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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)¹

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

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Abstract

Following a request from the European Commission, EFSA was asked to provide 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. This guidance document addresses the information and data to be submitted to EFSA on infant and follow-on formulae manufactured from protein hydrolysates with respect to the nutritional safety and suitability of the specific formula and/or the formula's efficacy in reducing the risk of developing allergy to milk proteins. The guidance will be further reviewed and updated with the experience gained from the evaluation of specific dossiers, and in the light of applicable Union guidelines and legislation. The guidance was adopted by the Panel on Dietetic Products, Nutrition and Allergies on 5 April 2017. Upon request from the European Commission in 2020, it has been revised to inform food business operators of the new provisions in the pre-submission phase and in the procedure set out in the General Food Law, as amended by the Transparency Regulation. This revised guidance applies to all dossiers submitted as of 27 March 2021 and shall be consulted for the preparation of dossiers intended to be submitted from that date onwards. For dossiers submitted prior to 27 March 2021, the previous guidance, published in May 2017 remains applicable.

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¹ The guidance was adopted on 5 April 2017 by the former Panel on Dietetic products, Nutrition and Allergies. The revision only aims to inform food business operators of the new provisions set out in the General Food Law (Regulation (EC) No 178/2002, as amended by Regulation (EU) 2019/1381 on the transparency and sustainability of the EU risk assessment in the food chain), and to guide to EFSA's practical arrangements implementing these new requirements. For this purpose, the revision concerns only the administrative part. The scientific content remains unchanged. The present guidance (revision 1) was endorsed on 21 January 2021 by the Panel on Nutrition, Novel Foods and Food Allergens (NDA): Dominique Turck, Jacqueline Castenmiller, Stefaan de Henauw, Karen-Ildico Hirsch-Ernst, John Kearney, Helle Katrine Knutsen, Alexandre Maciuk, Inge Mangelsdorf, Harry J McArdle, Androniki Naska, Carmen Pelaez, Kristina Pentieva, Alfonso Siani, Frank Thies, Sophia Tsaouri and Marco Vinceti.

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

Keywords: protein hydrolysates, infant formula, follow-on-formula, guidance, food allergy, milk proteins

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Summary

Following a request from the European Commission (EC), EFSA was asked to deliver a 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.

The guidance document addresses the information and data to be submitted to EFSA in relation to dossiers for evaluation of infant formulae (IF) and/or follow-on formulae (FOF) manufactured from protein hydrolysates. It covers dossiers for the assessment of the nutritional safety and suitability of the formula and dossiers on the product's efficacy in reducing the risk of developing allergy to milk proteins.

IF or FOF complying with the compositional requirements specified in the European Union (EU) legislation which have been manufactured from protein hydrolysate(s) already authorised for use in the EU do not need a separate assessment by the European Food Safety Authority (EFSA) with respect to their nutritional safety and suitability.

Out of the scope of this guidance is the scientific evaluation of:

- a) the efficacy of IF and/or FOF manufactured from protein hydrolysates in reducing the risk of developing allergy/allergic manifestations to allergens besides milk proteins;
- b) aspects of the composition of IF and FOF manufactured from protein hydrolysates which relate to nutrients or substances other than the protein hydrolysate;
- c) IF and FOF containing only mixtures of free amino acids which are intended for the dietary management of infants with a diagnosed disease/disorder or a medical condition and are covered by EU legislation on food for special medical purposes.

The following information should be provided in the dossier:

- Administrative data
- Public summary
- Technical dossier. The technical dossier should contain the following information:
 - Characterisation of the hydrolysed IF and/or a FOF (name and characteristics, list of ingredients, its energy and nutrient content), description of the manufacturing process, and stability information; characteristics and manufacturing process of the protein hydrolysate used to manufacture the hydrolysed IF and/or FOF.
 - Where applicable, information about the nutritional safety and suitability of the formula, including information on the history of use (if any), a comprehensive review of the scientific evidence, and a summary of pertinent growth studies performed in the target population for which the formula is intended.
 - Where applicable, information related to the product's efficacy in reducing the risk of developing allergy to milk proteins, including a comprehensive review of the scientific evidence and a summary of pertinent studies in the target population for which the formula is intended.
 - Full electronic copies of the references and the study reports identified by the applicant as being pertinent for the assessment together with the list of annexes and the list of references.

Where some of the information required by this guidance are not included in a particular dossier, justifications shall be provided.

