Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Ayanna Augustus at 301-796-3980 or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-8010.

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

October 2019
Drug Safety
Revision 1

Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

and/or

Office of Communication, Outreach, and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010; Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

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

October 2019
Drug Safety
Revision 1

TABLE OF CONTENTS

I. INTRODUCTION 1

II. BACKGROUND 3

A. FDA May Require Postmarketing Studies and Clinical Trials 3

B. Applicants Are Required to Report on the Status of Studies and Clinical Trials 4

III. IMPLEMENTATION OF POSTMARKETING STUDY AND CLINICAL TRIAL REQUIREMENTS UNDER SECTION 505(O)(3) OF THE FD&C ACT 6

A. Determining Whether Reports Under Section 505(k)(1) Are Sufficient 6

1. Postmarketing Adverse Event Reports and the FDA's Adverse Event Reporting Systems 6

2. FDA Considerations in Determining Whether FAERS and VAERS Are Sufficient for the Purposes Under Section 505(o)(3)(B) of the FD&C Act in a Specific Circumstance 7

B. Determining Whether the Active Postmarket Risk Identification and Analysis System Available Under Section 505(k)(3) Is Sufficient 8

1. The Sentinel System and the Active Postmarket Risk Identification and Analysis System 8

2. FDA Considerations in Determining Whether the ARIA System Is Sufficient 9

a. ARIA data characteristics needed to assess or identify a serious risk 9

b. ARIA analytic capabilities needed to assess or identify a serious risk 9

3. Other Considerations About the Sufficiency of ARIA 10

4. FDA Conduct of ARIA-Based Analyses of Similar Safety Concerns to Those Evaluated Under a PMR 10

5. FDA Conduct of Sentinel-Based Studies When a PMR Has Not Been Required 10

6. Applicant Conduct of Analyses Using Other Electronic Health Care Systems 10

C. Examples of Postmarketing Requirements Under Section 505(o) of the FD&C Act 11

D. Examples of Postmarketing Commitments 16

IV. BENEFIT-RISK ASSESSMENT 16

V. PROCEDURES 17

VI. DISPUTE RESOLUTION 18

VII. ENFORCEMENT OF REQUIREMENTS FOR POSTMARKETING STUDIES AND CLINICAL TRIALS 18

GLOSSARY 20

APPENDIX A: PMR AND PMC AUTHORITIES 22

Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act 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 provides information on the implementation of section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(o)(3)),[2] which authorizes FDA to require certain postmarketing studies and clinical trials[3] for prescription drugs approved under section 505(c) of the FD&C Act and biological products approved under section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262).[4]

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] Added by section 901 of Food and Drug Administration Amendments Act of 2007 (FDAAA).

[3] For purposes of implementing section 505(o)(3) of the FD&C Act, we distinguish between studies and clinical trials for the purposes described in this document.

[4] For the purposes of this guidance, all references to *drugs* include both human drugs and biological drug products regulated by CDER and CBER unless otherwise specified.

This guidance describes FDA's statutory authority to require certain postmarketing studies and clinical trials under section 505(o)(3) of the FD&C Act (i.e., postmarketing requirements (PMRs))[5] and provides an overview of the types and purposes of such studies and clinical trials. This guidance also describes those types of postmarketing studies and clinical trials that are agreed upon (i.e., postmarketing commitments (PMCs))[6] between FDA and the applicant.[7]

This draft guidance is a revision of the guidance for industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* published in April 2011. This revised guidance provides information on implementation of sections 505(o)(3)(D)(i) and (ii) of the FD&C Act. This guidance also reflects certain provisions enacted under the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act as they relate to postmarketing studies and clinical trials.[8] This guidance does not distinguish between prescription drugs with active ingredients that are controlled substances and other prescription drugs because, at this time, the Agency does not intend to treat controlled substances differently than other prescription drugs under 505(o). Once finalized, this guidance will replace the April 2011 guidance.

This guidance does not apply to nonprescription drugs approved under a new drug application or to generic drugs approved under section 505(j) of the FD&C Act.

The Glossary defines many of the terms for purposes of this guidance. Words or phrases found in the Glossary appear in bold italics at first mention.

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

[5] The term *postmarketing requirement* or PMR is used to describe all required postmarketing studies or clinical trials, including those required under FDAAA and those required under subpart H of 21 CFR part 314, subpart E of 21 CFR part 601, the Pediatric Research Equity Act, and the animal efficacy rule (see Appendix A: PMR and PMC Authorities).

[6] The term *postmarketing commitment* or PMC is used to describe studies and clinical trials that are agreed upon between FDA and the applicant (see Appendix A: PMR and PMC Authorities).

[7] For the purposes of this guidance, for ease of reference, the term *applicant* refers to a "responsible person" as defined in section 505(o)(2)(A) of the FD&C Act (i.e., the holder of an application for a prescription drug approved under section 505(c) of the FD&C Act, or pending, and biological products licensed under section 351 of the PHS Act (42 U.S.C. 262), or pending).

[8] See Section 3041 of Public Law 115-271.

II. BACKGROUND

A. FDA May Require Postmarketing Studies and Clinical Trials

FDA approves drugs based upon a demonstration that the drug is safe and effective when used under the conditions specified in the proposed labeling. In some instances, FDA may be aware of information and/or data at the time of approval or become aware of data and/or information in a postapproval setting that necessitates further assessment.

