PD CEN/TR 17612:2021

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Algae and algae products — Specifications for pharmaceutical sector applications

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National foreword

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English Version

Algae and algae products - Specifications for pharmaceutical sector applications

Algues et produits d'algues - Spécifications pour les applications dans le secteur pharmaceutique

Spezifikationen für Anwendungen im Nicht-Lebensmittel-/Futtermittelsektor

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European foreword

This document (CEN/TR 17612:2021) has been prepared by Technical Committee CEN/TC 454 “Algae and algae products”, the secretariat of which is held by NEN.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. CEN shall not be held responsible for identifying any or all such patent rights.

The European committee for Standardization (CEN) was requested by the European Commission (EC) to draft European standards or European standardization deliverables to support the implementation of Article 3 or Directive 2009/28/EC for algae and algae products or intermediates. The request presented as Mandate M/547, also contributes to the Communication on “Innovating for Sustainable Growth: A Bio economy for Europe”.

The former working group CEN Technical Board Working Group 218 “Algae” was created in 2016 to develop a work programme as part of the Mandate. The technical committee CEN/TC 454 “Algae and algae products” was established to carry out the work program the secretariat of which is held by NEN. CEN/TC 454 set up a number of topic specific working Groups listed below to develop standards for algae and algae products.

This document has been prepared by Working Group 5 “Specifications for the pharmaceutical applications sector” with the support of UNI as the secretariat, in close collaboration with the other CEN/TC 454 working groups:

CEN/TC 454/WG 1 “Terminology”;

CEN/TC 454/WG 2 “Identification”;

CEN/TC 454/WG 3 “Productivity”;

CEN/TC 454/WG 4 “Specifications for food/feed sectors applications”;

CEN/TC 454/WG 6 “Product test methods”.

Algae-based products and intermediates, in this TR referred to as ‘products’, are defined as whole biomass, extracts or derivatives from algae, including a.o. algae oil and algal meal.

This document will allow the stakeholders to have access to a clear point of reference on the use of algae in pharmaceutics.

Pharmacy had standards which date back to ancient Egypt; through the first pharmacopoeias which were the Arab one, the Totum continens (Elhavi) of ar-Razi, and that of the Salerno medical school.

Then national Pharmacopoieas developed in Europe in the Eighteenth Century.

Today pharmacetical industry has the European Pharmacopoiea (EP) [3], with legal status according medicinal regulatory framework (Annex A), being harmonized with American (USP) [4] and Japanese (JP) [5] through ICH [6].

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Introduction

The interest in algae and algae-based products or intermediates as a renewable and sustainable source of carbohydrates, proteins, lipids and pigments has increased significantly in Europe.

The purpose of this document prepared by WG 5 is to provide an overview on how quality indicating parameters for algae and algae-based products and intermediates relevant for pharmaceutical applications can be handled and to identify the need for any future standard developments for pharmaceutical applications. Algae are highly available and used in many countries as fertiliser, biostimulant, animal feed, medicine, cosmetic and food ingredients, and have different compounds depending on species.

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1 Scope

This document gives an overview of recommendations on product specifications, and other relevant information, for algae and algae products for pharmaceutical applications.

This document does not apply to food and feed applications.

This document does not provide instructions on handling of technical requirements in existing legislations.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

EN 16751, *Bio-based products - Sustainability criteria*

EN 16760, *Bio-based products - Life Cycle Assessment*

EN 16848, *Bio-based products - Requirements for Business to Business communication of characteristics using a Data Sheet*

EN 16935, *Bio-based products - Requirements for Business-to-Consumer communication and claims*

EN 17399, *Algae and algae products - Terms and definitions*

EN 17477[1], *Algae and algae products - Identification of the biomass of microalgae, macroalgae, cyanobacteria and Labyrithulomycetes - Detection and identification with morphological and/or molecular methods*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in EN 17399 and the following apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at http://www.electropedia.org/

3.1
algae and algae products
functional group of organisms consisting of microalgae, macroalgae, cyanobacteria, labyrinthulomycetes and products derived thereof

3.2
Raw Material Specification
RMS
several pages technical dossier about the product, usually prepared by manufacturer, directed to provide all product approval information to the customer and usually attached to commercial contract

[1] Under preparation. Stage at the time of publication: prEN 17477.

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Note 1 to entry: Examples of RMS for some algae categories are attached as Annex B.

3.3
Technical Data Sheet
TDS
one (few) page technical document showing the technical (biochemical) parameters adopted to characterize the product and therefore being the paradigm of the Certificate of Analysis (CoA)

Note 1 to entry: TDS includes ranges of different parameters used to define the product characteristics or applicable regulatory limits.

Note 2 to entry: Models of TDS for some algae categories are attached as Annex C.

