# Application for authorisation of an infant and/or follow-on formula manufactured from protein hydrolysates in Great Britain

Published 20 September 2021

This application form follows the approach of that provided by European Food Safety Authority (EFSA) for an infant and/or follow-on formula manufactured from protein hydrolysates to be used in the EU but with modifications appropriate for use in Great Britain.

Paragraph 21 of the introductory text of the Commission Delegated Regulation (EU) 2016/127,[[1]](#footnote-2) explains that manufacturers of infant formula (IF) and follow-on formula (FOF) which are made from protein hydrolysates must demonstrate the safety and suitability of each specific formula containing protein hydrolysates has been established by clinical evaluation. This requirement is also covered in Article 3 of the Regulation.

The process to submit an application seeking authorisation and approval of the safety and suitability of protein hydrolysates used to manufacture IF and FOF for use in GB has been agreed via the four-nation policy group established through the Nutrition Related Labelling, Composition and Standards (NLCS) common framework, and the wording of the framework will be updated appropriately to reflect this agreement.

Applications for IF and FOF which are made from protein hydrolysates for use in GB should be submitted to the appropriate GB authorities via the DHSC mailbox (which centrally coordinates applications for all GB nations). If you wish to submit an application for an infant and/or follow-on formula manufactured from protein hydrolysates to be authorised for use in:

* England only, please contact the competent authority via the DHSC mailbox at nutritionlegislation@dhsc.gov.uk
* Scotland only, please contact the competent authority via the Food Standards Scotland mailbox at labellingstandardsandregulatedproducts@fss.scot
* Wales only, please contact the competent authority via the Welsh Government mailbox at nutritionandhealthclaims@gov.wales

Manufactures of IF and FOF which are made from protein hydrolysates for use in the EU or Northern Ireland must continue to follow the requirements of Commission Delegated Regulation (EU) 2016/127.

IF and FOF are governed by the overarching Food for Specific Groups (FSG) legislation, Regulation (EU) No 609/2013 on food intended for infants and young children, food for special medical purposes, and total diet replacement for weight control,[[2]](#footnote-3) with the detailed labelling and compositional rules covered by Commission Delegated Regulation (EU) 2016/127.

Commission Delegated Regulation (EU) 2016/127 was adopted in 2016 and applied from 22 February 2020 except in respect of IF and FOF manufactured from protein hydrolysates, which was initially due to apply from 22 February 2021, but now applies from 22 February 2022 (in both [GB](https://www.legislation.gov.uk/uksi/2021/168/contents/made) and the EU).

## Part 1 - Administrative and technical data

### Comprehensive table of contents of the application

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### Identification form

Please use the identification form provided in [Appendix A](#_Appendix_A_–).

### Party responsible for the dossier

#### Company or organisation[[3]](#footnote-4)

Name of company or organisation

Enter your response here.

Address (in full) of company or organisation

Enter your response here.

#### Contact person authorised to communicate on behalf of the applicant[[4]](#footnote-5)

Name of contact person

Enter your response here.

Position or role of contact person

Enter your response here.

Address of contact person (if different to the one previously provided)

Enter your response here.

Telephone or mobile number of contact person

Enter your response here.

Email of contact person

Enter your response here.

### Scope of authorisation sought

This application is applicable to GB (England, Scotland, Wales).

If you do not wish for this application to be considered for all of GB, please delete the nations to which you are not applying:

England

Scotland

Wales

### Nature of the application

Please indicate the categories (which are listed below) that the application applies to and delete the categories which are not applicable:

An IF

A FOF

The efficacy of an IF and/or a FOF in reducing the risk of developing allergy to milk proteins.

#### Infant formula

Where appropriate, please explain in which way the formula does not comply with the specifications of an IF laid down in Commission Delegated Regulation (EU) 2016/127.1

Enter your response here.

#### Follow-on formula

Where appropriate, please explain in which way the formula does not comply with the specifications of an FOF laid down in Commission Delegated Regulation (EU) 2016/127.1

Enter your response here.

### Confidential data

Does the application include confidential data? (delete as applicable)

Yes

No

If yes, please specify the parts in the application (including unpublished studies) which contain confidential data, clearly stating sections and/or data sets, and page numbers, and verifiable reasons why the afore-mentioned information needs to be kept confidential.

Enter your response here (parts or elements, sections and page numbers and justifications).

Please indicate the confidential sections by writing “[CONFIDENTIAL: START]” at the start and “[CONFIDENTIAL: END]” at the end of each confidential section.

### Regulatory status outside GB

Please state whether the formula has been marketed within or outside GB. If so, provide information about the countries, areas or regions in which the formula is marketed and about the duration for which the product has been available on the market.

Enter your response here.

Please indicate whether the formula or its efficacy in reducing the risk of developing allergy to milk proteins has been scientifically evaluated by an authoritative or scientific body, either within or outside GB.

Enter your response here.

If so, provide a copy of the scientific evaluation in Part 5 of this form.

## Part 2 – Characteristics of the formula

### Name and characteristics of the formula

Please provide the specifications of the formula (for example physical and chemical properties, composition, and, where applicable, microbiological constituents), the list of ingredients and their sources, as well as the energy and nutrient content of the formula as consumed. The quantities should be given per 100ml ready-made formula and per 100kcal.

