Guidance on Gluten Labelling of Pharmaceutical Products

White Paper

Author:
Phil Kuhlman, Technical Specialist

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Abstract

The need to avoid the consumption of gluten by sufferers of coeliac disease has driven the food industry to implement rigorous labelling practices providing the tools for sufferers to limit gluten consumption. The Food and Drug Administration (FDA) has issued its guidance with regard to labelling within the pharmaceutical sector. This white paper considers the FDA's guidance, whilst also reflecting on RSSL's extensive experience and expertise in allergen management and testing.

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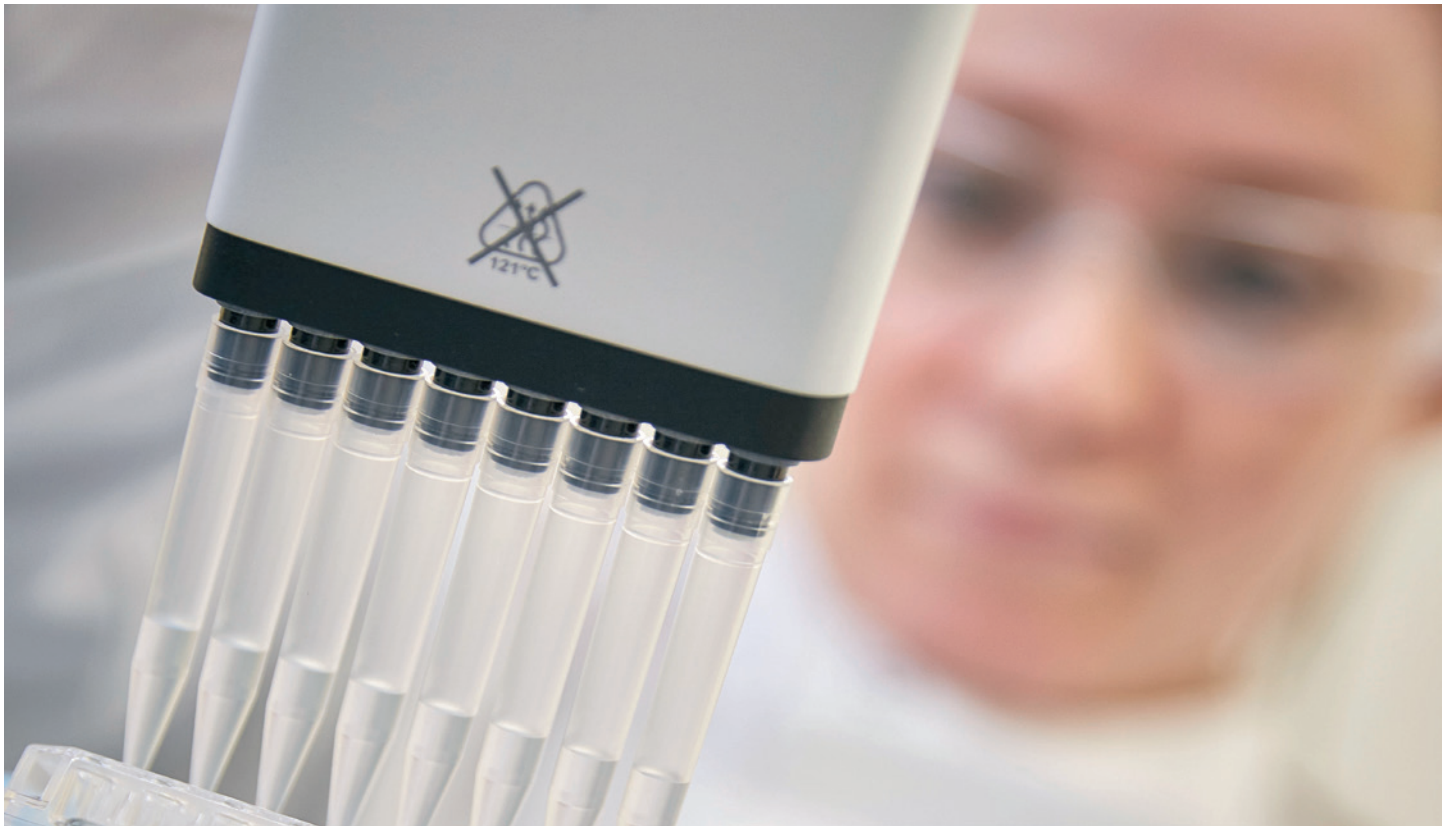
1. Introduction

