codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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Agenda Item 6 **CX/MAS 11/32/6**

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON METHODS OF ANALYSIS AND SAMPLING
Thirty-second Session
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USE OF PROPRIETARY METHODS IN CODEX STANDARDS

(Prepared within the Inter-Agency Meeting)

BACKGROUND

At the thirty-first Session of CCMAS the Inter-Agency Meeting (IAM) had prepared and presented a first discussion paper on the use of methods of analysis involving proprietary aspects within both the Standard Development Organisations and the Codex system. The draft paper was presented in the Annex to CRD 2. The paper noted that proprietary methods were not clearly defined, highlighted some concerns that could arise from their use, and in particular that: they might prevent further development of new and better techniques, distort competition between companies producing the reagents, and create difficulties for government authorities if particular reagents were not readily available for official methods. It was recalled that the R5 method for the determination of gluten illustrated some of these problems as the reagents were not generally available. Several approaches were proposed in CRD 2 to address this issue, including the use of the criteria approach in Codex.

In discussion in CCMAS it was noted that the IAM would proceed with its consideration of proprietary methods, invited wider contribution than only from IAM members and would provide an update to the next session of the Committee. Following on from the last Session of CCMAS all participants were asked for comment about the paper presented in the CRD and for comments generally. Some comments were received and these are in corporate in the following paper.

The discussion paper is structured such that it would be helpful to both members of the Inter-Agency Meeting and to participants in sessions of CCMAS.

RECOMMENDATIONS

It is recommended that CCMAS considers the attached discussion paper and decides:

- Whether it wishes to further discuss the subject in a future Session of CCMAS.
- Whether it wishes to define in the Codex Procedural Manual the characteristics that a proprietary method should be assessed.
- Whether it wishes to define in the Codex Procedural Manual additional characteristics that a proprietary method should meet, i.e. additional to those that a conventional method of analysis must meet as already described in the Codex Procedural Manual.
- Whether it is feasible to extend the criteria approach for the endorsement of methods of analysis in Codex to Type I, defining, methods of analysis.

PROPRIETARY METHODS IN CODEX STANDARDS AND IN STANDARD METHODS – HOW SHOULD THEY BE TREATED?

INTRODUCTION

Issues arising from the use of proprietary methods of analysis in Standard Methods adopted by the Standards Development Organisations (SDOs) or from their endorsement by CCMAS in Codex Standards have been discussed within CCMAS. Indeed, in the Report of the 30th Session of CCMAS it is stated:

Proprietary Methods Issues

159. The Chair of the IAM informed the Committee that several issues regarding proprietary methods had been discussed in the IAM and in some previous sessions of the Committee, such as the availability of reagents, restricted licensing of antibodies and the question of how to describe the method more generically for the purpose of use as a Codex method.

160. The Committee welcomed the offer from IAM to consider this issue among the standard setting organisations and invited delegates to provide their contribution, with a view to preparing a discussion paper on proprietary methods for consideration by the next session.

Members of the Inter-Agency Meeting were asked for comment as an aid to meeting the obligations stated above.

In addition, the Joint Research Centre, Geel, of the European Union and the Committee for European Normalisation, CEN, jointly sponsored a one-day Workshop in January 2010 entitled "*Possibilities and requirements for the standardization of proprietary methods of analysis"*. The issues will also be discussed in the IAM/MoniQa Workshop to be held 6th March, 2011 in Budapest.

This paper attempts to highlight some of the concerns that have been expressed with respect to the incorporation of propriety methods in legislation, including their endorsement within the Codex system, and in Standards published by the Standard Development Organisations.

The concerns with respect to proprietary methods include the following:

- Whether methods need to have an independent validation, not manufacturer's validation.
- Whether methods need to be "open", i.e. not be of a restricted commercial nature. This particularly applies when specific reagents are licensed to manufacturers.
- Whether there is the danger that the adoption of a proprietary method creates an anti-competitive situation.
- Whether the efficacy of a particular method is maintained over time.
- Whether the frequently used statement by an SDO to say that "any proprietary aspect within a Standard does not constitute an endorsement of that proprietary aspect (method etc)" is sufficient.
- Whether manufacturers should be listed or not as the project leaders when proprietary methods are being developed.

