minerals listed in the Annex to Directive 90/496/EEC, and substances which belong to or are components of one of those categories (as defined in the Regulation (EC) No 1924/2006).
Other substance	A substance other than a nutrient that has a nutritional or physiological effect (as defined in the Regulation (EC) No 1924/2006).

670

671 **APPENDICES**

672

673 **Notes to users:**

- 674 • **Information requested in Appendices P1.2 and P1.5 are**
675 **mandatory. Applicants are advised to follow the instructions given**
676 **and use the Templates provided.**
- 677 • For the remaining Appendices: Instructions are given for guidance to
678 applicants. This guidance is intended to assist applicants in preparing
679 and presenting in a well-structured format pertinent data that have been
680 identified and acquired to substantiate the claimed effect and to
681 facilitate review and evaluation of the results.
- 682 • Please note that the numbering of each Appendix corresponds to the
683 related Part/Section of the guidance document (see Diagram 1).
- 684 • For preparation of the application, refer also to suggested steps in
685 Diagram 2.

686

687 **Content:**

688	Appendix P1.2	Application form [Mandatory]
689	Appendix P1.5	Summary of the application [Mandatory]
690	Appendix P3	Overall summary of scientific data
691	Appendix P3.1.1	Tabulated summary of human data
692	Appendix P3.3	Tabulated summary of overall pertinent data
693		identified by study type
694	Appendix P4.1.1	Comprehensive review of human data
695	Appendix P4.1.1.6	Template provided to display the results of the
696		review of human data
697	Appendix P4.2.1	Synopsis of individual human studies
698	Appendix P4.2.2	Guidance for presenting non-human data

699 ***APPENDIX P1.2 – APPLICATION FORM***

700 **(i) Instructions for use:**

701 To be completed by the applicant for inclusion under **Part 1.2**.

702 It is **mandatory** to use the Template under (ii) of this Appendix and to give the required
703 information.

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705 **(ii) Template (provided in the next page):**

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Template P1.2

APPLICATION FORM



The application form should be used for an application for authorisation of a health claim made on food(s) for human use submitted pursuant to Article 14 of the Regulation (EC) No 1924/2006 to (a) a Member State in the European Union and (b) for the scientific evaluation by the European Food Safety Authority (EFSA).

A separate application form for each health claim is required.
Information should be provided where appropriate.

DECLARATION and SIGNATURE

- Application pursuant to Article 14 of the Regulation (EC) No 1924/2006 submitted to:**
- <Specify the Member State’s Competent Authority>**
- Food¹ (specify, provide common name and brand name as appropriate):**
- Proposed wording of the health claim:**
- Applicant²:**
- Contact person³:**

It is hereby confirmed that all existing data which are relevant to the health claim authorisation have been supplied in the application, as appropriate.

On behalf of the applicant

Signature	_____
Name	_____
Function	_____
Place	_____
	date (yyyy-mm-dd) _____

¹ “**food**” means a nutrient or other substance, or a combination of nutrients/substances, or a food or a category of food, for which a health claim is made.

² In case more than one company or organisation submitting an application: provide their names and addresses. EFSA requires only one contact person authorised to communicate with EFSA.

³ To facilitate communication purposes, EFSA requires having **only one contact person per application**.

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1. GENERAL INFORMATION

1.1 APPLICANT

1.1.1 Applicant⁴:

(Company) Name:
Address:
Country:

1.1.2 Person authorised for communication on behalf of the applicant with EFSA during the procedure (Notes: To facilitate communication purposes, EFSA requires having only one contact person):

Name:
Company name:
Address:
Country:
Telephone:
Telefax:
E-Mail:

1.2 SCOPE

1.2.1 THIS APPLICATION CONCERNS:

APPLICATION PURSUANT TO ARTICLE 14 OF THE REGULATION (EC) 1924/2006

Please specify:

- Reduction of disease risk claim
 Claim referring to children's development and health

1.2.2 INDICATE WHETHER THE APPLICATION INCLUDES:

Proprietary data:	<input type="checkbox"/> Yes	<input type="checkbox"/> No
If yes, has verifiable justification/declaration been provided?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
If yes, has the proprietary data in the application been located?	<input type="checkbox"/> Yes	<input type="checkbox"/> No

⁴ In case more than one company or organisation submitting an application: provide their names and addresses.

781

Confidential data:	<input type="checkbox"/> Yes	<input type="checkbox"/> No
If yes, has verifiable justification/declaration been provided?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
If yes, has the confidential data in the application been located?	<input type="checkbox"/> Yes	<input type="checkbox"/> No

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783

1.3 NATIONAL AND INTERNATIONAL STATUS

784

785 State whether approval for the health claim in this application has been already sought
786 through any authorising body, either in or outside the European Union.

