Contains Nonbinding Recommendations

Draft-Not for Implementation

Guidance for Industry

Providing Regulatory Submissions in Electronic or Paper Format to the Office of Food Additive Safety

Draft Guidance

You may submit written comments regarding this guidance at any time. Submit written comments on the guidance to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the title of the guidance document.

Additional copies are available from:
Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5001 Campus Drive
College Park, MD 20740
(Tel) 301-436-1200
http://www.fda.gov/FoodGuidances

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Food Safety and Applied Nutrition
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Guidance for Industry[1]
Providing Regulatory Submissions to the Office of Food Additive Safety in Electronic or Paper Format

This guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the telephone number listed on the title page of this guidance.

I. Introduction

This guidance document is intended to assist industry in transmitting regulatory submissions to the Office of Food Additive Safety (OFAS) in CFSAN at FDA. Although the guidance applies regardless of whether you transmit the submission in electronic format or in paper format, many of the details of this guidance are directed to specific format features associated with transmitting a submission in electronic format.

This guidance applies to the following types of regulatory submissions to OFAS:

- Food Additive Petition (FAP);
- Color Additive Petition (CAP);
- Food Master File (FMF);
- Color Master File (CMF);
- Food Contact Notification (FCN);
- Pre-Notification Consultation for a Food Contact Substance (PNC);
- Generally Recognized As Safe (GRAS) notice;
- Final Consultation for Food Derived From New Plant Varieties (Biotechnology Final Consultation); and
- Early Food Safety Evaluation of New Non-Pesticidal Proteins Produced by New Plant Varieties Intended for Food Use (New Protein Consultation).

[1] This guidance has been prepared by the Office of Food Additive Safety in the Center for Food Safety and Applied Nutrition at the U.S. Food and Drug Administration.

OFAS receives other types of submissions in addition to the submissions listed above. For example, OFAS receives "Threshold of Regulation" submissions in accordance with 21 CFR 170.39 and "Notification for a Food Contact Formulation" submissions in accordance with 21 CFR 170.106. This document does not provide any specific recommendations regarding these submissions because the number of these types of submissions is small. If you have questions about preparing a submission other than those listed above, you should contact us at the telephone number provided on the first page of this document.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Elements Common to All Regulatory Submissions

A. General

1. Where can I find the definitions of the regulatory submissions and terms covered by this document?

You can find the definitions of the regulatory submissions and terms covered by this guidance in Appendix 11.

2. Do any fees apply to my regulatory submission?

As of the date of this document, fees only apply to the submission of a CAP for the listing of a color additive (see 21 CFR 70.19).

3. Where do I send my regulatory submission?

Send all fully electronic submissions through FDA's Electronic Submission Gateway (ESG). For additional information about FDA's ESG, see Section III.B of this document.

Send a FCN, PNC, or FMF concerning a food contact substance (FCS) that is prepared in paper format, or prepared in electronic format but submitted on physical media (e.g., CD-ROM or DVD), to:

Notification Control Assistant
Office of Food Additive Safety
HFS-275
5001 Campus Drive
College Park, MD 20740-3835

Send all other regulatory submissions prepared in paper format, or prepared in electronic format but submitted on physical media (e.g., CD-ROM or DVD), to:

Office of Food Additive Safety
HFS-200
5001 Campus Drive
College Park, MD 20740-3835

4. May FDA refuse to accept my regulatory submission?

Yes. FDA may refuse to accept any regulatory submission that is transmitted in electronic format, if it is either inaccessible or contaminated with malicious elements such as a computer virus. FDA may also refuse to file a new submission if it is incomplete or if any data are lacking or not set forth so as to be readily understood (see, e.g., 21 CFR 71.1(d), 21 CFR 171.1(d), and 21 CFR 170.104(b)(1)).

B. Forms

5. Should I include a specific form with my regulatory submission?

Yes. You should include a specific form with any regulatory submission (including any new submission and any update, amendment, or supplement to a previous submission), regardless of whether you transmit the regulatory submission in electronic format or in paper format. You must use Form FDA 3480 when submitting a FCN (21 CFR 170.101(e)). If you are sending your submission in paper format, place your submission form at the beginning of the entire submission.

6. What is the purpose of the form I include with my regulatory submission?

The form prompts you to include certain elements of the particular type of regulatory submission in a standard format. A form you transmit in electronic format improves the efficiency of our administration of your submission, because it provides data and information that our systems can extract and upload directly into our databases.

The form also substitutes for the "Dear Sir" section of 21 CFR 71.1(c) (for a CAP) and 21 CFR 171.1(c) (for a FAP). However, the information on the form is not intended to substitute for the complete description of procedures, requirements, or recommendations included in the applicable regulation or guidance.

7. How do I find the correct form and applicable instructions for completing the form?

Table II-1 identifies the correct form to include with each type of regulatory submission, the Appendices where you can find each form, and the Appendices where you can find instructions for completing each form.

Table II-1

Where to Find the Correct Form for Your Regulatory Submission

Type of Submission	Form No.*	Where to Find the Instructions for Using the Form	Where to Find the Form
FAP, FMF	3503	Appendix 1	Appendix 2
CAP, CMF	3503	Appendix 1	Appendix 2
FCN, FMF for FCS, PNC	3480	Appendix 3a	Appendix 4a
Amendment to a FCN, PNC, or FMF for a FCS	3480-A	Appendix 3b	Appendix 4b
GRAS Notice	3667	Appendix 5	Appendix 6
Biotechnology Final Consultation	3665	Appendix 7	Appendix 8
New Protein Consultation	3666	Appendix 9	Appendix 10

***** For all original submissions and any additional information to those submissions (except those concerning FCS) use the same submission form.

8. How should I organize a new master file submission?

You should organize a new master file submission according to the items listed on the applicable form (i.e., Form FDA 3503 or Form FDA 3480). A summary of these items is listed in Table IV-1 of this document (for Form FDA 3503) and Table V-1 of this document (for Form FDA 3480) and described in the applicable instructions for the form (see Appendices 1, 3a and 3b).

C. Amendments, Updates, and Supplements

9. How are the terms "amendment," "update," and "supplement" used in the context of the regulatory submissions covered by this document?

The terms "amendment," update," and "supplement" are used as shown in Table II-2.

Table II-2
Use of the Terms "Amendment," Update," and "Supplement"

Submission	Amendment	Update	Supplement
FAP	Any data or information you submit to a filed FAP in response to a request from us for additional information or clarification	Any data or information submitted to a filed FAP on the initiative of the submitter (i.e., without a request from FDA)	N/A*
CAP	Any data or information you submit to a filed CAP in response to a request from us for additional information or clarification	Any data or information submitted to a filed CAP on the initiative of the submitter (i.e., without a request from FDA)	N/A
FCN	Any data or information you submit to an FCN	N/A	N/A
PNC	Any data or information you submit to a PNC	N/A	N/A
GRAS notice	Any data or information you submit regarding a filed GRAS notice before we respond to it	N/A	Any data or information you submit regarding a GRAS notice after we respond to it
Biotechnology Final Consultation	Any data or information you submit regarding a Biotechnology Final Consultation before we respond to it	N/A	Any data or information you submit regarding a Biotechnology Final Consultation after we respond to it
New Protein Consultation	Any data or information you submit regarding a New Protein Consultation before we respond to it	N/A	Any data or information you submit regarding a New Protein Consultation after we respond to it
FMF	Any data or information you submit to an FMF established for a FCS	Any data or information you submit to an FMF established for a substance other than a FCS	N/A
CMF	N/A	Any data or information you submit to an established CMF	N/A

*N/A means "Not applicable."

D. Table of Contents

10. Should I include a Table of Contents with my regulatory submission?

You should include a Table of Contents:

- With any submission regarding a GRAS notice, Biotechnology Final Consultation, or New Protein Consultation (whether the submission is a new submission or an amendment or supplement to a previous submission), regardless of whether the submission is transmitted in paper or electronic format;
- With any other regulatory submission transmitted in paper format; and
- Within individual Studies submitted as part of a regulatory submission.

11. How should I paginate a regulatory submission in paper format?

You should paginate a regulatory submission in paper format using continuous pagination. For an example of continuous pagination, see the example Table of Contents in Table II-3 in the next question.

12. How should I format the Table of Contents in a regulatory submission I transmit in paper format?

You should format the Table of Contents in a regulatory submission in paper format to show the overall page numbers for the entire submission. When there is more than one volume, the Table of Contents should include the volume number. Below, we provide examples of a Table of Contents for a FAP (Table II-3) and a safety study (Table II-4), respectively.

Table II-3
Example of a Table of Contents for a FAP Submitted in Paper Format

Title	Volume	Page No.
Proposed Regulation	I	1-2
Chemistry Information	I - VII	3-2560
• Identity	I	3-203
• Use and Technical Effect	I - III	204-1342
• Labeling	III	1343-1350
• Manufacturing Method	III	1351-1377
• Specifications	III	1378-1379
• Stability Studies	III - IV	1380 - 1753
• Studies Regarding Intended Effect	IV - V	1754 -2109
• Analytical Methods	V - VI	2110 -2531
• Chemistry References	VI	2532 -2560
Safety Information	VI - XXXI	2561-11671

Title	Volume	Page No.
• Toxicology Narrative	VI	2561-2575
• Genetic Toxicity Tests	VI	2576-2848
• Short Term Toxicity Studies in Rodents	VII	2849-3120
• Short Term Toxicity Studies in Non-Rodents	VII - VIII	3121-3170
• Subchronic Toxicity Studies in Rodents	VIII - IX	3171- 3552
• Subchronic Toxicity Studies in Non-Rodents	IX	3553-3853
• One Year Toxicity Studies in Non-Rodents	X	3854 - 4104
• Combined Chronic Toxicity/Carcinogenicity Studies in Rodents	X - XIX	4105-9948
• Multi-Generation Reproduction Study	XIX - XXX	9949-10970
• Immunotoxicity Studies	XXX	10971-11021
• Neurotoxicity Studies	XXX	11022-11202
• Metabolism and Pharmacokinetic Studies	XXX - XXXI	11203-11673
• Safety References	XXXI	11674-11678
Environmental Assessment	XXXI	11679-11792

Table II-4
Example of a Table of Contents for a One Year Toxicity Study in Non-Rodents Submitted in Paper Format

Title	Volume	Page No.
Authentication	X	1
Quality Assurance	X	2-3
Summary and Conclusions	X	4-10
Study Organization	X	11-13
Information on the Test and Control Article	X	14-18
Experimental Procedure	X	19-29
Evaluation of Data	X	30 - 40
Archives	X	41-43
Schedule of the Study	X	44-48
Comments and Deviations from The Original Protocol and Amendments	X	49- 51
Results	X	52-200
Tables of Mean Values	X	201-225
Appendices (individual results)	X	226 -245
Addenda	X	246 -249
Statement of Compliance	X	250

E. Information that is Exempt from Disclosure under the Freedom of Information Act (FOIA)

13. Should I designate in my regulatory submission information that I view as exempt from disclosure under the Freedom of Information Act?

Yes. We recommend that you designate information that you consider exempt from disclosure in writing (21 CFR 20.61(d)). However, if we disagree that the designated information satisfies the criteria for exemption from disclosure (see 21 CFR 20.27 and 21 CFR Part 20 Subparts D and E), the procedures in 21 CFR 20.61(e) will apply.

14. How should I designate information that I consider exempt from disclosure?

You should designate this information in a manner that will unambiguously communicate your view.

We recommend that you:

- Describe the information that you consider exempt from disclosure in a separate document (for the purposes of this guidance we are calling this document "Designation of Nondisclosable Information"). For example, the Designation of Nondisclosable Information included with a FAP could identify a particular quantitative formula you view as exempt from disclosure within the meaning of 21 CFR 171.1(h)(2)(iii). This would ensure that we know your view on this quantitative formula each and every time it appears. Such a separate document could, for example, both identify a quantitative formula you view as confidential and provide a list of places in the submission where the formula occurs.
- Identify information as exempt from disclosure at the place where it occurs in a submission (e.g., by highlighting). You may mark an entire page or set of pages as confidential (e.g., by a stamp at the top of each page) when you consider entire pages or multi-page documents as trade secret or confidential information (e.g., when describing a manufacturing process in a food additive petition). You should not mark an entire page or set of pages as confidential when the page or pages contain both confidential and non-confidential information. If you are unable to mark information on the electronic submission form as confidential (e.g., by highlighting), you should describe the information entered on the form you consider nondisclosable in a Designation of Nondisclosable Information document, as described above.