Enter your response here.

Please specify the methodology used to assess the energy and nutrient content of the specific product. Information on batch-to-batch variability of the formula should also be included.

Enter your response here.

If analytical methods are used to provide a quantitative analysis of the energy and nutrient content, please provide information on the measures in place to ensure the quality and consistency of the data.

Enter your response here.

Please also indicate whether the measurements have been performed in a competent facility that can certify the data. Whenever a quality system is in place for control and/or documentation, for example good laboratory practice (GLP) and ISO17025, the particular system should be indicated.

Enter your response here.

### Manufacturing process of the formula

Please provide a description of the manufacturing process of the formula.

This should also contain information about the addition of free amino acids, vitamins, minerals, fats, carbohydrates, and other substances. If the production follows a quality system (for example good manufacturing practice (GMP)), the particular system should be indicated. If the manufacturing process is claimed as confidential, a non-confidential summary of the manufacturing process should also be provided in the dossier for transparency reasons.

Enter your response here.

### Characteristics of the protein hydrolysate

#### Starting material

Please provide information on the protein source which is the basis of the hydrolysed protein and on whether a single protein or a mixture of proteins is used. Individual intact proteins (used as such or in mixtures for the preparation of the protein hydrolysate) should be identified by their molecular weight.

Enter your response here.

#### Protein hydrolysate

Please provide information on the degree of hydrolysis (DH) of the protein,[[5]](#footnote-6) the amount of residual protein, peptides and free amino acids, the molecular weight distribution of peptides and residual proteins, the overall amino acid pattern, the total nitrogen content, and the amino nitrogen content (including the ratio of amino nitrogen to total nitrogen).

Enter your response here.

Please provide a description of the methods used for hydrolysis and to measure the amount of residual protein, peptides and free amino acids, as well as the method used to assess the molecular weight distribution of peptides (for example, peptide mass fingerprinting (PMF)), high-performance liquid chromatography/mass spectrometry (HPLC/MS)) and residual proteins, together with a justification for the use of these methods. Information should also be provided on the batch-to-batch variability in relation to the described parameters.

Enter your response here.

### Manufacturing process of the protein hydrolysate

Please provide a detailed description of the procedure used to isolate the starting material, as well as of the manufacturing process of the protein hydrolysate. Please outline the hydrolytic conditions (for example enzymatic[[6]](#footnote-7)/chemical hydrolysis, pH, temperature, duration (hours)) used to produce the hydrolysate.

Enter your response here.

Please provide information on (type and amount of) degradation products or new products formed during the manufacturing process of the hydrolysate (for example Maillard reaction products, modified amino acids). If the production follows a quality system (such as GMP), the particular system should be indicated. If the manufacturing process is claimed as confidential, a non-confidential summary of the manufacturing process should also be provided in the dossier for transparency reasons.

Enter your response here.

### Stability information

Please provide a brief summary of the studies undertaken (this could include conditions, batches and analytical procedures), and of the results and conclusions of the stability studies carried out in the IF and/or FOF manufactured from the protein hydrolysate. Please include conclusions with respect to the process for safe and appropriate preparation, storage conditions and shelf-life.

Enter your response here.

### References

Please provide the references and supporting documentation quoted under Part 2 (including authors, title and publication year – no particular format is required), together with copies or reprints of published data and/or full reports of unpublished data.

Enter your response here.

## Part 3 – Nutritional safety and suitability of the hydrolysed formula

### Rationale for the use of the specific protein hydrolysate in the formula

Please provide a rationale for the use of the specific protein hydrolysate in a formula, indicating the measures taken to ensure that the formula is nutritionally adequate for the target population. If nutritional benefits could be expected from the use of the hydrolysate in the formula, a rationale and/or evidence on why such nutritional benefits could be expected.

Enter your response here.

### Preclinical data

If applicable, please provide information on *in vitro* or *in vivo* studies in animal models or other experimental settings if they may help to establish the nutritional adequacy, potential nutritional benefits, and/or the safety of the proposed formula (SCF, 2003).

### History of use

Data may be available on the use of the protein hydrolysate in IF and/or FOF in countries inside or outside of GB. Such data may provide information which could be considered for assessing the safety of the hydrolysed IF and/or FOF which is the subject of the application.

Information on the history of use could include a description of the extent of use of the protein hydrolysate and its duration, and of the group of infants who have consumed formula manufactured from the protein hydrolysate as the only source of nutrition (for IF) or in combination with complementary foods (for FOF).

A comprehensive literature review of human observational studies reporting on relevant safety outcomes could be performed[[7]](#footnote-8). Information on the search strategy, including the sources used to retrieve pertinent data (databases, other sources), the terms and limits used (such as publication dates, publication types, languages, population, default tags) should be provided, together with evidence that the IF and/or FOF consumed by infants in those studies were manufactured from protein hydrolysates complying with the specifications given in the section on the [characteristics of the protein hydrolysate](#_Characteristics_of_the) and [the manufacturing process of the protein hydrolysate](#_Manufacturing_process_of). Copies or reprints of full study reports should be provided, if available, in part 5 of this form.