In 2020, upon request from the European Commission, the guidance has been revised to inform food business operators of the new provisions set out in Regulation (EC) No 178/2002³ (i.e. the General Food Law, hereinafter 'GFL Regulation'), as amended by Regulation (EU) 2019/1381 on the transparency and sustainability of the EU risk assessment in the food chain (hereinafter 'Transparency Regulation'). They concern requirements in the pre-submission phase and submission application procedure that are applicable to all dossiers submitted as of 27 March 2021:

- possibility to request general pre-submission advice (Article 32a(1) of GFL Regulation);
- mandatory notification of information related to studies commissioned/carried out as of 27 March 2021 (Article 32b of GFL Regulation);
- publication of non-confidential version of all information submitted in support of the dossiers and related confidentiality decision-making process (Articles 38 and 39-39e of the GFL Regulation);
- public consultation on submitted dossiers (Article 32c(2) of GFL Regulation).

For detailed information, please refer to EFSA's Practical Arrangements on pre-submission phase and public consultations⁴ (EFSA, 2021a) and EFSA's Practical Arrangements concerning transparency and confidentiality⁵ (EFSA, 2021b) available on the EFSA website.

Food business operators should also note that as of 27 March 2021, dossiers shall be submitted through the e-submission system accessible through the European Commission's website or the EFSA's website.⁶

Before submitting a dossier, in conjunction with the present guidance, food business operators are also recommended to consult:

- EFSA's Explanatory note to the scientific and technical guidance for the preparation and presentation of an infant and/or follow-on formula manufactured from protein hydrolysates (with a view to amend Regulation (EU) 2016/127) (EFSA, 2020).⁷
- EFSA Administrative guidance for the processing of applications for regulated products (EFSA, 2021c) and the EFSA's Catalogue of support initiatives during the life-cycle of applications for regulated products (EFSA, 2021d)

This revised guidance applies to all dossiers submitted as of 27 March 2021 and shall be consulted for the preparation of dossiers intended to be submitted from that date onwards. For dossiers submitted prior to 27 March 2021, the guidance published on 11 May 2017⁸ remains applicable.

³ Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety, as amended by Regulation (EU) 2019/1381 of the European Parliament and of the Council of 20 June 2019 on the transparency and sustainability of the EU risk assessment in the food chain and amending Regulations (EC) No 178/2002, (EC) No 1829/2003, (EC) No 1831/2003, (EC) No 2065/2003, (EC) No 1935/2004, (EC) No 1331/2008, (EC) No 1107/2009, (EU) 2015/2283 and Directive 2001/18/EC, PE/41/2019/REV/1. OJ L 231, 6.9.2019, p. 1–28.

⁴ See [Decision of the Executive Director of the European Food Safety Authority laying down the practical arrangements on pre-submission phase and public consultations](#)

⁵ See [Decision of the Executive Director of the European Food Safety Authority laying down Practical Arrangements concerning Transparency and Confidentiality](#)

⁶ <https://www.efsa.europa.eu/en/applications/toolkit>

⁷ <https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/sp.efsa.2020.EN-1858>

⁸ <https://www.efsa.europa.eu/en/efsajournal/pub/4779>

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Background as provided by the European Commission in 2016

Commission Directive 2006/141/EC⁹ lays down requirements for infant formulae and follow-on formulae placed on the market in the European Union (EU). The Directive allows the use of protein hydrolysates as source of protein in infant formulae and follow-on formulae under certain conditions (Articles 5-7; Annex I, point 2.2; Annex II, point 2.2 and Annex VI). The Directive also lays down conditions for infant formulae manufactured from protein hydrolysates to bear a health claim describing the role of such products in reducing the risk of developing allergy to milk proteins (Article 13(6) and Annex IV, point 2.1).

Commission delegated Regulation (EU) 2016/127¹⁰ repeals Directive 2006/141/EC and revises the rules applicable to infant formula and follow-on formula, taking account of the opinion of the European Food Safety Authority (EFSA) of 2014 (EFSA NDA Panel, 2014a).

In that opinion, EFSA noted that 'the safety and suitability of each specific formula containing protein hydrolysates has to be established by clinical studies. Information on protein sources and the technological processes applied should also be provided. In this context, the Panel notes that one particular formula containing partially hydrolysed whey protein has been evaluated for its safety and suitability by the Panel[] (...) and has been authorised for use by Directive 2006/141/EC'. EFSA also noted that 'the criteria given in Directive 2006/141/EC alone are not sufficient to predict the potential of a formula to reduce the risk of developing allergy to milk proteins. Clinical studies are necessary to demonstrate if and to what extent a particular formula reduces the risk of developing short- and long-term clinical manifestations of allergy in at-risk infants who are not exclusively breast fed'.

In light of the above, Commission delegated Regulation (EU) 2016/127 establishes that infant formula and follow-on formula manufactured from protein hydrolysates should only be allowed to be placed on the market if their composition corresponds to the one already positively assessed by EFSA and prohibits the use of health claims describing the role of infant formula manufactured from protein hydrolysates in reducing the risk of developing allergy to milk proteins.