DEFINITION OF A PROPRIETARY METHOD

There is no accepted definition of a proprietary method. It could be stated that it a method/procedure/part of a method where control of intellectual property rights are involved.

NordVal defines a proprietary method to be:

1) A method where a party, or proprietor, exercises private ownership of the method.

2) A method with a registered trademark/brand name, which is owned and generally marketed by a commercial company.

However, for Codex purposes it is suggested that a clear distinction is made between:

"Alternative" proprietary methods, i.e. methods which would be classified as Type III methods within the Codex system and where the method can calibrated against an existing non-proprietary method, and

"Unique" proprietary methods, i.e. methods which would be classified as Type I methods within the Codex system and where the proprietary method adopted and endorsed is the only method which can be used as part of the Codex or other legislative Standard.

BACKGROUND TO PROPRIETARY METHODS OF ANALYSIS

The need for and attractiveness of proprietary methods in food control

Proprietary methods (frequently available as "test kits") are of increasing importance in the food industry and in official food control (especially within microbiology). The use of proprietary methods often means increased effectiveness, faster and less expensive analyses. The methods are ready to use, are frequently quicker to use than conventional procedures and often have simpler preparation steps; the methods descriptions are normally easy to follow. Proprietary methods often mean less costly and simpler instrumentation. Some analyses can even be carried out on site. In some areas there might not be any standard method (e.g. allergens), only proprietary methods.

There is a need for faster, more rapid and simpler methods for use by the Analytical Community and hence an increased demand for proprietary methods.

Availability of proprietary methods

There are a number of manufacturers of proprietary methods, both for microbiological and chemical methods. They have good marketing programmes and hence proprietary methods are easily available. Normally these are complete (whole) methods but in the past, in particular, they used to be "segments" of methods, e.g. immunoaffinity columns. However the later aspects are much less problematic given than it is relatively easy to define their performance characteristics.

Reliability of proprietary methods

Food authorities and users of proprietary methods have found it of vital importance that the proprietary methods are validated and certified by an independent party, in order to document the reliability of the method and to review that the performances of the methods meet their claims. For microbiological proprietary methods, there are five international standardisation organisations (AOAC International, AOAC Research Institute, AFNOR, MicroVal, NordVal) validating and certifying proprietary methods according to internationally accepted rules. For chemical methods, AOAC, NordVal and IDF:ISO/TC 34/SC 5 have established guidelines, and review proprietary methods for their reliability.

Inclusion of references to proprietary methods into Codex standards

There are advantages and disadvantages to including any reference to a proprietary method into Codex standards. Some of these are listed below:

Advantages:

- Easy to use.
- No frequent changes in the method are generally made.
- May be the only method to achieve a certain analytical goal.
- May reduce testing cost and may allow increasing testing frequency thus improving the rigour of compliance testing regimes.

Disadvantages

- Can become dated: a problem with the Codex method endorsement procedure is that sometimes a method becomes endorsed but is then not the method of choice for most analysts. The situation may arise for an analyst whereby a previously endorsed Codex method which might not be used routinely, and hence the analyst not trained to use, might have to be used in cases of dispute. This may cause particular difficulties if the endorsed method contains proprietary aspects which are then not readily obtainable.
- Fear of losing a method's endorsement: a manufacturer that has had his method endorsed might not want to revise/update it for fear of losing its endorsement. This may prevent newer and better techniques being taken into use by Codex. Further, the competitors will prioritise other fields of interest, as they have already lost the battle of getting their method endorsed. Proprietary methods should be reviewed/revised frequently by manufacturers so a method could very well be revised a couple of times before the Codex standard could be updated.
- If a reference to a proprietary method is included in a Codex standard, the manufacturer of that method gets significant financial advantages, which would not be very well received by competitors.
- It could lead to pressure (lobbying) on the members of the commodity committees and on CCMAS from test-kits manufacturers in order to get a reference to their product included in a standard.
- Governments come under pressure or criticism if particular reagents are not readily available even under license to any other manufacturer wishing to use them.

It is the financial advantages of having a particular proprietary method endorsed by Codex which should be of most concern to governments. The situation is slightly different for the SDOs in that they produce methods (Standards) with or without proprietary aspects, rather than endorsing/prescribing the use of such methods. It could be argued that not having a method available also costs money; but then the cost is on those responsible for compliance testing, food safety, etc., and this may well be a much greater disadvantage than the fact that some manufacturer are gaining financially by selling their methods.