### Clinical data

In order to demonstrate the safety and suitability of the formula manufactured from hydrolysed protein, at least one adequately powered clinical study in the target population is required.

### Guidance on the expected characteristics of such study is provided below

#### Study objectives

The objectives of the study should be to assess the effects of the formula manufactured from protein hydrolysate (hydrolysed formula) on measures of growth as compared to accepted growth standards and to a formula manufactured from intact protein or from protein hydrolysates complying with the compositional requirements laid down in Commission Delegated Regulation (EU) 2016/1271 (control formula).

#### Study products

The composition of the control formula should be as close as possible to the composition of the hydrolysed formula with respect to factors other than the protein fraction which could affect the study outcomes.

Evidence should be provided that the hydrolysed IF and/or FOF used in the study complies with the specifications provided in the section on the [manufacturing process of the formula](#_Manufacturing_process_of_1) with respect to the characterisation of the formula manufactured from hydrolysed protein that is the subject of the application.

Evidence should also be provided that the IF and/or FOF control formula used in the study complies with the compositional requirements laid down in Regulation (EU) No 609/2013 and Commission Delegated Regulation (EU) 2016/1271.

If the control formula does not comply with such requirements, please indicate in which way it deviates from them and whether it complies with the compositional requirements laid down in Commission Delegated Regulation (EU) 2016/1271.

#### Study design

At least one randomised, parallel study on the effects of the hydrolysed formula on measures of growth as compared to the control formula should be provided. Measures of growth in the hydrolysed and control formula groups should also be compared to accepted national or international growth standards or references. The inclusion in the study of a breast-fed reference group is not compulsory.

If the objective of the study is to detect similarity in growth between the hydrolysed and the control formula, the study should be designed and analysed as an equivalence study using a pre-defined margin of equivalence or non-inferiority. The appropriate Scientific Advisory Committees (SACs) note that different equivalence or non-inferiority margins have been suggested for use in infant growth studies[[8]](#footnote-9).Therefore, it is important to pre-define (at the protocol phase) the equivalence or non-inferiority margin used to calculate the number of subjects needed to ensure sufficient power of the study and to provide a rationale why such margin has been considered appropriate for that purpose.

The design of the study (in particular with respect to randomisation, allocation of subjects to groups, blinding, and sample size calculation) should be in line with generally accepted scientific principles.

In studies assessing the safety and suitability of hydrolysed IF, the intervention with the study formulas (hydrolysed and control) as the only source of nutrition should last at least 3 months. Studies assessing the safety and suitability of hydrolysed FOF should cover at least 3 months after complementary food is introduced.

#### Study group

The study group should be representative of the target population for which the hydrolysed formula is intended, which is healthy term infants in the general population.

#### Main outcome variables

The study should have sufficient power to test the effects of the hydrolysed formula as compared to the control formula on the following measures of growth:

1. Body weight (g)
2. Body length (mm)
3. Head circumference (mm)

These variables should be measured with a sufficient frequency during the study to establish the growth pattern of infants, ideally every 4 weeks, and provided as absolute values, as changes from baseline, and as the variable-for age z-scores at each assessment time point and for each study group, together with an indication of the growth standard used to calculate z-scores and the reasons for that choice.

Other outcome variables that should be assessed at different time points throughout the study include:

1. IF and/or FOF intake, together with information on the methods used to ascertain formula intake
2. Intake of complementary foods, where appropriate, together with information on the methods used to ascertain food intake
3. Tolerance of the study products and adverse events

Information on changes in laboratory values may provide additional information in certain circumstances, but it is not essential for assessing the safety and suitability of a formula manufactured from protein hydrolysates with respect to growth patterns.

#### Basic data set

All infants included in the clinical trials should be well characterised, especially with regard to factors that might affect the planned outcomes. In order to allow a comprehensive scientific assessment of the study, the following information which has been modified from (Aggett et al, 2003) should be provided:

* Infant sex
* Parity
* Delivery conditions (vaginal, C-section)
* Birth weight in grams
* Gestation in completed weeks
* Birth weight for gestation (z-score for sex and gestation)
* Date of birth
* Number of live born infants from the pregnancy
* Age at recruitment into the study
* Age at randomisation
* Age at baseline (meaning at the start of the intervention)
* Anthropometry at baseline (in absolute values and z-scores, together with an indication of the growth standard used to calculate z-scores)
* Body length
* Body weight
* Head circumference
* Date of, and age at, each assessment time point
* Anthropometry at each assessment time point (in absolute values and z-scores)
* Body length
* Body weight
* Head circumference
* Feeding history
* Whether breast or formula-fed
* Duration of exclusive human milk feeding
* Duration of partial human milk feeding
* Duration of exclusive formula feeding
* Types of formula used
* Maternal age and education
* Date and age when stopped participating as per protocol
* Reasons for non-compliance
* Age at withdrawal from the study
* Reasons for withdrawal from the study
* Advice given to parents with respect to the complementary feeding period, where relevant
* Age of introduction of complementary food, where relevant
* Amount of complementary feeding expressed in E% at each assessment time point, where relevant
* Information about infections
* Adverse events

It is acknowledged that, for studies for which the protocol was finalised before adoption of the present guidance, information may not be available for all the items indicated. As a minimum, information should be provided on: infant sex, birth weight in grams, gestation in completed weeks, age at baseline, anthropometry at baseline, date and age at each assessment time point, anthropometry at each assessment time point, feeding history, age at and reasons for withdrawal.