As explained in the Regulation's recitals, these requirements may be amended in the future in order to allow the placing on the market of formulae manufactured from protein hydrolysates with a composition different from the one already positively assessed, following a case-by-case evaluation of their safety and suitability by EFSA. In addition, if, after the assessment by EFSA, it is demonstrated that a specific formula manufactured from protein hydrolysates reduces the risk of developing allergy to milk proteins, further consideration will be given to how to adequately inform parents and caregivers about that property of the product.

The requirements of Commission delegated Regulation (EU) 2016/127 shall apply to infant formula and follow-on formula manufactured from protein hydrolysates from 2021. The Commission expects that, before that date, dossiers on formulae manufactured from protein hydrolysates will be presented by food business operators for assessment by EFSA with a view to request possible modifications to the conditions applicable to these products in the delegated Regulation.

In this context, it is considered necessary to consult EFSA regarding the type of data that food business operators should make available to the Authority in the future, when submitting such dossiers on formulae manufactured from protein hydrolysates.

Terms of Reference as provided by the European Commission in 2016

In accordance with Article 29 of Regulation (EC) No 178/2002¹¹, the European Commission requests EFSA to issue an opinion on scientific and technical guidance regarding the type of data that will be

⁹ Commission Directive 2006/141/EC of 22 December 2006 on infant formulae and follow-on formulae and amending Directive 1999/21/EC, OJ L 401, 30.12.2006, p. 1-33.

¹⁰ 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. 1-29.

¹¹ Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety, OJ L 31, 1.2.2002, p. 1-24.

considered appropriate by EFSA for providing scientific advice to the Commission on infant formulae and follow-on formulae manufactured from protein hydrolysates and, in particular, on:

- 1) the safety and suitability of a specific formula manufactured from protein hydrolysates and,
- 2) the product's efficacy in reducing the risk of developing allergy to milk proteins.

In preparing this scientific and technical guidance, EFSA is requested to take into account the requirements laid down in Regulation (EU) No 609/2013¹² and delegated Regulation (EU) 2016/127 and its opinion of 2014 on the essential composition of infant and follow-on formulae.

Background and Terms of Reference as provided by the European Commission in 2020

The European Commission (EC) asked EFSA to update the Scientific and technical guidance for the preparation and presentation of an application for authorisation of an infant and/or follow-on formula manufactured from protein hydrolysates¹³ in order to align it to Regulation (EU) 2019/1381 on the transparency and sustainability of the EU risk assessment in the food chain¹⁴, which applies as of 27 March 2021.

The guidance document has been identified to require updating as regards its administrative part. This request does not cover the scientific part of the document that has been left unchanged.

Scope

This guidance document addresses the information and data to be submitted to EFSA in relation to dossiers for evaluation of an infant formulae (IF) and/or follow-on formulae (FOF) manufactured from protein hydrolysates. It covers dossiers for the assessment of the nutritional safety and suitability of the formula and dossiers on the product's efficacy in reducing the risk of developing allergy to milk proteins.

IF or FOF complying with the compositional requirements specified in EU legislation which have been manufactured from protein hydrolysate(s) already authorised for use in the EU do not need a separate assessment by EFSA with respect to their nutritional safety and suitability.

Out of the scope of this guidance is the scientific evaluation of:

- a) the efficacy of IF and/or FOF manufactured from protein hydrolysates in reducing the risk of developing allergy/allergic manifestations to allergens besides milk proteins;
- b) aspects of the composition of IF and FOF manufactured from protein hydrolysates which relate to nutrients or substances other than the protein hydrolysate;
- c) IF and FOF containing only mixtures of free amino acids which are intended for the dietary management of infants with a diagnosed disease/disorder or a medical condition and are covered by EU legislation on food for special medical purposes¹⁵.

¹² Regulation (EU) No 609/2013 of the European Parliament and of the Council of 12 June 2013 on food intended for infants and young children, food for special medical purposes, and total diet replacement for weight control and repealing Council Directive 92/52/EEC, Commission Directives 96/8/EC, 1999/21/EC, 2006/125/EC and 2006/141/EC, Directive 2009/39/EC of the European Parliament and of the Council and Commission Regulations (EC) No 41/2009 and (EC) No 953/2009, OJ L 181/35, 29.6.2013, p. 1-22.

¹³ <http://www.efsa.europa.eu/en/efsajournal/pub/4779>

¹⁴ Regulation (EU) 2019/1381 of the European Parliament and of the Council of 20 June 2019 on the transparency and sustainability of the EU risk assessment in the food chain and amending Regulations (EC) No 178/2002, (EC) No 1829/2003, (EC) No 1831/2003, (EC) No 2065/2003, (EC) No 1935/2004, (EC) No 1331/2008, (EC) No 1107/2009, (EU) 2015/2283 and Directive 2001/18/EC (OJ L 231, 6.9.2019, p. 1).

