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4 Questions and answers on wheat starch containing gluten
5 in the context of the revision of the guideline on
6 'Excipients in the label and package leaflet of medicinal
7 products for human use' (CPMP/463/00 Rev. 1)
8 Draft

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Comments should be provided using this [template](#). The completed comments form should be sent to excipients@ema.europa.eu

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14 Questions and answers on wheat starch containing gluten 15 as an excipient in the context of the revision of the 16 guideline on 'Excipients in the label and package leaflet of 17 medicinal products for human use' (CPMP/463/00 Rev.1)

18 **1. Background**

19 Following the European Commission decision to revise the Annex of the guideline on 'Excipients in the
20 label and package leaflet of medicinal products for human use' (CPMP/463/00 Rev. 1) [1], a
21 multidisciplinary group of experts involving SWP (lead), QWP, PDCO, PRAC (ex PVWP), CMD(h), VWP,
22 BWP and BPWP was created in 2011.

23 The objective of this group is to update the labelling of selected excipients listed in the Annex of the
24 above mentioned EC guideline, as well as to add new excipients to the list, based on a review of their
25 safety. The main safety aspects to be addressed were summarised in a concept paper published in
26 March 2012 [2].

27 Q&A documents on excipients will be progressively released for public consultation. They will include
28 proposals for new or updated information for the labelling and package leaflet. Once a Q&A is finalised,
29 the corresponding background report supporting its review will also be published.

30 When the Q&As of all the selected excipients have been finalised, they will be grouped in a single Q&A
31 document. This information will be integrated in the updated Annex of the new revised EC guideline.

32 **2. What is wheat starch (containing gluten) and why is it 33 used as an excipient?**

34 Wheat starch is produced from wheat flour by removing proteins including gluten, meaning that wheat
35 starch only contains trace amounts of gluten and other proteins.

36 Wheat starch is occasionally used as an excipient in the formulation of medicinal tablets, capsules and
37 ointments in a variety of functions; as a diluent, a disintegrant, a glidant, or as a binder. Dependent on
38 the quality of the wheat starch, gluten can be present; however there is currently no regulatory
39 guidance in place on the acceptable levels of gluten in medicinal products. Gluten is covered only as a
40 constituent of wheat starch in the current guideline [1].

41 Gluten is a protein composite found in wheat and related grain species such as rye and barley.

42 Gluten proteins can be divided into two main fractions according to their solubility in aqueous alcohols:
43 the soluble gliadins and the insoluble glutenins. Both fractions consist of numerous, closely related
44 protein components characterized by high glutamine and proline contents [3].

45 In January 2009 a European Commission (EC) Regulation on gluten-free foods was adopted for foods
46 for special dietary use for persons intolerant to gluten. According to Commission Regulation (EC) No
47 41/2009, concerning the composition and labelling of foodstuffs suitable for people intolerant to gluten,
48 the following definitions are used to define levels of gluten in foodstuff. 'Very low gluten' or 'gluten-
49 free' is used for indicating respectively a content of gluten not exceeding 100 mg/kg and 20 mg/kg
50 (100 ppm and 20 ppm respectively) [4].

51 **3. Which medicinal products contain wheat starch?**

52 It is generally believed that only relatively few marketing authorisations are affected throughout the
53 EEA. For example, in the UK, a search of the MHRA database showed that there are 20 marketing
54 authorisations (MAs) that mention wheat starch as one of the excipients in the medicinal product. Most
55 of these (n=19) are oral dosage forms and one is a topical preparation which is applied as an ointment
56 to the skin. Similarly in several other countries, relatively few MAs containing wheat starch were found,
57 mainly products for oral use.