Under section 505(o)(3) of the FD&C Act, FDA, based on appropriate scientific data including information regarding chemically related or pharmacologically related drugs,[9] can require at the time of approval that an applicant conduct postmarketing ***studies*** or ***clinical trials***. FDA may also require that an applicant conduct postmarketing studies or clinical trials for a drug product covered under an approved application if FDA becomes aware of ***new safety information.***[10]

For example, in some cases, FDA may be concerned about a potential risk associated with the use of a drug and believe that the risk is serious but may not know enough about the risk, through adverse event reporting or otherwise, to determine how to address the risk in labeling and what information would be appropriate to include. In such cases, FDA can require an applicant to conduct a postmarketing study or clinical trial to obtain more information about the risk.

Postmarketing studies and clinical trials may be required for any or all of the following three purposes:[11]

- To assess a known ***serious risk*** related to the use of the drug
- To assess ***signals of serious risk*** related to the use of the drug
- To identify an ***unexpected serious risk*** when available data indicate the potential for a serious risk

For the purposes of this guidance,[12] clinical trials and studies are defined as follows:

[9] See section 505(o)(3)(A) of the FD&C Act.

[10] See section 505(o)(3)(C) of the FD&C Act. *New safety information* is defined at section 505-1(b)(3) of the FD&C Act.

[11] See section 505(o)(3)(B) of the FD&C Act.

[12] These definitions of postmarketing clinical trial and study do not affect whether the trials or studies are subject to the requirements of Title VIII of FDAAA (Clinical Trial Databases) and section 402(j) of the PHS Act (42 U.S.C. 282(j)).

- ***Clinical trials*** are any prospective investigations in which the applicant or investigator determines the method of assigning the drug(s) or other interventions to one or more human subjects.

- ***Studies*** are all other investigations, such as investigations with humans that are not clinical trials as defined above (e.g., observational epidemiologic studies), animal studies,[13] and laboratory experiments.

Before requiring a postmarketing study, FDA must find that adverse event reporting under section 505(k)(1) of the FD&C Act and the active postmarketing risk identification and analysis system as available under section 505(k)(3) of the FD&C Act will not be sufficient to meet the purposes described above.[14] Similarly, before requiring a postmarketing clinical trial, FDA must find that a postmarketing study or studies will not be sufficient to achieve these same purposes.[15]

In order to ensure that a study or clinical trial is well designed and adequate to address the serious risk, FDA describes the study or clinical trial to be conducted, including the study population and indication.

In general, the purposes of a PMR under section 505(o)(3) are related to serious risks. The term *serious risk* is defined for purposes of section 505(o) as a risk of a ***serious adverse drug experience***. This description does not mean that such postmarketing studies and clinical trials are limited to safety endpoints. Rather, in some cases, a postmarketing study or clinical trial with efficacy endpoints may be appropriate, for example, to further assess whether a potential lack of expected pharmacological effect, including reduced effectiveness, may result in a serious adverse drug experience.[16]

B. Applicants Are Required to Report on the Status of Studies and Clinical Trials

Under section 506B of the FD&C Act and 21 CFR 314.81(b)(2)(vii) and 601.70, applicants are required to report annually on the status of certain PMRs and PMCs, including PMRs required under section 505(o)(3) of the FD&C Act. Under sections 506B(c), FDA is required to track these PMRs and PMCs and report on them annually in the *Federal Register*.[17]

---

[13] We support the principles of the 3Rs (reduce/refine/replace) for animal use in testing when feasible. FDA encourages sponsors to consult with review divisions when considering a nonanimal testing method believed to be suitable, adequate, validated, and feasible. FDA will consider if the alternative method could be assessed for equivalency to an animal test method.

[14] See section 505(o)(3)(D)(i) of the FD&C Act.

[15] See section 505(o)(3)(D)(ii) of the FD&C Act.

[16] See sections 505(o)(2)(C) and 505-1(b)(5) of the FD&C Act.

[17] See the Postmarketing Requirements and Commitments web page at https://www.fda.gov/drugs/postmarket-requirements-and-commitments/postmarketing-requirements-and-commitments-reports.

Section 505(o)(3)(E)(ii) of the FD&C Act further delineates information that is required for PMRs that are issued under section 505(o)(3). This information must include the following:

- A timetable for completion

  A set of milestone dates[18] by which FDA measures progress of studies and clinical trials and compliance with requirements. These goal dates generally include, but are not limited to, final protocol submission date, study or clinical trial completion date, and final report submission date. Section 505(o)(3) of the FD&C Act does not include provisions allowing amendments to change milestone dates for purposes of required reporting.[19] Therefore, status reporting under these regulations will remain based on the *original* schedule.

- Periodic reports on the status of the study, including whether any difficulties in completing the study have been encountered

- Periodic reports on the status of the clinical trial, including the following:

  - Whether enrollment has begun
  - The number of participants enrolled
  - The expected completion date
  - Whether any difficulties completing the clinical trial have been encountered
  - Registration information with respect to the clinical trial under section 402(j) of the PHS Act (42 U.S.C. 282(j)).[20]

In addition, section 505(o)(3)(E)(ii) of the FD&C Act requires that applicants submit a report on each study and clinical trial "otherwise undertaken by the responsible person to investigate a safety issue," including postmarketing studies or clinical trials that are neither required by FDA nor agreed upon between FDA and the applicant. The studies and clinical trials may include investigations initiated by an applicant for many reasons without prior discussion with or

[18] For purposes of this guidance, milestone dates are a series of goal dates (e.g., final protocol submission, study or clinical trial completion date, final report submission) by which FDA measures progress of studies and clinical trials and compliance with requirements.