15. May I provide a redacted copy of some or all of my regulatory submission?

Yes. You may provide a redacted copy of your complete submission, or a redacted copy of only those parts of your submission containing information you view exempt from disclosure. If you provide a redacted copy of some or all of your regulatory submission, we nonetheless recommend that you also designate information exempt from disclosure as described above. This will help to ensure that we are aware of your view if, for example, you inadvertently did not redact all nondisclosable information.

16. Will FDA use my redacted copy when FDA responds to a request, under the FOIA, for a disclosable copy of my submission?

FDA may or may not use your redacted copy depending on whether the redacted copy satisfies the criteria for exemption under FOIA (see 21 CFR Part 20 at 20.27 and Subparts D and E) and on whether using your redacted copy will be the most efficient means for us to respond to FOIA requests (e.g., because of formatting issues).

17. Are the data and information in a master file submission available for public disclosure?

Whether the data and information in a master file submission are available for public disclosure is a case-by-case determination that we make in accordance with our regulations in 21 CFR part 20 and (when applicable) in submission-specific regulations such as 21 CFR 171.1(h). Whether specific data and information are exempt from disclosure depends on circumstances and, thus, may change as circumstances change.

F. Cover Letter

18. Should I include a cover letter with my regulatory submission?

We do not ask you to include a cover letter if you use the applicable form for the regulatory submission. If you choose not to use the applicable form, you should include a cover letter regardless of whether you transmit the submission in electronic format or in paper format and regardless of whether your submission is a new submission or an amendment, update, or supplement to an existing submission.

19. What should a cover letter include?

A cover letter should include the administrative information that would have been included with the applicable form. For FCN submissions, this information can be found in Part I of Forms 3480 and 3480-A. For all other regulatory submissions, this information can be found in Parts I, II, and III of the applicable form.

Examples of this administrative information include:

- The type of regulatory submission (e.g., FAP, New Protein Consultation);
- Whether the submission is a new submission or an amendment, update or supplement to a previous submission;
- The applicable regulation or guidance associated with the submission (e.g., a FAP is submitted in accordance with 21 CFR 171.1 and a New Protein Consultation is submitted in accordance with our Guidance to Industry entitled "Recommendations for the Early Food Safety Evaluation of New Non-Pesticidal Proteins Produced by New Plant Varieties Intended for Food Use" (Ref. 22));

- The format and mode of transmission (e.g., electronic format transmitted on physical media) and the number of any enclosed physical media (e.g., three CD-ROMs); and
- A statement that any electronic files have been checked and found to be virus-free.

In addition, when your submission is a CAP or a FAP, the cover letter should include the elements specified in the opening of 21 CFR 71.1(c) (for a CAP) or 21 CFR 171.1(c) (for a FAP).

G. References

20. How should I provide the Web site address when I refer to information available on the Internet?

You should provide the Web site address for information available on the Internet by including it in a list of references or web-based documents. For additional information on providing Web site addresses in electronic submissions, see Section III.E in this document.

III. General Considerations about Regulatory Submissions in Electronic Format

A. General Information

1. Should I use a password to protect a regulatory submission in electronic format?

No. Our internal security and archival processes will maintain the integrity of the files received.

2. Should I check a regulatory submission in electronic format for computer viruses?

Yes. The forms provide a checkbox prompting you to confirm that the submitted files have been checked and are free of computer viruses. If you are sending a cover letter refer to Section II.F above.

3. What is the size limit of electronic files I submit?

The size limit of electronic files you submit is 50 Megabytes (MB). You should divide any files larger than 50 MB into multiple files.

B. Transmission of a Regulatory Submission in Electronic Format

4. What is the FDA Electronic Submission Gateway (FDA ESG)?

The FDA ESG is an agency-wide portal mechanism for receiving submissions in electronic format. The FDA ESG enables the secure submission of regulatory information for review and provides for the receipt of a document.

5. How do I use the FDA ESG?

Complete instructions for use of the FDA ESG are available in FDA's Web site (Ref. 1).

6. Is the FDA ESG the only mechanism available for me to transmit my regulatory submission in electronic format?

No. You also may transmit a regulatory submission in electronic format by providing your electronic files on physical media (e.g., CD-ROM or DVD) and transmitting these physical media by means such as mail or a courier service.

7. What recommendations apply when I use physical media (such as CD-ROMs or DVDs) to transmit my regulatory submission in electronic format?

A regulatory submission transmitted in electronic format on physical media should be accompanied by a paper copy of any form or cover letter that you sign. At this time, we are not able to accept an electronic signature in documents transmitted on physical media.

You may "zip" files to provide as much information as possible on a single disc (or other physical medium). If you need to use more than one disc (or other physical medium), you should label each item (e.g., Disc 1 of 4, Disc 2 of 4, etc.).

C. File Formats and Names in an Electronic Regulatory Submission

8. What file formats should I use for my regulatory submission?

The type of file format to use depends on the type of data or information you are submitting. Table III-1 lists the file formats we recommend you use for the most common types of data and information. We generally are able to access formats listed in Table III-1 and data sets that are compatible with XML (extensible markup language) format. We recommend that you contact us before submitting data or information in any file format not listed in Table III-1. Doing so should minimize problems with your electronic submission.

The different Centers in FDA are in varying stages of implementing a pilot program for accessing files in Standard for Exchange of Nonclinical Data (SEND) and Study Data Tabulation Model (SDTM) (Ref. 14). The likelihood that OFAS will be able to receive files in SEND or SDTM increases as time goes on. Therefore, we recommend that you contact us before submitting files in SEND or SDTM formats. We can also receive files containing study data in XML format.

Additional information relevant to the use of electronic collection of clinical trial data is available in the Guidance to Industry - Computerized Systems Used in Clinical Investigations (Ref. 12).

Table III-1
Recommended File Formats

Type of Data or Information	Recommended File Format
General text	Portable Document Format (PDF)
Primary data or summary data (e.g., toxicological study reports)	Both PDF and, if available, spreadsheet format for tabular data (e.g., .xls).
Chemical structures	Molfiles (.mol) (preferred); or ChemDraw files (.cdx); or Structure & data files (.sdf) (Chemical structures may also be provided as images within PDF files)
Animal Study Data	In addition to PDF for full study reports, use templates when available and transmit the information in the completed template in PDF (Ref. 13); OR Use Standard for Exchange of Nonclinical Data (Ref. 14)
Clinical Trial Data Generated by Computerized Systems	Study Data Tabulation Model (SDTM) (Ref. 14)
References	PDF

9. What recommendations apply to files prepared in PDF format?

We recommend that you create PDF files directly from electronic source documents (rather than from scanned images) whenever possible. Such files require less memory space than scanned image files. Such files also help assure access to, and accurate searching of, text, tabular data and graphical objects.

If you scan a document to create a PDF file, we recommend that you capture text by optical character recognition (OCR) software so that the text of the resulting electronic documents is reasonably accessible and searchable.

10. How should I name files in a regulatory submission transmitted in electronic format?

You should name a file in a way that will help us to see what is in the file and when the file was prepared or submitted. Doing so will help us to store the file in our database in a way that our reviewers can easily find it and will improve the efficiency of our review.

In general, you should name a file using both generic elements (which relate to the type of information in the file, such as a toxicity study) and specific elements (which relate to your particular submission, such as the name of the substance that is the subject of the submission). The specific recommended conventions for naming files vary depending on factors such as:

- The type of data or information;
- Whether the data or information is transmitted in a new regulatory submission or in an amendment, update or supplement to a previous regulatory submission; and
- Whether the document that is the subject of the file exceeds 50 megabytes and, thus, is broken into more than one file.

You should refer to Appendix 12 and the detailed guidance for each type of regulatory submission (in Sections IV through VIII of this document) for more complete recommendations for naming files and for examples.

D. Roadmaps

11. What is an electronic submission "roadmap"?

An electronic submission "roadmap" is an organized grouping of electronic folders that you can download and use to structure an electronic submission.

12. Do different types of regulatory submissions have different roadmaps?

Yes.

13. Should I include a roadmap with each electronic regulatory submission I make?

Yes. You should include the applicable roadmap with each electronic regulatory submission (including a new submission and any update, amendment, or supplement to a previous submission). You should download a new roadmap each time you transmit an amendment, update or supplement to an existing submission. This will help us to distinguish the newly submitted information from the information in your original submission.

14. Where can I find the roadmaps for use in structuring regulatory submissions?

The roadmaps are available in Appendix 15.

15. Where can I find examples of representative roadmaps for the submissions described in this document?

Figures IV-1, V-1, VI-1, VII-1, and VIII-1 of this document (see Sections IV, V, VI, VII, and VIII of this document), which are submission outlines, depict examples of representative roadmaps for the submissions described in this document.

16. What would a roadmap look like when displayed on my computer?

Figures III-1 and III-2 provide examples of a roadmap as seen on your computer (Microsoft Windows). Figure III-1 shows a foldering structure and Figure III-2 shows files included within a particular folder. The information presented in this diagram depicts a set of folders in a food additive petition; an alternative presentation of Figure III-1 (in text format) is in Figure IV-1.

Figure III-1 shows a "Main directory" with "five first level folders" (Administrative, Administrative Technical, Chemistry, Safety and Environmental). The Administrative folder has three second level folders (Designation of Nondisclosable Information, Redacted Document and Incoming Correspondence). The Chemistry folder has two second level folders (Methods and References). The Safety folder has two second level folders (Studies and References). The Environmental folder has three second level folders (Confidential Environmental Info, Studies and References). The second level folders Incoming Correspondence, Chemistry, Safety and Environmental also contain third level folders. The third level Studies folder under the Safety folder has many fourth level folders.

Figure III-1 Example of the Main Directory of a FAP Submission Roadmap

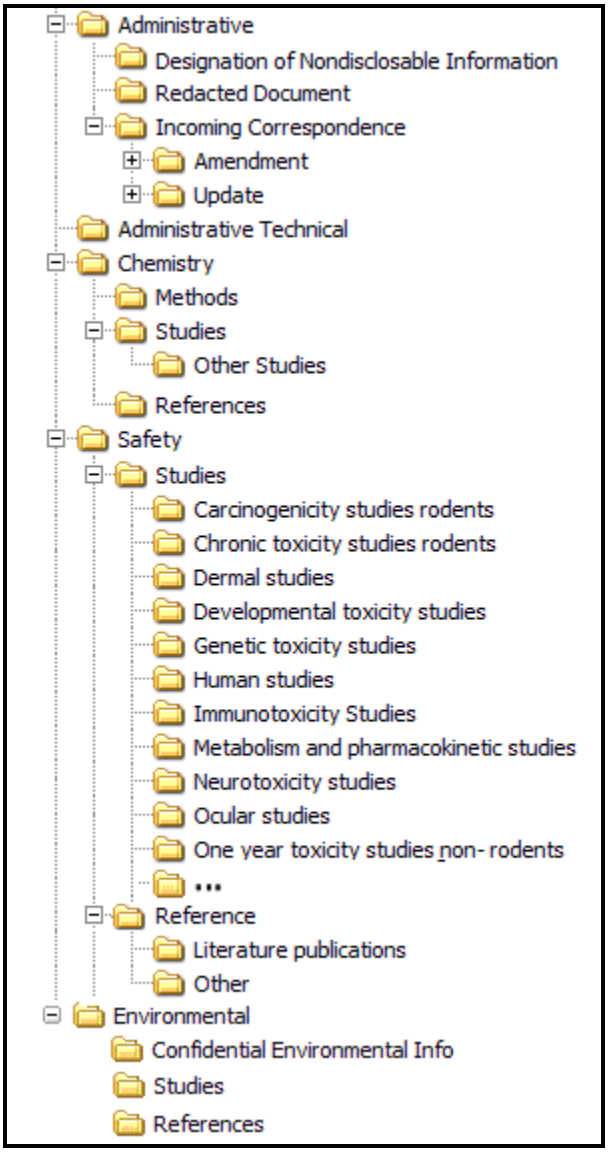
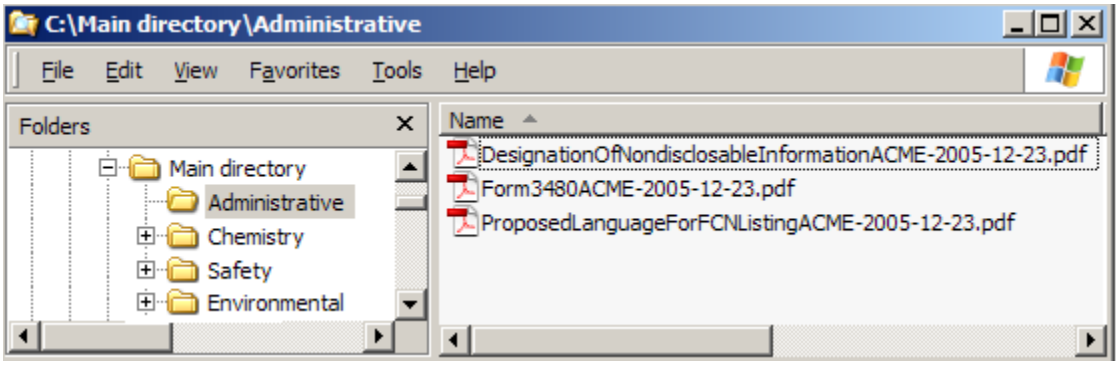


Figure III-2 Example of the Contents of the Administrative Subfolder in a FCN Submission Roadmap

Figure III-2 has two panels. The left panel of Figure III-2 shows a "Main directory" with four "first level folders" (i.e., Administrative, Chemistry, Environmental, and Safety folders). A "plus" sign precedes three folders (i.e., Chemistry, Safety, and Environmental folders), indicating that these folders contain second level folders.