787

<input type="checkbox"/> Yes	<input type="checkbox"/> No	
If yes, specify the status:		
Under consideration:	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Approved:	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Rejected:	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Withdrawn:	<input type="checkbox"/> Yes	<input type="checkbox"/> No

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2. HEALTH CLAIM PARTICULARS

791

2.1 SPECIFY THE FOOD⁵

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2.2 DESCRIBE THE RELATIONSHIP BETWEEN THE FOOD AND THE HEALTH CLAIM

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2.3 PROPOSAL OF THE WORDING OF THE HEALTH CLAIM

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2.4 SPECIFY THE TARGET POPULATION FOR THE HEALTH CLAIM

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2.5 SPECIFY THE CONDITIONS OF USE

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⁵ “**food**” means a nutrient or other substance, or a combination of nutrients/substances, or a food or a category of food, for which a health claim is made.

807 **2.6 INDICATE WHETHER THE HEALTH CLAIM COMPLIES WITH:**

808

809 The general principles referred to in Art 3 of the Regulation (EC) No
810 1924/2006811 The general conditions referred to in Art 5 of the Regulation (EC) No
812 1924/2006813 The specific conditions referred to in Art 10 of the Regulation (EC) No
814 1924/2006

815

816 **3. MARKETING / PROMOTION STATUS**

817

- 818 Labelling
 819 Brochure
 820 Internet marketing directed at consumers
 821 Expert documentation
 822 Advertisements
 823 Other forms of marketing, specify:

824

825

826 **4. CONSUMER UNDERSTANDING**

827

828 **4.1 INDICATE WHETHER SUPPORTING RATIONALE IS PROVIDED**

829

Yes No

830

831 **4.2 INDICATE WHETHER SURVEYS ON CONSUMER UNDERSTANDING HAVE BEEN
832 CARRIED OUT**

833

Yes No

834

835

836 **5. CONTENT OF THE APPLICATION**

837

838 Please provide the below information:

	Is the object of the application for a single health outcome only?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Parts/sections of the application:			
2.1.1	Has the nutrient or combination of nutrients and/or other substances for which the health claim is made been characterised?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
2.1.2	Has the food or category of food (i.e. the final product(s)) for which the health claim is made been characterised?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
2.2	Have analytical data for the final product for which the health claim is made been provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
2.3	Have relevant data and / or a supporting rationale that the food for which the health claim is made is in a form available to be used by	Yes <input type="checkbox"/>	No <input type="checkbox"/>

	the body been provided?		
3.1	Has a written summary of human data been provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
3.1.1	Has a tabulated summary of human data been provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
3.2	Has a written summary of non-human data been provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
3.3	Has a tabulated summary of overall pertinent data identified been provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
3.4	Have the overall conclusions clearly defining the health effects of the food as demonstrated by the totality of the data and weighing of the evidence been provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
4.1.1	Has the totality of the available scientific data been reviewed comprehensively?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
4.1.2	Has any proprietary data been identified?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
4.2	Have all pertinent data been identified?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
4.2.1.1	Are pertinent data coming from human intervention studies?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
4.2.1.2	Are pertinent data coming from human observational studies?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
4.2.2	Have any pertinent non-human data been identified?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Templates provided in the Appendices:			
P 1.2	Has the application form been provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
P1.5	Has the summary of the application been provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
P 3.1.1a	Has the tabulated summary of intervention studies in humans been provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
P 3.1.1b	Has the tabulated summary of observational studies in humans been provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
P 3.3	Has the tabulated summary of overall pertinent data identified by study type been provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
P 4.1.1.6	Have the tabulated results of the review of human data been provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
P 4.2.1.1	Has a synopsis of each human intervention study been provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
P 4.2.1.2	Has a synopsis of each human observational study been provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
	Is there sufficient evidence that the claimed beneficial effect of the food is relevant for human health?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
	Is there sufficient evidence that a cause and effect relationship is established between the consumption of the food and the health outcome in humans (including the strength, consistency, specificity, dose-response, and biological plausibility of the relationship)?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
	Is there sufficient evidence that the quantity of the food and pattern of consumption required to obtain the claimed beneficial	Yes <input type="checkbox"/>	No <input type="checkbox"/>

	effect could reasonably be achieved as part of a balanced diet?		
	Is there sufficient evidence that the study group(s) in which the evidence was obtained is representative of the target population for which the health claim is intended?	Yes <input type="checkbox"/>	No <input type="checkbox"/>

839

840

841

842

843 ***APPENDIX P1.5 – SUMMARY OF THE APPLICATION***

844 According to Articles 15(2b) and 15(3g) of the Regulation, the application shall be
845 accompanied by a Summary of the application, and EFSA shall make the Summary of the
846 application available to the public.

847 **(i) Instructions for use:**

848 To be completed by the applicant for inclusion under **Part 1.5**.

849 The Summary of the application should be presented in a standardised form. The language
850 used should be English. It shall be presented in an easily comprehensible and legible form. It
851 should be brief and concise. An electronic version of the Summary of the Application should
852 be provided.

853 The Summary of the Application should not contain parts which are considered to be
854 confidential as it will be published on the EFSA Website following receipt of the application
855 from a National Competent Authority of a Member State.

856 It is **mandatory** to use the Template provided under (ii) of this Appendix and to give the
857 required information.

858

859 **(ii) Template (provided in the next page):**

860

861 Template P1.5

862 **SUMMARY OF THE APPLICATION**



864 The Template provided should be used for the Summary for the application for
865 authorisation of a health claim made on food(s) for human use submitted pursuant to
866 Article 14 of the Regulation (EC) No 1924/2006 to (a) a Member State in the European
867 Union and (b) for the scientific evaluation by the European Food Safety Authority (EFSA).