#### Statistical analysis

The statistical analysis should be in line with generally accepted scientific principles.

Results should be provided for comparisons between the intervention and control groups for all outcome variables assessed. Growth patterns of the study groups should also be compared with accepted growth standards.

In particular, the following information should be provided:

1. descriptive and inferential statistics for each assessment time point for both the intention-to-treat (ITT)[[9]](#footnote-10) (or the Full Analysis Set (FAS)[[10]](#footnote-11)) and the per protocol (PP)[[11]](#footnote-12) analyses
2. the number of infants analysed at each time point for each analysis
3. the point estimate and the associated confidence interval for continuous outcome variables
4. the covariates used in the analysis, with appropriate justification for their use
5. the results of both the adjusted and the unadjusted analysis
6. reasons for dropouts or withdrawal of infants from the study by the investigators, together with an assessment or discussion of the impact of dropouts or withdrawals on the study results

### Published clinical studies not proprietary to the applicant

Published clinical studies on the safety and suitability of the formula manufactured from hydrolysed protein which are not proprietary to the applicant should be identified in a systematic and transparent manner through a comprehensive review of the scientific literature.7

Please provide a reference list and a brief summary of the studies identified through the comprehensive review of the scientific literature. Copies or reprints of pertinent published studies or articles not proprietary to the applicant should be provided in Part 5 of this form.

Enter your response here.

#### Clinical studies unpublished and/or proprietary to the applicant

Please provide a reference list and a summary of the studies (published or unpublished) on the safety and suitability of the formula manufactured from hydrolysed protein, which are proprietary to the applicant.

Enter your response here.

Applications should include the study protocol and the full study report of studies which are proprietary to the applicant in line with the information requested in [Appendix B](#_Appendix_B_-) of this guidance. The study protocol and the full study report should be provided in Part 5 of this form.

## Part 4 – Efficacy of the formula in reducing the risk of developing allergy to milk proteins

### Rationale for the use of the specific protein hydrolysate in the formula and the expected reduction in the risk of developing allergy to milk proteins

Please provide a rationale for the use of the specific protein hydrolysate in the formula, together with a rationale or evidence why reduction in the risk of developing allergy to milk proteins in the target population could be expected.

Enter your response here.

### Preclinical data

If applicable, please provide information on *in vitro* or *in vivo* studies in animal models or other experimental settings if they may help to establish the potential of the hydrolysed formula to reduce the risk of developing allergy to milk proteins.

Enter your response here.

### Clinical data

In order to demonstrate the efficacy of a formula manufactured from hydrolysed protein in reducing the risk of developing allergy to milk proteins (such as cow’s milk allergy, goat’s milk allergy), at least one adequately powered and designed clinical study is required.

Guidance on the expected characteristics of these studies is provided below.

### Guidance on the expected characteristics of clinical studies

#### Study objectives

The objectives of the study should be to assess the effects of the hydrolysed formula on the incidence of allergy to milk proteins as compared to a control formula manufactured from intact protein from the same source as the hydrolysate and complying with the compositional requirements laid down in Commission Delegated Regulation (EU) 2016/127.1

#### Study products

The composition of the control formula should be as close as possible to the composition of the hydrolysed formula with respect to factors other than the protein fraction which could affect the study outcomes.

Evidence should be provided that the hydrolysed IF and/or FOF tested in the study complies with the specifications provided in the section on the [manufacturing process of the formula](#_Manufacturing_process_of_1) with respect to the characterisation of the formula manufactured from hydrolysed protein that is the subject of the application.

Evidence should also be provided that the IF and/or FOF control formula used in the study complies with the compositional requirements for formula manufactured from intact protein laid down in Commission Delegated Regulation (EU) 2016/1271, and that the IF and/or FOF control formula has been manufactured from the same source as the hydrolysed formula that is the subject of the application.

If the control formula does not comply with the compositional requirements laid down in Commission Delegated Regulation (EU) 2016/1271, please indicate in which way it deviates from them and whether it complies with the compositional requirements laid down in Commission Delegated Regulation (EU) 2016/1271.

#### Study design

At least one randomised, parallel study on the effects of the hydrolysed formula on the incidence of allergy to milk proteins as compared to the control formula is required.

The study should be designed as a superiority study in line with generally accepted scientific principles (in particular with respect to randomisation, allocation of subjects to groups, blinding, and sample size calculation).