[19] 21 CFR 314.81(b)(2)(vii)(*a*)(*8*)(*ii-iii*) and 21 CFR 601.70(b)(8)(ii-iii).

[20] Section 402(j) requires that certain clinical trial information, including information regarding results of clinical trials, be submitted to the clinical trials data bank (https://www.ClinicalTrials.gov). Registration information for clinical trials required under section 505(o)(3) should include documentation that the PMR is registered in accordance with Title VIII of FDAAA. See the guidance for sponsors, industry, researchers, investigators, and FDA staff *Form FDA 3674 — Certifications to Accompany Drug, Biological Product, and Device Applications/Submissions* (June 2017).

notification to FDA. These studies and clinical trials may be summarized in a section of the annual report (drugs) or annual status report (biologics).

III. IMPLEMENTATION OF POSTMARKETING STUDY AND CLINICAL TRIAL REQUIREMENTS UNDER SECTION 505(o)(3) OF THE FD&C ACT[21]

As discussed in section II.A, FDA May Require Postmarketing Safety Studies and Clinical Trials, FDA can require postmarketing studies and clinical trials for the following purposes: to assess a known serious risk or signals of serious risk related to the use of the drug, or to identify an unexpected serious risk of a drug when available data indicate the potential for a serious risk. This determination will be based on scientific data deemed appropriate by FDA, including information regarding chemically related or pharmacologically related drug use.

Before requiring a postmarketing study or clinical trial under section 505(o)(3), FDA must find that the adverse event reporting under section 505(k)(1) of the FD&C Act and the analysis system under section 505(k)(3) of the FD&C Act (active risk identification and analysis (ARIA)) will not be sufficient to meet the aforementioned purposes. Further, before requiring a postmarketing clinical trial, FDA must find that a postmarketing study or studies will not be sufficient to meet those purposes.

FDA's determination of whether the information available under subsections (k)(1) and (k)(3) is sufficient is based on analysis of multiple factors, including the following: the nature of the serious risk, the appropriate type of investigation to assess or identify the particular serious risk(s), the strengths and limitations of electronic health data and adverse event report data to assess the specific serious risk, the scientific tools available to evaluate this data, and the extent to which the available data informs the serious risk.

Certain types of questions related to serious risk may only be answerable through specific types of studies or clinical trials, and the information available under subsections (k)(1) and (k)(3) would generally be considered insufficient to address those questions. For example, animal studies or clinical pharmacokinetic and pharmacodynamic trials may be the only means of determining whether a drug is carcinogenic or has the potential for interaction with other drugs, respectively.

A. Determining Whether Reports Under Section 505(k)(1) Are Sufficient

1. Postmarketing Adverse Event Reports and the FDA's Adverse Event Reporting Systems

[21] Applicants conducting postmarketing studies and clinical trials must continue to comply with 21 CFR parts 312 and 58 when applicable and Health and Human Services (HHS) and FDA human subject protection regulations at 45 CFR part 46 and 21 CFR parts 50 and 56 when applicable.

Section 505(k)(1) of the FD&C Act describes data that the applicant must report to FDA relating to clinical experience and other data or information associated with drugs.[22] The regulations implementing section 505(k)(1) include, among other things, a requirement for applicants to submit adverse event information, electronically, to FDA. The FDA Adverse Event Reporting System (FAERS) and Vaccine Adverse Event Reporting System (VAERS) databases[23] contain individual case safety reports (ICSRs) that applicants submit based on information provided by consumers, patients, and health care providers. These systems also contain ICSRs submitted directly to FDA by these reporters and ICSRs of adverse events reported in scientific literature and postmarketing studies. FAERS and VAERS data include reports of medication errors or drug quality problems when these are associated with adverse events.

2. FDA Considerations in Determining Whether FAERS and VAERS Are Sufficient for the Purposes Under Section 505(o)(3)(B) of the FD&C Act in a Specific Circumstance

The determination of the FAERS's and VAERS's sufficiency to meet the purposes described in section 505(o)(3)(B) of the FD&C Act is based, in the context of the serious risk related to the use of the particular drug, on considerations of the strengths and limitations of adverse event reports as information sources and on the particular data characteristics of the FAERS and VAERS systems. Therefore, FDA determines the FAERS's and VAERS's sufficiency for the purposes of whether to require a postmarketing study or clinical trial on a case-by-case basis for each serious risk.

Adverse event reports may be sufficient for identifying and assessing new (e.g., unexpected, unlabeled), serious adverse drug events that occur rarely and are closely linked in time to initiation of the drug and for which the background rate of events is low. Examples include Stevens-Johnson syndrome and toxic epidermal necrolysis.

Limitations of adverse event report data include the following:

- Cannot be used to calculate the actual incidence rate of an adverse event, including the incidence with a particular drug or to conduct comparisons between drugs on the rate of occurrence of an adverse event based on the total number of people exposed to the drug who experienced an adverse event (numerator) and the total number of people exposed to the drug (denominator). For example:

  - There is no certainty that a reported adverse event is due to the drug because FDA does not require a causal relationship between the drug and event be proven as part of the reporting requirements

[22] The requirements for postmarketing adverse event reporting are described in 21 CFR 310.305, 314.80, 314.81, 314.98, and 600.80.

[23] The regulations implementing section 505(k)(1) of the FD&C Act also refer to periodic adverse drug experience reports for approved drugs. Periodic safety reports summarize postmarket safety experience with a drug during a defined period of time and largely comprise listings and summary analyses of the adverse event reports submitted to the FAERS and VAERS. Consequently, FDA's determination of the sufficiency of the FAERS and VAERS encompasses the information that would generally be included in periodic safety reports.