¹⁵ In particular Commission Directive 1999/21/EC of 25 March 1999 on dietary foods for special medical purposes, OJ L 91, 7.4.1999, p. 29-36, to be replaced by Commission Delegated Regulation (EU) 2016/128 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 food for special medical purposes, OJ L 25, 2.2.2016, p. 30-43.

Objectives

The guidance presented in this document is intended to assist food business operators in the preparation and presentation of well-structured dossiers for the evaluation of IF and/or FOF manufactured from protein hydrolysates and for assessing the product's efficacy in reducing the risk of developing allergy to milk proteins.

It presents a common format for the organisation of the information to be provided and outlines:

- the information and scientific data which must be included in the dossier,
- the key issues which should be addressed in the dossier to substantiate the nutritional safety and suitability of the formula and/or its efficacy in reducing the risk of developing allergy to milk proteins.

It is intended that the guidance will be further updated as appropriate in the light of the experience gained with evaluations.

General principles

In the context of this guidance:

- 1) *Infant* means a child under the age of 12 months;

Infant formula (IF) means food intended for use by infants during the first months of life and satisfying by itself the nutritional requirements of such infants until the introduction of appropriate complementary feeding;

Follow-on formula (FOF) means food intended for use by infants when appropriate complementary feeding is introduced and which constitutes the principal liquid element in a progressively diversified diet of such infants;

Protein hydrolysates means products obtained by either chemical or enzymatic cleavage of peptide bonds of protein that are composed of free amino acids, peptides and residual intact protein in different proportions;

Hydrolysed formula means an IF or a FOF manufactured from a protein hydrolysate;

Control formula means a formula that is used in clinical studies as comparator and meets the requirements laid down in Regulation (EU) No 609/2013 and delegated Regulation (EU) 2016/127;

Allergy to milk proteins means adverse immunological responses to non-human milk proteins of different mammalian species (e.g. cow, goat). Allergic reactions to milk proteins can be broadly divided into immunoglobulin E (IgE)- and non-IgE-mediated, or mixed. These differ in clinical presentation, diagnostic testing, and prognosis.

- 2) This guidance presents a common format for the organisation of the information in order to assist the food business operator in the preparation of a well-structured dossier. Adherence to this format will also facilitate easy access to information and scientific data in the dossiers to help the EFSA NDA Panel to carry out its evaluation and to deliver its scientific advice in an effective and consistent way.
- 3) It is the duty of the food business operator to provide all available scientific data (including data in favour and not in favour) which are pertinent to the dossier. In its evaluation, the NDA Panel may use data which are not included in the dossier if they are considered pertinent to the claim. However, the NDA Panel should not be required to undertake any additional literature reviews, or to assemble or process data in order to evaluate the dossier. As such, the dossier should be comprehensive and complete. Each dossier will be considered on a case-by-case basis.
- 4) The dossier must contain information on the characteristics of the formula for which the dossier is made. This information should contain aspects such as the composition, physical and chemical characteristics, manufacturing process and stability. Measurements should be performed in a competent laboratory which can certify the data. Whenever a quality system is in place for performance/control/documentation (e.g. good manufacturing practice (GMP),

good laboratory practice (GLP), applicable ISO standard), the particular system should be indicated.

- 5) In order to substantiate the nutritional safety and suitability of a formula manufactured from protein hydrolysates, at least one human intervention study on outcomes of growth in the target population for which the formula is intended (i.e. healthy infants in the general population, whether or not they are considered to be at increased risk of developing allergy to milk proteins) should be provided.
- 6) In order to substantiate the efficacy of a product in reducing the risk of developing allergy to milk proteins, at least one human intervention study on the incidence of allergy to milk proteins in the target population for which the formula is intended (i.e. healthy infants in the general population, whether or not they are considered to be at increased risk of developing allergy to milk proteins) should be provided.
- 7) The nutritional safety and suitability of a formula manufactured from protein hydrolysates and the efficacy of the same formula in reducing the risk of developing allergy to milk proteins could be addressed in the same human intervention study provided that the study is adequately designed and has sufficient power for both purposes.
- 8) Data on the history of use of the product and non-human data could be submitted as part of the overall pertinent scientific evidence, but are not sufficient alone to substantiate the nutritional safety and suitability of an IF and/or a FOF or to establish the efficacy of a product in reducing the risk of developing allergy to milk proteins.
- 9) One dossier should be prepared for each IF or FOF manufactured from protein hydrolysates. If the proposed modification in the protein hydrolysate is the same for both IF and FOF, they may be addressed in the same dossier.
- 10) **Transparency and confidentiality** (Articles 38 and 39-39e of the GFL Regulation) - The Transparency Regulation introduced a general principle of proactive disclosure and transparency of information and data submitted to EFSA for scientific evaluation. In the light of this principle, and of the related provisions, EFSA must proactively disseminate all information shared by food business operators for the purposes of EFSA's scientific assessment, including that submitted during the assessment process. Specifically, EFSA is to make publicly available¹⁶ *inter alia* the following information¹⁷:
 - all its scientific outputs;
 - scientific data and other information supporting applications, including supplementary information, as well as other scientific data and information supporting requests from the Commission and the Member States for a scientific output;
 - the information on which its scientific outputs are based;
 - a summary of the advice provided to potential food business operators at pre-submission phase, if applicable.