Sufferers of Coeliac (Celiac) disease have a severe reaction to gluten when consumed in their diet. Currently, approximately 20 people in 100,000 (0.02%) have been diagnosed with this disease[1]. Grains such as wheat (Triticum species), Rye (Secale species) and Barley (Hordeum species) and all of their cross-breed species contain a set of proteins of the Prolamin and Glutamin families that together are termed 'gluten'. Gluten is also defined by the FDA as 'proteins that naturally occur in a gluten containing grain and that may cause adverse health effects in persons with celiac disiease'[2]. Gluten when ingested triggers the body's immune system to attack itself leading to damage to the gut lining and therefore reduced absorption of nutrients. For those suffering with the disease the only relief is living a gluten free lifestyle where gluten is avoided in all products consumed or placed directly on the skin. Severe suffers of Coeliac disease extend this life choice to all orally consumed products including drugs. The food industry has been regulated with regard to gluten labelling for many years. Food labelled as 'Gluten Free' is required to have less than 20 mg/kg of gluten to be compliant with the current FDA food labelling regulations[2]. Under these regulations a food product is 'gluten-free' if it meets the following criteria;

1. No ingredient is a gluten containing grain
2. Any ingredient that is in category (1) that has been processed to remove gluten
3. If in category (2) then the level of gluten is below 20 ppm (mg gluten per kg of food)

Products that contain wheat that has been processed to remove gluten; should be labelled with the statement below:

'The wheat has been processed to allow this food to meet the Food and Drug Administration (FDA) requirements for gluten-free foods'



In December of 2017 the FDA issued a guidance document considering the topic of drug labelling requirements with regard to the presence of gluten.

This guidance pertained only to human drug products that were either orally ingested, applied to or near the lips or were applied to the inside of the mouth. The guidance does not cover products that are solely regulated as cosmetics.

The guidance document considered the likely ingredients of oral drug products that would be relevant;

Table 1. Summary of the FDA's considerations and responses to the likelihood of gluten being incorporated into pharmaceutical products.

FDA Considered	FDA Response
Wheat gluten as an ingredient in the drug	Never/very rarely added as inactive ingredient.
Ingredient derived from wheat in the drug	Several ingredients would qualify (see below) Intentionally added gluten should be suitably labelled.
Adventitious contaminant within the drug	Products produced under cGMP should not be affected by contamination as there is a basic obligation to prevent contamination.

Table 2. Summary of the FDA's risk assessment of Ingredients derived from wheat that may be present within a drugs formulation;

Wheat Ingredient	FDA Risk Assessment
Wheat flour	Only rarely used. Would need labelling. Recommend suffers from Celiac disease to avoid.
Wheat starch	Only rarely used. Alternatives are available i.e. potato starch. Expect levels per unit dose to be less than 0.1 mg of gluten.
Ingredients derived from wheat starch	Modified starch, pregelatinized starch, sodium starch glycolate, starch hydrolysates (maltodextrin, dextrates, dextrose, maltose, sorbitol, xylitol, maltitol and mannitol as well as starch hydrolysates (mixtures of sugar alcohols). Expect levels per unit dose to be less than 0.5 mg of gluten.
Ingredient derived through fermentation	Processes based on fermentation of wheat products (i.e. citric acid) may contain gluten. Purification may eliminate the risk. Expect levels per unit dose to be less than 0.5 mg of gluten.
Wheat germ oil	Consider the content of gluten to be very low and the oral ingestion of gluten associated with a product to be insignificant.

2. FDA's guidance

The FDA considers the level of gluten in oral drugs to be less than a maximum 0.5 mg of gluten per unit dose which is less than the defined range of gluten (5 – 50 mg) consumed in a typical gluten-free diet[4,5]. Thereby patients that respond well to a gluten-free diet should have no concerns with taking oral drugs. Patients with hypersensitivity to gluten are most likely to avoid oral drugs with wheat derived ingredients.