233
234 – Lack of adequate detail on adverse events reported to FDA
235
236 – Underreporting of adverse events to FDA
237
238 – Stimulated reporting of adverse events (e.g., after significant publicity of a potential
239 drug risk)
240
241 – The FAERS and VAERS databases do not collect information about the total number
242 of people exposed to the drug
243
244 • Frequently have incomplete or missing information that affects the following:
245
246 – Assessment of potentially relevant risk factors and confounders necessary to
247 determine whether a causal relationship exists between a drug and an adverse event
248
249 – Identification of patient subpopulations (e.g., elderly patients, patients with specific
250 comorbidities) and evaluation of potential differential risk of the adverse event
251
252 – Evaluation of potential drug interactions
253
254 **B. Determining Whether the Active Postmarket Risk Identification and Analysis**
255 **System Available Under Section 505(k)(3) Is Sufficient**
256
257 *1. The Sentinel System and the Active Postmarket Risk Identification and Analysis*
258 *System*
259
260 FDA established the Sentinel System (Sentinel), a comprehensive active surveillance system, to
261 complement FDA's existing postmarket capabilities and to monitor the safety of approved drugs
262 using large sets of electronic health care data.[24] Sentinel's analytic capabilities are broad and
263 range from simple, rapid queries (e.g., counts of exposures) to sophisticated traditional
264 pharmacoepidemiologic studies that include medical record validation.
265
266 Within Sentinel, the ARIA system comprises predefined, parameterized, reusable routine
267 querying tools combined with the electronic data in the Sentinel Common Data Model.[25, 26]

[24] See the FDA's Sentinel Initiative Background web page at https://www.fda.gov/safety/fdas-sentinel-initiative/fdas-sentinel-initiative-background.

[25] Information about the ARIA analytic tools is available on the FDA's Sentinel web page at https://www.sentinelinitiative.org/active-risk-identification-and-analysis-aria.

[26] The Sentinel Common Data Model is the standardized data structure employed by all the Sentinel participants (Data Partners). The Data Partners transform the data in their local existing environments according to the Common Data Model, which enables them to execute standardized computer programs that run identically at each Data Partner site. Information about the Common Data Model is available at https://www.sentinelinitiative.org/sentinel/data/distributed-database-common-data-model.

FDA considers the ARIA system to be the "active postmarket risk identification and analysis system" for the purposes of section 505(k)(3) of the FD&C Act.

2. FDA Considerations in Determining Whether the ARIA System Is Sufficient

The determination of the ARIA system's sufficiency to meet the purposes described in section 505(o)(3)(B) of the FD&C Act, is based on an assessment of the capabilities of the system (i.e., a combination of the electronic health care data available in the Sentinel Common Data Model and analytic methods) that exist at the time of the sufficiency assessment. This determination is made on a case-by-case basis and takes into consideration multiple factors, some of which may be uncertain at the time of the sufficiency assessment (e.g., the future uptake of a newly approved drug, subsequent exposure of patients to a drug).

a. ARIA data characteristics needed to assess or identify a serious risk

With respect to the electronic health care data characteristics, FDA considers the following when determining the sufficiency of the ARIA system in a particular case:

- Is it possible to identify exposure to the drug within the available data?
- Is a validated or sufficiently defined health outcome of interest identifiable within the available data?
- Are sufficient data available in the ARIA system on important confounders, and to what extent might these confounders influence the outcome of the study?
- Is the population (i.e., cohort) of interest identifiable within the available data?
- Can an appropriate reference population be identified within the available data to make risk-based comparisons?
- Is there sufficient statistical power to assess the questions of interest?
- Is there sufficient patient follow-up time (i.e., duration of observation time after medical product exposure) in the ARIA system to inform the question of interest?

b. ARIA analytic capabilities needed to assess or identify a serious risk

FDA considers the following with respect to the analysis tools when determining the sufficiency of the ARIA system for the purposes under section 505(o)(3)(B):

- Are the analysis tools currently available through the ARIA system adequate for assessing the serious risk?

3. Other Considerations About the Sufficiency of ARIA

Another important consideration is whether electronic health care data systems available to FDA have the capacity to manage the FDA's need for multiple, concurrent, and relatively rapid ARIA queries. The number of proposed analyses may exceed ARIA's capacity. If this will occur, FDA may consider requiring a postmarketing study.

If, after the original determination of sufficiency, FDA determines the ARIA system's analytic methods and/or Sentinel's data are insufficient to meet the purposes in section 505(o)(3)(B) of the FD&C Act, FDA may require a postmarketing study or clinical trial.

4. FDA Conduct of ARIA-Based Analyses of Similar Safety Concerns to Those Evaluated Under a PMR

Even after requiring that an applicant conduct a postmarketing study or clinical trial for a particular purpose, FDA may also perform ARIA analyses as part of its pharmacovigilance activities for a drug to further evaluate the drug's safety. That is, even if the FDA considers the ARIA system insufficient to adequately address a specific serious risk (based upon the considerations above) and a PMR is issued, the ARIA system may still play a role in understanding a broader or related aspect of the issue.