The administrative folder in the left panel of Figure III-2 is highlighted to show that its contents are presented in the right panel of Figure III-2. The right panel of Figure III-2 contains three

PDF files (i.e.., for Designation of Nondisclosable Information, Form 3480, and Proposed Language for the FCN Listing for a food contact substance).



E. Organization of an Electronic Regulatory Submission

17. What format features should I include in the Table of Contents in a PDF file included in an electronic regulatory submission?

You should format the Table of Contents in a PDF file using bookmarks designed to help the reader navigate through the document efficiently.

18. How should I paginate the individual files in a regulatory submission in electronic format?

You should paginate each individual file transmitted in the regulatory submission. In most cases, you should paginate each submitted file so that it begins on page 1 – i.e., you should not incorporate any type of continuous pagination. This recommendation is in contrast to our recommendation for pagination of paper submissions, where continuous pagination is appropriate (see Section II.D of this document). See the next question for an exception associated with studies that are so large that you submit them in multiple files that use continuous pagination.

19. How should I organize information in large studies?

You should organize information in large studies as follows:

- Include a Table of Contents at the beginning of each study;
- Separate files by sections of the study rather than breaking in the middle of a section; and
- Preserve the pagination of a large study with each PDF file continuing the pagination where the previous PDF file left off.

For example, consider a study file with 2000 pages. If you split the file at the end of page 1500, the next file should start at page 1501. (See Appendix 12 for additional information on naming these files.)

20. How should I format the Web site addresses included in a reference list submitted in electronic format?

You should format Web site addresses in a reference list as hyperlinks and include the applicable Web site address as of the date when you accessed the reference from the Web site.

F. Preparation of Amendments, Updates, and Supplements in Electronic Format

21. What special recommendations apply to the submission of amendments, updates, or supplements in an electronic regulatory submission?

The following recommendations apply to amendments, updates, and supplements for all regulatory submissions prepared in electronic format.

- Use the applicable form.
- Download a new Roadmap and change the name of the "Main directory" to the number we assigned to your submission type (e.g., "FCN 009999" or "FAP 9A9999").
- Organize the information in the submission into one or more individual files as described in the specific guidance for your regulatory submission. (For example, an amendment or update to a FAP would include a separate file directed to each topic addressed in the amendment or update, whereas an amendment or supplement to a GRAS notice would include a single file regardless of the number of topics addressed in the amendment or supplement.)
- Begin each filename with the date (YYYY-MM-DD) the amendment, update or supplement is submitted.
- Place the files in appropriate folders according to the applicable roadmap.
- Do not include files already submitted.

Additional recommendations for amendments, updates or supplements are available in the specific guidance for each submission type as follows:

- FAPs/CAPs: Section IV.C;
- FCNs: Section V.C;
- GRAS notices: Section VI.C;
- Biotechnology Final Consultations: Section VII.C; and
- New Protein Consultation Submissions: Section VIII.C.

Following these recommendations will help us to store the data and information in the amendment, update or supplement in our database in a way that our reviewers can easily find it.

G. Electronic Signatures

22. Where can I find information about electronic signatures in a regulatory submission?

Information about electronic signatures in regulatory submissions to FDA is available in 21 CFR 11.200 and at the ESG (Ref. 1). For further information on the current status of electronic signatures, contact OFAS at 301-436-1200.

IV. Information Specific to Food or Color Additive Petition Submissions

Section IV of this document addresses FAP and CAP submissions (petition submissions). You must submit an FAP in accordance with 21 CFR 171.1 and a CAP in accordance with 21 CFR 71.1. We assign a number (FAP No. or CAP No., respectively) to your submission and review your submission to determine whether to establish a regulation for the use of a food additive or list a color additive in Title 21 of the Code of Federal Regulations.

A. General Information about Petition Submissions

1. How do the Parts on Form FDA 3503 relate to the elements of FAPs and CAPs?

Table IV-1 shows the elements of FAPs and CAPs and links each element to the applicable part of Form FDA 3503.

Table IV-1
Elements of FAPs and CAPs as Shown on Form FDA 3503

Element of FAPs and CAPs	Applicable Part on Form FDA 3503
Introductory information about the submission	I
Information about the petitioner (and any attorney or agent acting on behalf of the petitioner)	II
General administrative information	III
Information specific to Food Additive Petitions	IV.A
Information (including fees) specific to Color Additive Petitions	IV.B
Identity	V
Administrative	VI
Administrative Technical	VI
Chemistry	VI
Safety	VI
Environmental	VI
Signature	VII
N/A	VIII (List of Attachments)

2. How should I organize a new petition submission?

You should organize a new petition submission as a series of documents presenting the elements of a petition in an order corresponding to that of the elements listed on Form FDA 3503. A summary of these elements is listed in Table IV-1 of this document and described in the instructions for Form FDA 3503 (see Appendix 1). If you include any data or information not identified as an element on Form FDA 3503, you should place these data or information in a logical place in your submission based on the type of information.

3. Am I required to include a proposed regulation with my petition submission?

You must include a proposed regulation if your petition would alter an existing food additive regulation or color additive listing (see 21 CFR 171.1(c)G and 21 CFR 71.1(c)H). If your petition is for a new food additive regulation or color additive listing, you may include a proposed regulation (see 21 CFR 171.1(c)F and 21 CFR 71.1(c)F).

4. Am I required to include a proposed tolerance with my petition submission?

You must include a proposed tolerance with your petition if a tolerance is required to ensure safety (see 21 CFR 171.1(c)F and 21 CFR 71.1(c)F).

B. Petition Submissions in Electronic Format

General Questions and Answers about Petition Submissions in Electronic Format

5. How should I organize an electronic FAP or CAP submission?

You should organize an electronic FAP or CAP submission using the foldering structure available in a downloadable Petition Submission Roadmap (see instructions in Appendix 1 and the roadmap in Appendix 15). The entire Petition Submission Roadmap is organized under the folder entitled "Main directory." The "Main directory" includes six first-level folders, and several of these first-level folders include second-level and third-level subfolders. We show these folders and subfolders, using an outline format, in Figure IV-1, below.

Figure IV-1
Outline Representing the Folders and Subfolders in a Petition Submission Roadmap ("Main directory")

- Main directory
    - Administrative
        - Designation of Nondisclosable Information
        - Redacted Document
        - Incoming Correspondence
            - Amendment

- Update
- Administrative Technical
- Chemistry
  - Studies
    - Stability
    - Technical Effect
    - Migration
    - Other
  - Methods
  - References
- Safety
  - Studies
    - Genetic Toxicity Tests
    - Short Term Toxicity Studies Rodents
    - Short Term Toxicity Studies Non-Rodents
    - Subchronic Toxicity Studies Rodents
    - Subchronic Toxicity Studies Non-Rodents
    - One Year Toxicity Studies Non-Rodents
    - Chronic Toxicity Studies Rodents
    - Combined Chronic Toxicity/Carcinogenicity Studies Rodents
    - Carcinogenicity Studies Rodents
    - In Utero Exposure Phase for Addition to Carcinogenicity Studies Rodents
    - Reproduction Studies
    - Developmental Toxicity Studies
    - Immunotoxicity Studies
    - Metabolism and Pharmacokinetic Studies
    - Neurotoxicity Studies
    - Ocular Studies
    - Dermal Studies
    - Human Studies
    - Other Studies
  - References
    - Literature Publications
    - Other
- Environmental
  - Confidential Environmental Information
  - Studies
  - References
- Other

6. When should I use the specific folders and subfolders in the Petition Submission Roadmap ("Main directory")?

You should use the specific folders and subfolders as shown in Table IV-2. You should not place any specific files directly in "Main directory," which refers to the entire submission organized in the foldering structure (refer to Figure III-1 and Figure IV-1). "Main directory" only contains folders.

Table IV-2
When to Use Specific Folders and Subfolders in the "Main Directory" of a Petition Submission Roadmap*

Folder/Subfolder	When to Use it
Administrative folder	Any time you transmit a new submission, a file relating to fees associated with a CAP, or a redacted electronic file(s)
Designation of Nondisclosable Information folder	Any time you transmit data or information that satisfies the criteria for exemption from disclosure
Redacted Folder	Any time you submit a redacted copy, place it in the redacted subfolder under the Administrative folder, regardless of whether you are transmitting a new submission, an amendment, or an update
Incoming Correspondence folder	You should not place any specific files directly in the Incoming Correspondence folder. The Incoming Correspondence folder only contains subfolders
Incoming Correspondence/Submission Form Subfolder	Any time you transmit an amendment or update to your petition
Incoming Correspondence/ Amendment Subfolder	Only when the data or information you transmit to a filed submission in response to correspondence from us do not fall within the scope of any other folder, such as Chemistry, Safety, or Environmental
Incoming Correspondence/ Update Subfolder	Only when the data or information you transmit to a filed submission on your own initiative (i.e., not in response to correspondence from us) do not fall within the scope of any other folder, such as Chemistry, Safety, or Environmental
Administrative Technical Folder	Any time you transmit a proposed regulation, proposed tolerance, or information regarding exemption from batch certification for a color additive, regardless of whether you are transmitting a new submission, an amendment, or an update

Folder/Subfolder	When to Use it
Chemistry Folder and Applicable Subfolders	Any time you transmit chemistry data or information, regardless of whether you are transmitting a new submission, an amendment, or an update
Safety Folder and Applicable Subfolders	Any time you transmit safety data or information, regardless of whether you are transmitting a new submission, an amendment, or an update
Environmental Folder and Applicable Subfolders	Any time you transmit environmental data or information, regardless of whether you are transmitting a new submission, an amendment, or an update
Other Folder	Any time you transmit data or information in an original submission that does not fall within the scope of any other folders or subfolders

*If you are transmitting an amendment or update to your submission, you should rename "Main directory" to reflect the submission designation we assigned to it (i.e., FAP9A9999 or CAP 9C9999).

7. How should I name files in an electronic petition submission?

You should name each file using both generic and specific elements as described in Section III.C and Appendix 12 of this document. Generic elements in the file names specific to petition submissions are included in the examples in Tables IV-3 through IV-11 (below).

Questions and Answers about Files in the Administrative and Administrative Technical Folders in the original Petition Submissions

8. What subfolders and files should I place in the "Administrative" folder?

Table IV-3 shows the subfolders and files you should place in the "Administrative" folder.