Infants could be enrolled at any time from birth and prior to the introduction of milk proteins other than breast milk. The efficacy of hydrolysed IF and FOF on reducing the risk of developing allergy to milk proteins could be tested in the same study (for example hydrolysed IF given before the introduction of complementary feeding; hydrolysed FOF given at the time of introduction of complementary feeding and thereafter)

It should be noted that specific requirements cannot be set with respect to the duration of the intervention and/or the duration of the follow-up. However, reducing the risk of developing allergy to milk proteins during, at least, the first year of life would be clinically significant for the target population. Claims on the reduction of the risk of allergic disease for longer periods of time would require longer follow-ups.

Since factors other than the use of (hydrolysed or control) formula may affect the development of food allergy, including the development of allergic reactions to milk proteins such as breast feeding and mother’s diet, age of introduction of complementary foods, socioeconomic factors (EFSA, 2014b), care should be taken that such factors are taken into consideration in the study design.

#### Study group

The study group should be representative of the target population for which the hydrolysed formula is intended. Hydrolysed IF and FOF intended to reduce the risk of developing allergy to milk proteins should be tested in healthy term infants from the general population or in healthy term infants at increased risk of developing allergic diseases (for example having at least one parent or one sibling with ascertained allergic/atopic disease). Care should be taken to exclude from enrolment infants with established allergy to milk proteins.

#### Main outcome variables

The study should be adequately powered to test the effects of the hydrolysed formula as compared to the control formula on the risk of developing allergy to milk proteins.

The appropriate SACs are aware of past and ongoing studies assessing the efficacy of formulae manufactured from protein hydrolysates in reducing the risk of developing allergy or allergic manifestations in general (and not to milk proteins in particular) and considers that this outcome would be of public health relevance. It should be noted that in the context of this guidance, the diagnosis of allergy to milk proteins is needed for efficacy studies.

In this context, a careful family and clinical history are the basis for diagnosis of food allergy, including allergy to milk proteins. Food diaries, skin prick tests (SPTs), allergen specific IgE measurements, food elimination diets and food challenges are part of the standard protocol for the diagnosis of food allergy. A positive SPT indicates sensitisation to the tested food, but it is not diagnostic of food allergy. Allergen-specific serum IgE antibodies denote sensitisation to a particular food but are not diagnostic without a clinical history or food challenge. The use of atopy patch tests for the diagnosis of food allergy is controversial. Other available tests have no current role in the diagnosis of food allergy. Diagnosis is confirmed by exclusion of the suspected food and the subsequent amelioration of symptoms, and by the recurrence of symptoms on re-introduction of the offending food, ideally in double-blind placebo-controlled food challenges (DBPCFC), provided that the initial symptoms were not life threatening (EFSA, 2014b). Open-label food challenges controlled and evaluated by a physician may be sufficient for the confirmation of food allergy in infants and young children ≤ 3 years old under certain circumstances (Bindslev-Jensen et al, 2004; Sampson et al, 2012).

Guidelines for the diagnosis of food allergy and consensus papers aiming for the standardisation of oral challenge protocols have been published in Europe (Bindslev-Jensen et al, 2004; Muraro et al, 2014) and the USA (Sampson et al, 2012). Items highlighted in the section on [history of use](#_History_of_use) (basic data set) should also be considered, where applicable.

#### Statistical analysis

The statistical analysis should be in line with generally accepted scientific principles (see also the section on [history of use](#_History_of_use) (statistical analysis).

### Published clinical studies not proprietary to the applicant

Published clinical studies assessing the effects of the hydrolysed formula on the incidence of allergy to milk proteins which are not proprietary to the applicant should be identified in a systematic and transparent manner through a comprehensive review of the scientific literature.

Please provide a reference list and a brief summary of the studies identified through the comprehensive review of the scientific literature.

Enter your response here.

Copies or reprints of pertinent published studies and/or articles not proprietary to the applicant should be provided in Part 5 of this form.

### Clinical studies unpublished and/or proprietary to the applicant

Please provide a reference list and a summary of the studies (published or unpublished) assessing the effects of the hydrolysed formula on the incidence of allergy to milk proteins, which are unpublished and/or proprietary to the applicant.

Enter your response here.

Information should include the study protocol and the full study report of studies which are proprietary to the applicant in line with the information requested in Appendix B of this guidance. The study protocol and the full study report should be provided in Part 5 of this form.

## Part 5 – Copies and reprints

Please provide copies or reprints of pertinent published studies and/or articles not proprietary to the applicant.

Enter your response here.

Please provide copies and reprints of protocols and full study reports of clinical studies unpublished and/or proprietary to the applicant.

Enter your response here.

### Guidance

[Commission Delegated Regulation (EU) 2016/127 (supplementing Regulation (EU) No 609/2013): guidance](https://www.gov.uk/government/publications/infant-formula-and-foods-for-particular-nutritional-uses-parnuts-notification-requirements)

[EFSA Guidance on statistical reporting](https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2014.3908)

[EFSA Scientific and technical guidance for the preparation and presentation of a dossier for evaluation of an infant and/or follow‐on formula manufactured from protein hydrolysates (Revision 1)](https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2021.6556)

### References

AAP (1988) Clinical testing of infant formulas with respect to nutritional suitability for term infants. Report prepared under FDA contract 223-86-2117. Available from: <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/InfantFormula/ucm170649.htm>

Aggett, P, Agostoni, C, Axelsson, I, Goulet, O, Hernell, O, Koletzko, B, et al (2003). Core data for nutrition trials in infants: a discussion document - a commentary by the ESPGHAN Committee on Nutrition. Journal of Pediatric Gastroenterology and Nutrition. 36:338-342.