For example, evaluation of a specific safety concern may need to be assessed within both the intended general population and a subpopulation. FDA may require an applicant to conduct a postmarketing study or clinical trial to assess a serious risk in a specific subpopulation that cannot be identified in ARIA and FDA may perform its own assessment of the same safety concern in the general population using the ARIA system. In this example, FDA would issue a PMR focusing on the specific subpopulation but would not issue a PMR for the related assessment of the safety concern in the general population. The combination of the information obtained from the postmarketing study or clinical trial performed by the applicant with the information FDA obtains from its own assessment within ARIA would provide a more comprehensive understanding of the serious risk at issue.

5. FDA Conduct of Sentinel-Based Studies When a PMR Has Not Been Required

FDA may use analyses to study the safety of a drug using the Sentinel system when a PMR is not required. These studies may be useful to gather additional safety information or clarify observations that were made at the time of approval. FDA studies using Sentinel may also help identify and/or assess safety outcomes when drugs are used more broadly than was studied during drug development.

6. Applicant Conduct of Analyses Using Other Electronic Health Care Systems

An FDA determination, with regard to a particular drug, that the ARIA system is insufficient to meet the purposes under section 505(o)(3)(B) of the FD&C Act does not necessarily represent the following conclusions:

- That analyses using any type of administrative claims or electronic health care database will be insufficient to evaluate the serious risk.

  - The characteristics of, and the data contained within, electronic health care databases differ, as do available analytic methods.

  - FDA may determine that an applicant could conduct a postmarketing study utilizing data from other electronic health care systems and require a PMR.

- That the administrative claims and health care databases that comprise the ARIA system are insufficient as an information source. Safety evaluations that use non-ARIA analytic methods to analyze those databases may be appropriate. In those cases, FDA may determine that an applicant could conduct a postmarketing study using these other databases and require a PMR.

In summary, to obtain more information about a known serious risk, a signal of a serious risk, or an unexpected serious risk associated with the use of a drug, FDA can require applicants to conduct (1) a postmarketing study or studies after the Agency has determined that neither adverse event report data nor the ARIA system will be sufficient for such purpose, or (2) a postmarketing clinical trial or trials after it has determined that a postmarketing study or studies will not be sufficient for such purpose.

C. Examples of Postmarketing Requirements Under Section 505(o) of the FD&C Act

This section describes examples of postmarketing studies and clinical trials that FDA will generally consider requiring under section 505(o)(3) of the FD&C Act.

Examples of postmarketing *studies* include the following:

- Safety studies in animals investigating specific end-organ toxicities

  These studies include, but are not limited to, carcinogenicity and reproductive toxicity studies. Although in most instances applicants complete these studies before marketing approval, the studies could be conducted postapproval for certain drugs—for example, drugs intended to treat serious and life-threatening diseases.[27] If conducted postapproval, these studies would be required under 505(o) of the FD&C Act. Examples include studies designed to do the following:

  - Assess carcinogenic potential in appropriate species (e.g., mice and rats)

  - Assess the potential for reproductive toxicology in appropriate species (e.g., monkeys or rabbits)

[27] See the ICH guidance for industry *S1A The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals* (March 1996).

- In vitro laboratory safety studies designed to do the following:

  - Assess certain receptor affinities for any circulating or major metabolites, including conjugates, to evaluate the potential for off-target binding and resulting serious risk

  - Determine whether resistance to a drug has developed in those organisms specific to the labeled indication, resulting in increased serious risk

  - Define the mechanism of drug resistance for certain organisms

  - Assess the risk of cross contamination between drugs that could result from sharing drug-contacting equipment and parts

  - Validate the accuracy, precision, sensitivity, specificity, and robustness of an immunogenicity assay for a drug to assess an immunologic safety concern

- Observational pharmacoepidemiologic studies

  Such studies are generally designed to assess a serious risk associated with a drug exposure or quantify risk or evaluate factors that affect this risk (e.g., drug dose, timing of exposure, patient characteristics). Data sources for observational studies could include administrative health care claims data, electronic medical records, registries, prospectively collected observational data, or other sources of observational information.

  Applicants should consider the following when designing pharmacoepidemiologic studies.[28]

  - To facilitate interpretation of the findings, the studies should always have protocols (including a statistical analysis plan), should include control groups, and should test prespecified hypotheses. A control group may be omitted when there is a scientifically valid reason.

  - For a solely descriptive study, instead of one with a prespecified hypothesis, the protocol may include clearly stated objectives for describing the safety issue, including a defined upper bound for detectable risk, if applicable.

  Registries[29] are a type of prospective pharmacoepidemiologic study. Applicants should consider the following points in the use of registry studies:

[28] See also the guidance for industry and FDA staff *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data.* (May 2013).

[29] Registries established with the primary purpose of enrolling patients to mitigate a serious risk associated with a drug would be required as part of a REMS under section 505-1(f)(3)(F). When part of a REMS, they are an element necessary for the safe use of the drug and are not designed as a study with completion dates. These types of registries would not be required as PMRs and are not described further in this guidance.

