9 October 2017
EMA/CHMP/674221/2014
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on the draft 'Questions and answers on wheat starch (containing gluten)' (EMA/CHMP/704219/2013)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	MEB - Medicines Evaluation Board, the Netherlands
2	EFPIA – Sini Eskola (sini.eskola@efpia.eu)
3	BPI - Bundesverband der Pharmazeutischen Industrie (BPI e. V.)
4	MSD - Merck Sharp & Dohme
5	Tine Aarsen - Netherlands
6	AESGP - Association of the European Self-Medication Industry
7	DZG - Deutsche Zöliakie-Gesellschaft, Stuttgart
8	SciencePharma, Poland

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	It is not clear whether the Q&A will be a stand-alone document or should be read in addition to the current Guideline. In case the Q&A is intended to be a stand-alone document, an explanatory note to clarify the structure of the Table in Section 6 should be included. If it is to be read in conjunction with the current Guideline, this should be clearly mentioned.	We acknowledge your comment. The Q&A should be read in conjunction with the revised guideline and the report on "Wheat starch containing gluten".
1	The table in section 5 is useful to compare the information in the current document with the proposed text. However in the final document the table in section 5 may cause confusion. There is a risk that the information in this table will be used instead of the proposed information, especially because the table refers to "*current* information in the package leaflet". Therefore, it is advised to delete the table in section 5 in the final document.	We acknowledge your comment. It is currently only included for information. The title of the table has been changed.
1	The purpose of the last column of the Table included in Section 6 "Comments" is not clear. It is not clear when information is to be included in the SmPC, or when the information is included for the benefit of applicants and competent authorities. Any information considered relevant for health care professionals should be included in the SmPC, and hence reference to the SmPC should be included. It is suggested to replace the last column by two other columns; one for information to be included in the SmPC and a second column for additional comments for the benefit of applicants and competent authorities.	We acknowledge your comment and we have deleted the words "healthcare professionals". The purpose of this column is explained in the explanatory notes of the guideline. Article 59(1) requires that the package leaflet must be in accordance with the SmPC and shall be drawn up in accordance with the SmPC. Therefore, consistent information should be stated in both documents. This is taken into account at the time of writing the SmPC for all excipients. The exact wording of the SmPC statement and its location (SmPC section) will depend on product-specific aspects such as the actual quantity of the excipient, the duration of treatment, the type of disease and finally the benefit-risk of the medicinal product.

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1	In the title of this document and in the title of the guideline is mentioned '…Excipients in the label and package leaflet...' However also advice regarding the information to be included in the SmPC is given. Therefore, we propose to change "in the label and package leaflet" into 'in the product information'.	The title reflects the scope of the guideline. For some excipients a comment is included for adding a statement in the SmPC. The purpose is to reinforce or clarify the safety concerns and context (duration, patient population) in a more technical language. However it does not have the purpose to propose the exact wording for the SmPC (see above).
2	We welcome this Q&A document by the EMA. The focus on oral products is appropriate. It is important to reflect that 'gluten free' labelling may only be applied if wheat starch is used in the product, as wider labelling as such would be considered promotional. It may not be useful to apply 'gluten free' labelling to all products where wheat starch is not a component, and thus it is welcomed that the labelling expectation is not broadly applied. However, if this labelling change is being conducted to provide additional safety-critical information to patients then patients may be confused by a lack of 'gluten free' labelling on products that do not contain wheat starch. For example, a product may lack wheat starch and thus not be labelled as 'gluten free,' whilst other similar products on the market may contain wheat starch to some degree and be labelled with either 'gluten free' or 'contains very low levels of gluten.' Which product might a person with coeliac disease chose to use, based on the labelling information provided? We also note that below both 20 ppm and 100 ppm a product is considered suitable for people with coeliac disease (in line with previous labelling requirements) and, furthermore, compliance with the European Pharmacopoeia (PhEur) monograph for wheat starch	We acknowledge your comment. A standalone "gluten free" label is not desired for medicines. However, there is a need from patients and healthcare professionals to be informed about the presence or not of gluten in products containing wheat starch. Therefore, the packaging will mention the presence of wheat starch (only) and the PL will provide additional information on whether the content can be regarded as gluten-free or not This would allow for an informed choice to be made on whether or not to take the product. The work plan of the excipients working group give an idea on when a new label is expected to be finalised. The requirements for implementing the new wording is explained on the EMA website in a page dedicated to excipients labelling. In any case, implementation of a new wording is not required until its inclusion in the Annex to the guideline at the earliest.