Table IV-3
Subfolders and Files in the "Administrative" Folder of a Petition

Folder/subfolder	File Name	Information in File	Applicable Regulatory Citation
Administrative	*Form3503_..._YYYY-MM-DD.pdf*	Some specific information in the submission and a list of documents included	N/A

Folder/subfolder	File Name	Information in File	Applicable Regulatory Citation
Administrative	*CoverLetter_..._YYYY-MM-DD.pdf*	Letter accompanying the submission if you choose to send a letter in addition to Form FDA 3503	21 CFR 71.1 21 CFR 171.1
Administrative/ Designation of Confidential Information	*DesignationOfConfidentialInformation_..._YYYY-MM-DD.pdf*	A description of the data or information in your submission that you designated as nondisclosable information.	21 CFR 20.61(d)
Administrative/ Redacted	*RedactedBySubmitter_…_YYYY-MM-DD.pdf*	Data or information copied from one or more files in your submission and then modified by deletion of data or information you designated as nondisclosable information.	N/A*

*N/A means "Not applicable."

9. What files should I place in the "Administrative Technical" subfolder?

Table IV-4 shows the files you should place in the "Administrative Technical" folder.

Table IV-4
Files in the "Administrative Technical" Folder of a Petition Submission

File Name	Information in File	Applicable Regulatory Citation
ProposedRegulation_…_YYYY-MM-DD.pdf	Your proposed text for the food additive regulation or color additive listing.	21 CFR 71.1(c) H 21 CFR 171.1(c) G

File Name	Information in File	Applicable Regulatory Citation
ProposedTolerance_…_YYYY-MM-DD.pdf	Your proposed text for the tolerance provision of the food additive regulation or color additive listing, if a tolerance is required to ensure safety.	21 CFR 71.1(c) F 21 CFR 171.1(c) F
ExemptCertification_…_YYYY-MM-DD.pdf (CAP only)	The reasons why batch certification for a color additive is not necessary, including supporting data to establish the safety of the intended use (when applicable)	21 CFR 71.1(c) G

Questions and Answers about Files in the Chemistry, Safety and Environmental Folders of a Petition Submission

10. What files should I place directly in the "Chemistry" folder (rather than under any "Chemistry" subfolders)?

Table IV-5 shows the files you should place directly in the "Chemistry" folder.

Table IV-5
Files in the "Chemistry" Folder of a Petition Submission

File Name	Information in File	Applicable Regulatory Citation or Guidance
Identity_..._YYYY-MM-DD.pdf	The physical, chemical, and biological properties of the additive, as well as any information about the chemical identity and composition of the additive not included on Form FDA 3503	21 CFR 71.1(c) A 21 CFR 171.1(c) A
UseAndTechnicalEffect_..._YYYY-MM-DD.pdf	Information about the foods in which the additive will be used, the levels of use in such foods, and the purpose for which the additive will be used, and all directions, recommendations, and suggestions regarding the proposed use	21 CFR 71.1(c) B 21 CFR 171.1(c) B 21 CFR 170.3(n) 21 CFR 170.3(o)

File Name	Information in File	Applicable Regulatory Citation or Guidance
Labeling_..._ YYYY-MM-DD.pdf	• CAP: Specimens of the labeling proposed for the additive • FAP: Specimens of the labeling proposed for the additive and any labeling that will be required by applicable provisions of the Act on the finished food by reason of the use of the additive	21 CFR 71.1(c) B 21 CFR 171.1(c) B
ManufacturingMethod_..._ YYYY-MM-DD.pdf	Information about the manufacturing process and any person other than the petitioner who performs any manufacturing, processing, and packing operations for the additive	21 CFR 71.1(c) A 21 CFR 171.1(c) A 21 CFR 171.1(j)
Residues_..._ YYYY-MM-DD.pdf	How residues of the additive may occur in food when the additive would be used in packaging and what residues may reasonably be anticipated	21 CFR 71.1(c) B 21 CFR 171.1(c) B
Specifications_..._ YYYY-MM-DD.pdf	• CAP: Specifications prescribing the additive's component(s) and identifying and limiting the reaction byproducts and other impurities. • FAP: Specifications prescribing the minimum content of the desired component(s) and identifying and limiting the reaction byproducts and other impurities. Where such information is not available, you should include a statement as to the reasons why.	21 CFR 71.1(c) A 21 CFR 171.1(c) A Ref. 7 Ref. 8

File Name	Information in File	Applicable Regulatory Citation or Guidance
ExposureEstimates_..._ YYYY-MM-DD.pdf	• The basis for any alternative approach, other than the approach described in Refs. 7 and 9, that a petitioner wishes OFAS to use in estimating daily intake. • CAP: Complete data to allow us to consider the probable consumption of, and/or other relevant exposure from the additive and of any substance formed in or on food, drugs, or cosmetics because of such additive; and the cumulative effect, if any, of such additive in the diet of man or animals.	21 CFR 71.1(c) E Ref. 7 Ref. 9

11. What files should I place in the "Chemistry Studies" subfolders?

Table IV-6 shows the subfolders and files you should place in the "Studies" subfolder of the "Chemistry" folder.

Table IV-6
Subfolders and Files in the "Studies" Subfolder of the "Chemistry" Folder of a Petition

Folder/ Subfolder	File Name	Information in the File	Applicable Regulatory Citation or Guidance
Chemistry/ Studies/ Stability	*StabilityData_..._ YYYY-MM-DD.pdf*	Stability data and, when needed, the expiration period. A CAP also must include any packaging and labeling precautions needed to preserve stability.	21 CFR 71.1(c) A 21 CFR 171.1(c) A Ref. 7 Ref. 8

Folder/ Subfolder	File Name	Information in the File	Applicable Regulatory Citation or Guidance
Chemistry/ Studies/ Intended Effect	*IntendedEffect_..._ YYYY-MM-DD.pdf*	FAP Only: Data establishing that the food additive will have the intended physical or other technical effect or that it may reasonably be expected to become a component, or to affect the characteristics, directly or indirectly, of food and the amount necessary to accomplish this. These data should include information in sufficient detail to permit evaluation with control data.	21 CFR 171.1(c) C Ref. 7
Chemistry/ Studies/ Migration	*MigrationData_..._ YYYY-MM-DD.pdf*	Information sufficient to permit estimation of consumer exposure to a food additive.	21 CFR 171.1(c) B Ref. 7
Chemistry/ Studies/ Other	[Sweetness Potency]_..._ YYYY-MM-DD.pdf	Study of Sweetness Potency	N/A

12. What files should I place in the Chemistry "Methods" and "References" subfolders?

Table IV-7 shows the files you should place in the Chemistry "Methods" and "References" subfolders.

Table IV-7
Files in the Chemistry "Methods" and "References" Subfolders of a Petition Submission

Folder/ Subfolder	File Name	Information in the File	Applicable Regulatory Citation or Guidance
Chemistry/ Methods	*AnalyticalMethod_..._ YYYY-MM-DD.pdf*	FAP and CAP: A description of practicable methods to determine the amount of the additive in the raw, processed, and/or finished food and of any substance formed in or on such food because of its use. CAP: A description of practicable methods to determine the pure color and all intermediates, subsidiary colors, and other components of the color additive.	21 CFR 71.1(c) C 21 CFR 171.1(c) D Ref. 7 Ref. 8
Chemistry/ References	See Appendix 12	Any references to the scientific literature	Ref. 7 Ref. 8 Ref. 10 Ref. 2

13. What files should I place directly in the "Safety" folder (rather than under any "Safety" subfolders)?

Table IV-8 shows the files you should place in the "Safety" folder.

Table IV-8
Files in the "Safety" Folder of a Petition Submission

File Name	Information in File	Applicable Regulatory Citation or Guidance
ToxicologyNarrative_..._ YYYY-MM-DD.pdf	A summary of the results of, and conclusions from, safety studies included in your petition submission and relevant safety studies in the scientific literature.	Ref. 2

14. What files should I place in the "Safety Studies" subfolders?

Table IV-9 shows examples of the files you should place in the "Studies" subfolders.

Table IV-9
Folders and Files in the "Studies" Subfolder of the "Safety" Folder of a Petition Submission

Subfolder	Examples of File Names	Applicable Regulatory Citation or Guidance
Safety/Studies/ GeneticToxicityStudies	*Ames_..._YYYY-MM-DD.pdf*	21 CFR 71.1(c) D 21 CFR 171.1(c) E Ref. 15 Ref. 16
Safety/Studies/ ShortTermToxicity StudiesRodents	*ShortTermToxicity_..._YYYY-MM-DD.pdf*	21 CFR 71.1(c) D 21 CFR 171.1(c) E Ref. 15 Ref. 16
Safety/Studies/ ShortTermToxicity StudiesNon-Rodents	*ShortTermToxicity_..._YYYY-MM-DD.pdf*	21 CFR 71.1(c) D 21 CFR 171.1(c) E Ref. 15 Ref. 16
Safety/Studies/ SubchronicToxicity StudiesRodents	*SubchronicToxicity_..._YYYY-MM-DD.pdf*	21 CFR 71.1(c) D 21 CFR 171.1(c) E Ref. 15 Ref. 16
Safety/Studies/ SubchronicToxicity StudiesNon-Rodents	*SubchronicToxicity_..._YYYY-MM-DD.pdf*	21 CFR 71.1(c) D 21 CFR 171.1(c) E Ref. 15 Ref. 16
Safety/Studies/ OneYearToxicity StudiesNon-Rodents	*ChronicToxicity_..._YYYY-MM-DD.pdf*	21 CFR 71.1(c) D 21 CFR 171.1(c) E Ref. 15 Ref. 16
Safety/Studies/ ChronicToxicityOr CombinedChronic Toxicity/Carcinogenicity StudiesRodents	*ChronicToxicity_..._YYYY-MM-DD.pdf*	21 CFR 71.1(c) D 21 CFR 171.1(c) E Ref. 15 Ref. 16

Subfolder	Examples of File Names	Applicable Regulatory Citation or Guidance
Safety/Studies/ CarcinogenicityStudies Rodents	*Carcinogenicity_..._YYYY-MM-DD.pdf*	21 CFR 71.1(c) D 21 CFR 171.1(c) E Ref. 15 Ref. 16
Safety/Studies/ ReproductionStudies	*ReproductiveToxicity_..._YYYY-MM-DD.pdf*	21 CFR 71.1(c) D 21 CFR 171.1(c) E Ref. 15 Ref. 16
Safety/Studies/ DevelopmentalToxicity Studies	*ReproductiveToxicityTeratology_..._YYYY-MM-DD.pdf*	21 CFR 71.1(c) D 21 CFR 171.1(c) E Ref. 15 Ref. 16
Safety/Studies/ ImmunotoxicityStudies	*Immunotoxicity_..._YYYY-MM-DD.pdf*	21 CFR 71.1(c) D 21 CFR 171.1(c) E Ref. 15 Ref. 16
Safety/Studies/ MetabolismAnd PharmacokineticStudies	*PharmacokineticRats_..._YYYY-MM-DD.pdf*	21 CFR 71.1(c) D 21 CFR 171.1(c) E Ref. 15 Ref. 16
Safety/Studies/ NeurotoxicityStudies	*Neurotoxicity_..._MMMM-MM-DD.pdf*	21 CFR 71.1(c) D 21 CFR 171.1(c) E Ref. 15 Ref. 16
Safety/Studies/ HumanClinicalStudies	*HumanClinical_..._ YYYY-MM-DD.pdf*	21 CFR 71.1(c) D 21 CFR 171.1(c) E Ref. 15 Ref. 16
Safety/Studies/ EpidemiologyStudies	*Epidemiology_..._YYYY-MM-DD.pdf*	Ref. 15 Ref. 16
Safety/Studies/ OcularStudies	*OcularIrritation_..._YYYY-MM-DD.pdf*	Ref. 17
Safety/Studies/ DermalStudies	*Dermal_..._YYYY-MM-DD.pdf*	Ref. 17
Safety/Studies/ OtherStudies	*[DescriptiveName]_..._YYYY-MM-DD.pdf*	21 CFR 71.1(c) D 21 CFR 171.1(c) E

15. What files should I place in the "Environmental" folder of a petition?

Table IV-10 shows the files you should place in the "Environmental" folder.

