Over-the-Counter Monograph Order Requests (OMORs): Format and Content

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

April 2023
Over-the-Counter

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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Over-the-Counter Monograph Order Requests (OMORs): Format and Content Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to assist requestors[2] in preparing over-the-counter (OTC) monograph order requests (OMORs)[3] for submission to FDA under section 505G of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355h). This guidance provides FDA's recommendations on the format and content of the information that requestors should provide in an OMOR and identifies relevant guidance documents to assist requestors in preparing their OMORs.

This guidance provides an overview of the information that FDA may recommend for a sufficiently complete OMOR. This guidance is not intended to indicate the studies and related information that a requestor must submit in a specific OMOR.

Requestors can request a formal meeting with FDA to discuss specific data, studies, and related information to be submitted in the OMORs.[4]

In general, FDA's guidance documents 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

[1] This guidance has been prepared by the Office of Nonprescription Drugs in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] Under section 505G(q)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the term *requestor* refers to any person or group of persons marketing, manufacturing, processing, or developing an OTC monograph drug.

[3] An OMOR is a request for an order submitted under section 505G(b)(5) of the FD&C Act. See also section 744L(7) of the FD&C Act.

[4] See the draft guidance for industry *Formal Meetings Between FDA and Sponsors or Requestors of Over-the-Counter Monograph Drugs* (February 2022). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

On March 27, 2020, the President signed into law the Coronavirus Aid, Relief, and Economic Security Act (CARES Act). The CARES Act added section 505G to the FD&C Act. Section 505G reforms and modernizes the framework for the regulation of OTC monograph drugs. OTC monograph drugs may be marketed without an approved drug application under section 505 of the FD&C Act if they meet the requirements of section 505G of the FD&C Act, as well as other applicable requirements.[5]

Under the process set forth in section 505G(b) of the FD&C Act, FDA has the authority to issue a final order that adds, removes, or changes generally recognized as safe and effective (GRASE) conditions for an OTC monograph drug. Either FDA or a requestor can initiate the order process. A requestor can initiate the order process by submitting an OMOR with respect to certain drugs, classes of drugs, or combinations of drugs.[6] The OMOR may request issuance of an order determining the following: (1) whether a drug is GRASE or (2) whether a change to a condition of use of a drug is GRASE.[7]

The OMOR must be submitted to FDA in the form and manner specified by the Agency.[8] FDA will file the OMOR if FDA determines that the OMOR is sufficiently complete and formatted to permit FDA to conduct a substantive review.[9]

III. THE COMMON TECHNICAL DOCUMENT FORMAT AND CONTENT FOR AN OMOR

OMORs must be submitted in electronic format.[10] OMORs should follow the organizational structure and format outlined in the Common Technical Document for the Registration of Pharmaceuticals for Human Use (CTD). The CTD format was developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) to streamline the submission requirements for Japan, the European Union, and the United

[5] The CARES Act also added section 744M to the FD&C Act authorizing FDA to assess and collect user fees dedicated to OTC monograph drug activities.

[6] See section 505G(b)(5) of the FD&C Act.

[7] See section 505G(b)(5)(B) of the FD&C Act.

[8] See section 505G(b)(5)(B)(i) of the FD&C Act.

[9] See section 505G(b)(5)(A) of the FD&C Act.

[10] See section 505G(j) of the FD&C Act. See also the draft guidance for industry *Providing Over-the-Counter Monograph Submissions in Electronic Format* (September 2022). When final, this guidance will represent the FDA's current thinking on this topic.

States. The CTD organizes quality, safety, and efficacy information into a common format that has been adopted by ICH regulatory authorities. The CTD format is sufficiently flexible to accommodate a variety of types and sources of information that may be included in OMORs.

FDA has issued guidance documents specific to CTD[11] for organizing certain applications that will be submitted to FDA. The recommendations provided in these guidance documents are also applicable to OMORs. Although, in general, requestors should follow the recommendations provided in previously issued CTD guidance documents, this guidance highlights additional format and content recommendations specific to an OMOR.