3.4
Certificate of Analysis
CoA
one (few) page document issued from laborator(ies) and reporting test results for a specific lot, usually in front of TDS parameters, including references to test method

3.5
Material Safety Data Sheet
MSDS or SDS
document issued with the aim of providing information about product compliance in respect of human health and safety at the workplace and protection of the environment

3.6
sustainable development
development that meets the environmental, social and economic needs of the present without compromising the ability of future generations to meet their own needs

[SOURCE ISO Guide 82:2019, 3.2]

3.7
algae as herbal raw material
whole, fragmented or cut algae, in an unprocessed state, usually in dried form but sometimes fresh, precisely defined by the botanical scientific name according to the binomial system (genus, species, strain, (variety) and author)

3.8
extracts
concentrated preparations of liquid, solid or intermediate consistency, usually obtained from dried algae matter

Note 1 to entry: For some preparations, the matter to be extracted undergo a preliminary treatment, for example, inactivation of enzymes, grinding or defatting.

3.9
algal drug preparations
products obtained by subjecting herbal drugs to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation, including comminuted or powdered herbal drugs, tinctures, extracts, essential oils, expressed juices and processed exudates

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3.10
active principles of algal origin
substances having proven clinical activity

3.11
pesticides
any substances or mixture of substances intended for preventing, destroying or controlling any pest, unwanted species of plants or animals causing harm during or otherwise interfering with the production, processing, storage and transport or marketing of vegetable drugs

Note 1 to entry: Pesticides include substances intended for use as growth-regulators, defoliants or desiccants and any substance applied to crops either before or after harvest to protect the commodity from deterioration during storage and transport.

4 Product characteristics

4.1 Product purity

4.1.1 General

The product characteristics specified from 4.2 to 4.6 should comply with the relevant Pharmacopeia (e.g. European Pharmacopea (EP) [3], US Pharmacopea (USP) [4] and Japanese Pharmacopea (JP) [5]), depending on the product final destination Country. This condition is applicable to algae and algae products extracts.

In case the product characteristics are referred to algae and algae products raw materials, the compliance applies after processing (extraction, refining).

The product purity is defined by the percentage of specific component in the total amount of product or, in case of whole algae biomass, by species/strain amount as percentage of the total dry weight of the product. Any other substances should be specified in the technical data sheet.

The purity percentage is specified by mass fraction (kg/kg). When this is not possible according to the state in which the product is presented, it can be expressed by volume fraction (m^3/m^3) or cell fraction (cell counts/all cell counts) or their corresponding concentrations if more appropriate.

The presence of GMO material in algae and algae products is to be considered as impurity (ref to EU Reg on GMO).

The presence of not organic material in organic algae and algae products is to be considered as impurity (ref to EU Reg on organic production).

NOTE 1 Purity is referred to contractual limits. Purity is generally not directly related to contamination since the latter is often of small extent and does not affect the amount of required substance.

NOTE 2 Purity is related to species identification and test methods. For methods on the identification of species refer to EN 17477[1].

When a product is not pure, this impurity can be detected by different types of detection methods listed in Table 1.

Macroscopical/microscopical characterization includes features, which distinguish the algae material from potential non-specified substances. Identification tests need to be specifically validated for algae and are usually a combination of methods depending on the algae species. Identification tests include macroscopical characters, microscopical characters, chromatographic procedures and physicochemical analysis. Automated tools might help like cell counters or cell flow cytometers.

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The development of tests based on nucleic acids characteristics (microsatellites, NGS, barcoding, RAPD, AFLP, etc.) to be sequenced from product samples would provide simple and fast tools for the identification of multiple targeted species and would help to indicate the presence of other nucleic acids than those of the algal material. In general, there is a lack of algae databases for the identification of foreign matter.

Currently these tests are not yet standardized and available for routine testing. Therefore, quality assurance methods aimed at reduction / prevention of risk of impurity like good farming practices (GFP), good manufacturing practices (GMP), traceability and Chain of Custody systems are essential to monitor the level of purity for algae and algae products.

An overview of the currently available methods for qualitative and quantitative determination of algae purity is shown in Table 1. The reliability of these different methods depends on the complexity of the species and impurities and are not necessarily sufficient for each case.

The following substances affecting the purity of a product can be addressed:

— Physical foreign matter (i.e. (micro) plastic fragments, wires from fishing nets and ropes, feathers from birds, shells);

— Other algae (including toxin-producing cyanobacteria), bacteria or organic materials (i.e. grass, proteins or oils from other species);

— Algae from other location then stated (i.e. from Asia instead of Europe). Most promising test to detect the presence of algae from other regions then stated, is the use of stable isotopes. However, first databases with the characterization of isotopes from different regions need to be established.

Macroscopic examination is suitable for determining the presence of particles of foreign matter in whole or cut (macro)algae. Foreign matter are all materials which are not part of the (macro)algae biomass. Additional aids (like UV-light, sieving, centrifugation) might be helpful to find the foreign matter.