POSSIBLE WAYS FORWARD FOR CODEX

Alternative Methods (Codex Type II/III, Rationale, Methods)

For the "alternative" propriety methods of analysis there appears to be little advantage in specify such methods in legislation, including in Codex Standards. Here a defined chemical entity is being considered.

Such methods will be Codex Type III methods. Rather than specify/endorse a proprietary method in any standard it would be better to increase the pace of the introduction of the criteria approach when endorsing methods of analysis in Codex Standards.

Unique Methods (Codex Type I, Defining, Methods)

Here there are a number of possibilities:

1. To define the proprietary chemical used in the method.

As examples, in the milk sector the two methods for the determination of phosphatase methods state the commercial reagents in detail, i.e.:

EN ISO 11816-1|IDF 155-1:2006

Milk and milk products - Determination of alkaline phosphatase activity - Part 1: Fluorimetric method for milk and milk-based drinks

4.1 Fluorophos® substrate, in bottles, each containing 144 mg of Fluorophos® substrate powder.

This is a non-fluorescent aromatic monophosphoric ester substrate, 2'-[2-benzothiazolyl]-6'-hydroxybenzothiazole phosphate (Fluorophos®).

The Fluorophos® substrate remains stable for 2 years when stored in unopened bottles at between 2 °C and 8 °C.

and

EN ISO 22160|IDF 209: 2007

Milk and milk-based drinks - Determination of alkaline phosphatase activity - Enzymatic photo-activated system (EPAS) method

4.1 Non-chemiluminescent dioxetane ester substrate

[0,2 mol/l 3-(2'-spiroadamantanane)-4-methoxy-4-(3"-phosphate phenyl-1,2 dioxetane disodium salt in DEAE buffer with 1 % fluorosine], is commercially available [e.g. as Charm reagent AP® liquid].

2. To define the analyte in terms of a structure.

It may be possible in some situations to define the analyte of interest in terms of its chemical structure. In the Appendix dealing with the gluten an attempt has been made to define do this – i.e. to identify the chemicals involved rather than simply considering a reactivity to a particular set of antibodies.

3. To not endorse the proprietary procedure

To not endorse a proprietary procedure would appear to be very drastic and would probably deprive the Analytical Community of valuable analytical procedures.

QUALITY STANDARDS TO BE APPLIED TO THE VALIDATION OF PROPRIETARY METHODS TAKEN FOR CODEX PURPOSES

The characteristics that have to be assessed for non-proprietary methods of analysis used for Codex purposes are given in the Codex Procedural Manual. The most critical of these is generally considered to be the assessment of the precision characteristics of the method as determined (estimated) through a collaborative trial. It would be unreasonable for the same characteristics not to be assessed for proprietary methods of analysis – thus a simple comparison within a single laboratory of the performance characteristics of an existing Codex Type II/III method with a proposed proprietary method is insufficient. It would be expected that because such comparisons can only occur if the methods are Codex Type II/III methods, then the need to endorse such proprietary methods within the Codex system should be considered on a case-by-case basis rather than replacing all references to specific methods by performance criteria (i.e. the "criteria approach").

It is also important to consider whether any of the normally determined characteristics should be emphasised for proprietary methods, selectivity being an obvious example. Consideration should be given as to whether additional performance characteristics should be required for proprietary methods, e.g. replacement reagent stability and consistency.

CONCLUSIONS

It is recommended that CCMAS considers the following:

- Where there is no absolute need for that proprietary method, CCMAS should generally not adopt a proprietary method unless there are other considerations that make it desirable to adopt such a method.

- That method performance criteria should be established for proprietary methods in the same way as is already established for conventional methods. Such performance criteria should be those stipulated in the Codex Procedural Manual for conventional methods with additional criteria to be discussed.

- That proprietary methods being validated and reviewed by an independent third party according to international recognised protocols may not be sufficient when such methods are to be used for Codex purposes. If a proprietary method is validated by such a procedure it should be brought into the Codex system as a Codex Type IV method. Type IV methods are candidate or could be "suggested" methods as has happened with some natural mineral waters methods.