An OMOR should be organized into five modules as follows:

- Module 1: Administrative Information
- Module 2: Summaries
- Module 3: Quality
- Module 4: Nonclinical Study Reports
- Module 5: Clinical Study Reports

CTD is designed to accommodate multiple types of regulatory applications; it contains section headings and section subheadings that may not be pertinent to all OMORs. Therefore, an OMOR may not include all the information identified for an applicable module, section, or subsection described in this guidance or other CTD guidance documents. In those circumstances, a requestor should indicate that no information is being submitted for a given module or a section or subsection of a module.

A. MODULE 1: ADMINISTRATIVE INFORMATION

1. Format

Module 1: Administrative Information should contain six sections in the following order:

- Table of Contents
- Cover Letter
- Administrative Information
- References
- Meetings
- Labeling

[11] For guidances for industry that address CTD, see the FDA guidance web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. At this time, submission of OMORs should not be done through the electronic CTD (eCTD), which is the standard format for electronic regulatory submissions for new drug applications (NDAs), abbreviated new drug applications (ANDAs), certain biologics license applications (BLAs), and certain investigational new drug applications. See the guidances for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (February 2020) and *Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act* (December 2014). See also section 745A(a) of the FD&C Act (21 U.S.C. 379k-1(a)).

2. Content

a. Table of contents

An OMOR should have a comprehensive table of contents (TOC) for the entire submission. The comprehensive TOC significantly enhances the usefulness of the document. It should include a complete list of all documents provided in the submission by module.

b. Cover letter

In general, the cover letter should contain pertinent information that aids communication regarding the review of the OMOR. At minimum, the cover letter should address the following:

- Indicate the applicable OTC monograph or request and rationale for creation of a new OTC monograph.
- Describe the change(s) to the OTC monograph condition(s) being proposed in the OMOR.
- Indicate the proposed classification of the OMOR as a Tier 1 or Tier 2 OMOR.[12]
- Provide the name and the full contact information of the requestor(s).
- Indicate the OMOR submission date.
- Provide information about the proposed OTC monograph condition of use including active ingredient(s), pharmacological class, intended use, strength, specific dosage form, route of administration, directions for use, and any other pertinent information.
- Describe the data and information included in the OMOR to support the proposed change to the OTC monograph condition of use.

[12] This information is relevant to the requirements under sections 505G(b)(5)(A)(i) and 505G(b)(5)(C)(iv)(II) of the FD&C Act. Section 744L of the FD&C Act defines Tier 1 and Tier 2 OMORs. A Tier 1 OMOR is any OMOR not determined to be a Tier 2 OMOR. See section 744L(8) of the FD&C Act. A Tier 2 OMOR is a request for the following: (1) reordering of existing information in the Drug Facts label of an OTC monograph drug; (2) addition of information to the "Other Information" section of the Drug Facts label of an OTC monograph drug (subject to certain limitations); (3) modification to the "Directions" section of the Drug Facts label of an OTC monograph drug, consistent with changes made pursuant to section 505G(c)(3)(A) of the FD&C Act; (4) standardization of the concentration or dose of a specific finalized ingredient within a particular finalized monograph; (5) change to ingredient nomenclature to align with nomenclature of a standards-setting organization; or (6) addition of an interchangeable term in accordance with 21 CFR 330.1 (or any successor regulations). See section 744L(9) of the FD&C Act.

- Provide a certification that the requestor has submitted all evidence, both positive and negative, related to whether the ingredient or other condition of use is GRASE.[13]

- Indicate whether the requestor is seeking market exclusivity under section 505(G)(b)(5)(C) of the FD&C Act for a change subject to a final order, and provide the rationale.

- Indicate whether FDA reviewed any protocols or held formal meetings with the requestor during the development of the OMOR, and if so, indicate the date(s).

- Provide a statement listing the approximate size of the electronic submission (e.g., 2 gigabytes) and a statement that the submission is virus-free with a description of the software (name, version, and company) that was used to check the files for viruses.

- Provide the name, title, address, phone, fax, and email of the individual the Agency should contact about issues related to the submission. If there are separate regulatory and technical points of contact, include this information for both individuals.