Currently there is no definition of 'gluten-free' for drug products due to limits not currently being established and difficulties in substantiating the claim. In addition, the question of whether 'gluten' should apply only to the intact protein molecules or also peptides derived from them has not been resolved

3. Current ingredient labelling regulations and practice

Nonprescriptive (over-the-counter) oral drug products
The drug facts label should have a section for 'inactive ingredients' which must list 'the established name of each inactive ingredient'

- **Prescriptive oral drug products**
  The 'description' section of the prescribing information would usually contain a list of inactive ingredients. In addition, biological products are required to identify certain types of inactive ingredient (preservatives, known sensitising substances and inactive ingredients when a safety factor). The FDA interprets 'when a safety factor' as meaning that wheat gluten and wheat flour must be identified by those names if they are orally administered biological products.

4. FDA recommendation for a voluntary gluten label

'Contains no ingredient made from a gluten-containing grain (wheat, barley or rye).'

This statement should only be used when it is true and can be substantiated. This would include information from suppliers confirming the origins of the source materials used in the production of the ingredients. The FDA go on to indicate that raw materials that are derived from wheat may be tested to determine the level of protein or gluten as a means of substantiating any gluten claims. Any such testing needs to be included with the manufacturing records and be readily available to the FDA for authorised inspection.

5. Parallels and contrast with the food industry

The food industry has a long history and vast experience in managing the production of gluten free products in a complex supply chain and manufacturing environment. Testing is applied by manufacturers and retailers alike to substantiate the gluten free status of their raw materials and finished products, and to ensure that all controls to prevent contamination of gluten are effective.

The term 'gluten' is used to refer to the complexes of proteins from the glutenin and gliadin protein families. The limited solubility of gluten in aqueous solutions makes its extraction and accurate detection difficult, something that has proven to be problematic to the food industry. Given the increased demand for gluten testing in recent years, improvements have been made and extraction buffers have been developed that are more efficient at extracting gluten, even from complex matrices such as cooked food products.

RSSL has extensive experience in carrying out analysis of allergens, and have performed gluten testing for food manufacturers seeking to make 'gluten-free' claims for a number of years. Typically, gluten testing is performed using a commercial sandwich ELISA kit and is quantified against a standard curve. RSSL use the r-biopharm RIDASCREEN® Gliadin sandwich ELISA kit that has a sensitivity of 5 – 80 ppm for gluten. The kit is robust and can reliably detect gluten in both raw and cooked products.

Demand for gluten testing within the pharmaceutical industry is beginning to increase, as awareness of conditions such as coeliac disease grows. Within pharmaceuticals the most likely source of contaminating gluten is derived from the process of hydrolysing or fermenting wheat products in order to prepare raw ingredients. The consequence of this processing is the fragmentation of the 'gluten' protein into peptides which are less likely to be detected using the standard 'R5 Mendez' sandwich ELISA. However, more suitable competition ELISA kits have been developed for the brewing industry that are able to detect even the presence of small fragments of the gluten proteins. These competition ELISAs are therefore more suited to the application of gluten quantitation in pharmaceutical raw ingredients.

Another consideration when choosing a commercial ELISA kit to analyse for gluten is the source of the antibodies used in the kit. Polyclonal antibodies offer greater coverage of antigens which would increase robustness and reliability of detection. This has advantages for the food industry, however, preparation of new batches of polyclonal antibodies are prone to variability. The use of monoclonal antibodies has the advantage of reliable supply and consistency between batches although these will only recognise a single epitope (recognised region of a peptides that the antibody will bind to). Where possible the use of competition ELISA kits based on monoclonal antibodies would be preferred for any GMP analysis application due to the consistency between batches.

A selection of ELISA kits are commercially available for the detection of 'gluten'. The majority use the sandwich approach as this has been identified as the best format for detection of 'gluten' in food. The competition type ELISA, which is more suited to pharmaceutical analysis is significantly less common.