868 Information should be provided where appropriate.

869 **1. GENERAL INFORMATION**

870
871 **1.1 APPLICANT**

872 **Applicant¹:**

873 (Company) Name:

874 Address:

875 Country:

876
877
878 **1.2 SCOPE**

879 **THIS APPLICATION CONCERNS:**

880 APPLICATION PURSUANT TO ARTICLE 14 OF THE REGULATION (EC)
881 1924/2006

882 **Please specify:**

883 Reduction of disease risk claim

884 Claim referring to children's development and health

885
886 **1.3 MEMBER STATE OF APPLICATION**

887 <Specify the Member State's Competent Authority>

888
889 **1.4 NATIONAL AND INTERNATIONAL STATUS**

890 State whether approval for the health claim in this application has been already sought
891 through any authorising body, either in or outside the European Union.

892 Yes No

¹ In case more than one company or organisation submitting an application: provide their names and addresses.

If yes, specify the status:			
Under consideration:	<input type="checkbox"/>	Yes	<input type="checkbox"/> No
Approved:	<input type="checkbox"/>	Yes	<input type="checkbox"/> No
Rejected:	<input type="checkbox"/>	Yes	<input type="checkbox"/> No
Withdrawn:	<input type="checkbox"/>	Yes	<input type="checkbox"/> No

893

894 **2. HEALTH CLAIM PARTICULARS**

895 **2.1 SPECIFY THE FOOD²**

896

897 **2.2 DESCRIBE THE RELATIONSHIP BETWEEN THE FOOD AND THE HEALTH CLAIM**

898

899 **2.3 PROPOSAL OF THE WORDING OF THE HEALTH CLAIM**

900

901 **2.4 SPECIFY THE TARGET POPULATION FOR THE HEALTH CLAIM**

902

903 **2.5 SPECIFY THE CONDITIONS OF USE**

904

905 **3. CONSUMER UNDERSTANDING**

906 **SUMMARISE SUPPORTING RATIONALE, AND/OR RELEVANT DATA IF AVAILABLE**

<NOTES: Filling of this section should not exceed 550 words (~ 3500 characters with spaces>

907

908 **4. FOOD CHARACTERISTICS**

909 *<NOTES: Filling of the sections 4.1 to 4.3 should not exceed 1100 words (~ 7000 characters with spaces>*

910

911 **4.1 CHARACTERISATION**

The nutrient or combination of nutrients and/or other substance – intentionally

² “**food**” means a nutrient or other substance, or a combination of nutrients/substances, or a food or a category of food, for which a health claim is made.

added to foods – for which the health claim is made:
The food or category of food for which the health claim is made:

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913

4.2 SUMMARISE RELEVANT ANALYTICAL INFORMATION

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916

4.3 SUMMARISE RELEVANT INFORMATION AND/OR SUPPORTING RATIONALE ON BIOAVAILABILITY

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917

5. SCIENTIFIC SUBSTANTIATION OF THE HEALTH CLAIM

918 As specified in the Regulation, health claims should be substantiated by taking into account
919 the totality of the available scientific data and by weighing the evidence, subject to the
920 specific conditions of use.
921

SUMMARISE TO WHICH EXTENT:

922 *<NOTES: Filling of the sections 5.1 to 5.4 should not exceed 1100 words (~ 7000 characters*
923 *with spaces>*
924

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5.1 THE CLAIMED BENEFICIAL EFFECT OF THE FOOD IS RELEVANT FOR HUMAN HEALTH

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5.2 A CAUSAL AND EFFECT RELATIONSHIP IS ESTABLISHED BETWEEN THE CONSUMPTION OF THE FOOD AND THE HEALTH OUTCOME IN HUMANS (INCLUDING THE STRENGTH, CONSISTENCY, SPECIFICITY, DOSE-RESPONSE, AND BIOLOGICAL PLAUSIBILITY OF THE RELATIONSHIP)

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5.3 THE QUANTITY OF THE FOOD AND THE PATTERN OF CONSUMPTION REQUIRED TO OBTAIN THE CLAIMED BENEFICIAL EFFECT COULD REASONABLY BE ACHIEVED AS PART OF A BALANCED DIET

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937
938
939

5.4 THE EVIDENCE OBTAINED FROM THE SPECIFIC STUDY GROUP(S) CAN BE GENERALISED TO THE TARGET POPULATION FOR WHICH THE CLAIM IS INTENDED

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940

941 **APPENDIX P3 – OVERALL SUMMARY OF SCIENTIFIC DATA**

942 **(i) Instructions for use:**

943 This guidance is applicable to **Part 3** and is intended to assist applicants in summarising the
944 scientific data that have been acquired under Part 4.2.

945 Therefore, it is advisable to start with the preparation and completion of Part 4 prior to
946 starting Part 3.

947

948 **(ii) General principles:**

949 The overall summary is intended to provide a summary of all the pertinent scientific data
950 identified in Part 4.2, and which form the basis for the substantiation of the health claim. The
951 summary of the data identified should establish that the relationship between the food and the
952 health claim is substantiated by the totality of the scientific data and by weighing the
953 evidence.

