



Commentary

Food Chemicals Codex (FCC), Tenth Edition, Third Supplement

September 1, 2017

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts (CoE Rules), and except as provided in Section 8.01(e) *Immediate Standards*, USP publishes proposed revisions to the *Food Chemicals Codex (FCC)* for public review and comment in the *FCC Forum (FCCF)*, USP’s venue for providing public notice and receiving public comment on an *FCC* proposed standard. After comments are considered and incorporated as the Food Ingredients Expert Committee (FIEC) deems appropriate, the proposal may advance to effective status or be republished in *FCCF* for further notice and comment, in accordance with the CoE Rules. In cases when proposals advance to effective status without republication in the *FCCF*, a summary of comments received and the FIEC’s responses are published in the *Commentary* section of the USP.org website at the time the revision is published.

The *Commentary* is not part of the text of the monograph or general test or assay. Rather, it explains the basis of the FIEC’s response to public comments. If there is a difference between the contents of the *Commentary* section and the monograph or general test or assay, the text of the monograph prevails. In case of a dispute or question of interpretation, the language of the monograph text, alone and independent of the *Commentary*, prevails.

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Comments were received for the following when they were proposed in the Food Chemicals Codex (FCC):

- Appendix XVIII: Guidance On Developing and Validating Non-Targeted Methods For Adulteration Detection
- Appendix XVI: Nonprotein Nitrogen Determination For Skim Milk Powder And Nonfat Dry Milk
- Plant Stanol Esters
- Taurine
- Vanillyl Butyl Ether

No Comments were received for the following when they were proposed in the Food Chemicals Codex (FCC):

- Propyl Gallate
- Sodium Saccharin

Monograph/Section: Appendix XVI: Nonprotein Nitrogen Determination for Skim Milk Powder and Nonfat Dry Milk/Principle

Expert Committee: Food Ingredients

Expert Committee-initiated Change #1: In *Principle*, include a reference to public standard of identity of skim milk powder and nonfat dry milk.

Monograph/Sections: Appendix XVIII: USP Guidance on Developing and Validating Non-Targeted Methods for Adulteration Detection/Multiple Sections

Expert Committee: Food Ingredients

No. of Commenters: 20

General Comments

Comment Summary #1: The commenter suggested incorporating Raman spectroscopy, surface-enhanced Raman spectroscopy, and mass spectrometry (MS) in the *Guidance*, and suggested adding an MS-based example to the *In Scope* method section.

Response: Comment partially incorporated. A note was included stating that a non-targeted method applies to any test that provides a pattern or quantitative measurement. An MS example was added to the *In Scope* section.

Comment Summary #2: The commenter suggested specifying that the *Guidance* is for statistical classification and that not all non-targeted methods require a statistical component.

Response: Comment not incorporated. The commenter's suggestions were based on a different definition of "non-targeted methods" from that in the *Guidance*.

Comment Summary #3: The commenter suggested adding the following reference as evidence for using one-class classification for authentication: "Rodionova, O. Y., Titova, A. V., & Pomerantsev, A. L. (2016). Discriminant analysis is an inappropriate method of authentication. *TrAC Trends in Analytical Chemistry*, 78, 17-22."

Response: Comment incorporated.

Comment Summary #4: The commenter suggested adding content on “data storage/data back-up,” which is applicable to liquid chromatography mass spectrometry (LC-MS) data storage.

Response: Comment not incorporated. The Expert Committee found the current description to be sufficient.

Comment Summary #5: The commenter suggested considering what metadata to incorporate, although not strictly needed for a single-class model.

Response: Comment incorporated. A statement was added to the text.

Comment Summary #6: The commenter suggested including an example of the process, which would reflect the key points of each section and some of the advised limits.

Response: Comment not incorporated. Inclusion of an example in the next version will be considered.

Comment Summary #7: The commenter suggested adding a statement to the *Applicability Statement* section or the *Defining the Reference Set* section on the variability in authentic food samples among different geographic locations.

Response: Comment not incorporated. The Expert Committee determined that the related information already in the *Guidance* was sufficient.

Comment Summary #8: The commenter suggested including a bulleted list briefly describing the most important actions of each step in the flow chart in Appendix 2, to provide an overview of the process.

Response: Comment not incorporated. The Expert Committee determined that the proposed edit would not enhance the understanding of that section.