- Provide the signatory's name and contact information

c. Administrative information

The requestor should provide the appropriate administrative documents and information in the OMOR. Examples of administrative documents and information include the following:

- U.S. agent letter of appointment, if applicable.[14]

- A statement that all information considered by the requestor to be confidential has been identified in the OMOR, including a description of the method used to identify the information as confidential. See section VI., Confidential Information, of this guidance for details on limitations associated with confidential information submitted under the OTC monograph order process.[15]

[13] See the Over-the-Counter Monograph User Fee Program Performance Goals and Procedures — Fiscal Years 2018–2022 document, which discusses content and format of monograph submissions, available at https://www.fda.gov/media/106407/download.

[14] If the requestor does not reside or have a place of business in the United States, an agent that resides or maintains a place of business in the United States should countersign the OMOR.

[15] Pursuant to section 505G(d) of the FD&C Act, FDA must make all information in an OMOR, with certain exceptions, public at the time of a proposed order. See section VI., Confidential Information.

- An environmental assessment[16] or the claim of categorical exclusion[17] and the justification for the exclusion. A claim of categorical exclusion must (1) "include a statement of compliance with the categorical exclusion criteria" and (2) "state that to the applicant's knowledge, no extraordinary circumstances exist."[18] See section V., Environmental Assessment, of this guidance.

- Statement of claimed exclusivity.

d. References

The References section should include the following information, as applicable:

- Letter of authorization. If providing reference to a third party's new drug application (NDA), abbreviated new drug application (ANDA), biologics license application (BLA), or drug master file (DMF), include letter(s) of authorization by the owner(s) of information giving authorization for the information to be used by the requestor in connection with the OMOR.[19] If authorization to an NDA, ANDA, BLA, or DMF is not available, justify why the reference is still relevant.

- Statement of right of reference. If providing reference to a third party's NDA, ANDA, BLA, or DMF, the requestor should include a statement indicating the NDA, ANDA, BLA, or DMF to which the requestor has a right of reference and identify the section(s) of the OMOR for which the letter(s) of authorization is relevant.

- Previously submitted information to FDA, including the following:

  — Indicate whether the OMOR references data or information from any approved NDA or ANDA, licensed BLA, or DMF.

  — Identify data or information previously provided to FDA (such as data submitted to another OMOR, public comment(s) submitted to an order, or a citizen petition) for FDA to consider when reviewing the OMOR, including the submission date and file number.[20]

[16] See 21 CFR 25.20.

[17] 21 CFR 25.31.

[18] 21 CFR 25.15(a).

[19] The owner of the information should be aware that in general the OTC monograph order process is a public process. Under this order process, section 505G(d) of the FD&C Act limits the information that can remain confidential after submission to FDA in connection with proceedings on an order, including an OMOR. See section VI., Confidential Information.

[20] The requestor should provide a complete copy of the previously submitted information in the appropriate module.

e. Meetings

The Meetings section should contain a listing of all meetings with FDA, including complete copies of meeting background materials and meeting correspondence, pertaining to the specific OMOR. The requestor should identify all meetings that pertain to the specific OMOR and identify any information that it considers to be confidential, if applicable.

f. Labeling

The Labeling section should include the following:

- An example of proposed labeling that reflects the OTC monograph condition(s) of use proposed in the OMOR
- The proposed OTC monograph that reflects the OTC monograph condition(s) of use proposed in the OMOR

B. MODULE 2: SUMMARIES

1. Format

Module 2: Summaries should contain seven sections in the following order:

2.1 Table of Contents
2.2 Introduction to the Summary Documents
2.3 Quality Overall Summary
2.4 Nonclinical Overview
2.5 Clinical Overview
2.6 Nonclinical Written and Tabulated Summaries
2.7 Clinical Summary

2. Content

a. Table of contents

The comprehensive TOC should list all the documents provided in the OMOR for Modules 2 through 5.

b. Introduction to the summary documents

The Introduction section to the summary documents should provide a concise narrative summary of (1) the positive safety and effectiveness data supporting a determination that a specific drug, class of drugs, or combination of drugs with the proposed active ingredient or other condition of use is GRASE for the intended nonprescription use, and (2) the negative safety and effectiveness data that are not supportive of a determination that the specific drug, class of drugs, or combination of drugs or other condition of use is GRASE. The introduction should clearly

identify and address each of the major topics addressed in the submission. The introduction should include a summary table listing all studies included in the submission with their corresponding titles (as they appear in the study reports), study numbers, and location in the submission (with hyperlinks to each study). There should be one clearly identified study number for each study submitted.