954

955 **(iii) Sequence of information:**

956 The overall summary of the totality of pertinent data identified (including the data in favour
957 and the data not in favour) should be presented in the following order:

- 958 • *Written summary of human data*
- 959 • *Tabulated summary of human data*
- 960 • *Written summary of non-human data*
- 961 • *Tabulated summary of overall pertinent data identified*
- 962 • *Overall conclusions*

963

964 **Written summary for human data**

965 This section is applicable to **Part 3.1**.

966 The written summary is intended to provide a summary of the human data presented under
967 Part 4.2.1. The summary should include pertinent information resulting from the
968 comprehensive review, including unpublished or proprietary data. Cross-referencing to more
969 detailed presentations provided in Part 4.2.1 is encouraged.

970 The results from all pertinent studies, including studies with inconclusive or negative results,
971 which were considered for evaluation of the health claim should be summarised as follows,
972 quoting the appropriate references identified in section 4.2 when needed:

973 **First, the relationship** between the consumption of the food and the claimed health outcome
974 **should be characterised** by considering, i.e.:

- 975 ➤ the magnitude of the effect and its physiological relevance,
- 976 ➤ the study population in which the effect has been observed and whether a
977 broader generalisation of the results to the target population is possible,
- 978 ➤ the conditions under which the effect has been achieved or observed
979 (metabolic room, clinical setting, free-living subjects, etc.),
- 980 ➤ the sustainability of such effect over time,

981 ➤ the amount of food used to achieve the effect, the usual intakes of food in the
982 target population and whether these amounts could be reasonable consumed as
983 part of a healthy diet.

984 **Second**, to what extent the data substantiate **a causal relationship** between the consumption
985 of the food and the claimed health outcome should be addressed by considering:

- 986 ➤ the consistency of results across studies,
- 987 ➤ the magnitude of the effect, its statistical significance, the presence/absence of
988 equally strong evidence, neutral or against,
- 989 ➤ if available, an effective dose.
- 990 ➤ Elements to be considered are the biological plausibility, alternate explanations
991 for the observed effect and the specificity of the cause-effect relationship.

992

993 **Tabulated summary for human data**

994 This section is applicable to **Part 3.1.1**. Please use the Templates and follow the guidance
995 provided in **Appendix P3.1.1**.

996

997 **Written summary for non-human data**

998 This section is applicable to **Part 3.2**. It is recommended to complete the Overview of
999 individual non-human studies presented in Part 4.2.2 prior to starting the Written Summary
1000 required in Part 3.2. The written summary is intended to provide an overall integrated
1001 summary of the non-human data presented under Part 4.2.2

1002 The results from all pertinent studies considered to support the health claim, should be
1003 summarised, and should be arranged in a logical order so that all relevant data elucidating a
1004 certain effect are brought together.

1005 Cross-referencing to more detailed information provided in **Part 4.2.2** should be given.

1006

1007 **Tabulated summary of overall pertinent data identified**

1008 This section is applicable to **Part 3.3** and is based on the human data presented under Part
1009 4.2.1 and includes non-human data presented under Part 4.2.2.

1010 Please use the Template provided in the **Appendix P3.3**.

1011

1012 **Overall conclusions**

1013 This section is applicable to **Part 3.4**.

1014 The overall conclusions should clearly define how and to what extent human data are
1015 supported by other available data. Any important limitations of the studies presented should
1016 be discussed here.

1017 **The analyses provided in previous sections should not be reiterated here. This section**
1018 **can be brief**, but it should clearly define the health effects of the food as demonstrated by the
1019 totality of the data (including evidence in favour and not in favour) and by weighing the
1020 evidence to arrive at logical, well-argued conclusions substantiating the relationship between
1021 the food and the health effect.

1022 **APPENDIX P3.1.1 – TABULATED SUMMARY FOR HUMAN DATA**1023 **(i) Instructions for use:**1024 This guidance is applicable to **Part 3.1.1**.1025 It is advisable to start with the preparation and completion of Part 4.2.1 prior to preparing Part
1026 3.1.1.1027 It is advisable to use the Templates below as appropriate: **Appendix P3.1.1.a** for human
1028 intervention studies and **Appendix P3.1.1.b** for observational studies.

1029

1030 **(ii) Appendix P3.1.1.a - Template provided for “Tabulated summary of**
1031 **intervention studies in humans”**1032 **1.** Provide a table summarising the results of human intervention studies for the health
1033 outcome. If more than one intervention (i.e. different doses of food) is reported in the same
1034 study, use more than one line for that study indicating which intervention group is being
1035 considered (see table below as an example). List intervention studies by hierarchy of study
1036 design as follows: randomised controlled studies, other randomised studies (non-controlled),
1037 controlled non-randomised studies, other intervention studies.