441 – FDA may approve a drug with a requirement for a registry that would collect data for
442 a study required as a PMR (under section 505(o)(3) of the FD&C Act). When a
443 pharmacoepidemiologic study using registry data meets the statutory criteria for a
444 PMR described in section III., Implementation of Postmarketing Study and Clinical
445 Trial Requirements Under Section 505(o)(3) of the FD&C Act, FDA intends to
446 require the registry and the study as a PMR.
447
448 – A sponsor can voluntarily create a registry to serve as a repository for clinical data,
449 such as an outcomes registry, that is not part of a PMR issued under section 505(o)(3)
450 of the FD&C Act. However, if FDA becomes aware of new safety information in the
451 postapproval setting, FDA could require the sponsor to conduct a PMR study, which
452 may utilize the registry data.
453
454 Other examples of required observational pharmacoepidemiologic studies include, but are
455 not necessarily limited to, studies designed to do the following:
456
457 – Provide estimates of absolute risk (e.g., incidence rates) for a serious adverse event or
458 toxicity or provide estimates of relative risk
459
460 – Obtain long-term clinical outcome data, including information about potentially rare
461 serious adverse events, in patients exposed to the drug compared to patients not
462 exposed to the drug
463
464 – Identify risk factors (e.g., patient characteristics, duration of drug use) associated with
465 the occurrence of adverse events among patients exposed to specified drugs
466
467 – Compare pregnancy incidence, pregnancy outcomes, and/or child outcomes for
468 patients exposed to the drug compared to patients not exposed to the drug
469
470 • Meta-analyses
471
472 Meta-analyses[30] are studies that can be designed to evaluate a safety endpoint by
473 statistical analysis of data from completed studies or clinical trials. A meta-analysis
474 should use a prospectively designed study protocol and analysis plan with a
475 comprehensive selection of relevant studies or clinical trials and appropriate statistical
476 methodology. An example of a required meta-analysis is one designed to:
477
478 – Evaluate the occurrence of all-cause mortality, cardiovascular death, and cancer
479 incidence and identify potential predictive factors in patients treated with the drug
480 compared to control therapies in all completed randomized clinical trials that include
481 the drug
482

[30] See the draft guidance for industry *Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products* (November 2018). 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.

Postmarketing *clinical trials* required under section 505(o)(3) of the FD&C Act to assess or identify a serious risk typically have a safety endpoint evaluated with prespecified assessments and are adequately powered to analyze the serious risk identified by FDA. In some cases, when a serious risk relates to failure of expected pharmacological action, including reduced effectiveness, the trial might be designed with an efficacy endpoint, for example, to further assess whether a potential failure of expected pharmacological action, including reduced effectiveness, may result in a serious adverse drug experience.

Examples of clinical trials designed with safety endpoints include trials intended to:

- Evaluate, in a controlled clinical trial, the occurrence of asthma exacerbations associated with potential serious adverse effects of the irritative component of an inhalation treatment for asthma
- Determine the incidence of myocardial infarction in patients treated with the approved drug in a follow-on clinical trial after approval, using the original randomized population
- Evaluate differences in safety outcomes between patients who are randomized after a defined period of treatment to either placebo or continued treatment (randomized withdrawal trial)
- Evaluate the potential for QT interval prolongation in a thorough QT clinical trial
- Measure growth and neurocognitive function in pediatric patients treated chronically with the drug[31]
- Evaluate safety in a particular racial or ethnic group or vulnerable population such as the immunocompromised[31]
- Evaluate the safety of the drug in pregnant women[31]
- Evaluate drug toxicity in patients with hepatic or renal impairment[31]
- Evaluate long-term safety of cell and gene therapy products depending on the type of vector used and the inherent risk of integration
- Evaluate the safety of a drug in patients with HIV-1 coinfected with hepatitis C or B[31]

Examples of clinical trials intended to further assess or identify a serious risk related to failure of expected pharmacological action, including reduced effectiveness, could be designed to do the following:

[31] Patients are treated with the drug at a dose and schedule specified in the clinical trial protocol.

- Determine whether extending the treatment duration of an antiviral drug, which is indicated to treat a serious viral infection, mitigates the risk for relapse after completing the course of treatment

- Evaluate a newly identified potential drug-drug interaction that may reduce the systemic exposure of a drug approved to reduce the risk of cardiovascular events

- Evaluate a newly identified antidrug antibody response to a biological drug product approved to treat a serious disease, when information suggests that the antibody may reduce the drug's effectiveness either by altering its pharmacokinetics or by binding to domains of the drug critical to its functional activity

- Evaluate a new signal that a subgroup of patients (e.g., defined by age, sex, race, biomarker) with a life-threatening cancer may not respond to a drug that had been approved based on a clinically meaningful effect in the overall population with the cancer, such that certain patients may be exposed to toxicity with less prospect for benefit

The following describe examples of evaluations designed for the purposes under section 505(o)(3) of the FD&C Act that could be required as either a postmarketing study or clinical trial, depending on the type of information and/or data necessary to assess the risk being addressed by the PMR:

- PMRs designed to evaluate the pharmacokinetics of the drug in the labeled population or in a subpopulation at potential risk for high drug exposures that could lead to toxicity. These could include studies or clinical trials designed to do the following:

  - Determine the optimal dose for maintenance therapy in patients with chronic renal disease, a population at risk for drug accumulation

  - Study the pharmacokinetic profile in a rodent model of hepatic dysfunction to evaluate the potential for toxicity in patients with liver impairment

- PMRs designed to evaluate drug interactions or bioavailability when scientific data indicate the potential for a serious safety risk. These could include studies or clinical trials to do the following:

  - Assess in vitro whether drugs are p-glycoprotein substrates and therefore could lead to increased drug concentrations and toxicity

  - Assess potential interactions of an approved drug with a frequently concomitantly prescribed medication

  - Evaluate whether multiple doses of an approved drug alter the metabolism of a sensitive cytochrome P450 2C9 substrate