c. Quality overall summary

The Quality Overall Summary section should provide a summary of all chemistry and manufacturing data included in the submission. It should not include information, data, or justification that was not included in Module 3 (the quality module). It should include a discussion of key issues that integrates information from sections in Module 3 and supporting information from other modules, including cross-referencing to volume and page number in other modules. Most of the information in this section, including tables, figures, or other items, can be imported directly from Module 3.

For content and format recommendations for the Quality Overall Summary section for an OMOR, requestors should refer to the ICH guidance for industry *M4Q: The CTD — Quality* (August 2001).

d. Nonclinical overview

The Nonclinical Overview section should present an integrated and critical assessment of the pharmacologic, pharmacokinetic, and toxicologic evaluation of the active ingredient or other conditions of use. Where relevant guidances on the conduct of studies exist, requestors should take these guidances into consideration and discuss any deviation from the recommendations in these guidances. The nonclinical testing strategy should be discussed and justified. There should be comments on the good laboratory practice status of the studies submitted, taking into consideration which studies are pivotal to support the safety of the ingredient. Requestors should indicate any association between nonclinical findings and the quality assessment, the results of clinical studies, or the effects seen with related drug products or ingredients, as appropriate.

For content and structural format recommendations for the Nonclinical Overview section for an OMOR, requestors should refer to the ICH guidance for industry *M4S: The CTD — Safety* (August 2001).

e. Clinical overview

The Clinical Overview section should present an integrated and critical assessment of all the clinical data included in the OMOR (e.g., clinical effectiveness studies, biopharmaceutics, clinical pharmacology data, safety studies, consumer behavior studies, postmarketing safety data). The Clinical Overview section should provide the rationale for the OTC monograph drug development program and a succinct discussion and interpretation of the clinical findings together with any other relevant information (e.g., pertinent animal data or drug product quality issues that may have clinical implications) necessary to present the conclusions and implications of the data. The Clinical Overview section should (1) present the strengths and limitations of the

OTC monograph drug development program and study results, (2) analyze the benefits and risks of the conditions of use proposed in the OMOR for the OTC monograph drug for its intended use, and (3) describe how the study results support critical parts of the labeling.

For content and format recommendations for the Clinical Overview section for an OMOR, requestors should refer to the ICH guidance for industry *M4E(R2): The CTD — Efficacy* (July 2017).

f. Nonclinical written and tabulated summaries

The Nonclinical Written and Tabulated Summaries section should provide data summaries, not a complete exposition. Only in unusual cases should the narrative parts of the Nonclinical Overview section be the same as the summaries found in the nonclinical study reports in Module 4. In general, the narrative parts of the Nonclinical Written and Tabulated Summaries section should be different from those in the Nonclinical Overview section.

For recommendations on general presentation of this section such as the order of presentation of information within each section, use of tables and figures, length of written nonclinical summaries, and sequence of written summaries and tabulated summaries, requestors should refer to the ICH guidance for industry *M4S: The CTD — Safety*.

Nonclinical written summaries

The nonclinical written summaries should include a narrative summary of all the nonclinical data included in the submission. This includes nonclinical pharmacology, pharmacokinetics, and toxicology.

For recommendations on the content for each nonclinical written summary, requestors should refer to the ICH guidance for industry *M4S: The CTD — Safety*. Requestors should modify the format, if needed, to provide the best possible presentation of the information and to facilitate the understanding and evaluation of the results.

Nonclinical tabulated summaries

Requestors should follow the order of presentation given for the nonclinical written summaries for the preparation of the tables for the nonclinical tabulated summaries.

The summary tables for the nonclinical information submitted in an OMOR should be provided in the format outlined in the ICH guidance for industry *M4S: The CTD — Safety*.