1038

1039 Outcome:

Studies*	Intervention**	Intervention n/N	Control n/N	RR (95%CI)	Cross-reference to relevant sections within Parts 4 and 5
Study 1	Intervention 1				
Study 1	Intervention 2				
Study 2					
Study <i>n</i>					

1040 **Indicate first author and publication year.*1041 *** To be filled only for studies with more than one intervention groups*1042 *RR (95%CI) = Relative risk (95% confidence interval)*

1043

1044 **2.** If possible, provide a graphical analysis (e.g. forest plot) summarising the results of human
1045 intervention studies for the health outcome. Specify whether the graphical analysis is
1046 presented:

1047 a. Without meta-analysis

1048 b. With meta-analysis (fixed effect model)

1049 c. With meta-analysis (random effects model)

1050

1051 In cases b. and c., where a metaanalysis of the studies is identified/performed, the
1052 protocol followed in conducting the analysis should be clearly detailed.

1053

1054 **3.** If available, published pooled analyses or meta-analyses of human intervention studies
 1055 should be presented here (in **Part 3.1.1**), indicating the source and the protocol used to
 1056 conduct the meta-analysis, and summarising the relevant results. A full report, if available,
 1057 should be annexed under **Part 5.2**, and cross-reference should be given.

1058

1059 **(iii) Appendix P3.1.1.b - Template provided for “Tabulated summary of human**
 1060 **observational studies”**

1061 **1.** Provide a table summarising the results of observational studies for the health outcome. If
 1062 more than one level of exposure (i.e. different doses of food) is reported in the same study,
 1063 use more than one line for that study indicating which exposure group is being considered
 1064 (see table below as an example). List observational studies by hierarchy as follows: cohort
 1065 studies, case-control studies, cross-sectional studies, other observational studies.

1066

1067 Outcome:

Studies*	Exposure**	Exposure n/N	Control n/N	OR (95%CI)	Cross-reference to relevant sections within Parts 4 and 5
Study 1	Exposure 1				
Study 1	Exposure 2				
Study 2					
Study <i>n</i>					

1068 **Indicate first author and publication year.*1069 *** To be filled only for studies with more than one level of exposure*1070 *OR (95%CI) = Odd ratio (95% confidence interval)*

1071

1072 **2.** If possible, provide a graphical analysis (e.g. forest plot) summarising the results of
 1073 observational studies for the health outcome. Specify whether the graphical analysis is
 1074 presented:

- 1075 a. Without meta-analysis
 1076 b. With meta-analysis (fixed effect model)
 1077 c. With meta-analysis (random effects model)

1078
 1079 In cases b. and c., where a meta-analysis of the studies is identified/performed, the
 1080 protocol followed in conducting the analysis should be clearly detailed.

1081

1082 **3.** If available, published pooled analyses or meta-analyses of observational studies should be
 1083 presented here (in **Part 3.1.1**), indicating the source and the protocol used to conduct the
 1084 meta-analysis, and summarising the relevant results. A full report, if available, should be
 1085 annexed under **Part 5.2**, and cross-reference should be given.

1086 **APPENDIX P3.3 – TABULATED SUMMARY OF OVERALL PERTINENT DATA**1087 **(i) Instructions for use:**1088 This guidance is applicable to **Part 3.3**.1089 It is advisable to start with the preparation and completion of Parts 4.2.1 and 4.2.2 prior to
1090 preparing Part 3.3. Please use the Template below under (ii).1091
1092 **(ii) Appendix P3.3 - Template provided for “Tabulated summary of overall pertinent
1093 data identified by study type”**1094 To be completed by the applicant for inclusion under **Part 3.3**. Individual studies included in
1095 any meta-analysis should be presented separately.

1096

Study type	Number of pertinent studies	Cross-reference to relevant sections within Parts 4 and 5
1. Human studies¹ (Total 1.1 to 1.4)		
1.1 Experimental intervention studies (Total a to c)		
a. RCT (full randomisation ²)		
b. RCT (concealed allocation)		
c. RT (non-controlled)		
1.2 Quasi-experimental intervention studies (Total a+b)		
a. Non-randomised, controlled		
b. Non-randomised, non-controlled		
1.3 Observational studies (Total a to d)		
a. Cohort studies		
b. Case-control studies		
c. Cross-sectional studies		
d. Other (e.g. Case reports)		
1.4 Other ³		
2. Non-human studies (Total 2.1 to 2.3)		
2.1 Animal studies ⁴		
2.2 <i>ex vivo/in vitro</i> studies ⁵		
2.3 Other ⁶		
Total (1 + 2)		

1097 *RCTs = Randomised controlled trials*1098 *RT = Randomised trials*1099
1100 ¹ Human studies dealing with the effect of the food on the health outcome.1101 ² Method of randomisation reported as coin toss, computer generated numbers, random number tables or similar.1102 ³ Human studies dealing with the mechanisms by which the food could be responsible for the health outcome
1103 (mechanistic studies), or studies on bioavailability.1104 ⁴ Animal studies dealing with e.g.: the mechanisms by which the food could be responsible for the health
1105 outcome (mechanistic studies), including studies on bioavailability.1106 ⁵ These include: *ex vivo* and *in vitro* studies based on either human or animal biological samples.1107 ⁶ Studies reporting any combination of the above or non classifiable among the above.