Table IV-10
Folders and Files in the "Environmental" Folder of a Petition Submission Roadmap

Folder/ Subfolder	File Name	Information in the File	Applicable Regulatory Citation or Guidance
Environmental	*EA_ …_YYYY-MM-DD.pdf*	Concise public document that provides sufficient evidence and analysis for FDA to determine whether to prepare an Environmental Impact Statement (EIS) or a Finding of No Significant Impact (FONSI)	21 CFR 71.1(c) J 21 CFR 171.1(c) H 21 CFR 25.40 Ref. 19
Environmental	*ClaimCategorical Exclusion_..._YYYY-MM-DD.pdf*	(1) The section of the CFR under which the categorical exclusion is claimed; (2) A statement of compliance with the categorical exclusion criteria; and (3) A statement that, to the submitter's knowledge, no extraordinary circumstances exist that require submission of an Environmental Assessment.	21 CFR 71.1(c) J 21 CFR 171.1(c) H 21 CFR 25.15 21 CFR 25.30 21 CFR 25.32 Ref. 19
Environmental/ Confidential Environmental Information	*MarketVolume_ …_YYYY-MM-DD.pdf*	Data and information that are protected from disclosure under 18 U.S.C. 1905, 21 U.S.C. 331(j) or 360j(c)	21 CFR 25.51 Ref. 19
Environmental/ Studies	*…_YYYY-MM-DD.pdf*	Study reports of environmental fates or effects studies	Ref. 19
Environmental/ References	*…_YYYY-MM-DD.pdf*	Environmental literature references (published studies, excerpts)	Ref. 19

C. Electronic Amendments and Updates to Petition Submissions

16. What recommendations apply to amendments and updates to petition submissions?

You should refer to Section III.F of this document for general recommendations applying to amendments and updates in electronic format.

When transmitting any amendment or update to a petition submission, you should organize your submission into individual files addressed to specific topic areas (administrative, chemistry, safety, or environmental), even if an amendment responds to multiple questions we sent you in a single letter. You then should place these files in appropriate folders/subfolders according to the Petition Submission Roadmap.

For example, an amendment to a FAP could include two Chemistry files (one to revise specifications and another to revise an analytical method), a Safety file responding to our questions about a subchronic toxicity study conducted in dogs, and a file containing a revised Environmental Assessment. In this example, you would:

- Place the file containing revised specifications directly in the "Chemistry" folder;
- Place the file containing the revised analytical method in the Chemistry/Methods subfolder;
- Place the file containing the response to our questions about the toxicology study in the Safety/Studies/Subchronic Toxicity Non-Rodents subfolder; and
- Place the revised Environmental Assessment in the Environmental Assessment folder.

17. What files should I place in the "Incoming Correspondence" subfolder?

Table IV-11 shows the files you should place in the two subfolders of the "Incoming Correspondence" folder.

Table IV-11
Files in the "Additional Information/Incoming Correspondence" Subfolder for a Petition Submission

Subfolder	File Name	Information in the File
IncomingCorrespondence/ Amendment	*YYYY-MM-DD_ Form3503_….pdf*	Form with responsive material completed for an amendment.
	YYYY-MM-DD_Amendment_…pdf	An amendment that does not fit in any of the other folders (e.g. Chemistry, Safety, Environmental,etc)
IncomingCorrespondence/ Update	*YYYY-MM-DD_ Form3503_….pdf*	Form with responsive material completed for an update.

Subfolder	File Name	Information in the File
	YYYY-MM-DD_Update_…pdf	An update that does not fit in any of the other folders (e.g. Chemistry, Safety, Environmental, etc)

18. Where can I find an example of a foldering structure with an amendment for a FAP?

Below is an example of an amendment to an existing, fictional FAP (FAP 0A9999), arranged in the standard roadmap. Folder names are in bold and file names are in italics; for clarity, we omitted empty folders. In this example, the amendment responds to an FDA letter dated 11-20-2006, which requested further information. Note that each file name begins with the date the amendment is submitted (see Section III.C and Appendix 12 of this document for file naming conventions). We would place these amendment documents in the corresponding folders in our database file for FAP 0A9999, alongside documents previously submitted. (You should not re-submit any previously submitted documents.)

- **FAP 0A9999**
  - **Administrative**
    - **Incoming Correspondence**
      - **Amendment**
        - *2006-12-07_Form FDA 3503_InResponseToFDA2006-11-20 Letter.pdf*
  - **Chemistry**
    - **Methods**
      - *2006-12-07_ResponsesToFDA2006-11-20ChemistryQuestions_(AnalyticalMethod_ …).pdf*
  - **Safety**
    - **Studies**
      - **SubchronicToxicityStudies**
        - *2006-12-07_SubchronicToxicity_Study5567_ EmulsifierX_Rats_OralGavage_ 2000-11-08.pdf*
  - **Environmental**
    - *2006-12-07_EA_Revised_EmulsifierX.pdf*

D. Food and Color Master Files

19. How do the parts on Form FDA 3503 relate to the elements of FMFs and CMFs?

Table IV-12 shows the elements of FMFs and CMFs and links each element to the applicable part of Form FDA 3503.

Table IV-12
Elements of FMFs and CMFs as Shown on Form FDA 3503

Element of FMFs and CMFs	Applicable Part on Form FDA 3503
Introductory information about the submission	I
Information about the company responsible for the master file (and any attorney or agent acting on behalf of that company)	II
General administrative information	III
Information specific to Food or Color Master Files	IV.C
Identity	V
Administrative Technical (when a submission is in advance of a planned FAP or CAP)	VI
Chemistry	VI
Safety	VI
Environmental	VI
Signature	VII
N/A	VIII (List of Attachments)

20. How should I organize an electronic master file submission prepared according to the elements on Form FDA 3503?

You should organize an electronic master file submission prepared according to the elements on Form FDA 3503 using the foldering structure available in a downloadable Petition Roadmap (see instructions in Appendix 1 and the roadmap in Appendix 15). In general, you should follow the recommendations in Sections III and IV.B of this document for more detailed information about organizing an electronic master file submission according to the elements of Form FDA 3503.

V. Information Specific to Food Contact Notification Submissions and Pre-Notification Consultation Submissions

Section V of this document addresses FCN and PNC submissions for food contact substances. You must submit an FCN in accordance with 21 CFR 170.101. You voluntarily submit a PNC prior to submitting a FCN to facilitate your preparation of a FCN. We assign a file number (FCN No. or PNC No., respectively) to your submission and review your submission. If we do not object to your FCN within 120 days, your FCN becomes effective. If we object to your FCN, we will send you an FCN objection letter; if we do so within 120 days, your FCN will not become effective. If we and you agree that you may submit a food additive petition proposing the approval of the FCS for the use in your FCN, we will consider that you have withdrawn your FCN on the date we receive your petition.

A. General Information about Food Contact Notification Submissions

1. When do I use Form FDA 3480?

You must use Form FDA 3480 when transmitting an original FCN submission (21 CFR 101.101).

You should use Form FDA 3480 when transmitting:

- A PNC as described in Ref. 5; and
- A FMF regarding a food contact substance.

2. When should I use Form FDA 3480-A?

You should use Form FDA 3480-A when transmitting an amendment to a previously submitted FCN, PNC, or FMF regarding a FCS. Form FDA 3480-A is much shorter than Form FDA 3480.

3. How do I determine whether to send FDA a Pre-Notification Consultation for a FCS or a Food Master File for a FCS?

You should send us a PNC if your reason for providing us with information relevant to a FCS is to consult with us to facilitate preparation of a complete FCN in the future (Ref. 5).

You should send us a FMF if your reason for providing us with information relevant to a FCS is outside the context of your own preparation of a complete FCN. For example, you would submit a FMF submission for a FCS if you are providing confidential data or information in support of a FCN submitted to us by a manufacturer who does not have access to these confidential data or information.

4. How do the parts on Form FDA 3480 relate to the elements of a FCN?

Table V-1 shows the elements of FCNs and links each element to the applicable part of Form FDA 3480.

Table V-1
Elements of FCNs as Shown on Form FDA 3480

Element of FCNs	Applicable Part on Form FDA 3480
General information	I
Chemistry information	II
Safety information	III
Environmental	IV
Certification	V
List of Attachments	VI

5. How should I organize a new FCN submission?

You should organize a new FCN submission as a series of documents presented in an order corresponding to that presented on Form FDA 3480. If you include any data or information not identified on Form FDA 3480 (e.g., raw material specifications and technical bulletins), you should place these data or information in a logical place in your submission based on the type of information.

6. What should I include for the proposed language for the FCN listing?

You should include the language that you propose for your FCN in our "Inventory of Effective Food Contact Substance (FCS) Notifications" (the Inventory), including the FCS identity, notifier, manufacturer/supplier(s), and limitations and specifications. See the Inventory for examples (Ref. 3).

7. Why should I include proposed language for the FCN listing?

Including proposed language for the FCN listing will help to ensure that we understand the conditions of use that are the subject of your FCN. Under 21 CFR 170.101(b), your FCN must include all data and other information that form the basis of the determination that the FCS is safe under the intended conditions of use.

B. Food Contact Notification Submissions in Electronic Format

8. How should I organize an electronic FCN submission?

You should organize an electronic FCN submission using the foldering structure called the FCN Submission Roadmap (see instructions in Appendix 3a and the roadmap in Appendix 15). The entire FCN Submission Roadmap is organized under the folder entitled "Main directory." The "Main directory" includes four first-level folders. Three of these first-level folders include second-level subfolders, and one of these folders (i.e., the Safety folder) includes third-level and fourth-level subfolders. We show the FCN Submission Roadmap, using an outline format, in Figure V-1, below. In the various subfolders, Figure V-1 uses the convention "[Etc]" to mean that there are more folders in the FCN Roadmap (not shown in the outline) that continue the pattern of the outline.

Figure V-1
Outline Representing the FCN Submission Roadmap

- Main directory
  - Administrative
  - Chemistry
    - Studies
    - References
  - Environmental
    - Confidential Environmental Information
    - Studies
    - References
  - Safety
    - Chemical Name 1*
      - References
      - Studies
        - Genetic Toxicity Studies
        - Short Term Toxicity Studies Rodents
        - Short Term Toxicity Studies Non-Rodents
        - Subchronic Toxicity Studies Rodents
        - Subchronic Toxicity Studies Non-Rodents
        - One Year Toxicity Studies Non-Rodents
        - Chronic Toxicity or Combined Chronic Toxicity/Carcinogenicity Studies Rodents
        - Carcinogenicity Studies Rodents
        - Reproduction Studies
        - Developmental Toxicity Studies
        - Immunotoxicity Studies
        - Metabolism and Pharmacokinetic Studies
        - Neurotoxicity Studies
    - Chemical Name 2*
      - References
      - Studies
        - [Etc]

- [Etc]

* The original FCN Submission Roadmap includes 10 "Chemical Name #" folders. You would rename the Chemical Name 1, Chemical Name 2, etc. folders to specific chemical names of substances (e.g., the FCS or impurities) for which you have included safety studies (see Conventions for Naming Files in Appendix 12). You may delete or ignore remaining Chemical Name # folders that you do not use. Our system will not import empty folders.

9. When should I use the specific folders and subfolders in the FCN Submission?

You should use these folders and subfolders as shown in Table V-2. You should not place any specific files directly in "Main directory." "Main directory" only contains folders.

Table V-2
When to Use Specific Folders and Subfolders in the "Main Directory" of a FCN Submission Roadmap*

Folder/Subfolder	When to Use it
Administrative folder	Any time you transmit a new submission, an amendment, or a redacted electronic file(s)
Chemistry Folder and Applicable Subfolders	Any time you transmit chemistry data or information, regardless of whether you are transmitting a new submission or an amendment
Environmental Folder and Applicable Subfolders	Any time you transmit environmental data or information, regardless of whether you are transmitting a new submission or an amendment
Safety Folder and Applicable Subfolders	Any time you transmit safety data or information, regardless of whether you are transmitting a new submission or an amendment

* If you are transmitting an amendment to your submission, you should re-name the "Main directory" to the file number we assigned to it (e.g. FCN000999).

10. How should I name files in an electronic FCN submission?

You should name each file using both generic and specific elements as described in Section III.C and Appendix 12 of this document. Generic elements in the file names specific to FCN submissions are included in Tables V-3 through V-9 (below). See Appendix 12 for examples of complete file names..

11. What files should I place in the "Administrative" folder of a FCN submission?

Table V-3 shows the files you should place in the "Administrative" folder.