For the recommended formats for the tables in the nonclinical tabulated summaries, requestors should refer to Appendices B and C in the ICH guidance for industry *M4S: The CTD — Safety Appendices* (August 2001). However, requestors should modify the format, if warranted, to provide the best possible presentation of the information and to facilitate the understanding and evaluation of the results.

g. Clinical summary

The Clinical Summary section should provide a detailed, factual summary of all of the clinical information in the OMOR. This includes information provided in clinical study reports; information provided in consumer behavior study reports; information obtained from any meta-analyses or other cross-study analyses for which full reports have been included in Module 5; and postmarketing data for drugs that have been marketed in the United States or in other regions including data from both the prescription and nonprescription settings. When summarizing postmarketing data for drugs that have been marketed in the nonprescription setting in other regions, the requestor should provide the regulatory status of the drug for each region including information about whether there are limitations or restrictions on access (e.g., pharmacy only, pharmacist only, general sales).

For recommendations on the content and format for each subsection in the Clinical Summary section, requestors should refer to the ICH guidance for industry *M4E(R2): The CTD — Efficacy*.

C. MODULE 3: QUALITY DATA

1. Format

Module 3: Quality Data should be organized according to the following general section outline:

3.1 Module 3 Table of Contents
3.2 Body of Data
3.3 Literature References

For recommendations on the format of information in Module 3 and its organizational placement within the module, requestors should refer to the ICH guidances for industry *M4Q: The CTD — Quality* and *M4: The CTD — Quality Questions and Answers/Location Issues* (June 2004).

2. Content

Module 3 should discuss the chemistry, manufacturing, and controls reports for both drug substance and drug product.

For recommendations on content to include in Module 3 of the OMOR, requestors should refer to the ICH guidance for industry *M4Q: The CTD — Quality*.

In addition, for the drug substance, Module 3 should also include the compendial status of the active ingredients in the United States Pharmacopeia (USP) National Formulary (NF). If there is no USP monograph for the active ingredient(s), then the requestor should provide a proposed USP monograph including a complete validation of the methods.

D. MODULE 4: NONCLINICAL STUDY REPORTS

1. Format

Module 4: Nonclinical Study Reports should be organized according to the following general section outline:

4.1 Module 4 Table of Contents
4.2 Study Reports
4.3 Literature References

For recommendations on the structural format and organization of nonclinical study reports in an OMOR, requestors should refer to the ICH guidance for industry *M4S: The CTD — Safety*.

2. Content

Module 4 should include data and reports from the nonclinical studies.

a. Nonclinical studies

The nonclinical studies that may be necessary to support an OMOR include the following: (1) pharmacology studies, (2) general toxicity studies, (3) toxicokinetic and nonclinical pharmacokinetic studies, (4) reproduction toxicity studies, (5) genotoxicity studies, and (6) an assessment of carcinogenic potential. Requestors should conduct other nonclinical studies to assess phototoxicity, immunotoxicity, juvenile animal toxicity, and abuse liability on a case-by-case basis.

For recommendations on the types of nonclinical safety studies that should be conducted to support an OMOR and their relation to the conduct of human clinical studies, requestors should refer to the ICH guidance for industry *M3(R2): Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010).

b. Individual study reports

Each individual nonclinical study report should include its own TOC and summary. Requestors should include complete data sets (not selected or summary data) in the submission.[21] Data from studies provided only in summary form will generally not be sufficiently informative to support a determination that the condition of use is GRASE.

[21] Although Standard for Exchange of Nonclinical Data (SEND) data sets and CTD tables are not required for OMORs, we recommend that requestors submit both data sets and tables in their submissions to facilitate review of the data. See the FDA Data Standards Advisory Board web page at https://www.fda.gov/industry/fda-resources-data-standards.

E. MODULE 5: CLINICAL STUDY REPORTS

1. Format

Module 5: Clinical Study Reports should be organized according to the following general section outline:

5.1 Module 5 Table of Contents
5.2 Tabular Listing of All Clinical Studies
5.3 Clinical Study Reports
5.4 Literature References

For recommendations on the specific organization and placement of clinical study reports and related information in Module 5, requestors should refer to the ICH guidance for industry *M4E(R2): The CTD — Efficacy*.