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	will prevent higher levels of gluten being present. On balance therefore we propose either that no change to the labelling requirement is made (as it may falsely suggest a 'gluten free' benefit to some products) or alternatively that no pharmaceutical products should be considered to be at risk from gluten content and thus no products should need any labelling for gluten content. Either approach would prevent any false impression of valuable (even promotional) 'gluten free' status being applied to some wheat starch containing products. Additionally, it is unclear what type of variation would be required to submit these types of changes. It would be helpful if there is a phased-in approach to bring all labels into compliance with these set of new additions to the excipient guideline, and not to have to do each update one-by-one.	
4	Merck acknowledges the need for and supports the revision of the guideline and the text concerning the excipient in question. We completely agree with your scientific conclusions. Nevertheless, we have some concerns that the information planned for the package leaflet is far too complicated for the patients and could therefore cause confusion or worries.	We acknowledge your comments. These have been addressed in the point below.
4	We acknowledge the need for and welcome the update of the guideline and the declaration of wheat starch/gluten in the patient information leaflet based on the following principles: The text will only be applied to those products which include wheat starch as excipient. Absence of wheat starch will not be declared.	We acknowledge your comment and the text has been simplified. We can confirm that: - The text will only be applied to those products which include wheat starch as excipient. - Absence of wheat starch will not be declared. - The text is only used for products administered

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	The text should only be used for oralia. Nevertheless, our experience with questions coming from patients shows that the proposed text might cause some problems. The text as proposed would be preferable for inclusion in the SmPC. The regulation that absence of wheat starch is not declared will not be known by patients, i.e. they would wonder, why products without any wheat starch are not labelled as "gluten-free".	orally. See also above response to previous comments on the same issue.
5	I would like to comment on the new proposal for labeling medicine products with information about gluten and the suitability for patients with celiac disease. In our household, two persons have celiac disease, my 14 year old son and me, his mother. We have great difficulties in finding medicinal products and supplements that contain no gluten at all. Several times we became ill from medications. And I think medications are supposed to make you better, not to make you ill, or more ill than you already were. I hear you asking, how do you know that the amount of gluten is the issue? That is very simple. I can give two examples of products that made us ill. The first one: my son suffered from migraine attacks. His pediatrician told us, to give him a double dose paracetamol as soon as the first signs of such an attack became evident (blind on one eye and fingers feeling pinched). So I gave him 2 paracetamol tablets for children from Roter (1000 mg total dose). Soon after that, he became nauseous, and started to vomit. He told me, that he became much sicker after he took these two tablets. At first I did not take his complaints very seriously, but lying on my bed later that night, I thought, what if it is true? If this medication really contains gluten that makes him (more) ill? So I contacted the manufacturer, they looked at the ingredients and explained to me, that the mannitol in	We acknowledge your comment and we sympathise with your situation, and the issues that have arisen as described. This document will not be able to address every specific example that may arise in a clinical setting. The excipient guideline is to cover issues broadly and the majority of people affected.