Table V-3
Files in the "Administrative" Folder of a FCN Submission

File Name	Information in File	Applicable Regulatory Citation and Guidance
Form3480_..._YYYY-MM-DD.pdf	Some specific information in the submission and a list of documents included	21 CFR 170.101 Ref.5
CoverLetter_..._YYYY-MM-DD.pdf	Letter accompanying the submission if you choose to send a letter in addition to Form FDA 3480	N/A*
DesignationOfNondisclosableInformation_..._YYYY-MM-DD.pdf	A document describing the data or information in your submission that you view as nondisclosable (see Section II.E of this document)	21 CFR 20.61(d)
ProposedLanguageForFCNListing_..._YYYY-MM-DD.pdf	Proposed Language for your FCN listing	21 CFR 170.101(b)
RedactedBySubmitter_..._YYYY-MM-DD.pdf	Copy(ies) of one or more files in your submission modified by deletion of data or information you view as trade secret or confidential information, if you choose to include these	N/A

* N/A means "Not applicable."

12. What files should I place directly in the "Chemistry" folder (rather than in any Chemistry subfolders)?

Table V-4 shows the files you should place directly in the "Chemistry" folder.

Table V-4
Files in the "Chemistry" Folder of a FCN Submission

File Name	Information in File	Applicable Item on Form FDA 3480 and Guidance*
Identity_..._YYYY-MM-DD.pdf	A description of the FCS, including chemical formula(s), structure(s) and molecular weight(s)	Form FDA 3480 II.A.5 (Description) Ref. 10
Structure_..._YYYY-MM-DD.mol	A structure for the FCS and for substances that may migrate into food from use of the FCS (see Part III.C of this guidance for file formats)	Form FDA 3480 II.A.5 (Description) Ref. 10
IR_..._YYYY-MM-DD.pdf *NMR_..._YYYY-MM-DD.pdf* *MassSpec_..._YYYY-MM-DD.pdf*	Spectroscopic data characterizing the FCS	Form FDA 3480 II.A.6 (Characterization) Ref. 10
ManufacturingProcess_..._YYYY-MM-DD.pdf	A complete description of the manufacturing process	Form FDA 3480 II.B.1 (Manufacturing Process) Ref. 10
RawMaterialSpecs_..._ YYYY-MM-DD.pdf	Specifications for reagents, solvents, catalysts, purification aids, etc., used in the manufacturing process	Ref. 10
Impurities_…_YYYY-MM-DD.PDF	Supporting data used to arrive at the levels of impurities reported on Form FDA 3480, and/or information supporting that no migration to food is expected	Form FDA 3480 II.C.1 (Impurities) Ref. 10

File Name	Information in File	Applicable Item on Form FDA 3480 and Guidance*
Specifications_…_YYYY-MM-DD.pdf	Physical and chemical specifications for the FCS	Form FDA 3480 II.C.2 (Specifications) Ref. 10
MolWeightProfile_..._YYYY-MM-DD.pdf	The maximum percentage of oligomeric species (not including residual monomers, reactants, or solvents) below 1000 Daltons and supporting data and analytical methods	Form FDA 3480 II.A.7 (Molecular Weight Profile) Ref. 10
IntendedUse_..._ YYYY-MM-DD.pdf	Use level of the FCS, the types of food contact articles in which it may be used, types of food, conditions of use, etc.	Form FDA 3480 II.D.1,2 (Intended Use) Ref. 10
TechnicalEffect_..._ YYYY-MM-DD.pdf	A description of the intended technical effect of the FCS; summary of data showing the FCS will achieve the intended technical effect and that the proposed use level is the minimum level required to accomplish the intended technical effect	Form FDA 3480 II.D.3 (Intended Technical Effect) Ref. 10
Stability_..._YYYY-MM-DD.pdf	Description of any chemical breakdown process that the FCS may undergo during either its intended use in the manufacture of a food contact article or during migration testing**	Form FDA 3480 II.E (Stability of the FCS) Ref. 10
MigrationCalculation_..._YYYY-MM-DD.pdf	A description of the mathematical approach used in estimating migration levels of the FCS to food and/or any of its constituents.	Form FDA 3480 II.F.2 (Migration Calculation Option) Ref. 10
ExposureCalculation_..._ YYYY-MM-DD.pdf	Representative calculations for the dietary concentration (DC) and estimated daily intake (EDI) for all substances migrating to food as a result of the intended use of the FCS	Form FDA 3480 II.G (Estimated Daily Intake) Ref. 10

* The applicable section of the regulation is 21 CFR 170.101(b).
** When applicable, a study on the stability of the FCS is placed in the "Studies" subfolder of the "Chemistry" folder (see Table V-5).

13. What files should I place in the "Studies" and "References" subfolders of the "Chemistry" folder of a FCN submission?

Table V-5 shows the files you should place in the "Studies" and "References" subfolders of the "Chemistry" folder.

Table V-5
Files in the "Studies" and "References" Subfolders of the "Chemistry" Folder of a FCN Submission Roadmap

Folder/ Subfolder	File Name	Information in the File	Applicable Item on Form FDA 3480 and Guidance*
Chemistry/ Studies	*StabilityStudy_..._YYYY-MM-DD.pdf*	A study on the stability of the FCS **	Form FDA 3480 II.E (Stability of the FCS) Ref. 10
Chemistry/ Studies	*MigrationStudy_..._YYYY-MM-DD.pdf*	A study determining the expected levels of migration of the FCS or its components to food	Form FDA 3480 II.F.1 (Migration Testing Option) Ref. 10
Chemistry/ References	See Appendix 12	Any references to the scientific literature	Ref. 10

* The applicable section of the regulation is 21 CFR 170.101(b).
** When applicable, a narrative description of a chemical breakdown process that the FCS may undergo during either its intended use in the manufacture of a food contact article or during migration testing is placed directly in the "Chemistry" folder (see Table V-4).

14. What file should I place directly in the Safety folder of a FCN submission (rather than in any Safety subfolders)?

Table V-6 shows the file you should place directly in the Safety folder.

Table V-6
Files in the "Safety" Folder of a FCN Submission

Folder/Subfolder	File Name	Information in File	Applicable Item on Form FDA 3480 and Guidance
Safety	*SafetyNarrative_..._YYYY-MM-DD*.pdf	A summary describing the	Form FDA 3480 III.1 (Safety Narrative)

		scientific basis of your determination that the food contact substance (FCS) is safe under the conditions of use	Ref. 18

15. What files should I place directly in the subfolder for a specific chemical in the "Safety" folder of a FCN submission (rather than in any subfolder for that chemical)?

Table V-7 shows the files you should place directly in the subfolder for a specific chemical in the "Safety" folder.

Table V-7
Files in the Subfolder for a Specific Chemical in the "Safety" Folder of a FCN Submission Roadmap

Folder/Subfolder	File Name	Information in File	Applicable Item on Form FDA 3480 and Guidance*
Safety/*ChemicalName1*	*CTP_..._.pdf*	A Comprehensive Toxicology Profile (CTP), for the specific chemical, including detailed study summaries	Form FDA 3480 III.2 Ref. 18
Safety/*ChemicalName1*	*LiteratureSearch_..._.pdf*	Data or information that the notifier relies upon to prepare the CTP	Ref. 18

* The applicable section of the regulation is 21 CFR 170.101(a).

16. What files should I place in the Studies and References subfolders for a specific chemical in the Safety folder?

Table V-8 shows the files you should place in the subfolders of the "Studies" subfolder of the "Safety" subfolder for a given chemical.

Table V-8
Example Subfolder and File in the Safety/*Chemical Name* 1/ "Studies" Subfolder and files in the Safety/*Chemical Name* 1/ "References" subfolder of an FCN Submission

Subfolder	Examples of File Names	Applicable Regulatory Citation, Part on Form FDA 3480, and Guidance
Safety/ *ChemicalName1*/Studies/ GeneticToxicityStudies	*Ames_..._YYYY-MM-DD.pdf*	Form FDA 3480 III.3 Ref. 18 Ref. 16
Safety/*ChemicalName1*/References	(Titles of the reference, citation,…) See Appendix 12	Ref. 18 Ref. 16

17. What files should I place in the "Environmental" folder of a FCN submission?

Table V-9 shows the files you should place in the "Environmental" folder, and in the "Confidential Environmental Information", "References" and "Studies" subfolders.

Table V-9
Folders and Files in the "Environmental" Folder of a FCN Submission

Folder/ Subfolder	File Name	Information in the File	Applicable Regulatory Citation, Part on Form FDA 3480, and Guidance
Environmental	*EA…-YYYY-MM-DD.pdf*	Concise public document that provides sufficient evidence and analysis for FDA to determine whether to prepare an Environmental Impact Statement (EIS) or a Finding of No Significant Impact (FONSI)	21 CFR 170.101(d) Form FDA 3480 Part IV 21 CFR 25.40 Ref. 19
Environmental	*FIFRA Label_..._ YYYY-MM-DD .pdf*	(1) A copy of the current FIFRA registration label for the substance that has the same use requested in the submission; and (2) The proposed FIFRA registration label that includes the food contact use for which the sponsor intends to request an amendment from EPA.	21 CFR 170.101(d) Form FDA 3480 IV 21 CFR 25.32(q) Ref. 19

Folder/ Subfolder	File Name	Information in the File	Applicable Regulatory Citation, Part on Form FDA 3480, and Guidance
Environmental/ Confidential Environmental Information	*MarketVolume…-YYYY-MM-DD.pdf*	Data and information that are protected from disclosure under 18 U.S.C. 1905, 21 U.S.C. 331(j) or 360j(c)	21 CFR 170.101(d) Form FDA 3480 IV Ref. 19
Environmental/ Studies	*…YYYY-MM-DD.pdf*	Study reports of environmental fates or effects studies	Ref. 19
Environmental/ References	*…YYYY-MM-DD.pdf*	Environmental literature references (published studies, excerpts)	Ref. 19

C. Electronic Amendments to Food Contact Notifications

18. What recommendations apply to electronic amendments to FCN submissions?

You should first refer to Section III.F of this document for general recommendations applying to amendments in electronic format.

You should use Form FDA 3480-A (rather than Form FDA 3480) when transmitting an amendment to a FCN. Form FDA 3480-A is much shorter than Form FDA 3480.

When transmitting any amendment to a FCN submission, you should organize your submission into individual files, each addressed to specific topic areas (administrative, chemistry, safety, or environmental), even if your amendment responds to multiple questions we sent you in a single letter. You then should place these files in the appropriate folders/subfolders (according to the content of the file) in the FCN Submission Roadmap.

For example, an amendment to a FCN might include two Chemistry files (one to revise specifications and another to revise a migration study), a Safety file responding to our questions about the toxicity of an impurity, known as 3-AP-PEG (CAS Reg. No. 34901-14-9), and a file containing a revised Environmental Assessment. In this example, you would:

- Place the file containing revised specifications directly in the Chemistry folder;
- Place the file containing the migration study revisions in the Chemistry/Studies subfolder;
- Place the file containing the response to our questions about the toxicity of 3-AP-PEG in the Safety/3-AP-PEG (34901-14-9) subfolder ; and
- Place the revised Environmental Assessment in the Environmental folder.

(See the file structure for this example under the next question.)

19. May I see an example of the file structure for a complete amendment to a FCN?

The outline below is an example of an amendment to an existing, hypothetical FCN (FCN 009999), arranged in the standard submission roadmap. Folder names are in bold and file names are in italics; for clarity, we omitted empty folders. In this example, the amendment responds to an FDA letter dated 11-20-06, which requested further information. Note that each file name begins with the date the amendment is submitted (i.e., the date entered on page 1 of Form FDA 3480-A) (see Section III.C and Appendix 12 of this document for recommendations for naming files). FDA would place these amendment documents in the corresponding folders in our database file for FCN 009999, alongside documents previously submitted. (You should not re-submit any previously submitted documents.)

- **FCN 009999**
  - **Administrative**
    - *2006-12-07_Form FDA 3480-A_InResponseToFDA2006-11-20 Letter.pdf*
  - **Chemistry**
    - *2006-12-07_ResponsesToFDA2006-11-20ChemistryQuestions_(Impurities_MigrationStudy_ …).pdf*
    - *2006-12-07_ImpuritiesBatchData(TIPA, 34901-14-9, catalyst)_Chromatograms&Calculations.pdf*
  - **Studies**
    - *2006-12-07_MigrationStudy_RevisedChromatograms_….pdf*
  - **Environmental**
    - *2006-12-07_EA_Revised_HPNH_ InPolypropylene.pdf*
  - **Safety**
    - **3-AP-PEG (34901-14-9)**
      - *2006-12-07_Response to FDA2006-06-20Question-Toxicity of 3-AP-PEG*

D. Pre-Notification Consultations and Food Master Files for Food Contact Substances

20. How do the parts on Form FDA 3480 relate to the elements of PNCs and FMFs for FCSs?

Table V-10 shows the potential elements of PNCs and links each element to the applicable part of Form FDA 3480. PNCs and FMFs sometimes contain only a subset of the information (e.g., specific chemistry information) that would be included in a FCN for a FCS.