58 The gluten content in MAs already approved should be determined as it is likely that protein levels are
59 confused with gluten levels. Many calculations provided assumed a gluten level of 0.3% in PhEur
60 compliant wheat starch, however this is an incorrect assumption. The PhEur states that wheat starch
61 should contain no more than 0.3% protein [5]. In literature it has been reported that at levels between
62 0.23% and 0.34% protein, the gluten content varied between <0.01 to 0.05% [6]. Following
63 communication with EDQM, it is assumed that a gluten content of no more than 100ppm is present in
64 wheat starch, when complying with the wheat starch monograph levels of 0.3% protein. This is based
65 on notes provided by EDQM, when working on the Wheat Starch PhEur monograph. The notes provided
66 indicate that there is a correlation between total protein limit and gluten content, based on the Kjeldahl
67 paper [6], but also on additional tests conducted by experts at the time.

68 **4. What are the safety concerns?**

69 Coeliac sprue, also known as coeliac disease, is an autoimmune disorder of the digestive tract that
70 occurs in genetically pre-disposed people of all ages from infancy. Coeliac disease is caused by a
71 reaction to gliadin, a prolamin (gluten protein) found in wheat, and similar proteins found in crops like
72 barley and rye.

73 It is a chronic disorder that results in an inability to tolerate gliadin. When patients with coeliac disease
74 ingest gliadin, an immunologically mediated inflammatory response occurs that damages the mucosa
75 of the intestines resulting in maldigestion and malabsorption [7-10].

76 Coeliac disease occurs in adults and children and the rate of occurrence in the population is around 1%
77 and prevalent all over the world [11-19]. In most affected people, coeliac disease remains
78 undiagnosed [20] although the rate of diagnosis is increasing [21].

79 The only known effective treatment is a lifelong gluten-free diet. When a patient with coeliac disease is
80 exposed to gluten, the patient may develop symptoms that include pain and discomfort in the digestive
81 tract, chronic constipation and diarrhoea, failure to thrive (in children), anaemia, weight loss,
82 weakness and fatigue, but these may be absent, and symptoms in other organ systems can develop.
83 The extraintestinal symptoms include osteopenia, osteoporosis, skin disorders, neurological and
84 hormonal disorders [8-10].

85 Upon exposure to gliadin, and specifically to three peptides found in prolamin, the enzyme tissue
86 transglutaminase modifies the protein, and the immune system cross-reacts with the small-bowel
87 tissue, causing an inflammatory reaction. That leads to a truncating of the villi lining the small intestine
88 (called villous atrophy). This interferes with absorption of nutrients because the intestinal villi are
89 responsible for absorption [8-10, 21].

90 The total exposure needed to trigger the symptoms is not exactly known and may differ between
91 people. However a review of available literature suggests that consumption of less than 10 mg of
92 gluten per day is highly unlikely to trigger disease activity [22-26].

93 **5. What are the reasons for updating the information in the**
94 **package leaflet?**

95 According to the current guideline, if the medicinal use in itself is unlikely to trigger disease activity,
96 but still contains gluten, then there are no requirements on the levels of gluten to be mentioned (see
97 table below). However, as patients with coeliac disease are likely to have additional low levels of
98 exposure to gluten in their daily diet, it is important to inform on the levels of gluten in a particular
99 medicine to allow patients and doctors to make the right choice.

100 It is proposed that the gluten levels should be determined in the wheat starch excipient only and not
101 as part of the drug product specification.

102 Where wheat starch that contains gluten is used, we recommend using the same definitions for levels
103 of gluten in medicines, as are used in Commission Regulation 41/2009, which concerns the
104 composition and labelling of foodstuffs suitable for people intolerant to gluten. This would make it clear
105 for people involved with or affected by coeliac disease to understand the gluten content definitions
106 used and to take into account their total intake of gluten when taking medicine and plan their diet
107 accordingly, i.e. 'very low gluten content', up to 100 ppm (100 µg/g), and 'gluten-free', up to 20 ppm
108 (20 µg/g).