572 – Evaluate bioavailability of an oral drug in the presence of food
573
574 **D. Examples of Postmarketing Commitments**
575
576 In general, the following types of studies or clinical trials can be considered for agreed-upon
577 PMCs:
578
579 • Drug and biologic product quality studies, including manufacturing, stability, and
580 immunogenicity studies that do not have a primary safety endpoint, such as studies
581 designed to do the following:
582
583 – Develop an optical rotation test, collect data on commercial batches, and use the data
584 to update drug substance specification standards
585
586 – Evaluate immune response to concomitant vaccination or vaccinations that are a part
587 of routine U.S. immunization practice
588
589 • Pharmacoepidemiologic studies designed to examine the natural history of a disease or to
590 estimate background rates for adverse events in a population not treated with the drug
591 that is the subject of the marketing application
592
593 • Studies and clinical trials conducted with vaccines, such as surveillance and observational
594 pharmacoepidemiologic studies when data do not suggest a serious risk or signals of
595 serious risk related to the use of the vaccine and when available data do not indicate the
596 potential for serious risk, such as the following:
597
598 – A surveillance study of cases of the infectious disease targeted by the approved
599 vaccine occurring in vaccinated populations using product-specific surveys and
600 calculating product-specific rates of infectious disease within the monitored
601 population
602
603 – A clinical trial conducted with vaccines in which the objective is a further
604 characterization of the safety profile and the primary endpoint is not related to a
605 serious risk identified by FDA under section 505(o) of the FD&C Act
606
607
608 **IV. BENEFIT-RISK ASSESSMENT**
609
610 The intent of a PMR is to achieve a better understanding and more fully characterize a serious
611 risk, if one exists. FDA will review the data and/or information obtained under a PMR and
612 assess its effect on the benefit-risk profile of the drug in the context of the serious risk being
613 evaluated. This may result, for example, in labeling changes under section 505(o)(4) of the
614 FD&C Act.
615
616

V. PROCEDURES

The following general PMR and PMC procedures apply to PMRs issued under section 505(o)(3) of the FD&C Act.

For new marketing applications, FDA plans to inform the applicant of the planned target date for communication of feedback from the review division regarding PMRs and PMCs in the filing communication letter.[32]

In both the pre- and postapproval settings, FDA plans to communicate a list of potential PMRs and PMCs, clearly delineated as to which are required and which may be agreed upon, to the applicant along with a brief rationale for why FDA thinks these studies and clinical trials are appropriate. The list should also include a request for a proposed timetable for completion.

The applicant will have the opportunity to discuss the design and conduct of the PMRs and PMCs, as well as the overall goal, with the FDA review team. The applicant should provide prompt feedback and engage in discussion as needed with the FDA review team to facilitate completion of clearly written and well-designed PMRs and PMCs. The applicant should also provide a timetable for completion of the study or clinical trial for the PMRs and a schedule for milestone submissions and final reports for PMCs. For PMRs and PMCs, the first milestone is generally the "final protocol submission" date. FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial. Thus, the date for this milestone should be selected to allow for the discussion period needed to create a well-designed study or clinical trial. As described in section II.B., Applicants Are Required to Report on the Status of Studies and Clinical Trials, public status of PMRs and PMCs is based on the original schedule, so appropriate and realistic dates should be proposed.

The FDA review team intends to (1) review the potential study or clinical trial designs to make sure they will serve the purposes of the study or clinical trial and (2) assess whether the proposed timetable will be realistic and will provide for timely completion of the study or clinical trial.

Section 505(o)(3) of the FD&C Act gives FDA the authority to require PMRs without prior agreement from the applicant. For PMCs, the applicant should submit a written agreement to conduct the PMCs. FDA intends to include the PMRs and PMCs and their milestones and dates in the action letter issued at the completion of the application review. In the postapproval setting, FDA intends to include the new PMRs and PMCs and their milestones and dates in the letter establishing the PMRs and PMCs.

[32] See CDER Manual of Policies and Procedures (MAPP) 6010.8 Rev. 1 *NDAs and BLAs: Communications to Applicants of Planned Review Timelines.* For this and other MAPPs, see the CDER MAPPs web page at: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-manual-policies-procedures-mapp.

VI. DISPUTE RESOLUTION

The applicant may appeal a requirement to conduct a postmarketing study or clinical trial using the usual dispute resolution procedures (see the guidance for industry and review staff *Formal Dispute Resolution: Appeals Above the Division Level* (November 2017))[33] (see section 505(o)(3)(F) of the FD&C Act).

VII. ENFORCEMENT OF REQUIREMENTS FOR POSTMARKETING STUDIES AND CLINICAL TRIALS

FDA has authority to enforce the section 505(o)(3)(E)(ii) requirements for postmarketing studies and clinical trials.[34] An applicant's failure to comply with the timetable, periodic report submissions, and other requirements of section 505(o)(3)(E)(ii) of the FD&C Act will be considered a violation unless the applicant demonstrates good cause for the noncompliance. Section 505(o)(3)(E)(ii) of the FD&C Act provides that FDA shall determine what constitutes good cause. In addition, under section 505(p)(2) of the FD&C Act, failure to conduct a postmarketing study or clinical trial required under section 506B of the FD&C Act and subparts H and E (21 CFR 314.510 and 601.41) may result in enforcement action.

Enforcement action could include one or more of the following:

- Charges under section 505 of the FD&C Act. A responsible person[35] may not introduce or deliver into interstate commerce the drug involved if the person is in violation of section 505(o) (postmarketing study and clinical trial requirements) (see section 505(o)(1) of the FD&C Act) or 505(p)(2) (certain postmarketing studies).

- Misbranding charges. A drug is misbranded under section 502(z) of the FD&C Act (21 U.S.C. 332(z)) if the applicant for that drug violates postmarketing study or clinical trial requirements, including those outlined in section II.B., Applicants Are Required to Report on the Status of Studies and Clinical Trials.