The algae harvesting and farming company should provide the purity on a CoA for each batch of algae.

4.1.2 Purity of microalgae and cyanobacteria

Microscopy is a suitable tool for microalgae, cyanobacteria and all powdered materials. Reduction of particle size or powdering materials can hide the presence of non-specified substances and make it more difficult to detect. Also diluted samples cannot be qualified and need a quantification step.

The determination of purity in fresh sample can be possible using inverted microscopy (Utermöhl technique according to EN 15204) to determine the microalgae and cyanobacteria biovolume. This European Standard describes the necessary methods for measuring cell dimensions and for the calculation of cell or counting unit volumes to estimate the biovolume (wet weight biomass) in phytoplankton samples. This method has been successfully used by French spirulina producers to monitor the quality and purity of their biomass.

Where available, methods based on nucleic acid analysis of specific species, fingerprinting or metabarcoding (using 1 or 2 markers) may provide information on purity of any algae powder.

Currently these methods are not yet available for routine tests.

4.1.3 Purity of macroalgae

By their very nature, macroalgae growing in the wild may be found to grow interspersed with other species. Therefore, it is not always practical to obtain a harvest of macroalgae that is 100 % pure.

Macroscopic examination is suitable for determining the presence of foreign matter in whole or cut macroalgae. This applies also to algae cultivated in tanks.

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Visual inspection is suitable for freshly harvested algae as the intact cells can be recognized as a whole. When the holdfast is removed, or when epiphytic organisms are present on the surface visual inspection may not be sufficient to identify the species after harvesting. For ground algae, cells are disrupted and algae type can no longer be recognized nor be quantified.

Microscopy is indispensable for all powdered materials. Reduction of particle size or powdering materials can hide the presence of non-specified substances and make it more difficult to detect. Also diluted samples cannot be qualified and need a quantification step.

The most reliable way to monitor the purity of macroalgae is for companies to assess the freshly harvested raw material by visual, macroscopic means. Purity should be expressed as the percentage of the target macroalgae of interest over the total weight of the harvested biomass. In case the growth of other algae/bacteria on the macroalgae is noticed, some follow-up test may be needed (microscopical for instance) in order to check for potential impurities from hazardous organisms to verify if the product is safe for the purpose of the product.

It is noted that macroalgae harvested from the wild may contain up to 10 % of other species that grow alongside and co-occur with the main species that is harvested; of course, if the composition of such products is fit for use, it can still be considered a single ingredient product, defined by its 90 % component, because the presence of other macroalgae is not regulated by specific limits provided all the macroalgae is safe for intended use.

4.1.4 Purity of algae derivatives or extracts

Pure algae extract can include a range of compounds present in the algae and/or it may refer to a pure fraction containing one ore more compounds. Purified extracts with single components or a small number of components can be responsible for the product efficacy. In complex mixtures of natural origin (extracts) the efficacy may be related to synergistic effects of several components of the raw material and not to a single molecule.

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Table 1 — Types of impurities and detection methods

Impurity	Fresh materials		Dry materials or powder	
	Qualitative	**Quantitative**	**Qualitative**	**Quantitative**
Physical foreign matter	Visual inspection	Visual inspection	Visual inspection	Visual inspection
	Microscopical inspection	Microscopical inspection	Microscopical inspection	Microscopical inspection
	Additional tools	Additional tools	Additional tools	Additional tools
Other algae, bacteria and organic materials	Visual inspection	Visual inspection	Visual inspection	Visual inspection
	Microscopical inspection	Microscopical inspection	Microscopical inspection	Microscopical inspection
	Nucleic acid analysis	--	Nucleic acid analysis	--
	Chemical fingerprinting[a]	--	Chemical fingerprinting[a]	--
Regional identity	Isotopic analysis	Isotopic analysis[b]	Isotopic analysis	Isotopic analysis[b]

[a] chemical fingerprinting includes different techniques, for example: IR spectra, NMR, TLC, Mass Spectrometry, fatty acid profile.

[b] methods to be developed.

4.1.5 Methods of analysis

The inventory of available methods and recommendation for prioritizing future method development on purity of algae and algae products are listed in Tables F.1 and F.2.

Specific gaps to use these methods are lack of respectively [7]:

— sampling strategies for visual inspection and microscopy;

— quantification method for microscopy;

— databases, algae selective primers and protocols for nucleic acid identification; and

— databases for molecular and chemical fingerprinting and isotope analysis (see Annex F).

In addition to the gap per analysis methodology, methods are lacking for the quantification of the found foreign matter. Furthermore, protocols describing what to do with the product if the presence of a foreign matter is detected, are lacking.

It is recommended to further develop and standardize the following protocols [7]:

— sample strategies for quality control of fresh materials and of dry/powdered materials;

— quality control protocols describing which other checks have to be done when foreign matter is found;

— visual inspection protocols for fresh materials and for dry/powdered materials;

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