Bindslev-Jensen, C, Ballmer-Weber, BK, Bengtsson, U, Blanco, C, Ebner, C, Hourihane, J, et al (2004). Standardization of food challenges in patients with immediate reactions to foods – position paper from the European Academy of Allergology and Clinical Immunology. Allergy. 59(7):690-697.

EFSA (2010). Application of systematic review methodology to food and feed safety assessments to support decision making. EFSA Journal. 8(6):1637.

EFSA (2014a). Guidance on Statistical Reporting. EFSA Journal. 12(12):3908.

EFSA (2014b) Scientific Opinion on the evaluation of allergenic foods and food ingredients for labelling purposes. Available from: <https://efsa.onlinelibrary.wiley.com/doi/abs/10.2903/j.efsa.2014.3894>

Muraro, A, Werfel, T, Hoffmann-Sommergruber, K, Roberts, G, Beyer, K, Bindslev-Jensen, C, et al (2014). EAACI Food Allergy and Anaphylaxis Guidelines: diagnosis and management of food allergy. Allergy. 69(8):1008-1025.

Sampson, H, van Gerth Wijk, R, Bindslev-Jensen, C, Sicherer, S, Teuber, S, Burks, A, et al (2012). Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. Journal of Allergy and Clinical Immunology. 130:1260-1274.

SCF (2003) Report of the Scientific Committee on Food on the revision of essential requirements of infant formulae and follow-on formulae. Available from: <https://ec.europa.eu/food/system/files/2020-12/sci-com_scf_out199_en.pdf>

## Appendix A – Identification form (mandatory)

### Identification form

The identification form should be used for a dossier on a specific food product for a scientific evaluation by UK SACs as required in the context of Commission Delegated Regulation (EU) 2016/1271.

### Declaration and signature

Name of the specific food product

Enter your response here.

Nature of the request

Enter your response here.

Party responsible for the dossier (company or organisation) name

Enter your response here.

Address of party responsible for the dossier (in full)

Enter your response here.

Contact person’s name

Enter your response here.

Address (in full)

Enter your response here.

Telephone number

Enter your response here.

Email address

Enter your response here.

It is hereby confirmed, to the best of our knowledge, that all existing data which are relevant to the dossier have been supplied, as appropriate.

On behalf of the applicant:

Signature

Enter your signature here.

Name

Enter your name here.

Title

Enter your response here.

Place and date (dd-mm-yyyy)

Enter your response here.

## Appendix B - Information to be presented in a full study report for clinical studies unpublished and/or proprietary to the applicant

A study report can be considered complete when it contains at least the information outlined in this Appendix. This Appendix has been adapted from the International Conference on Harmonisation (ICH) guideline E3 on the structure and content of clinical study reports[[12]](#footnote-13) for the purpose of this guidance. Study reports which follow the full structure of ICH E3 are also acceptable.

Study reports not complying with the requirements outlined below may not allow a scientific evaluation of the study by UK SACs as required.

### Title page

The title page should include information on hydrolysed IF and/or FOF under investigation, the primary outcome variables studied, the methods used to assess the outcome variables, the study design (such as double or single-blind, two or more arms, single or multicentre), the study group, the study initiation and completion dates, the place in which the study was conducted, the name of the sponsor, the funding source and its exact role and contribution to the study (such as in the design, conduct, analysis and/or reporting of the study, if any), the name of the principal investigator, the name of the author of the report, and the date when the report was signed off.

### Summary

### Table of contents

### List of abbreviations and definition of terms

### Ethical considerations

This should include information about the review and approval of the study by an ethics committee. Information about the ethical conduct of the study, and about how the informed consent was obtained from participants, should be provided.

### Trial registration

It should be specified whether the study was registered in a trial registry. If so, the trial registration number should be given. In case the study was not registered, explanation should be provided.

### General information about the study

In this section, the name and affiliation of the investigators and other people with a major role in the study (for example staff carrying out observations related to the outcome variables under investigation), the statisticians and the authors of the report, should be provided. Information about the facilities which were used (for example for multicentre studies: information about the study sites and about the use of a central laboratory vs non-central sample analyses), and on whether a contract research organisation has been tasked to carry out the work should also be included.

### Study objectives

The objectives of the study and the hypothesis to be tested should be specified in this section.

### Study design

This section should outline whether the study was planned such as open-label, single-blind (specifying who was blinded) or double-blind study, as a single- or multi-centre study (with a specification about the number of study sites). Information about the country setting, the type of control used (and the reasons why it was considered appropriate in the context of the study), the study duration and a discussion on the choice of the study design for investigating the selected outcomes should also be provided. In case the study was planned with an adaptive design, it should be specified which kind of adaptations at which time points were planned in the protocol and whether a Data Monitoring Committee was involved in the implementation of the plan.