Table 3. Summary of the FDA's risk assessment of Ingredients derived from wheat that may be present within a drugs formulation;

Name of Kit	Manufacturer	Catalogue number	Type of ELISA	Type of Antibody	Range (ppm)
RIDASCREEN® Gliadin	R-Biopharm AG	R7001	Sandwich	R5 monoclonal	2.5 - 40 ppm gliadin
RIDASCREEN® FAST Gliadin	R-Biopharm AG	R7002	Sandwich	R5 monoclonal	5 – 40 ppm gliadin
RIDASCREEN® FAST Gliadin sensitive	R-Biopharm AG	R7051	Sandwich	R5 monoclonal	1.25 - 20 ppm gliadin
RIDASCREEN® Gliadin competitive	R-Biopharm AG	R7021	Competitive	R5 monoclonal	5 – 135 ppm gliadin
AgraQuant® Gluten G12TM	Romer Labs	COKAL0200	Sandwich	G12 monoclonal	4 -220 ppm gluten
AgraQuant® Gluten	Romer Labs	COKAL0248	Sandwich	Polyclonal	4 -120 ppm gluten
Wheat /Gluten (gliadin)	Morinaga	M2103	Sandwich	Polyclonal	0.31 – 20 ppm wheat protein
Veratox® for Gliadin	Neogen	8480	Sandwich	Polyclonal	5 – 50 ppm gliadin
Veratox® for Gliadin R5	Neogen	8510	Sandwich	R5 monoclonal	2.5 – 40 ppm gliadin
Gluten	ELISA systems	ESGLUT-48	Sandwich	Polyclonal	1 -20 ppm gliadin
Gluten-Check	Bio-Check (UK)	R6098/ R6099	Sandwich	R5 monoclonal	2.5 – 50 ppm gluten
Gluten-Tec® ELISA	EuroProxima	5171GT	Competitive	Monoclonal (α-20 epitope of gliadin)	0.156-5 ng

The most appropriate point to test for gluten within a pharmaceutical manufacturing process is the in-coming raw materials. Generally, by testing raw ingredients, the concentration of gluten will be at its greatest and the reduced level of processing allows the 'gluten' to be more easily detected. The principles of good manufacturing practice (GMP) clearly state the need for adequate control of all stages in the manufacturing process including confirmation of the identity of all raw ingredients. Greater control of raw ingredients reduces the possibility of accidental introduction of gluten contamination into the drug manufacturing process. The most likely introduction of gluten into the manufacturing process would be accidental contamination of a raw material where the food and pharmaceutical supply chains overlap (e.g. in the production for starches from commodities like wheat and potato). These types of contamination are relatively easy to detect at the incoming raw ingredient stage of the process when testing is applied.

6. Conclusion

Testing of food products for the presence of gluten has been successfully performed for the past 13 years at RSSL using the standard 'R5 Mendez' sandwich ELISA. Although this is the 'gold standard' in the food industry for assessing the levels of gluten, the highly processed, hydrolysed or fermented nature of the raw ingredients used for pharmaceutical products means that competition ELISAs are more suitable. Several commercial gluten competition ELISAs are available which are based on monoclonal antibodies making them suitable for the GMP analysis of gluten. The validation of a test kit in conjunction with the suitable sample extraction conditions would need to be performed for each product. RSSL have extensive experience and the capabilities to provide both full validation as well as routine gluten analysis of raw ingredients and if needed gluten determination within drug products and active pharmaceutical ingredients (APIs) as well.

About the author

Phil Kuhlman, Biopharmaceutical Technical Specialist

Phil has seventeen years' industry experience, built on eight years of academic experience in protein-protein interaction and characterisation, having graduated in 1993 from Leicester University with a PhD in Biochemistry. He has gained a broad knowledge of the characterisation and use of proteins and nucleic acids through working in academia prior to moving into the biotechnology sector and then into a CRO. Phil's main expertise is in characterisation of biologics throughout the complete drug lifecycle with an emphasis on forced degradation studies for determining comparability between biosimilars and setting critical quality attributes (CQA's).

7. References

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About Reading Scientific Services Ltd (RSSL)

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Tel: **+44 (0)118 918 4076** Email: **enquiries@rssl.com** Web: **www.rssl.com**

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Reading Scientific Services Ltd
The Reading Science Centre, Whiteknights Campus,
Pepper Lane, Reading, Berkshire RG6 6LA

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