By derogation from the general principle of proactive disclosure and transparency, EFSA may grant confidential status to certain elements of dossiers, provided food business operators submit a verifiable justification, and EFSA accepts the confidentiality request. The items on which confidentiality requests may be made are set out in Article 39(2) of the GFL Regulation. This guidance is to be read in conjunction with Union law and case law, as well as with **EFSA's Practical Arrangements concerning transparency and confidentiality**, which provide a comprehensive description of applicable procedures and provision.

¹⁶ The proactive disclosure of the above information does not imply permission or licence for their re-use, reproduction, or exploitation in breach of the relevant existing rules concerning intellectual property rights or data exclusivity. EFSA cannot be held liable or responsible for any use of the disclosed data by third parties in breach of any existing intellectual property rights.

¹⁷ For an exhaustive list of the types of information, documents or data which is made proactively available, please refer to Articles 5 and 6 of Decision of the Executive Director of the European Food Safety Authority laying down practical arrangements concerning transparency and confidentiality (EFSA, 2021b).

For each document for which confidentiality is requested, the food business operators are required to upload in the e-submission system:

- **a request to treat certain item(s) as confidential**, specifying: the confidentiality ground(s) and conditions, justification, excerpt of the text, location in the file.
- **a version of the concerned document with all information visible and no blackening applied**. In this version, all information claimed to be confidential by the applicant should be boxed or earmarked (confidential version, not for public disclosure);
- **a non-confidential version with all elements claimed to be confidential blackened** (public version).

The non-confidential (public) version of the dossier will be made publicly available in the OpenEFSA portal¹⁸ as soon as the application is declared valid.

- Upon publication of the non-confidential version of the application by EFSA following the implementation of EFSA's confidentiality decision, EFSA will launch **public consultation with third parties** on the EFSA website (Article 32c(2) of GFL Regulation).

Before submitting a dossier, food business operators are also advised to consult the following:

- EFSA Administrative guidance for the processing of applications for regulated products (EFSA, 2021c) and the EFSA's Catalogue of support initiatives during the life-cycle of applications for regulated products (EFSA 2021d).

Structure of the dossier

The following information should be provided in the dossier and the structure should follow the pre-filled table of content required by the e-submission system available through the EFSA's¹⁹ and European Commission's websites, to be used for submitting the dossier.

Data provided in the dossier should be organised as follows:

Administrative data

The following information should be provided in the dossier:

- Food business operator's contact details (name of entity, email, address, post-code, phone, country, website)²⁰;
- Person responsible for the dossier contact details (name of person responsible/representative, name of entity, email, address, post-code, phone, country, website)²¹;
- Manufacturer's contact details (name of entity, email, address, post-code, phone, country, website);
- Subject of the request;
- Scope of the dossier (Assessment of the nutritional safety and suitability of an IF and/or a FOF manufactured from protein hydrolysates/ Assessment of the efficacy of an IF and/or a FOF in reducing the risk of developing allergy to milk proteins)
- Existing authorisations at Member States level (country, status, reference of the authorisation);
- Existing authorisations in non-EU countries (country, status, reference of the authorisation);
- Information on data sharing agreement in place, if any;
- Cover Letter, specifying the content of the submission.

¹⁸ <https://open.efsa.europa.eu>

¹⁹ <https://www.efsa.europa.eu/en/applications/toolkit>

²⁰ In case more than one company or organisation submits dossier, provide their names and addresses. Only **one contact person** is authorised to communicate with EFSA.

²¹ To facilitate communication, EFSA requires that there be only **one contact person per application**.

Public summary

A short summary of the dossier should be provided. This document should not contain any confidential information. The public summary will be published together with the non-confidential version of the dossier on the OpenEFSA portal.²²

Technical dossier²³

It should include:

Pre-application information²⁴

All relevant pre-application identification(s) received by EFSA in the pre-submission phase for the regulated product which is the subject matter of the dossier and information required with regard to notification of studies obligation should be provided.