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	this product is derived from wheat. I know that the amount of gluten is very small in wheat derivatives. But I also know that my son cannot eat any candy or other food product with maltodextrin, glucose or dextrose or any other wheat derivative, because they all contain too much gluten for him. I had never heard of mannitol before. I wrote my experiences down and send it to the Ducth governmental College ter Beoordeling van Geneesmiddelen (CBG). I did so after testing this product myself. It will not surprise you that I became ill of this very small amount of gluten too. The second example comes from tablets for a sore throat (from VSM). I used these many years for my son. But all at once, we became ill from these tablets. I contacted the manufacturer, and found out that they used glucose from maize in the past, and turned to glucose from wheat in the present product. This sounded very familiar for me. My son had eaten candy for 8 years, all the time he was at primary school. But the last year, in 2011/ 2012, he became ill from one candy after another (the same year his migraine attacks started). I contacted many food manufacturers, and they all told me the same story: they used maize derivatives in the past, and they changed this and used wheat derivatives instead. So instead of a drawer full with special gluten-free candy, no candy remained for him at all. Apparently the same development which happened with food products happened to medications as well. I still did not understand why this change took place. But the university of Wageningen (WUR) made things clear to me: wheat is the cheapest ingredient at this moment. And the production of wheat has doubled the last ten years, as well as the production of 'vital wheat gluten' with more concentrated wheat proteins. Besides that, new EU regulations had introduced taxes for sugar. So wheat became an attractive	

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	alternative for sugar, because it is possible to make sweeteners from wheat. The governmental agricultural organization 'Productschap Akkerbouw' told me that a large manufacturer of glucose syrup from the United States (Cargill) had closed its doors in the Netherlands in 2011/ 2012, and that glucose from then on was made from wheat from farmers in Germany and France (instead of maize). In the United States, wheat derivatives are no threat to patients with celiac disease. I obtained information from the e-book 'Jump-start your gluten-free diet' from the Chicago Celiac Disease Center; in this book I read that the two large manufacturers of glucose, dextrose and so on made these products with maize, not with wheat. Of special concern is the use of 'vital wheat gluten' in many products. During 8 years at primary school, my son was sick now and then, but it was manageable. But when wheat became cheaper than maize, our situation worsened drastically. Now my son cannot go to school 2 or 3 days a week. His growth has stagnated, while he should be growing rapidly at the age of puberty. The reason: an incredible amount of food products contain gluten. One third contains gluten that is labeled on the package as wheat. And in other cases wheat starch is used (below or above 20 ppm in the end product). In more other cases wheat derivatives are used. I collected many of them the last years, becoming an expert in this field. We became ill from traces of gluten in brown sugar (caramel from wheat), tea (aroma sticks with maltodextrin from wheat), lemonade, coffee milk, baking powder, salmon, chocolate, candy, ice, desserts, meat products, toothpaste, and so on, and so on. Even gluten-free products contain too much gluten for us. But one question remains: is it all gluten? So the Dutch celiac organsation (NCV) and the governmental food agency Voedsel- en	

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	Warenautoriteit (VWA) were so kind to check things. The VWA came to my home and took the chocolate sprinkles that made my son ill for two days (with no gluten mentioned on the package). They contain 5 ppm gluten, they told me. I did not know that anyone could become ill from such a small amount of gluten. In fact, I realized that he can become ill from as little as 0.04 mg gluten. That is such a small amount, you actually can't see it. In the next years, the VWA tested more products: gluten-free flour contained 6 a 7 ppm gluten, and the sweets with maltodextrin at the front of the ingredients list contained gluten between 3 and 10 ppm. They even tested Ritalin (for someone else) and found out that it contains between 3 and 10 ppm gluten. So what did docters say? Is it possible to react to such small amounts of gluten? Yes, it is possible, said the well-known Dutch celiac disease expert dr. Mulder (VUmc). He pointed to a study named 'a milligram of gluten a day, keeps the mucosal recovery away' from a non who took hosties with a very small amount of gluten in it and did not recover. I looked at the medical literature and found other studies with very small amounts of gluten that made patients with celiac disease ill: Chartrand et al. (1997) 1,5 mg/dag Ciclitira et al. (1985) 4 mg/ dag Biagi et al. (2004) 1 mg/dag Scotta et al. (1982) 1,4 mg/ dag So apparently a subset of celiac disease patients cannot tolerate a very tiny amount of gluten. But what about the 20 ppm amount of gluten that is considered safe to many celiac disease patients? I read the famous Catassi study, on which the current 20 ppm level is	