2. Content

Module 5 in the OMOR should include full reports of the following: (1) all clinical effectiveness and safety studies and other clinical data, (2) all clinical pharmacology and human toxicokinetic data, (3) all consumer behavior studies, and (4) postmarketing experience. In addition to actual study reports, the requestor should include all other types of clinical data (e.g., from literature searches, scientific articles, other published materials) in this module.[22]

a. Clinical studies and related information

For recommendations on the types of clinical studies and related information that can be included in Module 5 of an OMOR, requestors should refer to the ICH guidance for industry *M4E(R2): The CTD — Efficacy*.

In addition to the clinical studies referenced in the ICH guidance for industry *M4E(R2): The CTD — Efficacy*, requestors may also need to include consumer behavior study reports or other information demonstrating prima facie safe nonprescription marketing and use[23] in Module 5 of the OMOR.

[22] Requestors should include a hyperlink to a full copy of the referenced article or other referenced published material. If the scientific article or other published material is not accessible online, the requestor should include a complete copy in the submission.

[23] See section 505G(b)(6)(C) of the FD&C Act.

Consumer Behavior Studies

While not all consumer behavior studies are clinical studies, all consumer behavior study reports should be included in Module 5. Consumer behavior studies include label comprehension studies,[24] self-selection studies,[25] actual use studies, and human factors studies.[26]

Safe nonprescription marketing and use

Some OMORs may propose that a drug is GRASE if the drug contains an active ingredient not previously incorporated in a drug specified in section 505G(a)(1), (a)(2), or (a)(3) of the FD&C Act, subject to a final order under section 505G(b) of the FD&C Act, or subject to a final sunscreen order (as defined in section 586(2)(A) of the FD&C Act).[27] For such OMORs, Module 5 must include information demonstrating prima facie safe nonprescription marketing and use, including the following, as applicable:[28]

1) Information demonstrating that the drug has a history of being marketed and safely used by consumers in the United States as a nonprescription drug under comparable conditions of use must be included.[29]

2) If the drug has not been previously marketed in the United States as a nonprescription drug, the requestor must include information sufficient for a prima facie demonstration that the drug was marketed and safely used under comparable conditions of marketing and use in a country listed in section 802(b)(1)(A) of the FD&C Act or designated by FDA in accordance with section 802(b)(1)(B) of the FD&C Act.[30] The time period of marketing and use must provide reasonable assurances concerning the safe nonprescription use of the drug. Additionally, the requestor should provide evidence that during the time period of nonprescription use, the drug was subject to sufficient monitoring by a regulatory body considered acceptable by FDA for such monitoring, including for adverse events associated with nonprescription use of the drug.[31]

[24] See the guidance for industry *Label Comprehension Studies for Nonprescription Drug Products* (August 2010).

[25] See the guidance for industry *Self-Selection Studies for Nonprescription Drug Products* (April 2013).

[26] See the draft guidance for industry and FDA staff *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development* (February 2016). When final, this guidance will represent the FDA's current thinking on this topic.

[27] See section 505G(b)(6)(B) of the FD&C Act.

[28] See section 505G(b)(6)(C) of the FD&C Act.

[29] See section 505G(b)(6)(C)(i) of the FD&C Act.

[30] See section 505G(b)(6)(C)(ii) of the FD&C Act.

[31] See section 505G(b)(6)(C)(ii) of the FD&C Act.

3) If FDA determines that information described in (1) or (2) above is not needed to provide a prima facie demonstration that the drug can be safely marketed and used as a nonprescription drug, the requestor must submit other information FDA determines is sufficient for such purposes.[32]

If the OMOR fails to include such information, FDA will refuse to file the OMOR and require that the nonprescription marketing of the drug be pursuant to an approved application under section 505 of the FD&C Act.[33]

b. Reports of postmarketing experience

For drug products or active ingredients that are currently marketed, Module 5 should include reports that summarize the marketing experience relevant to the OTC monograph condition of use proposed in the OMOR, including detailed information for relevant safety observations.

Module 5 should include all relevant postmarketing data available to the requestor (published and unpublished, including periodic safety update reports if available). The requestor should provide in Module 5 a tabulation of serious adverse events reported after the drug is marketed, including any potentially serious drug interactions. The requestor should describe any postmarketing findings in subgroups. The requestor should provide safety information from various safety databases such as the FDA Adverse Event Reporting System, World Health Organization VigiBase, American Association of Poison Control Centers, other country's or region's safety database, or a requestor's (or their affiliate's) safety database.