1108

1109

1110 **Do not include numbers in grey rows in totals of columns. Several cells in the above table might not be
1111 applicable.**

1112 ***APPENDIX P4.1.1 – COMPREHENSIVE REVIEW OF HUMAN DATA***

1113

1114 **(i) Instructions for use**

1115 This guidance is applicable to **Part 4.1.1**. Applicants are advised to read this carefully to
1116 complete Part 4.1.1.

1117 It is intended to assist applicants in conducting a comprehensive review of the totality of
1118 scientific data in a systematic and transparent manner in order to identify the pertinent human
1119 data to substantiate the claimed effect.

1120

1121 **(ii) Information required in Part 4.1.1 when conducting a comprehensive review of**
1122 **the totality of scientific data:**

1123 To be completed by the applicant and presented under Part 4.1.1:

1124 **1. Authorship.** Name, affiliation, conflict of interests' declaration and signature of the
1125 reviewer(s) responsible for the comprehensive review.

1126 **2. Background**

1127 2.1. Define the nutrient(s)/substance/food/food category relevant to the effect for which a
1128 health claim is made

1129 2.2. Define the health outcome relevant to the effect for which a health claim is made

1130 2.3. In case of a health outcome that cannot be measured directly, define any marker(s)
1131 being selected as surrogate of the health outcome, if any, e.g.: plasma cholesterol
1132 concentrations being used as marker of cardiovascular disease risk, bone density
1133 being used as marker of osteoporosis risk, etc.

1134 2.4. Provide information and a rationale for selecting the above marker(s) of health
1135 function (if any) as surrogate for the health outcome in point 2.2. State their relevance
1136 to the health claim. For both endpoints and markers of health outcome, state whether
1137 they are methodologically valid with respect to their analytical characteristics.

1138 **3. Brief description of the hypothesis tested, i.e.: Food-health relationship**

1139 **4. Literature search**

1140 4.1. List of electronic databases searched

1141 4.1.1. General Health and Medical databases

1142 4.1.2. Selected databases with a specific focus

1143 4.1.3. Research registers

1144 4.1.4. Review registers

1145 4.1.5. Other

1146 4.2. Search strategy

1147 4.2.1. Standard search terms (and combination of terms) used.

1148 4.2.2. Additional search terms (for databases not allowing complex search strategies)

- 1149 4.2.3. Search limits. Specify whether (and which) search limits were used, if any.
- 1150 a. Dates of publication.
- 1151 b. Publication type
- 1152 c. Language
- 1153 d. Population subgroup (s)
- 1154 e. Default tag (Title, Abstract, Full text, other)
- 1155 f. Other
- 1156 4.2.4. Website searches (for relevant organisations publishing reviews /guidelines
- 1157 /consensus opinions relevant to the topic).
- 1158 4.2.5. Hand searching and grey literature. Specify what efforts were made to obtain
- 1159 scientific data that are not indexed in the major electronic databases.
- 1160 4.3. Identify when the search was performed
- 1161 **5. Identification of pertinent literature**
- 1162 5.1. Detailed **exclusion and inclusion criteria** applied to select pertinent references with
- 1163 clear identification of the references excluded by each exclusion criteria either before
- 1164 or after evaluation of the full text.
- 1165 5.2. List of all references identified potentially pertinent to the topic. Indicate author(s),
- 1166 title, journal/book/other, publication year, volume, pages. For book and book chapters
- 1167 indicate also editor, publisher and city.
- 1168 **Important notice:**
- 1169 a. Journal abstracts and articles published in newspapers, magazines, newsletters or
- 1170 handouts that have not been peer-reviewed **should not** be cited.
- 1171 b. Books or chapters of books for consumers or the general public **should not** be cited.

1172 **APPENDIX P4.1.1.6 – TEMPLATE PROVIDED TO DISPLAY THE RESULTS OF THE**
 1173 **REVIEW OF HUMAN DATA**

1174 **“Number of pertinent references identified by publication type”**

1175 To be completed by the applicant for inclusion under **Part 4.1.1.6**.
 1176
 1177

Publication type	Number of pertinent publications
Human data¹ (Total 1 to 8)	
1 Original research (Total a+b)	
a. Intervention studies	
b. Observational studies	
2 Pooled analysis of human intervention studies	
3 Meta-analysis of human intervention studies	
4 Pooled analysis of human observational studies	
5 Meta-analysis of human observational studies	
6 Review articles	
7 Guidelines/consensus opinions/text book chapters	
8 Other ²	

1178
 1179 ¹ Articles reporting Human studies dealing with the effect of the food on the health outcome underlying the
 1180 claim.
 1181 ² Articles reporting Human studies dealing with the mechanisms by which the food could be responsible for the
 1182 health outcome (mechanistic studies), or studies on bioavailability.
 1183

1184 **Do not include numbers in grey rows in total of columns. Some cells in the above table might not be**
 1185 **applicable.**

1186 **APPENDIX P4.2.1 – SYNOPSIS OF INDIVIDUAL HUMAN STUDIES**1187 **(i) Instructions for use:**

1188 Applicants are advised to use the following Templates for presenting the synopsis of
1189 individual human studies requested under **Part 4.2.1**.

1190 For human intervention studies (randomised controlled, randomised non-controlled, and
1191 controlled non-randomised studies), go to (ii)-**Appendix P4.2.1.1**.