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	based. Although the 'double blind, placebo controlled' study has great value, it is based on a very small group of patients, and what's more: only healthy patients are involved: people with healed intestines, negative antibody test results, and no complaints in daily life. The American Food and Drug Association made comments on this. In an overview of threshold levels the FDA argues that this is not a representative group; they assume that the most sensitive patients are not involved: the ones with positive antibodies, a low Marsh score (1/2) and/or complaints in daily life. A large group of patients has their celiac disease not well controlled (35 up to 50 % according to other studies). But their individual level of tolerance has not been investigated. What struck me in the Catassi study is that one person stopped with participating in the study, because he became ill form an amount of 10 mg of gluten per day. That represents our situation, and that of other supersensitive patients. But also the opposite is the case: two persons, who took a daily amount of 50 mg. gluten, had intestines that recovered, instead of worsened. So in my opinion, there is a wide spectrum of tolerability levels, some patients being more sensitive to gluten and some patients being less sensitive to gluten. But the goal of the study was to find a 'one size fits all' approach. Not to find a limit that suits all celiac disease patients. The conclusion of Catassi is, that 20 ppm is a safe product for the **majority of** celiac disease patients (of note: he never said that it suits **all** patients). In real life, there is a 'range of tolerability levels'. And we belong to the very small group that cannot tolerate any gluten at all. Interesting of the Catassi study is that only products that replace bread, biscuits and pasta, the so-called grain-based products, are supposed to contain some small amounts of gluten. All other products are	

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	supposed to contain no gluten at all. But that was Italy, many years ago. How are we doing at this point? My son and I cannot eat 90% of the products in the supermarket. Some investigations have been made to check out the gluten content of all kinds of flour in Canadian supermarkets. It turned out that 10% of these flours (from maize, rice, and so on) contain gluten above 20 ppm (not gluten-free) 57% contain gluten at al level between 3 and 20 ppm and 19% contain no detectable gluten (below 3 ppm). Many food products contain ingredients that are contaminated with gluten, because they come into contact with wheat or products with wheat in the same factory or in the transport line. Now back to medication. You can easily say, such a small tablet or dosage unit contains so little gluten that cannot harm you. But do you realize that 90% of the products in the supermarket contain very small amounts of gluten? And all these small amounts of gluten together may be a threat to the health of celiac disease patients. So please change your scope from medications to the patients taking these medications. Your pill is not the only thing we put in our mouth in a day. In fact, many celiac disease patients have different pills, many need supplements with vitamins, calcium, iron, and so on, to have a better nutritional status. Many suffer from complications like osteoporose, hyperthyroidy and other auto-immune conditions. Taking more medications and supplements can make the amount of gluten ingested higher. Of even more concern is the question whether the medication can be effective, when it is packed in a small dose of gluten. I have great doubts about that. Medications do not work properly by many celiac	

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	disease patients, because their intestines are not healed very well, and not all stuff is absorbed. In fact, the gluten in the medication can prevent the medication to work properly. Unfortunately, there is no study in this field (giving celiac disease patients with ADHD Ritalin with and without gluten traces (wheat starch) for example, or give patients with osteoporosis calcium supplementation with and without gluten traces (most times sorbitol). In my opinion, medications for celiac disease patients should not contain any (detectable) traces of wheat or gluten. RIKILT (the Dutch Food safety organization) has compared different tests that measure the amount of gluten (in behalf of the VWA). The present ELISA R5 antibody test which belongs to the Codex Alimentarius as the 'preferred method' actually did not perform very well at very low amounts of gluten (according to R5 no gluten was present in Ritalin, but according to G12 antibody testing there was a detectable amount of gluten between 3 and 10 ppm). You mention that the amount of gluten can be determined 'using a suitable method' but the question is, which method is that? In my opinion, when any traces of gluten can be found (with a sensitive method), it should be mentioned on the package leaflet. Going back to wheat derivatives. They are very common. And are used in so many products that I have lost count. I will give you my list of wheat derivatives, I collected them the last few years: - glucose - dextrose - maltodextrine	