Table V-10
Elements of PNCs and FMFs as Shown on Form FDA 3480

Element of PNCs and FMFs	Applicable Part on Form FDA 3480
General information	I
Chemistry information	II
Safety information	III
Environmental	IV
Certification	V
List of Attachments	VI

21. How should I organize an electronic PNC submission?

You should organize an electronic PNC submission using the foldering structure available in a downloadable FCN Submission Roadmap (see instructions in Appendix 3a and the roadmap in Appendix 15). In general, you should follow the recommendations in Sections III and V.B of this document for more detailed information about organizing an electronic PNC submission.

VI. Information Specific to Generally Recognized as Safe Notice Submissions

Section VI of this document addresses submission of GRAS notices. The GRAS notification procedure[2] is a voluntary procedure in which you inform us of your view that a particular use of a substance is exempt from the premarket approval requirements of the Act based on your determination that such use is GRAS in accordance with 21 CFR 170.30. We assign a file number (GRAS Notice No. (GRN)) to your submission and respond to you by letter.

A. General Information about Generally Recognized as Safe Notice Submissions

1. How do the parts on Form FDA 3667 relate to the elements of a GRAS notice?

Table VI-1 shows the elements of a GRAS notice and links each element to the applicable part of Form FDA 3667.

Table VI-1
Elements of a GRAS Notice as Shown on Form FDA 3667

Element of a GRAS Notice	Applicable Part on Form FDA 3667
Introductory information about the submission	I

[2] We have issued a proposed rule that would establish this procedure in 21 CFR 170.36 (*Federal Register* of April 17, 1997; 62 FR 18938). As of the date of this guidance publication we have not yet issued a final rule based on that proposed rule.

Element of a GRAS Notice	Applicable Part on Form FDA 3667
Information about the notifier (and any attorney or agent acting on behalf of the notifier)	II
General administrative information	III
Intended use	IV
Identity	V and VI
Method of manufacture	VI
Specifications	VI
Dietary exposure	VI
Self-limiting levels of use	VI
Common use in food before 1958 (if applicable)	VI
Comprehensive discussion of the basis for the GRAS determination	VI
Bibliography	VI
Signature	VII
N/A	VIII (List of Attachments)

2. How should I organize a new GRAS notice submission?

You should organize a new GRAS notice as a document presenting the elements of a GRAS notice in an order corresponding to that of the elements listed on Form FDA 3667. A summary of these elements is listed in Table VI-1 of this document and described in the instructions for Form FDA 3667 (see Appendix 5). If you include any data or information not identified on Form FDA 3667, you should place these data or information in a logical place in your submission based on the type of information.

B. Generally Recognized as Safe Notice Submissions in Electronic Format

3. How should I organize an electronic GRAS notice submission?

You should organize an electronic GRAS notice submission using the foldering structure available in a downloadable GRAS Notice Submission Roadmap (see instructions in Appendix 5 and the roadmap in Appendix 15). The entire GRAS Notice Submission Roadmap is organized under the folder entitled "Main directory." The "Main directory" includes three first-level folders, entitled "Administrative," "GRAS Notice," and "Incoming Correspondence." The "Incoming Correspondence" folder includes three second-level subfolders entitled "Submission Form," "Amendment" and "Supplement." We show these folders and subfolders, using an outline format, in Figure VI-1, below.

Figure VI-1
Outline Representing the Folders and Subfolders in the "Main directory" of a GRAS Notice Submission Roadmap

- Main directory

- Administrative
- GRAS Notice
- Incoming Correspondence
  - Submission Form
  - Amendment
  - Supplement

4. When should I use the specific folders and subfolders in the GRAS Notice Submission Roadmap?

You should use these folders and subfolders as shown in Table VI-2. You should not place any specific files directly in "Main directory." "Main directory" only contains folders.

Table VI-2
When to Use Specific Folders and Subfolders
in the "Main Directory" of a GRAS Notice Submission Roadmap*

Folder/Subfolder	When to Use it
Administrative	Any time you transmit a new GRAS notice and submission form or a redacted electronic file(s)
GRASNotice	Only when you transmit a new GRAS notice
IncomingCorrespondence	You should not place any specific files directly in the Incoming Correspondence folder. The Incoming Correspondence folder only contains subfolders.
Incoming Correspondence/Submission Form	Any time you transmit information while we are reviewing your GRAS notice or after we have responded to your GRAS notice
IncomingCorrespondence/ Amendment	Any time you transmit information while we are reviewing your GRAS notice
IncomingCorrespondence/ Supplement	Any time you transmit information after we have responded to your GRAS notice

* If you are transmitting an amendment or supplement to your GRAS notice, you should re-name "Main directory"to reflect the file number we assigned to your notice.

5. How should I name files in an electronic GRAS notice submission?

You should name each file using both generic and specific elements as described in Section III.C and Appendix 12 of this document. Generic elements in the file names specific to GRAS notice submissions are included in the examples in Table VI-3 (below).

6. What files should I place in each folder and subfolder?

Table VI-3 shows the files you should place in each folder and subfolder.

Table VI-3
Placement of Files in the GRAS Notice Submission Roadmap

Folder/Subfolder	File Name	Information in File
Administrative	*Form3667_..._YYYY-MM-DD.pdf*	Form FDA 3667 with responsive material completed
Administrative	*CoverLetter_..._YYYY-MM-DD.pdf*	Letter accompanying the submission if you choose to send a letter in addition to Form FDA 3667
Administrative	*DesignationOfConfidential Information_..._YYYY-MM-DD.pdf*	A description of the data or information in your submission that you designated as nondisclosable information (21CFR 20 Subpart D)
Administrative	*RedactedBySubmitter_…_YYYY-MM-DD.pdf*	Copy(ies) of one or more files in your submission modified by deletion of data or information you designated as nondisclosable information
GRASNotice	*GRASNotice_..._YYYY-MM-DD.pdf*	File containing the following information not placed on the form: • Table of Contents • Any additional information about identity not covered in Part V of Form FDA 3667 • Method of manufacture • Specifications for food-grade material • Dietary exposure • Self-limiting levels of use • Common use in food before 1958 (if applicable) • Comprehensive discussion of the basis for the determination of GRAS status • Bibliography • Other Information
GRASNotice	*[Miscellaneous]_..._YYYY-MM-DD.pdf*	One or more files containing miscellaneous information you ask FDA to consider in evaluating your GRAS notice (e.g., technical bulletins)
IncomingCorrespondence/ Submission Form	*YYYY-MM-DD-Form3667_..._.pdf*	Form FDA 3667 with responsive material completed

Folder/Subfolder	File Name	Information in File
IncomingCorrespondence/ Amendment	*YYYY-MM-DD_Amendment_....pdf*	When applicable, file(s) containing the information you submit to us during our review of your GRAS notice. An amendment addressing more than one topic should include a Table of Contents.
IncomingCorrespondence/ Supplement	*YYYY-MM-DD_Supplement_....pdf*	When applicable, file containing the information you submit to us after we respond to your GRAS notice. A supplement addressing more than one topic should include a Table of Contents.

C. Electronic Amendments and Supplements to GRAS Notice Submissions

7. What recommendations apply to amendments and supplements to GRAS notice submissions?

You should refer to Section III.F of this document for general recommendations applying to amendments and supplements in electronic format.

When transmitting any amendment or supplement to a GRAS notice, you should organize your submission as a single file. If an amendment or supplement addresses more than one topic, the file should include a Table of Contents with bookmarks to aid in navigating through the submission. You then should place this file in the Incoming Correspondence/Amendment or Incoming Correspondence/Supplement subfolder in the GRAS Notice Submission.

VII. Information Specific to Biotechnology Final Consultation Submissions

Section VII of this document addresses Biotechnology Final Consultation submissions, A Biotechnology Final Consultation is a voluntary procedure for foods derived from new plant varieties. Information about that consultation procedure is available in our guidance entitled "Guidance on Consultation Procedures. Foods Derived From New Plant Varieties" (the consultation procedures) (Ref. 20). We assign a file number (Biotechnology Notification File No. (BNF)) to your submission and respond to you by letter.

A. General Information about Biotechnology Final Consultation Submissions

1. How do the parts on Form FDA 3665 relate to the elements of a Biotechnology Final Consultation?

Table VII-1 shows the elements of a Biotechnology Final Consultation and links each element to the applicable part of Form FDA 3665.

Table VII-1
Elements of a Biotechnology Final Consultation as Shown on Form FDA 3665

Element of a Biotechnology Final Consultation	Applicable Part on Form FDA 3665
Introductory information about the submission	I
Information about the person responsible for the submission (and any attorney or agent acting on behalf of that person)	II
General administrative information	III
Information about the food and the new plant variety from which it is derived	IV
Identity of new substances in the new plant variety	V
Summary of safety and nutritional assessment	VI
Signature	VII
N/A	VIII (List of Attachments)

2. How should I organize a Biotechnology Final Consultation?

You should organize a new Biotechnology Final Consultation as a document presenting the elements of a Biotechnology Final Consultation in an order corresponding to that of the elements listed on Form FDA 3665. These elements are also listed in Table VII-1 of this document and described in the instructions for Form FDA 3665 (see Appendix 7). If you include any data or information not identified as an element on Form FDA 3665, you should place these data or information in a logical place in your submission based on the type of information.

B. Biotechnology Final Consultation Submissions in Electronic Format

3. How should I organize an electronic Biotechnology Final Consultation submission?

You should organize an electronic Biotechnology Final Consultation submission using the foldering structure available in the downloadable Biotechnology Final Consultation Submission Roadmap (see instructions in Appendix 7 and the roadmap in Appendix 15). The entire Biotechnology Final Consultation Submission Roadmap is organized under the folder entitled "Main directory" in the Biotechnology Final Consultation Submission Roadmap. The "Main directory" contains three first-level folders, entitled "Administrative," "Submission," and "Incoming Correspondence." The "Incoming Correspondence" folder includes three second-level subfolders entitled "Submission Form," "Amendment" and "Supplement." We show these folders and subfolders, using an outline format, in Figure VII-1, below.

Figure VII-1
Outline Representing the Folders and Subfolders in the "Main directory" of a Biotechnology Final Consultation Submission Roadmap

- Main directory
  - Administrative
  - Submission
  - Incoming Correspondence
    - Submission Form
    - Amendment
    - Supplement

4. When should I use the specific folders and subfolders in the Biotechnology Final Consultation Submission Roadmap?

You should use these folders and subfolders as shown in Table VII-2. You should not place any specific files directly in "Main directory." "Main directory" only contains folders.

Table VII-2
When to Use Specific Folders and Subfolders in the "Main Directory" of a Biotechnology Final Consultation Submission Roadmap*

.

Folder/Subfolder	When to Use it
Administrative	Any time you transmit a new Biotechnology Final Consultation and submission form or a redacted copy(s)
Submission	Only when you transmit a new Biotechnology Final Consultation
IncomingCorrespondence	You should not place any specific files directly in the Incoming Correspondence folder. The Incoming Correspondence folder only contains subfolders.

Folder/Subfolder	When to Use it
Incoming Correspondence/Submission Form	Any time you transmit information while we are reviewing your Biotechnology Final Consultation or after we have responded to your Biotechnology Final Consultation
Incoming Correspondence/ Amendment	Any time you transmit information while we are reviewing your Biotechnology Final Consultation
Incoming Correspondence/ Supplement	Any time you transmit information after we have responded to your Biotechnology Final Consultation

*If you are transmitting an amendment or supplement to your Biotechnology Final Consultation, you should re-name the Main directory to reflect the file number we assigned to your submission.

5. How should I name files in an electronic Biotechnology Final Consultation submission?

You should name each file using both generic and specific elements as described in Section III.C and Appendix 12 of this document. Generic elements in the file names specific to Biotechnology Final Consultation submissions are included in Table VII-3 (below).