1192 For human observational studies, go to (iii)-**Appendix P4.2.1.2**.

1193

1194 **(ii) Appendix P4.2.1.1: Template provided for “Synopsis of each human intervention
1195 study”**

1196 Please provide one synopsis for each study.

1197 To be included under **Part 4.2.1.1**.

1198 **1. Identification of the study**

1199 1.1. Authors:

1200 1.2. Article title:

1201 1.3. Source (journal, conference, etc.) Year/Volume/pages/Country of origin:

1202 1.4. Institutional affiliation (first author) and/or contact address:

1203 1.5. Conflict(s) of interest declared:

1204 1.6. Good Clinical Practice status / ethical consideration:

1205 **2. Report status.** Please check as appropriate:1206 Published Unpublished

1207 **3. Verification of study eligibility** (check if the intervention study meets inclusion criteria defined in 5.1 of
1208 the Appendix P4.1.1 on Comprehensive Review of Human Data):

1209 **4. Description of the study population**

1210 4.1. Population subgroup (if not general population):

1211 4.2. Age range:

1212 4.3. Sex:

1213 4.4. Ethnicity:

1214 4.5. Inclusion criteria:

1215 4.6. Exclusion criteria:

1216 4.7. Setting:

1217 4.8. Geographical region:

1218 **5. Study design:**

1219 5.1. Design: randomised controlled trials, cross-over studies, other.

1220 5.2. Intervention arm(s): *(fill boxes below as appropriate. Use N/A when not applicable)*

1221

	Food	Food matrix, if applicable	Daily intake (nutrient(s)/substance)	Daily intake (food/food category, if applicable)	Duration of intervention
Intervention 1 = control					
Intervention 2					
Intervention <i>n</i>					

1222

1223 5.3. Number of subjects allocated to each intervention arm:

1224 5.4. Primary outcome: State the variable used for power calculations, if any.

1225 5.5. Secondary outcome(s): variable 1, variable 2, variable *n*

1226 5.6. Comparability of subjects between study groups (arms) at baseline. Variables checked for: variable 1,
1227 variable 2, variable *n*

1228 **6. Study outcomes:**

1229 6.1. Duration of follow-up:

1230 6.2. Drop outs by intervention arm (including controls, if applicable):

1231 6.3. Adverse effects in the control and intervention arms, if any reported:

1232 6.4. Pre-test and post-test values (means/medians \pm SD/SEM/interquartile ranges), mean differences (\pm
1233 SD/SEM/95%CI) for primary/secondary outcomes, and statistical significance of the results.
1234

Variable 1	Pre-test	Post-test	Mean difference	P-1*	P-2**
Controls					
Intervention 1					
Intervention 2					
Intervention <i>n</i>					
Variable 2	Pre-test	Post-test	Mean difference	P-1*	P-2**
Controls					
Intervention 1					
Intervention 2					
Intervention <i>n</i>					

1235 Values are expressed as: (state means/medians \pm SD/SEM/interquartile ranges/95%CIs, as
1236 appropriate)

1237 * **P-1**= Significance for changes in the variable considered during each treatment.

1238 ****P-2** = Significance for changes in the variable considered during each treatment **as compared to**
1239 **the control group.**

1240 6.5. Address the biological relevance of the results.

1241

1242 **7. Study quality.** Please check the appropriate columns in the table below

	Yes	Partially	No	Unknown	N/A ¹
1. Power calculations performed					
2. Baseline characteristics of subjects reported					
3. Subjects inclusion and exclusion criteria specified					
2. Information on background dietary habits provided					
3. Information on physical activity provided					
4. Information on smoking/alcohol drinking provided					
5. Information on medication use provided					
6. Information on other risk factors provided					
7. Randomisation					
a. Random sequence generation					
b. Treatment allocation concealed					
8. Control and intervention(s) group(s) comparable at baseline for relevant risk factors/outcome variables.					
9. Blinding of subjects					
10. Blinding of care givers ²					
11. Blinding of outcome assessors ³					
12. Compliance of subjects with the intervention reported					
13. Duration of intervention(s) adequate to test the hypothesis					
14. Point estimates and variability of main outcome variable reported.					
15. Endpoints/Markers of health outcome(s) validated analytically					
16. Endpoint/Markers of health outcome(s) validated biologically					
17. Analyses include an intention to treat analysis					
18. Adjustment for potential confounders performed					

1243 ¹ N/A=Not applicable

1244 ² Appropriate placebo available
 1245 ³ Investigators in charge of assigning laboratory values and of evaluating complementary exams (ECG,
 1246 ultrasounds, etc.) blinded to subjects' allocation arm.
 1247

1248 **8. Conclusions** (15 lines maximum)

1249

1250

1251 **(iii) Appendix P4.2.1.2: Template provided for “Synopsis of each observational**
 1252 **human study”**

1253 Please provide one synopsis for each study.

1254 To be included under **Part 4.2.1.2.**

1255 **1. Identification of the study**

1256 1.1. Authors:

1257 1.2. Article title:

1258 1.3. Source (journal, conference, etc.) Year/Volume/pages/Country of origin:

1259 1.4. Institutional affiliation (first author) and/or contact address:

1260 1.5. Conflict(s) of interest declared:

1261 1.6. Good Epidemiological Practice status / ethical consideration:

1262 **2. Report status.** Please check as appropriate:

1263 Published Unpublished

1264 **3. Verification of study eligibility (check if observational study meets inclusion criteria):**

1265 **4. Description of the population**

1266 4.1. Population subgroup (if not general population):

1267 4.2. Age range(s):

1268 4.3. Sex:

1269 4.4. Ethnicity:

1270 4.5. Inclusion criteria (for cases and controls, if appropriate):

1271 4.6. Exclusion criteria (for cases and controls, if appropriate):

1272 4.7. Recruitment procedures used (consecutive, arbitrary, unreported, other):

1273 4.8. Setting(s):

1274 4.9. Geographical region(s):

1275 **5. Study design:**

1276 5.1. Design: cohort, case-control, case-reports, cross-sectional

1277 5.2. Data collection (prospective, retrospective, unreported, other).

1278 5.3. Exposure (s): *(fill boxes below as appropriate. Use N/A when not applicable)*

1279

	Food	Food matrix, if applicable	Daily intake (nutrient(s)/substance)	Daily intake (food/food category, if applicable)	Duration of exposure
Exposure 1= control					
Exposure 2					
Exposure <i>n</i>					

1280

1281 5.4. Number of subjects (total, per cohort, per group):

1282 5.5. Primary outcome: State the variable used for power calculations, if any.

1283 5.6. Secondary outcome(s): variable 1, variable 2, variable *n*

1284 5.7. Comparability of subjects between study groups (arms) at baseline. Variables checked for: variable 1,

1285 variable 2, variable *n*

1286

- 1287 **6. Outcome measures and results:**
 1288 6.1. Duration of follow-up:
 1289 6.2. Drop outs in total, by group:
 1290 6.3. Adverse effects being reported:
 1291 6.4. Measure of effect of the exposure: report measure of effect for outcome variables as appropriate.
 1292 6.5. Address the biological relevance of the results.

- 1293 **7. Study quality.** Please check the appropriate columns in the table below.
 1294
 1295

	Yes	Partially	No	Unknown	N/A ¹
1. Power calculations performed					
2. Baseline characteristics of subjects reported					
3. Subjects inclusion and exclusion criteria specified					
4. Definition of cases explicit					
5. Condition of cases reliably assessed and validated					
6. Controls selected from the source of population of the cases					
7. Information on background dietary habits provided					
8. Information on physical activity provided					
9. Information on smoking/alcohol drinking provided					
10. Information on medication use provided					
6. Information on other risk factors provided					
11. Information on the distribution of prognostic factors provided					
12. Groups comparable at baseline for relevant risk factors/potential confounding variables					
13. Exposure ascertained					
14. Dose-response relationship between exposure and outcome demonstrated					
15. Outcome assessors blinded to exposure status					
16. Appropriate duration of follow-up for outcome to occur					
17. Endpoint/Markers of health outcome(s) validated analytically					
18. Endpoint/Markers of health outcome(s) validated biologically					
19. Drop out rates and reasons similar among groups					
20. Adequate adjustment for the effects of confounding variables					
21. Statistical methods appropriate					
22. Dose-response relationship between exposure and outcome statistically significant					

1296 ¹ N/A=Not applicable

- 1297
 1298 **8. Conclusions** (15 lines maximum)
 1299

1300 **APPENDIX P4.2.2 – GUIDANCE FOR PRESENTING NON-HUMAN STUDIES**

1301 **(i) Instruction for use:**

1302 This guidance is applicable to **Part 4.2.2** and is intended to assist applicants in the preparation
1303 and presentation of non-human data that have been identified and acquired to support the
1304 health claim.

1305

1306 **(ii) Sequence of information:**

1307 The sequence of information to be presented under Part 4.2.2 is described below:

- 1308 • Animal data
 - 1309 ○ Studies investigating aspects related to absorption / distribution /
 - 1310 metabolism / excretion
 - 1311 ○ Mechanistic studies
 - 1312 ○ Other
- 1313 • *Ex vivo* or *in vitro* data (i.e. meaning studies based on either human or animal
- 1314 biological samples related to the mechanisms of action)
- 1315 • Other studies
- 1316 • List of references

1317

1318 **(iii) Content of information:**

1319 For each individual study, a **brief and concise overview should be given**, addressing if
1320 applicable:

- 1321 ➤ Testing model
- 1322 ➤ Good Laboratory Practice status where appropriate
- 1323 ➤ The quality and relevance of “test food(s)”, dose, route of administration,
- 1324 duration of exposure
- 1325 ➤ The principal findings (e.g. mechanism of action) and their relevance for
- 1326 humans.
- 1327 ➤ Any potential side effects identified

1328

1329 Copies of article/reprint of references and full study reports for unpublished studies should
1330 **not** be given under Part 4.2.2. They should be annexed in **Part 5.2**. Full study reports for
1331 unpublished studies should be annexed under **Part 5.3**. Cross-reference should be given.

1332

1333

1334

1335

1336

1337