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	- fructose - caramel (kleurstof E150) - mannitol (zoetstof E421) - xylitol (zoetstof E967) - sorbitol (zoetstof E420) - maltitol (zoetstof E965) - ascorbinezuur/ vitamine C (antioxydant E300) - melkzuur (voedingszuur E270) - maltitol - lactitol - isomalt The nice thing about this is, that they can be made from other sources as well, maize, rice, potatoes, and so on. Then it is no problem for us. But I would really like to know if there are any wheat derived ingredients in my medication. So I prefer that you mention this on your package leaflet as well, like this: glucose (wheat), for the small group of patients with celiac disease that are very sensitive. Then another issue. I have already mentioned that the 20 ppm level is suitable to **most** patients with celiac disease. And it is necessary to declare this clearly on your label. In real life, patients with celiac disease decide if they eat gluten-free, or gluten-free and wheatstarch-free. Unfortunately, there are no studies that reveal the amount of patients that cannot tolerate gluten-free wheat starch, and maybe the amount of gluten in wheat starch may even be different in	

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	different nations. In the Netherlands, it is common to start with a gluten-free diet, and after 12 months a medical evaluation takes place. Some patients have antibodies that are too high, their intestines do not heal well, or their symptoms do not disappear. Doctors have agreed that this group of patients should not eat gluten-free wheat starch, to see if their symptoms of ongoing disease activity disappear, which happens in the majority of cases (CBO Richtlijn Coeliakie en DH van maagdarmleverartsen http://www.mdl.nl/uploads/240/442/richtlijn_Coeliakie_definitief.pdf) So when you eat gluten-free and wheatstarch-free every day, it should be very strange to get medications that contain wheat starch. And in fact, the insurance company will not give you an alternative, because your present proposed text considers it to be safe… So in this case, patients have to pay for other medications that do not make them ill. There should be a possibility that when a celiac disease patient follows a gluten-free and wheatstarch-free diet, this also applies to medications. That's why it is so important to add that 20 ppm is considered safe for **most** patients with celiac disease. And of note: the gluten-free products with wheat starch are also tested below the level of 20 ppm gluten. Still a considerable amount of Dutch celiac disease patients do not eat gluten-free products with wheat starch. In your proposal, you mention that the amount of 100 ppm gluten (low gluten) is suitable for patients with celiac disease. I have a pretty good overview of products 'low in gluten' in the Netherlands, and I only know one item (biscuits) with that claim; hundreds of other products contain less than 20 ppm gluten. Products with 100 ppm of gluten are not considered to be safe in our country. Doctors and dietitians have the opinion that this higher amount of gluten is	

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	actually not safe. The Dutch doctor Kneepkens states that products in the range of 20 to 100 ppm gluten 'should not appear on the menu of celiac disease patients'. I don't see why an exception should be made for medications, knowing that in many food products traces of gluten are hidden (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3378840/). On line 73 you mention gliadin, not glutenin, but also glutenin can make patients with celiac disease ill. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3349865/ And I miss recent information about the fragments in gluten that make celiac patients ill: celiac disease toxic epitopes; 31 are known and newer ones will follow. In the future newer methods to detect gluten will search for these specific epitopes. Sources: - Biagi F et al. A milligram of gluten a day keeps the mucosal recovery away: a case report. Nutr Rev. 2004. 62(9): 360-363 - Catassi C, Fabiani E, Iacono G et al. A prospective, double-blind, placebo-controlled trial to establish a safe gluten threshold for patients with celiac disease. Am.J.Clin.Nutr.2007;85:160-6. - Chartrand L et al. Wheat starch intolerance in patients with celiac disease. 1997. J Am Diet Assoc 97(6): 612-618 - Ciclitira PJ et al. Evaluation of gliadin-containing gluten-free products in coeliac patients. 1985. Hun Nutr Clin Nutr 39C: 303-308 - FDA, Health hazard assessment for gluten exposure in individuals with celiac disease: determination of tolerable daily	

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	intake levels and levels of concern for gluten. 2011 - Hollon JR et al. Trace gluten contamination may play a role in mucosal and clinical recovery in a subgroup of diet-adherent non-responsive celiac disease patients. BMC Gastroenterology 2013, 13-40 doi:10.1186/1471-230x-13-40 - Koerner TB et al. Gluten contamination of naturally gluten-free flours and starches used by Canadians with celiac disease, Food Additives & Contaminants: Part A, 2013 http://dx.doi.org/10.1080/19440049.2013.840744	
6	AESGP supports the proposals for new or updated information for the labelling and package leaflet regarding gluten as an excipient in human medicines.	We acknowledge your comment.