If data are available for different combinations of active ingredients, different doses, different dosage forms, significantly different formulations, or different populations of use, the requestor should provide separate tabular summaries in Module 5.

The reports of postmarketing experience should include discussions and analyses of the postmarketing data along with the conclusions and implications of the data as it pertains to the OTC monograph condition of use proposed in the OMOR. The reports should also include any relevant safety discussions and analyses from the literature, if available.

Reports that are heavily redacted or do not provide clear drug product identification are unlikely to provide useful information.

c. Individual study reports

Each individual clinical study report should include its own TOC and summary. The requestor should include complete subject-level data sets (not selected or summary data). Each study should have its own data sets for efficacy and safety data, and there should be integrated datasets for safety and, if applicable, integrated datasets for efficacy. In general, we expect that data from studies provided only in summary form will not be sufficiently informative to support a

[32] See section 505G(b)(6)(C)(iii) of the FD&C Act.

[33] See section 505G(b)(6)(A) of the FD&C Act.

conclusion that a drug, class of drugs, or combination of drugs is GRASE for the intended nonprescription use.

Each individual study should describe the statistical evaluation of clinical data (e.g., information concerning the description and analysis of each controlled clinical study and the documentation and supporting statistical analyses used in evaluating the controlled clinical studies; information concerning a summary of information about the safety of the drug, the documentation and supporting statistical analyses used in evaluating the safety information).

Each individual study report should include all necessary appendices including but not limited to study information (e.g., full protocols and protocol amendments, list of all independent ethics committees or institutional review boards consulted, documentation of statistical methods), patient data listings, and case report forms.

For additional guidance on the structure and content of clinical study reports, requestors should refer to the ICH guidance for industry E3 *Structure and Content of Clinical Study Reports* (July 1996).

IV. GENERAL CONSIDERATIONS FOR AN OMOR

A. Language

The OMOR should be in the English language. If any portion of a submission is in a foreign language, the requestor should provide a complete and accurate English translation, including English translations of any references.

B. Fonts

Font size for text and tables should be of a style and size that is large enough to be easily legible, even after photocopying or when provided electronically. We recommend that narrative text be submitted in Times New Roman 12 point font. Generally, font sizes 9 to 10 points are considered acceptable in tables, but requestors should avoid fonts smaller than 12 points whenever possible. When choosing a font size for tables, it is important to balance the desirability of providing sufficient information on a single page to facilitate data comparisons with that of maintaining a font size that remains readable. If the font size is too large, data comparisons may be complicated because data may be presented in multiple tables. We recommend 10 point font for footnotes.

C. Paper size

Generally, the requestor should format an OMOR to standard U.S. letter size paper (8.5 by 11 inches). Occasionally, a requestor may format individual pages larger than standard paper size to present a floor plan, synthesis diagram, batch formula, or manufacturing instructions.

D. Pagination

Page numbering should be at the document level and not at the module level. (The entire submission should never be numbered consecutively by page.) In general, all documents should have page numbers. Because the page numbering is at the document level, there should only be one set of page numbers for each document.

If the OMOR includes a document within a document, such as a protocol within a study report, the document to be included (in this case, the protocol) should be attached as an appendix.

E. OMOR Searchability

The entire OMOR submission should be electronically searchable. An OMOR should not contain nonsearchable text or images.

F. Hyperlinks to References

All items in reference lists and all in-text references citing scientific articles or other published materials should include a hyperlink to a full copy of the referenced article or other referenced published material. Requestors should place hyperlinks to scientific articles and other published materials in the relevant sections by subject.

V. ENVIRONMENTAL ASSESSMENT

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impacts of their actions and to ensure that the interested and affected public is informed of environmental analyses. FDA complies with NEPA by evaluating environmental impacts of agency action such as decisions on applications or petitions as a part of its regulatory process.