Comment Summary #9: The commenter suggested adding content to the *Purpose* section indicating that the information in the *Guidance* is insufficient to design a validation protocol and that the number of samples depends on the complexity of the model.

Response: Comment partially incorporated. Caution text was added to indicate that “the number of samples depends on the complexity of the model.”

Purpose

Comment Summary #10: The commenter suggested revising the following text: "This guidance is intended for use specifically for food fraud/economically motivated adulteration (EMA). This is due to the fact that EMA related adulterants are typically present in concentrations consistent with the sensitivity limits of non-targeted methods" to "As EMA-related adulterants are typically present..., this guidance document is intended specifically for food fraud/EMA."

Response: Comment partially incorporated. The wording in the related text was changed.

Comment Summary #11: The commenter suggested adding an explanation of what “typically” means or under which conditions to see 0.1% for sensitivity limits "typically above 0.1% concentration."

Response: Comment not incorporated. The Expert Committee determined that the context provided clarity and the proposed edit would not enhance the understanding of the section.

Overview

Comment Summary #12: The commenter suggested adding the following text to the introduction of the *Typical and Atypical* section: "Typical, implying a lower probability of adulteration," and "Atypical, implying an increased probability of adulteration."

Response: Comment incorporated.

Comment Summary #13: The commenter suggested adding explanation in the text on the quotient "Typical/Atypical" in *Figure 1*.

Response: Comment incorporated.

Comment Summary #14: The commenter suggested expanding and deleting some of the definitions in the *Glossary of Terms*.

Response: Comment partially incorporated. The terms "Test Set," "Reference Set," "Atypical sample," "Typical sample," "Correct Typical results," "Correct Atypical results," "Multiclass (or Two-class) classification," and "One-class classification" were added, and "Limit of Detection" was deleted.

Comment Summary #15: The commenter suggested defining what is truly "non-targeted" and "semi-targeted" in the *Non-targeted Method* section.

Response: Comment not incorporated. The Expert Committee determined that the proposed edit would not enhance the understanding of the section.

Comment Summary #16: The commenter indicated that the term "one-class classification (OCC)" is inappropriate as a synonym for "non-targeted." The commenter indicated that the method development and validation processes described in the *Guidance* are that of a supervised two-class classification model because both Atypical and Typical samples are involved.

Response: Comment partially incorporated. The wording was changed to avoid the confusion of "one-class classification" used as a synonym for "non-targeted."

Comment Summary #17: The commenter suggested moving the glossary terms directly after the title.

Response: Comment not incorporated. The Expert Committee determined that the proposed edit would not enhance the understanding of the section.

Steps for Development and Validation—The Generic Thought Process

Comment Summary #18: The commenter suggested removing *Figure 2* or clarifying the text.

Response: Comment incorporated. *Figure 2* was removed and the related text was changed.

Comment Summary #19: The commenter suggested indicating in the *Reference Set* section that the set should encompass all sources of potential variation but the applicability statement may focus on a narrow question.

Response: Comment incorporated.

Comment Summary #20: The commenter indicated that it is unclear how to obtain and use the receiver operating characteristic (ROC) curve in *Figure 3*. The commenter suggested clarifying the link between the ROC curve and the limit of detection (LOD).

Response: Comment incorporated. The text was modified, and USP General Chapter <1039> *Chemometrics* was referenced.

Comment Summary #21: The commenter suggested revising the first sentence to focus on the process of defining the scope of the method.

Response: Comment not incorporated. The Expert Committee found the current text to be sufficient.

Comment Summary #22: The commenter suggested revising the second paragraph of the *Establish an Applicability Statement* section to form two separate sentences as follows: (1) “Setting model boundaries inevitably is a tradeoff between....” and (2) “This trade-off has direct implications for the company or organization making use of the result of this analysis: setting the specificity rate too low can result in a higher rate of incorrect Atypical results...”

Response: Comment incorporated.

Comment Summary #23: The commenter recommended differentiating between spiked and incurred samples, with preference given to incurred samples if the adulterant is expected to be altered during processing.

Response: Comment incorporated.

Comment Summary #24: The commenter suggested changing "true typical" to “typical” in the *Specificity Rate* text.

Response: Comment incorporated.

Comment Summary #25: The commenter suggested adding to the *Applicability Statement* section that it is easier to detect adulteration when the screening is performed close to the source of adulteration.

Response: Comment incorporated.