General/Scientific Information

- Characterisation of the hydrolysed IF and/or a FOF (name and characteristics, list of ingredients, its energy and nutrient content), description of the manufacturing process, and stability information; characteristics and manufacturing process of the protein hydrolysate used to manufacture the hydrolysed IF and/or FOF.
- Where applicable, information about the nutritional safety and suitability of the formula, including information on the history of use (if any), a comprehensive review of the scientific evidence, and a summary of pertinent growth studies performed in the target population for which the formula is intended.
- Where applicable, information related to the product's efficacy in reducing the risk of developing allergy to milk proteins, including a comprehensive review of the scientific evidence and a summary of pertinent studies in the target population for which the formula is intended.
- Full electronic copies of the references and the study reports identified by the food business operator as being pertinent for the assessment together with the list of annexes and the list of references (see also Section 4)

Where some of the information required by this guidance are not included in a particular dossier, justifications shall be provided.

List of annexes and references

A list of all the unpublished studies and documents as well as a list of all the published studies submitted in support of the dossier should be uploaded.

A list of all studies notified (in accordance to Article 32b of GFL Regulation) via the database available on the EFSA website^{25, 26} should also be uploaded.

²² <https://open.efsa.europa.eu/>

²³ Please see General principle 10.

²⁴ See [Decision of the Executive Director of the European Food Safety Authority laying down the practical arrangements on pre-submission phase and public consultations](#)

²⁵ <https://www.efsa.europa.eu/en/applications/toolkit>

²⁶ See [Decision of the Executive Director of the European Food Safety Authority laying down the practical arrangements on pre-submission phase and public consultations](#)

General/Scientific information²⁷

1. Characterisation of the formula

1.1. Name and characteristics of the formula

Please provide the specifications of the formula (e.g. 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 100 mL ready-made formula and per 100 kcal. Please specify the methodology used to assess the energy and nutrient content of the specific product. Batch-to-batch variability of the formula should also be addressed.

If analytical methods are applied 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. 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/documentation (e.g. GLP and ISO17025), the particular system should be indicated.

1.2. 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 (e.g. GMP), the particular system should be indicated.

1.3. 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.

Protein hydrolysate

Information on the degree of hydrolysis (DH) of the protein,²⁸ 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), should be provided.

A description of the methods used 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 (e.g. peptide mass fingerprinting (PMF), high-performance liquid chromatography/mass spectrometry (HPLC/MS)) and residual proteins should be provided, 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 parameters described above.

1.4. Manufacturing process of the protein hydrolysate

A detailed description of the procedure used to isolate the starting material, as well as of the manufacturing process of the protein hydrolysate, should be provided. The hydrolytic conditions (e.g. enzymatic/chemical hydrolysis, pH, temperature, duration (hours)) used to produce the hydrolysate should be outlined. Information on (type and amount of) degradation products or new products

²⁷ Please see General principle 10.

²⁸ i.e. the percentage of cleaved peptide bonds, defined as $DH (\%) = \frac{h}{htot} \cdot 100$, where "htot" is the total number of peptide bonds per protein equivalent and "h" is the number of hydrolysed peptide bonds.

formed during the manufacturing process of the hydrolysate should also be provided (e.g. Maillard reaction products, modified amino acids).

If the production follows a quality system (e.g. GMP), the particular system should be indicated.

1.5. Stability information

A brief summary of the studies undertaken (e.g. 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, should be provided. Conclusions with respect to storage conditions and shelf-life should be given.

Supporting documentation and references quoted under Section 1 should be uploaded here (see also Notes to Food Business Operators under Section 4).

2. Nutritional safety and suitability of the hydrolysed formula

2.1. Rationale for the use of the specific protein hydrolysate in the formula

A rationale for the use of the specific protein hydrolysate in a formula should be provided, 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/evidence on why such nutritional benefits could be expected should be provided.

2.2. Preclinical data

Information on *in vitro* or *in vivo* studies in animal models or other experimental settings should be provided if they may help to establish the nutritional adequacy, potential nutritional benefits, and/or the nutritional safety of the proposed formula (SCF, 2003).

2.3. 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 the EU. Such data may provide information which could be considered for assessing the nutritional 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 nutritional safety outcomes could be performed.²⁹ Information on the search strategy, including the sources used to retrieve pertinent data (databases, other sources), the terms and limits used (e.g. 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 Sections 1.3 and 1.4 of the dossier.

Electronic copies of full study reports should be provided, if available, as indicated in Section 4.

2.4. Clinical data

In order to demonstrate the nutritional 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.

²⁹ Food business operators 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).

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 the EU legislation (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 Section 1.2 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 delegated Regulation (EU) 2016/127.

If the control formula does not comply with such requirements, please indicate in which way(s) it deviates from them and whether it complies with the compositional requirements laid down in Commission Directive 2006/141/EC.