8	It is necessary to provide patients with appropriate information about pharmacotherapy, including potential risks. Having regard to the above statement, patient should be informed about gluten content in medicinal products. In the discussed document, it is assumed that in wheat starch containing no more than 0.3% protein, gluten level is up to 100 ppm. However, the cited results of Skerritt (1992) study show that the gluten content can be significantly higher. It is not clear what the basis of the presented assumption was. If any additional tests, confirming gluten level in wheat starch were available, it would be recommended to present the results in the discussed document (i.e. notes provided by EDQM).	We acknowledge your comment. EDQM previously established that 0.3% protein in wheat starch corresponded to 100 ppm gliadin. The results obtained were based on studies conducted, the Skerrit paper and the methods used in the article.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 63-64	8	**Comment:** In the document, it is assumed that a gluten content of no more than 100 ppm is present in wheat starch, when complying with the wheat starch monograph levels of 0.3% protein. It would be recommended to support this assumption by exemplary study results.	Partly accepted. The assumptions were made by the EDQM based on literature and laboratory testing conducted. The information was used to set the limit of 0.3% protein that is currently in place.
Line 73-74	5	Please see **General Comments:** "On line 73 you mention gliadin, not glutenin, but also glutenin can make patients with celiac disease ill […]"	Accepted. The text has been amended to include glutenin.
Line 73-74	7	**Comment:** The glutenin should be added because according to studies conducted in the last years they have an equal toxic effect as gliadin. **Proposed change:** It is a chronic disorder that results in an ~~in~~ability to tolerate gliadin **and glutenin**. When patients with coeliac disease ingest **these proteins** ~~gliadin~~, …	Partly accepted. The word "inability" should be kept in the text and not be replaced with "ability". We agree with the other amendments proposed. The text amended is as follows: It is a chronic disorder that results in an inability to tolerate gliadin and glutenin. When patients with coeliac disease ingest these proteins, …
Line 93-138	2	**Comment:** While question 5 includes reasons for updating the information in package leaflets, it does not provide a timeline for implementation or whether the changes are to take effect immediately or as a phased-in approach.	Accepted. We agree the timeline should be phased in. The EMA will agree timelines.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Please specify an implementation timeline to update SPC details to be consistent with the information contained in question 5 of the Q&A.	
Line 100-101	1	**Proposed change:** It is proposed that the gluten levels should be determined **(either by calculation or analytical method)** in the wheat starch excipient only and not as part of the drug product specification.	Accepted.