6. What files should I place in each folder of the "Main directory?"

Table VII-3 shows the files you should place in each folder and subfolder..

Table VII-3
Placement of Files in the Biotechnology Final Consultation Submission Roadmap

Folder/Subfolder	File Name	Information in File
Administrative	*Form3665_..._YYYY-MM-DD.pdf*	Form FDA 3665 with responsive material completed
Administrative	*CoverLetter_..._YYYY-MM-DD.pdf*	Letter accompanying the submission if you choose to send a letter in addition to Form FDA 3665
Administrative	*DesignationOfConfidentialInformation_..._YYYY-MM-DD.pdf*	A description of the data or information in your submission that you designated as nondisclosable information (21CFR 20 Subpart D).
Administrative	*RedactedBySubmitter_..._YYYY-MM-DD.pdf*	Copy(ies) of one or more files in your submission modified by deletion of data or information you designated as nondisclosable information.

Folder/Subfolder	File Name	Information in File
Submission	*Submission_..._YYYY-MM-DD.pdf*	File containing the following information not placed on the form • Table of Contents • Summary of Safety and Nutritional Assessment • Other Information
Incoming Correspondence/ SubmissionForm	*YYYY-MM-DD_ Form3665_..._.pdf*	Form FDA 3665 with responsive material completed
Incoming Correspondence/ Amendment	*YYYY-MM-DD_Amendment_....pdf*	When applicable, file containing the information you submit to us during our review of your Biotechnology Final Consultation. An amendment addressing more than one topic may include a Table of Contents.
Incoming Correspondence/ Supplement	*YYYY-MM-DD_Supplement_....pdf*	When applicable, file containing the information you submit to us after we respond to your Biotechnology Final Consultation. A supplement addressing more than one topic may include a Table of Contents.

C. Electronic Amendments and Supplements to Biotechnology Final Consultation Submissions

7. What recommendations apply to amendments and supplements to Biotechnology Final Consultation submissions?

You should refer to Section III.F of this document for general recommendations applying to amendments and supplements in electronic format.

When transmitting any amendment or supplement to a Biotechnology Final Consultation, you should organize your submission as a single file. If an amendment or supplement addresses more than one topic, the file may include a Table of Contents with bookmarks to aid in navigating through the submission. You then should place this file in the Incoming Correspondence/Amendment or Incoming Correspondence/Supplement subfolder in the Biotechnology Final Consultation Submission Roadmap.

VIII. Information Specific to New Protein Consultation Submissions

Section VIII of this document addresses submissions about the early food safety evaluation of a new non-pesticidal protein produced by a new plant variety **(**New Protein Consultation). The New Protein Consultation is a voluntary procedure for proteins derived from a new plant variety. Information about the consultation procedure is available in our guidance entitled "Recommendations for the Early Food Safety Evaluation of New Non-Pesticidal Proteins Produced by New Plant Varieties Intended for Food Use" (Ref.22). We assign a file number (the NPC number) to your submission and respond to you by letter.

A. General Information about New Protein Consultation Submissions

1. How do the parts on Form FDA 3666 relate to the elements of a New Protein Consultation?

Table VIII-1 shows the elements of a New Protein Consultation and links each element to the applicable part of Form FDA 3666.

Table VIII-1
Elements of a New Protein Consultation as Shown on Form FDA 3666

Element of a New Protein Consultation	Applicable Part on Form FDA 3666
Introductory information about the submission	I
Information about the person responsible for the submission (and any attorney or agent acting on behalf of that person)	II
General administrative information	III
Information about the new protein	IV
Information about genetic material	V
Scientific evaluation of the food safety of the new protein	VI
Other pertinent information	VI
Signature	VII
N/A	VIII (List of Attachments)

2. How should I organize a New Protein Consultation?

You should organize a New Protein Consultation as a document presenting the elements of a New Protein Consultation in an order corresponding to that of the elements listed on Form FDA 3666. These items are also listed in Table VII-1 of this document and described in the

instructions for Form FDA 3666 (see Appendix 9). If you include any data or information not identified as an element on Form FDA 3666, you should place these data or information in a logical place in your submission based on the type of information.

B. New Protein Consultation Submissions in Electronic Format

3. How should I organize an electronic New Protein Consultation submission?

You should organize an electronic New Protein Consultation submission using the foldering structure available in a downloadable New Protein Consultation Submission Roadmap (see instructions in Appendix 9 and the roadmap in Appendix 15). The entire New Protein Consultation Submission Roadmap is organized under the folder entitled "Main directory." The "Main directory" contains three first-level folders, entitled "Administrative," "Submission," and "Incoming Correspondence." The "Incoming Correspondence" folder includes three second-level subfolders entitled "Submission Form," "Amendment" and "Supplement." We show these folders and subfolders, using an outline format, in Figure VIII-1, below.

Figure VIII-1
Outline Representing the Folders and Subfolders in the "Main directory" of a New Protein Consultation Submission Roadmap

- Main directory
  - Administrative
  - Submission
  - Incoming Correspondence
    - Submission Form
    - Amendment
    - Supplement

4. When should I use the specific folders and subfolders in the New Protein Consultation Submission Roadmap?

You should use these folders and subfolders as shown in Table VIII-2.You should not place any specific files directly in "Main directory." "Main directory" only contains folders.

Table VIII-2
When to Use Specific Folders and Subfolders
in the "Main Directory" of a New Protein Consultation Submission Roadmap*

Folder/Subfolder	When to Use it
Administrative	Any time you transmit a (new) New Protein Consultation and submission form or a redacted copy(s)
Submission	Only when you transmit a (new) New Protein Consultation

Folder/Subfolder	When to Use it
IncomingCorrespondence	You should not place any specific files directly in the Incoming Correspondence folder. The Incoming Correspondence folder only contains subfolders.
Incoming Correspondence/Submission Form	Any time you transmit information while we are reviewing your New Protein Consultation or after we have responded to your New Protein Consultation
IncomingCorrespondence/ Amendment	Any time you transmit information while we are reviewing your New Protein Consultation
IncomingCorrespondence/ Supplement	Any time you transmit information after we have responded to your New Protein Consultation

*If you are transmitting an amendment or supplement to your New Protein Consultation, you should re-name the Main directory to reflect the file number we assigned to your submission.

5. How should I name files in an electronic New Protein Consultation submission?

You should name each file using both generic and specific elements as described in Section III.C and Appendix 12 of this document. Generic elements in the file names specific to New Protein Consultation submissions are included in the examples in Table VIII-3 (below).

6. What files should I place in each folder of the "Main directory?"

Table VIII-3 shows the files you should place in each folder and subfolder of the "Main directory."

Table VIII-3
Placement of Files in the New Protein Consultation Submission Roadmap

Folder/Subfolder	File Name	Information in File
Administrative	*Form3666_..._YYYY-MM-DD.pdf*	Form FDA 3666 with responsive material completed
Administrative	*CoverLetter_..._YYYY-MM-DD.pdf*	Letter accompanying the submission if you choose to send a letter in addition to Form FDA 3666
Administrative	*DesignationOfConfidentialInformation_..._YYYY-MM-DD.pdf*	A description of the data or information in your submission that you designated as nondisclosable information (21CFR 20 Subpart D).

Folder/Subfolder	File Name	Information in File
Administrative	*RedactedBySubmitter_..._YYYY-MM-DD.pdf*	Copy(ies) of one or more files in your submission modified by deletion of data or information you designated as nondisclosable information.
Submission	*Submission_..._YYYY-MM-DD.pdf*	File containing • Table of Contents • Scientific evaluation of the food safety of the new protein • Other pertinent information
Incoming Correspondence/ SubmissionForm	*YYYY-MM-DD_Form3666_..._.pdf*	Form FDA 3666 with responsive material completed
Incoming Correspondence/ Amendment	*YYYY-MM-DD_Amendment_....pdf*	When applicable, file containing the information you submit to us during our review of your New Protein Consultation. An amendment addressing more than one topic may include a Table of Contents.
Incoming Correspondence/ Supplement	*YYYY-MM-DD_Supplement_....pdf*	When applicable, file containing the information you submit to us after we respond to your New Protein Consultation. A supplement addressing more than one topic may include a Table of Contents.

C. Electronic Amendments and Supplements to New Protein Consultation Submissions

7. What recommendations apply to amendments and supplements to New Protein Consultation submissions?

You should refer to Section III.F of this document for general recommendations applying to amendments and supplements in electronic format.

When transmitting any amendment or supplement to a New Protein Consultation, you should organize your submission as a single file. If an amendment or supplement addresses more than one topic, the file may include a Table of Contents with bookmarks to aid in navigating through the submission. You then should place this file in the Incoming Correspondence/Amendment or

Incoming Correspondence/Supplement subfolder in the New Protein Consultation Submission Roadmap.

IX. FDA Web Site References

As of January 28, 2010, FDA had verified the Web site addresses for the references it makes available as hyperlinks from the Internet copy of this guidance.

A. Administrative Information Web Site References

1. FDA Electronic Submissions Gateway (ESG). Information on setting up an FDA ESG Account (Webtrader and AS2).

2. Guidance for Industry - Questions and Answers About the Petition Process.

3. Inventory of Effective Food Contact Substance (FCS) Notifications.

4. Definitions of Food Types and Conditions of Use for Food Contact Substances.

5. Guidance for Industry - Preparation of Food Contact Notifications: Administrative.

6. Guidance for Industry - Frequently Asked Questions About GRAS.

B. Chemistry Information Web Site References

7. Guidance for Industry - Recommendations for Submission of Chemical and Technological Data for Direct Food Additive Petitions.

8. Guidance for Industry - Color Additive Petitions. FDA Recommendations For Submission Of Chemical And Technological Data On Color Additives For Food, Drugs, Cosmetics or Medical Devices.

9. Guidance for Industry - Estimating Dietary Intake of Substances in Food.

10. Guidance for Industry - Preparation of Premarket Submissions for Food Contact Substances: Chemistry Recommendations.

11. Enzyme Preparations: Chemistry Recommendations For Food Additive And Gras Affirmation Petitions.

C. Safety Study Information Web Site References

12. Guidance to Industry - Computerized Systems Used in Clinical Investigations.

13. Guidance for Industry: Templates for Reporting Toxicology Data.

14. Standard for Exchange of Non-Clinical Data.

15. Guidance for Industry - Summary Table of Recommended Toxicological Testing for Additives Used in Food.

16. Guidance for Industry and Other Stakeholders - Toxicological Principles for the Safety Assessment of Food Ingredients. Redbook 2000.

17. Appendix E - Color Additives For Medical Devices.

18. Preparation of Food Contact Notifications for Food Contact Substances: Toxicology Recommendations.

D. Environmental Information Web Site References

19. Guidance for Industry - Preparing a Claim of Categorical Exclusion or an Environmental Assessment for Submission to the Center for Food Safety and Applied Nutrition.

E. Biotechnology Information Web Site References

20. Guidance on Consultation Procedures. Foods Derived From New Plant Varieties.

21. Statement of Policy: Foods Derived From New Plant Varieties.

22. Guidance for Industry - Recommendations for the Early Food Safety Evaluation of New Non-Pesticidal Proteins Produced by New Plant Varieties Intended for Food Use.

X. Appendices

Appendix 1: Instructions for Completing Form FDA 3503 Food/ Color Additives and Master Files
Appendix 2: Food and Color Additive Petition and Master File Form FDA 3503 (available in PDF)
Appendix 3a: Instructions for Completing Food Contact Substance Form FDA 3480
Appendix 3b: Instructions for Completing Food Contact Substance Form FDA 3480-A for Amendments
Appendix 4a: Notification for New Use of a Food Contact Substance under Premarket Notification submission Form FDA 3480: (available in PDF)
Appendix 4b: Notification for New Use of a Food Contact Substance under Premarket Notification submission Form FDA 3480-A for amendments (available in PDF)
Appendix 5: Instructions for Completing GRAS Notice Form FDA 3667
Appendix 6: GRAS Notice Form FDA 3667 (available in PDF)
Appendix 7: Instructions for Completing Biotechnology Notification FORM FDA 3665
Appendix 8: Biotechnology Final Consultation Form FDA 3665 (available in PDF)
Appendix 9: Instructions for Completing New Protein Consultation Form FDA 3666
Appendix 10: New Protein Consultation Form FDA 3666 (available in PDF)