### Study group

The inclusion and exclusion criteria should be described, including the diagnostic criteria (and their validation) used to select subjects, if applicable. The appropriateness of the study group for the particular purpose of the study should be discussed. Any predefined criteria for excluding subjects from the study after randomisation should also be given, together with information on how these subjects were intended to be followed-up.

### Study products

A detailed description of the hydrolysed IF and/or FOF under investigation and of the control formula, including information on the mode of administration and the amounts used, should be provided.

### Method of assigning subjects to groups

Details on the method used to assign subjects to the study groups (randomisation or minimisation) should be given. It should be specified whether allocation was done in a centralised or decentralised way, whether it was stratified (and if so by which factors) or whether the allocation was done in blocks. Information on the measures taken to conceal the allocation should also be described.

### Blinding

Information on the strategy used to ensure blinding should be provided, for example measures taken to ensure that the study products were not distinguishable by smell, taste or packaging; information on how products were labelled (for example by subject individual codes or other). Information should be given on who had access to the product codes, whether there were any pre-defined circumstances in which the blinding could be broken, and who from the team of investigators would be unblinded in case of such a need. If proper blinding could not be achieved, please discuss and justify why this was not possible. For studies with an adaptive design, it should be reported how it was ensured that the study personnel remained blinded to the interventions, especially if the pre-planned adaptation required unblinding of the data. In such a case, it should be justified why the particular adaptation made it necessary to unblind the data, and why the same aim could not have been achieved with statistical methods not requiring such unblinding.

### Concomitant medication or interventions

Any concomitant medication or non-pharmacological intervention allowed by the study protocol should be described.

### Compliance with the intervention and the protocol

This section should include a detailed description of the measures taken to ensure and assess compliance with the intervention and the protocol.

### Outcome variables measured

Information about the pre-defined primary outcome variables, secondary outcome variables and all other outcomes planned to be measured should be presented in this section. The methods used to assess the outcome variables should be specified. Information about the timing of the measurements (for example a flowchart), and a justification of the appropriateness of the outcome variables chosen to achieve the objectives of the study should also be included.

### Data quality assurance

Any measures taken with respect to the quality assurance of the data collected should be addressed.

### Pre-planned statistical analyses

This section refers to the statistical analysis planned before the implementation of the study and should specify whether any subgroup analyses were pre-planned. The choice of each statistical technique should be appropriately justified. The data analysis sets (for example ITT, FAS, PP) should also be defined. It should be specified which of the analyses presented have been pre-specified as the main analysis in case several alternative analyses for one outcome are planned (for example ITT vs PP or different models used). The reasons for the choice of the analysis should be given. If imputation of missing data is foreseen, information should be given on how it is planned to assess the robustness of the assumptions made with respect to the imputation of data. For studies for which an adjustment for multiple comparisons is needed in order to preserve the family-wise type I error rate, the pre-planned approach towards adjusting for multiplicity should be specified. In case of studies with an adaptive design, the number and time-points of pre-specified interim analyses, as well as the statistical methods used to conserve the type I error rate, should be given. The appropriateness of the statistical method used for the design of the study should be discussed. Finally, it should be stated which analyses were planned to be confirmatory and which ones exploratory.

### Determination of sample size

Detailed information on how the planned sample size of the study was calculated should be provided. This should include information about the expected size of the effect, the assumed standard deviation of the population, the significance level chosen, the anticipated power of the study, and the statistical tests (to be performed) to which the sample size calculation relates. In addition, information should be given on whether equal or unequal allocation to groups has been accounted for in the sample size calculation (if unequal allocation is foreseen) and whether any allowance for dropout has been made. Finally, the programme used to calculate the sample size should be identified. In case of studies with adaptive design allowing for sample size re-estimation, the planned method for re-estimating sample size should be described.

### Protocol amendments, deviations and violations or deviations from the planned approaches and analyses

Non-adherence or changes made during or after the study with respect to the pre-planned approaches or pre-planned analyses should be specified. Any protocol amendments (meaning a systematic change in the protocol after approval), protocol deviations and violations (meaning unplanned unsystematic deviations from the protocol with either minor effects (deviations) or affecting the scientific integrity (violations)) should be outlined.

A protocol amendment may, for example, relate to a systematic change of the pre-established inclusion and exclusion criteria, the planned study design, addition or deletion of endpoints, sample size, the planned statistical approaches or the definition of data analysis sets (such as ITT vs PP). If no protocol amendments have been made, it should be confirmed that the study was carried out according to the protocol.

Protocol deviations and violations may relate, for example, to inadequate or not-timely collected informed consent, inclusion of subjects not meeting the eligibility criteria, improper breaking of the blind, improper assessment of an outcome, incorrect or missing tests, rescheduled or missed study visits, visits outside the permitted window, inadequate record keeping, use of not permitted medication or a non-pharmacological intervention.

Any additional exploratory analyses conducted which were not part of the (amended) protocol (such as unplanned subgroup analyses to inform a subsequent study) should also be recorded.

### Subject flow

A clear description of the number of subjects screened, the number of subjects recruited, the number of subjects randomised, the number of subjects who entered and completed each study phase, the number of dropouts and the number of withdrawals should be specified. The reasons for subjects dropping out of the study or for having been withdrawn from the study by the investigators should be stated. Information about whether and when the blind was broken (if so) should also be provided.