Comment Summary #26: The commenter suggested revising the *Reference Set* section to include an additional precaution to perform an initial analysis (modeling) of the Reference Set and to remove the most extreme 1–2% of the samples.

Response: Comment partially incorporated. The Expert Committee indicated in the text that only extreme outliers should be removed.

Comment Summary #27: The commenter suggested clarifying in the *Test Set* section whether "in silico" is described in the literature as a practical method in relation to non-targeted modeling.

Response: Comment partially incorporated. An in silico reference was added to the text.

Comment Summary #28: The commenter indicated in the *Test Set and Atypical Samples* section that test set (and validation set) samples do not need to be equally distributed between Typical and Atypical.

Response: Comment not incorporated. The established practice is to have an approximately equal distribution of samples across Typical and Atypical groups to ensure that there is an equivalent robustness in the Sensitivity and Specificity rates.

Comment Summary #29: The commenter indicated in the *Test Set and Atypical Samples* section that “three samples for each adulterant” is insufficient.

Response: Comment partially incorporated. The phrase “at least three samples” was added to the text.

Comment Summary #30: The commenter suggested adding “authentic adulterated samples” (purchased as such, or obtained during a routine analysis) to the *Test set and Atypical Samples* section, because these are the preferred samples, if available.

Response: Comment incorporated.

Comment Summary #31: The commenter suggested spiking atypical rather than near-centroid samples in the *Test set and Atypical Samples* section. The commenter

indicated that adding an adulterant can cause the sample to move in a particular direction and that a random selection (greater than three) is needed.

Response: Comment partially incorporated. A note was added indicating that one of the spiked samples must be spiked enough to exceed twice the threshold.

Comment Summary #32: The commenter recommended adding the requirement to check for agreement between real and virtual “results” to the *Test Set – In silico methods* section.

Response: Comment partially incorporated. An in silico reference was added to the text. The Expert Committee will consider future revisions to this *Guidance* upon the receipt of relevant data.

Comment Summary #33: The commenter indicated in the *Performance Criteria* section that although the final result is binary, the result of the evaluation phase (test and validation) should be the non-rounded number (i.e., the distance or probability from the model).

Response: Comment not incorporated. The Expert Committee will consider future revisions to this *Guidance* upon the receipt of relevant data.

Comment Summary #34: The commenter indicated that there is an inconsistency in the ROC plots: the text mentions that it is generated for different levels of adulterations, whereas the figure caption mentions different discrimination thresholds, and the glossary of terms mentions “model boundaries.”

Response: Comment incorporated.

Comment Summary #35: The commenter suggested addressing modification of the applicability statement because the development and validation could cause changes to the original applicability statement.

Response: Comment incorporated.

Comment Summary #36: The commenter suggested that *Figure 4* should be cited in the *Establish an Applicability Statement* section.

Response: Comment incorporated.

Comment Summary #37: The commenter suggested that the *Reference Set* section should mention the minimum number of samples to describe the entire variance of the sample set (amount per “subclass”).

Response: Comment not incorporated. The Expert Committee determined that the current description is sufficient.

Comment Summary #38: The commenter suggested using respective algorithms such as Kennard-Stone or DUPLEX to select samples in the *Test Set* section, instead of selecting samples near the model centroid, in order to cover the entire natural variance of a material and to avoid overly optimistic results for heterogeneous materials.

Response: Comment incorporated.

Comment Summary #39: The commenter suggested revising the following paragraph in the *Establish Performance Criteria* section: “Using the samples from ...Incorrect Typical result rate.” For example, in the sentence “...each sample is tested multiple times across all facilities...,” clarify whether all samples (test set) should be analyzed at all available facilities. In the sentence “the replicate results are pooled for each sample,” indicate specifically how to calculate the result rates.

Response: Comment incorporated. The performance criteria were reworded.

Comment Summary #40: The commenter suggested revising the *Atypical samples* section to clarify if the Atypical samples in the Validation set differ from the Atypical samples in the Test set.

Response: Comment incorporated.

Comment Summary #41: The commenter suggested including information in the *Reference set* section on how to define a typical sample and how to ensure authenticity.

Response: Comment incorporated.

Comment Summary #42: The commenter suggested providing an example of the heterogeneous material described in the third paragraph of the *Test Set* section. The commenter indicated that a random selection of samples is not relevant.

Response: Comment not incorporated. The Expert Committee determined that the proposed edit would not enhance the understanding of the section.