Line 100-101	2	*"...it is proposed that the gluten levels should be determined in the wheat starch excipient only and not as part of the drug product specification..."* **Comment:** This guidance clearly positions this as an excipient risk (which is helpful). It would be helpful to extend this statement in order to clarify that drug substances/APIs are also out-of-scope of the requirements for gluten assessment. This would be of benefit (even if this is limited to chemically synthesised molecules where no vegetable materials are used). **Proposed change:** "...it is proposed that the gluten levels should be determined in the wheat starch excipient only and not as part of the drug product **or drug substance** specification..."	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 100-101	6	*"It is proposed that the gluten levels should be determined in the wheat starch excipient only and not as part of the drug product specification."* **Comment:** This guidance clearly positions this as an excipient risk (which is helpful). It would be helpful to extend this statement in order to clarify that drug substances/APIs are also out-of-scope of the requirements for gluten assessment (even if this is limited to chemically synthesised molecules where no vegetable materials are used). **Proposed change:** "It is proposed that the gluten levels should be determined in the wheat starch excipient only and not as part of the drug product **or drug substance** specification."	Accepted.
Line 107 and 141	1	**Comment:** It is mentioned that definitions on 'very low gluten content' and 'gluten-free' are based on the Commission Regulation 41/2009 concerning the composition and labelling of foodstuffs suitable for people intolerant to gluten. It is recommended to include this information not only in the package leaflet (as is now proposed) but in the SmPC as well. **Proposed change:**	Accepted. This information has to be included section 2 of the SmPC according the SmPC guideline (http://ec.europa.eu/health/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Additional comment in Comments column: **To be added to the SmPC as relevant:** **This product is regarded as "gluten-free" i.e. it contains less than 20 ppm (ug/g) of gluten.** **This product is regarded as "very-low gluten" i.e. it contains less than 100 ppm (ug/g) of gluten.**	
Line 131	1	**Proposed change:** […] into account a maximum level of gluten of 100 ppm in PhEur compliant wheat starch. Alternatively, the gluten content in the wheat starch can be determined using a suitable analytical method.	Accepted.
Line 141 Column "Comments"	1	**Comments:** In the comments column (section 6) it is mentioned that gluten content can be based on the Ph.Eur. Monograph, i.e. maximum amount of 100 ppm or can be determined by a suitable method. The latter does not become clear from the text in chapter 5 and it should be added there.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 141 "Information for the PL"	2	**Comment:** Wording is not considered patient friendly (which could impact readability test). -The unit "ppm" could be difficult to understand by a patient. The "ppm" is probably not useful here. -"should": QRD recommends the use of "should" is avoided. Also, we are often reminded by QRD that "should" is not easy to translate in Roman language. **Proposed change:** This product is regarded as "gluten-free" ~~**(less than 20 ppm (ug/g) of gluten)**~~ and is suitable for people with coeliac disease.	Accepted. The unit mg/kg is used in Commission Regulation (EC) No 41/2009, whereas in this paper both ppm and ug/g are used to put the values into perspective. Quantitative concentration are now mentioned only in the "comments" column which will be understood by regulators, industry and healthcare professionals. The following text has been proposed: This product is regarded as "gluten-free" and is suitable for people with coeliac disease.
Line 141	2	**Comment:** The guideline is not consistent with the food regulations. The food regulations state that <20ppm gluten is classified as "gluten free". In order to avoid a mixed message the threshold should be changed to ≤20ppm. **Proposed change:** Threshold: ~~**Zero**~~ **≤20ppm** and the wording amended as follows: This product is regarded as "gluten-free~~**" (less than 20 ppm (ug/g) of gluten)**~~ and is suitable for people with coeliac disease.	Partly accepted. The threshold zero means that the information should be present whatever the quantity of wheat starch. Depending on the amount of gluten the mention "regarded as gluten-free" will be added or not. The wording of the text has been amended slightly as proposed in the updated Q&A.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Threshold: ~~**20ppm (µg/g)>20ppm≤100ppm**~~ and the wording amended as follows: 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.**~~ **(a maximum of 100ug/g) and is unlikely to trigger disease activity in patients with Coeliac disease.**	
Line 141 Column "Threshold"	3	**Comment:** We suggest to define better the thresholds - the threshold corresponding to "gluten-free" category: 0–19 ppm (µg/g) instead of 'zero' - the threshold corresponding to "very low gluten content" category: 20–100 ppm (µg/g) instead of '20 ppm (µg/g)'.	Not accepted. See above and updated Q&A.