FDA's regulations in 21 CFR part 25 specify that environmental assessments (EAs) must be submitted as part of applications or petitions that request FDA action, unless the action qualifies for categorical exclusion.[34] Because an OMOR is a request for agency action analogous to an application or petition, the requestor must accompany such a request with either an EA or a claim of categorical exclusion.[35]

[34] 21 CFR 25.15(a).

[35] As stated in 21 CFR 25.15, "all applications or petitions requesting agency action require the submission of an EA or a claim of categorical exclusion." Under 21 CFR 25.31, the same categorical exclusion criteria apply to "actions on OTC monographs" as apply to applications like NDAs and ANDAs. See the final rule, "National Environmental Policy Act; Revision of Policies and Procedures" (NEPA final rule), published July 29, 1997 (62 FR 40570 at 40578). It follows that the requirement to submit an EA, when not categorically excluded, would similarly apply to requests for actions on OTC monographs. FDA "will treat like actions alike, regardless of the avenue through which the actions are requested" (NEPA final rule at 40578).

Regulation 21 CFR 25.31 sets forth the classes of actions related to human drugs and biologics that are subject to categorical exclusions and, therefore, ordinarily do not require the preparation of an EA. Barring extraordinary circumstances,[36] the OMORs described below each have a claim of categorical exclusion:

- The OMOR does not propose to increase the use of the active moiety.[37]

- The OMOR proposes to increase the use of active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion.[38]

- The OMOR is for a substance that occurs naturally in the environment, and the OMOR does not propose to alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.[39]

If none of these categorical exclusions apply, then the requestor must prepare an EA that addresses the relevant environmental issues and include the EA in the OMOR.[40] An adequate EA is one that contains sufficient information to enable FDA to determine whether the proposed action may significantly affect the quality of the human environment.[41]

Requestors must comply with the requirements as set forth in 21 CFR 25. In addition, requestors should refer to the guidances for industry *Environmental Assessment of Human Drug and Biologics Applications* (July 1998) and *Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity* (March 2016) for general recommendations on how to prepare EAs for submission. For further information see regulations promulgated by the Council of Environmental Quality at 40 CFR part 1500.

VI. CONFIDENTIAL INFORMATION

In general, the OTC monograph order process is a public process. Under this order process, section 505G(d) of the FD&C Act limits the information that can remain confidential after submission to FDA in connection with proceedings on an order, including an OMOR.

[36] As described in 21 CFR 25.21, an EA is required for an action that ordinarily would be excluded if certain extraordinary circumstances indicate that the proposed action may significantly affect the quality of the human environment. When "extraordinary circumstances" exist, then the requestor of an OMOR that otherwise would be categorically excluded is required to submit an EA consistent with 21 CFR 25.21.

[37] 21 CFR 25.31(a).

[38] 21 CFR 25.31(b).

[39] 21 CFR 25.31(c).

[40] See 21 CFR 25.15(a), 21 CFR 25.21, and 21 CFR 25.31.

[41] 21 CFR 25.15(a).

In general, until disclosure is triggered under section 505G(d)(2) of the FD&C Act, any information, including reports of testing conducted on the drug or drugs involved, that is submitted by a requestor in connection with proceedings on an order under section 505G and is a trade secret or confidential information subject to 5 U.S.C. 552(b)(4) or 18 U.S.C. 1905 will not be disclosed to the public unless the requestor consents to that disclosure.[42] However, FDA generally must make any information submitted by a requestor in support of an OMOR (e.g., the contents of the OMOR) available to the public not later than the date on which the proposed order is issued.[43] Nonetheless, the information will remain confidential if (1) the information pertains to pharmaceutical quality information, unless such information is necessary to establish standards under which a drug is GRASE; (2) the information is of the type contained in raw datasets; (3) the information is submitted in a requestor-initiated request, but the requestor withdraws the request in accordance with withdrawal procedures established by FDA before FDA issues the proposed order; or (4) FDA requests and obtains the information under section 505G(c) of the FD&C Act and the information is not submitted in relation to an order under section 505G(b) of the FD&C Act.[44]

[42] See section 505G(d)(1) of the FD&C Act.

[43] See section 505G(d)(2)(A)(i) of the FD&C Act.

[44] See section 505G(d)(2)(B) of the FD&C Act.