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/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/non-inferiority. The Panel notes that different equivalence/non-inferiority margins have been suggested for use in infant growth studies.³⁰ Therefore, it is important to pre-define (at the protocol phase) the equivalence/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 nutritional 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 nutritional 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)

³⁰ E.g. 0.5 z-score difference (SCF, 2003), 3 g/day difference in weight gain over a 3 to 4 month period (AAP, 1988).

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:

- 4) IF and/or FOF intake, together with information on the methods used to ascertain formula intake
- 5) Intake of complementary foods, where appropriate, together with information on the methods used to ascertain food intake
- 6) 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 nutritional 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 information³¹ 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 (i.e. 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
 - Type(s) of formula used
- Maternal age and education
- Date and age when stopped participating as per protocol
- Reason/s for non-compliance
- Age at withdrawal from the study

³¹ Modified from Aggett et al. (2003).

- Reason/s 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)³² (or the Full Analysis Set (FAS)³³) and the per protocol (PP)³⁴ 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 drop-outs or withdrawal of infants from the study by the investigators, together with an assessment/discussion of the impact of drop-outs/withdrawals on the study results.

2.4.1. Published clinical studies not proprietary to the food business operator

Published clinical studies on the nutritional safety and suitability of the formula manufactured from hydrolysed protein which are not proprietary to the food business operator should be identified in a systematic and transparent manner through a comprehensive review of the scientific literature³⁵. A reference list and a brief summary of the studies identified through the comprehensive review of the scientific literature should be given.

Electronic copies of pertinent published studies/articles not proprietary to the food business operator should be provided, as indicated in Section 4.

2.4.2. Clinical studies unpublished and/or proprietary to the food business operator

A reference list and a summary of the studies (published or unpublished) on the nutritional safety and suitability of the formula manufactured from hydrolysed protein, which are proprietary to the food business operator, should be given.

³² All infants randomised.

³³ All infants which were fed at least once with the study products.

³⁴ All infants which completed the protocol as planned.

³⁵ Food business operators 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).

Dossiers should include the study protocol and the full study report of studies which are proprietary to the food business operator in line with the information requested in Appendix A of this guidance. The study protocol and the full study report should be provided, as indicated in Section 4.

3. Efficacy of the formula in reducing the risk of developing allergy to milk proteins

3.1. 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

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

3.2. Preclinical data

Information on *in vitro* or *in vivo* studies in animal models or other experimental settings should be provided if they may help to establish the potential of the hydrolysed formula to reduce the risk of developing allergy to milk proteins.

3.3. 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 (e.g. 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.

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 EU legislation.

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 Section 1.2 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) 2016/127, 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 Regulation (EU) 2016/127, please indicate in which way(s) it deviates from them and whether it complies with the compositional requirements laid down in Commission Directive 2006/141/EC.

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 (e.g. hydrolysed IF given before the introduction of complementary feeding; hydrolysed FOF given at the time of introduction of complementary feeding and thereafter).

The Panel cannot set specific requirements with respect to the duration of the intervention and/or the duration of the follow-up. However, the Panel considers that 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 (e.g. breast feeding and mother's diet, age of introduction of complementary foods, socioeconomic factors; EFSA NDA Panel, 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 (e.g. 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 Panel is aware of past and ongoing studies assessing the efficacy of formulae manufactured from protein hydrolysates in reducing the risk of developing allergy/allergic manifestations in general (and not to milk proteins in particular), and considers that this outcome would be of public health relevance. The Panel considers, however, 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 NDA Panel, 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 Section 2.4 (basic data set) should also be considered in this section, where applicable.

Statistical analysis

The statistical analysis should be in line with generally accepted scientific principles (see also Section 2.4. Statistical analysis).

3.3.1. Published clinical studies not proprietary to the food business operator

Published clinical studies assessing the effects of the hydrolysed formula on the incidence of allergy to milk proteins which are not proprietary to the food business operator should be identified in a systematic and transparent manner through a comprehensive review of the scientific literature.¹⁰ A reference list and a brief summary of the studies identified through the comprehensive review of the scientific literature should be given.

Electronic copies of pertinent published studies/articles not proprietary to the food business operator should be provided, as indicated in Section 4.

3.3.2. Clinical studies unpublished and/or proprietary to the food business operator

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 food business operator, should be given.

Applications should include the study protocol and the full study report of studies which are proprietary to the food business operator in line with the information requested in Appendix A of this guidance. The study protocol and the full study report should be provided, as indicated in Section 4.

4. Annexes to the dossier

Electronic copies of all pertinent studies (published and unpublished, proprietary and not proprietary) submitted in support of the dossier, including electronic copies of protocols and full study reports of clinical studies unpublished and/or proprietary to the food business operator should be uploaded in the e-submission system (in alphabetical order of first authors) as part of the technical dossier (i.e. under 'General/Scientific information' section).