109 Taking into account the relatively small amount (weight) of medicinal products consumed daily
110 compared to a daily diet, we would expect that very low levels of gluten content in medicinal products
111 would be acceptable, i.e. 100 ppm, without affecting the daily diet considerations of people with coeliac
112 disease. The package label and leaflet should reflect this information in line with what is already in
113 place in the excipients guideline and the following information should be considered: For products
114 which contain gluten at levels below 20 ppm, it is recommended that a gluten-free statement is
115 included on the label and additional text is included in the PIL.

116 For products which contain gluten levels between 21 ppm and 100 ppm, a statement should be
117 included that the product contains only very low levels of gluten, to a maximum of 100 ppm, and is
118 suitable for people with coeliac disease. One dosage unit or one daily dose contains no more than xx
119 mcg gluten.

120 As has been outlined previously, the maximum content of protein in pharmaceutical grade wheat
121 starch is limited to 0.3% protein and it is therefore assumed that the gluten content will be maximum
122 100 ppm. Therefore all statements and labelling information relate to situations where the content of
123 gluten is maximum 100 ppm.

124 If the wheat starch excipient contains gluten levels below 20 ppm, the wheat starch should be labelled
125 as gluten free, whereas if the wheat starch contains gluten below 100ppm (but above 20 ppm), the
126 wheat starch should be labelled as containing very low gluten content.

127 Levels higher than 100 ppm of gluten should not occur as PhEur compliant wheat starch will not
128 exceed 100 ppm which means that only if the product would consist of 100% wheat starch a
129 concentration of 100 ppm could be reached based on a worst-case scenario.

130 The gluten content may be calculated based on the content of wheat starch in the product and taking
131 into account a maximum level of gluten of 100 ppm in PhEur compliant wheat starch.

132 Calculation of gluten content will be in practice a 'worst-case' calculation with the assumption of a
133 maximum 100 ppm content in wheat starch as the actual gluten content may vary in wheat starch on a
134 batch-to-batch basis. Statements in the SmPC, on the labelling and in the PIL regarding the gluten

135 content must only be applied to those medicines which include wheat starch as an excipient. Products
136 which do not contain wheat starch may not make any reference to the absence of gluten as this would
137 be considered promotional.

138 For companies already with a MA, and whose medicinal products contain wheat starch, gluten warnings
139 in line with what has been outlined above should be included in the SmPC, PIL and label.

140 **Current information in the package leaflet**

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Wheat Starch	Oral	Zero	<p>Suitable for people with coeliac disease.</p> <p>Patients with wheat allergy (different from coeliac disease) should not take this medicine.</p>	<p>Wheat Starch may contain gluten, but only in trace amounts, and is therefore considered safe for people with coeliac disease. (Gluten in wheat starch is limited by the test for total protein described in the PhEur monograph.)</p>

141 **6. Proposal for an updated information in the package leaflet**

Name	Route of Administration	Threshold*	Information for the Package Leaflet	Comments
Wheat Starch containing gluten	Oral	Zero	<p>This product is regarded as “gluten-free” (less than 20 ppm (ug/g) of gluten) and is suitable for people with coeliac disease.</p> <p>Patients with wheat allergy (different from coeliac disease) should not take this medicine.</p>	<p>Gluten in wheat starch is assumed to be limited by the test for total protein described in the PhEur monograph, whereby compliance with the protein limit of 0.3% is considered to imply that there is no more than 100 ppm of gluten present in the wheat starch.</p>
		20 ppm (µg/g)	<p>This product contains only very low levels of gluten, a maximum of 100 ppm (100 µg/g), and is suitable for people with coeliac disease.</p> <p>One dosage unit contains no more than xx mcg gluten.</p> <p>Patients with wheat allergy (different from coeliac disease) should not take this medicine.</p>	<p>Alternatively, the gluten content in the wheat starch can be determined using a suitable method.</p> <p>Based on this information, the maximum level of gluten in the medicinal product can be determined when it is known what levels of wheat starch are used in the product.</p>

142 *Note: The threshold is a value, equal to or above which it is necessary to provide the information stated.
 143 A threshold of 'zero' means that it is necessary to state the information in all cases where the excipient is present in the medicinal product [1].

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