- Civil monetary penalties. Under section 303(f)(4)(A) of the FD&C Act (21 U.S.C. 333(f)(4)(A)), an applicant that violates postmarketing study or clinical trial requirements may be subject to civil monetary penalties of up to $250,000 per violation, but no more than $1 million for all violations adjudicated in a single proceeding. These penalties increase if the violation continues more than 30 days after FDA notifies the applicant of the violation. The penalties double for the following 30-day period and continue to

[33] 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.

[34] FDA has the authority to review records upon inspection of postmarketing studies and clinical trials, including underlying data and source documents (see section 505(k) of the FD&C Act).

[35] Defined at section 505(o)(2)(A) of the FD&C Act.

695 double for subsequent 30-day periods, up to $1 million per period and $10 million for all
696 violations adjudicated in a single proceeding. In determining the amount of a civil
697 penalty, FDA will consider the applicant's efforts to correct the violation (see section
698 303(f)(4)(B) of the FD&C Act).
699

GLOSSARY[1]

Adverse drug experience is any adverse event associated with the use of a drug in humans, whether or not considered drug related, including:

(A) an adverse event occurring in the course of the use of the drug in professional practice;

(B) an adverse event occurring from an overdose of the drug, whether accidental or intentional;

(C) an adverse event occurring from abuse of the drug;

(D) an adverse event occurring from withdrawal of the drug; and

(E) any failure of expected pharmacological action of the drug, which may include reduced effectiveness under the conditions of use prescribed in the labeling of such drug, but which may not include reduced effectiveness that is in accordance with such labeling.

Clinical trials are any prospective investigations in which the applicant or investigator determines the method of assigning the drug or drugs or other interventions to one or more human subjects. Clinical trials are one type of clinical investigation, as defined at 21 CFR 312.3(b).

New safety information with respect to a drug, means information derived from a clinical trial, an adverse event report, a postapproval study (including a study under section 505(o)(3) of the FD&C Act), or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 505(k) of the FD&C Act; or other scientific data deemed appropriate by FDA about—

(A) a serious risk or unexpected serious risk associated with use of the drug that FDA has become aware of (that may be based on a new analysis of existing information) since the drug was approved, since the risk evaluation and mitigation strategy was required, or since the last assessment of the approved risk evaluation and mitigation strategy for the drug; or

(B) the effectiveness of the approved risk evaluation and mitigation strategy for the drug obtained since the last assessment of such strategy.

[1] The definitions in this glossary are presented for purposes of this guidance only. The definitions of the following terms are adapted from section 505-1(b) of the FD&C Act (21 U.S.C. 355-1(b)): adverse drug experience, new safety information, serious adverse drug experience, serious risk, signal of a serious risk and unexpected serious risk. FDA considers these definitions to include safety information related to a class effect, not apparently limited to a single member of the class for structural, mechanistic, or other reasons.

Serious adverse drug experience is an adverse drug experience that—

(A) results in—
(i) death;
(ii) an adverse drug experience that places the patient at immediate risk of death from the adverse drug experience as it occurred (not including an adverse drug experience that might have caused death had it occurred in a more severe form);
(iii) inpatient hospitalization or prolongation of existing hospitalization;
(iv) a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
(v) a congenital anomaly or birth defect; or

(B) based on appropriate medical judgment, may jeopardize the patient and may require a medical or surgical intervention to prevent an outcome described under subparagraph (A).

Serious risk means a risk of a serious adverse drug experience.

Signal of a serious risk means information related to a serious adverse drug experience associated with use of a drug and derived from —

(A) a clinical trial;

(B) adverse event reports;

(C) a postapproval study, including a study under section 505(o)(3) of the FD&C Act;

(D) peer-reviewed biomedical literature;

(E) data derived from the postmarket risk identification and analysis system under section 505(k)(4) of the FD&C Act;

(F) other scientific data deemed appropriate by the Secretary.

Studies are all other (not clinical trial) investigations, such as investigations with humans that are not clinical trials as defined above (e.g., observational epidemiologic studies), animal studies, and laboratory experiments.

Unexpected serious risk means a serious adverse drug experience that is not listed in the labeling of a drug or that may be symptomatically and pathophysiologically related to an adverse drug experience identified in the labeling, but differs because of greater severity, specificity, or prevalence.

781 **APPENDIX A: PMR AND PMC AUTHORITIES**
782

Postmarketing Requirement (PMR) Authorities	Postmarketing Commitment (PMC) Authorities
Pediatric Research under section 505B of the Federal Food, Drug, and Cosmetic Act (the FD&C Act):[1] • 21 CFR 314.55(b) (drugs) • 21 CFR 601.27(b) (biologics)	Agreed -upon postmarketing studies and clinical trials: • 21 CFR 312.85
Accelerated approval regulations:[2] • 21 CFR 314.510, Subpart H (drugs) • 21 CFR 601.41, Subpart E (biologics)	
Animal Rule: [3] • 21 CFR 314.610(b)(1), Subpart I (drugs) • 21CFR 601.91(b)(1), Subpart H (biologics)	
Food and Drug Administration Amendments Act of 2007 (FDAAA), section 901. • Section 505(o)(3) of the FD&C Act	

783

[1] See the draft guidance for industry *How to Comply with the Pediatric Research Equity Act* (September 2005). 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.

[2] See the guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014).

[3] See the guidance for industry *Product Development Under the Animal Rule* (October 2015).