Line 141	4	**Comments on Threshold:** The levels/thresholds of gluten content are not understood by patients. In particular also the unit "ppm" will not be understood. Therefore we suggest making no difference between "less than 20 ppm" and "less than 100 ppm". For both instances, only the content per dosage unit would be meaningful for the patient. **Comments on PL Zero:** The term "gluten free" is confusing for patients. They	Partially accepted. See above responses and updated Q&A.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		struggle to understand that a very low level of gluten can be regarded as "gluten-free". Therefore we suggest avoiding this term. **Comments on PL 20 ppm:** The differentiation between allergy and coeliac disease is not known or diagnosed for all patients with relevant symptoms / problems. Also in the treatment and nutrition in daily life, no real differentiation can be made in practice. Therefore, we would refrain from making any comments or recommendation on taking or not taking the product. It can be explained that the information is relevant for both groups. "Wheat starch may cause problems for patients with coeliac disease or wheat allergy." In conclusion, we would recommend only one text for the package leaflets of wheat starch containing products, regardless of thresholds: **Proposed changes:** ~~**Contains wheat starch. Wheat starch may cause problems for patients with coeliac disease or wheat allergy. This product contains very small quantities of gluten, i.e. one dosage unit contains less than xxx microgram gluten.**~~	
Line 141	5	**Threshold: zero**	Partly accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Information for the PL		This product is regarded as 'gluten-free' (less than 20 ppm of gluten) and is suitable for ~~**people**~~ **the majority of/ most of the patients** with coeliac disease	The text proposed has been amended. This product is regarded as 'gluten-free' (if less than 20 ppm of gluten) and is generally suitable for patients with coeliac disease.
Line 141 Information for the PL	5	**Threshold: 20 ppm** This product contains only very low levels of gluten, a maximum of 100 ppm and is **not** suitable for patients with coeliac disease**/is suitable for less sensitive patients with coeliac disease.**	Partly accepted. The text proposed has been amended.
Line 141 Column "Comments"	5	**Comments:** Ingredients derived from wheat in the medicinal product must name the origin of the grain, like this: mannitol (wheat), because the most sensitive patients with celiac disease cannot tolerate it.	Not accepted. The proposals mentioned are outside the scope of this guideline review.
Line 141 Column "Comments"	5	*'using a suitable method'* **–** please see **General Comments**	Not accepted. It is not proposed that a specific method is stated in the guideline, as several analytical methods can be used to determine the gluten content in wheat starch, and additional methods may be developed in the future.
Line 141 Column "Thresholds"	6	**Comment:** We suggest defining the thresholds better. - the threshold corresponding to "gluten-free" category: 0–19 ppm (µg/g) instead of 'zero' - the threshold corresponding to "very low gluten	Partially accepted. See above and updated Q&A.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		content" category: 20–100 ppm (µg/g) instead of '20 ppm (µg/g)'.	
Line 141 Column "Comments"	7	**Comment:** The mentioned protein limit (0.3 %) is not very reliable for the definition of the exact gluten content of a product. The reason is that there is no linear relationship between the protein and the gluten content. So by focussing only on the protein limit the gluten content in the remaining protein part may be highly underestimated. "gluten content…can be determined using a suitable method". **Proposed change:** The first paragraph should be entirely deleted. Instead, we propose to specify the approved and standardized method of the Codex Alimentarius namely the R5-Sandwich-ELISA as a single method for the determination of the gluten content in wheat starch. The result of such test may not exceed 20 ppm.	Not accepted. It is not proposed that a specific method is stated in the guideline, as several analytical methods can be used to determine the gluten content in wheat starch, and additional methods may be developed in the future.