- That some consideration is given to developing method criteria for Codex Type I methods in the same way as currently exists for Codex Type II and III methods. It is appreciated that this is a contradiction with the straight interpretation of the Codex General Principles for Methods of Analysis, as first discussed in Codex in 1977. However, since 1977 analytical performance considerations have advanced and some consideration should now be given to avoiding "locking in" a proprietary method that has been adopted as Type I by Codex. It would be necessary to give some consideration as to how far different Type I methods can differ before being considered non-comparable or irreconcilable.

- That preference should be given to endorsing those procedures which are in an "open" system, i.e. where the reagents are comprehensively described in the method. This would then avoid the criticism that such methods are "black-box" methods.

- That no approach is taken which then makes it look as if the method is endorsed by Codex to the detriment of other potential methods; that preference is given to adopting suitable method criteria rather than endorsing a specific proprietary method of analysis.

APPENDIX: DEFINITIONS OF GLUTEN

What is definition of gluten in the Codex Standard?

For the purpose of the Codex standard, "gluten" is defined as a protein fraction from wheat, rye, barley, oats or their crossbred varieties and derivatives thereof, to which some persons are intolerant and that is insoluble in water and 0.5M NaCl.

Prolamins are defined as the fraction from gluten that can be extracted by 40 - 70% of ethanol. The prolamin content of gluten is generally taken as 50%, but this can vary.

What is the legal definition of gluten according to the EU Gluten Regulation – 41/2009/EC

Gluten means a protein fraction from wheat, rye, barley, oats or their crossbred varieties and derivatives thereof, to which some persons are intolerant and which is insoluble in water and 0.5 M sodium chloride solution.

What does the R5 Elisa (Mendez method) measure?

The monoclonal antibody R5 raised against a secalin extract can recognize the potential coeliac-toxic epitope QQPFP, which occurs repeatedly in the prolamine proteins α-, γ- and ω-gliadins, hordeins and secalins. The method is a highly sensitive and specific sandwich ELISA to quantify low levels of wheat, barley and rye prolamins in foods for coeliacs. The ELISA does not detect the prolamine protein from oats (avenin).

R5-ELISA is able to identify gliadins, hordeins and secalins with assay sensitivities of 0.78, 0.39 and 0.39 ng/ml, respectively. The assay's detection limit was 1.5 ng gliadins/ml (1.56 ppm gliadins, 3.2 ppm gluten). The system proved insensitive to the non-coeliac-toxic cereals maize, rice and oats, and was non-cultivar-dependent. It was also able to detect gliadins and hordeins in unprocessed and heat-processed wheat- and barley-based products, and to estimate the gluten content of hydrolysed foods (see note 1).

What is a more general scientific definition of gluten?

The *Triticeae* species contains the major gluten containing cereals which includes wheat, rye and barley as well as in hybrid grains such as triticale and ingredients derived from these grains. Gluten is found in the protein portion of the cereal grains and the seed proteins are known to fall into four groups:

- albumins
- globulins
- prolamins
- glutelins

The major fractions in gluten are the glutelins and prolamines. The type of glutelin will vary among grains, the most well know are glutenin in wheat, hordenin in barley and avenin in oats. Prolamine fractions from each of the gluten containing grains, are also given specific names, these include gliadin in wheat, secalin in rye and hordein in barley. It is thought that the ability of the grain to elicit mucosal damage depends the structure of the prolamine and the amount present in each cereal (see note 2).

Way Forward

When the R5 method was being progressed though the Codex Standard some consideration could have been given to identifying the specific chemical structure being analysed and deciding whether the analysis could have been described in those terms.

Comment of Typing of the R5 Method

It is interesting to note that when the R5 method was being discussed and endorsed in CCMAS there was only a consensus that it should be classified as a Type I method. Some delegates thought that it should be described as a Type II method. If the method had been classified as a Type II method then many of the problems that subsequently arose could have been avoided, or certainly reduced.

Notes

1. Report of a collaborative trial to investigate the performance of the R5 enzyme linked immunoassay to determine gliadin in gluten-free food. European Journal of Gastroenterology & Hepatology, October 2005, Volume 17, Issue 10, Pages 1053-1063. E, Méndez, C, Vela, U, Immer, F, Janssen.

2. The pathogenesis of celiac disease. *Gastroenterology*, Volume 115, Issue 1, Pages 206-210. A.Godkin, D.Jewell