Comment Summary #43: The commenter suggested deleting the *In silico methods* section because its applicability is very limited.

Response: Comment not incorporated. The Expert Committee determined that the proposed edit would not be beneficial.

Comment Summary #44: The commenter suggested revising the *Reference Set* section to emphasize the authenticity of the samples and to add a method for assessing the authenticity of the samples.

Response: Comment incorporated.

Comment Summary #45: The commenter suggested that rather than setting a confidence level, all authentic samples, as well as extra space, should be included in the boundary.

Response: Comment not incorporated. The Expert Committee determined that the current description is sufficient.

Comment Summary #46: The commenter suggested revising the *Reference Set* section to include a manual inspection during modeling and to include annotation of the outliers.

Response: Comment incorporated.

Using/Maintaining/Monitoring/Revalidation

Comment Summary #47: The commenter suggested adding “operator-induced variability” to the text.

Response: Comment incorporated.

Comment Summary #48: The commenter suggested changing “validation” to “verification” in the following text in the *Frequency of Monitoring* section: "the form of an experiment similar to validation but on a smaller scale."

Response: Comment incorporated.

Comment Summary #49: The commenter suggested that *Figure 4: Flowchart of critical steps in non-targeted method development and validation* should be cited in the *Establish an Applicability Statement* section.

Response: Comment not incorporated. The Expert Committee determined that the proposed edit would add unnecessary details.

Comment Summary #50: The commenter suggested using examples to provide more detail on the term "Charting."

Response: Comment incorporated. The term was changed to “control charting,” and a reference was included.

Comment Summary #51: The commenter suggested expanding the *Internal Control Plan* section. The commenter indicated that the cumulative sum control chart (CUSUM) is typically only used for numerical data, and it is unclear how to proceed in the case of non-numerical data.

Response: Comment not incorporated. The Expert Committee determined that the current description is sufficient.

Comment Summary #52: The commenter suggested clarifying the definition of "class of sample."

Response: Comment incorporated.

Comment Summary #53: The commenter suggested that the *Charting* section should include parameters for the daily mean/median to be used.

Response: Comment not incorporated. The Expert Committee determined that the current description is sufficient.

Comment Summary #54: The commenter recommended that if samples are significantly changed, a new model should be created instead of adding or updating the method.

Response: Comment incorporated.

Comment Summary #55: The commenter suggested addressing the importance of keeping the reference and test sets up to date and suggested methods for obtaining atypical samples.

Response: Comment not incorporated. The Expert Committee determined that the proposed edit would not be in the scope of the *Guidance*.

Comment Summary #56: The commenter suggested adding repeatability in addition to reproducibility.

Response: Comment incorporated.

Interpretation and Next Steps for a “Hit” (An atypical result indicating that U is atypical)

Comment Summary #57: The commenter indicated that better examples should be included.

Response: Comment incorporated. The examples were modified.

Appendix 1&2

Comment Summary #58: The commenter suggested moving *Table 2: Comparison of Non-Targeted Methods* to the section on *Other Approaches Used in Authentication* because it is not cited in the text and the statements in the table are not clear.

Response: Comment incorporated.

Comment Summary #59: The commenter indicated that *Figure 4* was not cited in the text, and there was an open end within the logical scheme. The commenter suggested clarifying how to proceed if the variability cannot be reduced and a new analytical approach cannot be implemented, as well as modifying the text to reflect changing of the applicability statement after method development.

Response: Comment incorporated.

Minor editorial comments

Comment Summary #60: The commenter suggested rewording the text in the *Overview* as follows: "An adulterated sample could show as Atypical, however, an authentic, unadulterated sample with....could also show as Atypical."

Response: Comment incorporated.

Comment Summary #61: The commenter suggested changing the word "creation" to "design" in the *Overview*.

Response: Comment incorporated.

Comment Summary #62: The commenter suggested deleting the phrase "(though not necessarily)" from the *Outline and Scope* section.

Response: Comment incorporated.

Comment Summary #63: The commenter suggested omitting the word "seller" or defining that the gain is typically only for the fraudster, not for the subsequent re-seller (e.g., retailer, etc.) in the EMA definition in the *Outline and Scope* section.

Response: Comment incorporated.

Comment Summary #64: The commenter suggested deleting the word "truly" in "truly adulterated" in *In Scope 2* of the *Outline and Scope* section.

Response: Comment incorporated.