### Data sets analysed

Information should include a clear definition of each analysis set used for final analysis (such as ITT, FAS, PP), including information on the number of subjects available for each analysis at each assessment time point. In case PP analyses are presented, information should be given on the extent to which the subjects included in this analysis set could have deviated from the protocol, and the reasons why they were still eligible for inclusion in the PP analysis set. Finally, the reasons for excluding subjects from each analysis at each time point should be provided.

### Baseline characteristics of the study group

Information on the baseline characteristics of the study group for all analysis sets should be given (such as ITT, FAS, PP, completers, other): overall and by study centre for multi-centre studies.

### Results of assessment of compliance with the intervention and the protocol

Information on the results of the assessment of compliance with the intervention and with the protocol should be provided.

### Statistical analysis carried out

A detailed description of the statistical analysis carried out should be provided, in line with EFSA’s guidance on statistical reporting (EFSA, 2014a). This description should include, among other, information on:

* the statistical programme used (version number and operating system)
* the type of statistical tests/models used
* the test/model selection
* the appropriateness of the test/model used for the type of data generated
* the handling of missing data (including a detailed description of the potential mechanism for missing data and of how the missing data were handled). If missing data were imputed
* please describe the methods used to do so and specify which sensitivity analyses were carried out, if any
* the variables or factors used as fixed or as random effects (if appropriate)
* the assumed covariance structure for longitudinal analyses
* the adjustment for covariates (and justification about the covariates used)
* the handling of data stemming from multicentre trials
* whether any issue with respect to multiple comparisons arises (in case of multiple primary outcomes or multiple group comparisons, or if a secondary outcome is intended to be used as the primary efficacy criterion instead of the primary outcome); this should include a description of the method chosen for adjusting the analysis for multiple comparisons and information on the number of outcomes for which the analysis has been adjusted.

### Results of the study

Information on results for all the outcome variables assessed and for all analysis sets investigated should be presented. The results should be given as estimates with associated confidence intervals and p-values (if corrected for multiple comparisons, both the uncorrected and corrected results (confidence intervals and p-values accounting for multiple comparisons) should be provided).

Results should be presented for all groups under investigation and for each assessment time point if foreseen in the prespecified analysis plan; otherwise descriptive statistics should be included. The information should be presented in a tabular format, and not only graphically. For multicentre trials, results or descriptive statistics for the individual centres should be presented (if prespecified). The number of subjects included in each analysis and assessment time point should be provided.

In case of data imputation, the results of the related sensitivity analyses should be included. The full outputs of the statistical analyses, together with the associated codes used for programming, should be provided via a separate Annex. A full list of the abbreviations used to denominate variables or factors in the programming should also be given, so that the statistical outputs are self-explanatory.

### Adverse events

Information on adverse events should be clearly reported (indicating those which may be related to the intervention and those which may not be related to the intervention), together with information on the (diagnostic) criteria used to ascertain them[[13]](#footnote-14)

1. Commission Delegated Regulation (EU) 2016/127 of 25 September 2015 supplementing Regulation (EU) No 609/2013 of the European Parliament and of the Council as regards the specific compositional and information requirements for infant formula and follow-on formula and as regards requirements on information relating to infant and young child feeding, OJ L 25, 2.2.2016, p. 1 to 29. [↑](#footnote-ref-2)
2. [https://www.legislation.gov.uk/eur/2013/609/introduction#](https://www.legislation.gov.uk/eur/2013/609/introduction) [↑](#footnote-ref-3)
3. In case more than one company or organisation submits a dossier, provide their names and addresses. Only one contact person is authorised to communicate with the competent authority. [↑](#footnote-ref-4)
4. To facilitate communication, only one contact person should be indicated per dossier. [↑](#footnote-ref-5)
5. This means the percentage of cleaved peptide bonds, defined as DH (%) = h/htot 9 100, where ‘htot’ is the total number of peptide bonds per protein equivalent and ‘h’ is the number of hydrolysed peptide bonds. [↑](#footnote-ref-6)
6. For information on the approval of food enzymes used in the production of protein hydrolysate please see <https://www.food.gov.uk/business-guidance/regulated-products/food-enzymes-guidance>. Any extraction solvent used in the production process must also be compliant with GB law. [↑](#footnote-ref-7)
7. Applicants could consider the EFSA guidance on the application of systematic review methodology to food and feed safety assessments to support decision making for that purpose (EFSA, 2010). [↑](#footnote-ref-8)
8. For example a 0.5 z-score difference (SCF, 2003), 3 g/day difference in weight gain over a 3 to 4-month period (AAP, 1988). [↑](#footnote-ref-9)
9. All infants randomised. [↑](#footnote-ref-10)
10. All infants which were fed at least once with the study products. [↑](#footnote-ref-11)
11. All infants which completed the protocol as planned. [↑](#footnote-ref-12)
12. http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html [↑](#footnote-ref-13)
13. For reporting of safety-related data, see also ICH-E3- Structure and content of study reports. [↑](#footnote-ref-14)