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

The applicant must ensure that terms and conditions asserted by any rightsholder of studies, information or data submitted to EFSA are fully satisfied. The applicant may consult with copyright licensing authorities (i.e. at national level) for guidance on purchasing the appropriate licenses to provide studies, information or data to EFSA, taking into account the proactive disclosure requirements as detailed above. For publications already available to the public upon payment of fees (e.g. studies published in scientific journals) for which the applicant does not have or cannot obtain intellectual property rights for the purposes of the proactive public disclosure requirements, the applicant must provide (a) a copy of the relevant publications along with the relevant bibliographic references/citations for scientific assessment purposes only, in the confidential version of its application and (b) these relevant bibliographic references/citations where these publications are available to the public in the non-confidential version of its application for public dissemination on the OpenEFSA portal³⁶.

³⁶ <https://open.efsa.europa.eu>

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Abbreviations

AAP	American Academy of Pediatrics
DBPCFC	Double-blind placebo-controlled food challenge
EC	European Commission
EFSA	European Food Safety Authority
EU	European Union
FAS	Full Analysis Set
FOF	Follow-on formula
GFL	General Food Law (Regulation (EC) No 178/2002)
GLP	Good Laboratory Practice
GMP	Good manufacturing practice
HPLC/MS	High-performance liquid chromatography coupled to mass spectrometry
IF	Infant formula
IgE	Immunoglobulin class E
ISO	International Organization for Standardization
ITT	Intention to treat analysis
NDA	Panel on Nutrition, Novel Foods and Food Allergens
PP	per protocol analysis
SCF	Scientific Committee on Food
SPT	Skin prick test
TR	Transparency Regulation

Appendix A – Information to be presented in a full study report for clinical studies unpublished and/or proprietary to the food business operator

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 reports³⁷ 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 the NDA Panel.

1. Title page

The title page should include information on hydrolysed IF and/or FOF under investigation, the primary outcome variable(s) studied, the method(s) used to assess the outcome variable(s), the study design (e.g. 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 (e.g. 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.

2. Summary

3. Table of contents

4. List of abbreviations and definition of terms

5. 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.

6. 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 given.

7. General information about the study

In this section, the name/affiliation of the investigators and other people with a major role in the study (e.g. staff carrying out observations related to the outcome variable(s) under investigation), the statisticians and the authors of the report, should be provided. The section should also include information about the facilities which were used (e.g. 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.

8. Study objectives

The objective(s) of the study and the hypothesis to be tested should be specified in this section.

9. Study design

This section should outline whether the study was planned e.g. 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 outcome(s) 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.

³⁷ <http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html>

10. 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.

11. 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.

12. 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 here.

13. Blinding

Information on the strategy used to ensure blinding should be provided, e.g. measures taken to ensure that the study products were not distinguishable by smell, taste or packaging; information on how products were labelled (e.g. 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.

14. Concomitant medication or interventions

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

15. 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.

16. Outcome variable(s) measured

Information about the pre-defined primary outcome variable(s), secondary outcome variable(s) and all other outcomes planned to be measured should be presented in this section.

The methods used to assess the outcome variable(s) should be specified.

This section should also include information about the timing of the measurements (e.g. flowchart), and a justification of the appropriateness of the outcome variables chosen to achieve the objective(s) of the study.

17. Data quality assurance

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

18. Preplanned 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 (e.g. 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 (e.g. 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 preplanned 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.

19. Determination of sample size

Detailed information on how the planned sample size of the study was calculated should be given here. 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 drop-out 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.

20. Protocol amendments, deviations and violations/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 here.

Any protocol amendments (i.e. a systematic change in the protocol after approval), protocol deviations and violations (i.e. 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 (e.g. 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 (e.g. unplanned subgroup analyses to inform a subsequent study) should also be recorded.

21. 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 drop-outs 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 given here.

22. Data sets analysed

This section should include a clear definition of each analysis set used for final analysis (e.g. 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 given.

23. Baseline characteristics of the study group

In this section, baseline characteristics for all analysis sets should be given (e.g. ITT, FAS, PP, completers, other) - overall and by study centre for multicentre studies.

24. Results of assessment of compliance with the intervention and the protocol

Results of the assessment of compliance with the intervention and with the protocol should be given here.

25. 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.³⁸ 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.

26. Results of the study

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 given). 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 given as an 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.

27. Adverse events

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.³⁹

³⁸ <https://www.efsa.europa.eu/it/efsajournal/pub/3908>

³⁹ For reporting of safety-related data see also ICH-E3-'Structure and content of study reports'.