Comment Summary #65: The commenter suggested rewording "human expert" in *In Scope 5* of the *Outline and Scope* section.

Response: Comment incorporated.

Comment Summary #66: The commenter suggested changing the words "hoax leveled" into "threat" in *Out of Scope 3* of the *Outline and Scope* section.

Response: Comment incorporated.

Comment Summary #67: The commenter suggested revising the following sentence in the *Steps for development and validation—The generic thought process* section to form shorter sentences: "For non-targeted methods, the validation process does not limit the scope of applicability of the method, but does give a degree of calibration for those adulterants validated."

Response: Comment incorporated.

Comment Summary #68: The commenter suggested deleting or rephrasing "what must it do to be useful in your specific application" to "...the scope/applicability statement of the method entails key aspects of expected achievements for the specific situation/circumstances..." in the *Establish an Applicability Statement* section.

Response: Comment incorporated.

Comment Summary #69: The commenter suggested changing "intended purpose" to "scope" in the first sentence of the *Establish an Applicability Statement* section.

Response: Comment incorporated.

Comment Summary #70: The commenter suggested changing "Key points to cover are the intended matrix, the purpose, and an indication of sensitivity, specificity, and significance" into bullet points in the *Establish an Applicability Statement* section.

Response: Comment not incorporated. The Expert Committee determined that the proposed edit would not enhance the understanding of the section.

Comment Summary #71: The commenter suggested changing the word "organization" to "user" in the second paragraph of the *Establish an Applicability Statement* section.

Response: Comment incorporated.

Comment Summary #72: The commenter suggested changing the words "a good sample" into "an authentic sample" in the *Steps for development and validation—the generic thought process* section.

Response: Comment incorporated.

Comment Summary #73: The commenter suggested replacing the sentence "Agents used for intentional adulteration would typically be expected at concentrations below the sensitivity limits of most non-targeted methods" with "Agents used for such intentional modification would also be expected at concentrations below the sensitivity limits of most non-targeted methods" in the *Purpose* section.

Response: Comment incorporated.

Comment Summary #74: The commenter suggested replacing "contaminants" with "adulterants" in the first bullet of the *Reference Set* section.

Response: Comment incorporated.

Expert Committee-initiated Change #1: Replace the section title "*Monitoring*" with "*Quality assurance/control measures.*"

Expert Committee-initiated Change #2: In *Atypical Samples*, list the full name of IBDU as isobutylidene diurea.

Expert Committee-initiated Change #3: In *Confirmatory analyses*, the word "accredited" should be changed to "qualified." The phrase "legally credible" should be changed to "scientifically defensible."

Monograph/Sections: Plant Stanol Esters/Multiple sections

Expert Committee: Food Ingredients

No. of Commenters: 1

Comment Summary #1: The commenter recommended that the peroxide value be changed from NMT 0.5 mEq/kg to NMT 5.0 mEq/kg to reflect the typical shelf-life value.

Response: Comment incorporated.

Expert Committee-initiated Change #1: Replace the sentence "They are insoluble in water and soluble in non-polar solvents such as hexane, iso-octane and 2-propanol" in the *Description* section with "They are insoluble in water and soluble in hexane, iso-octane and 2-propanol" because 2-propanol is not a non-polar solvent.

Expert Committee-initiated Change #2: Add the test for Free Fatty Acid to the *Specific Tests* section with the acceptance criteria of NMT 0.1% because there was no test for the acid value.

Monograph/Sections: Taurine/Multiple Sections

Expert Committee: Food Ingredients

Expert Committee-initiated Change # 1: Delete thin layer chromatography (TLC) from the *Identification* section. Because infrared spectroscopy and high-performance liquid chromatography (HPLC) are sufficient for identifying taurine, TLC has become unnecessary for *Identification*. Revise the TLC in the *Related Substances* section accordingly to add the content on TLC that was deleted from the *Identification* section.

Expert Committee-initiated Change # 2: In the *Assay* section, correct the formula under the *Assay* to reflect the fact that the linearity of the method is obtained by plotting the logarithms of taurine peak responses against the logarithms of the concentrations.

Monograph/Section: Vanillyl Butyl Ether/Description of Odor

Expert Committee: Food Ingredients

Expert Committee-initiated Change #1: In the *Description of Odor* section, list only “weak vanillic” and remove “weak” and “acidic” because these terms are not specific odor descriptors.