
Best Practices in Drug and Biological Product Postmarket Safety Surveillance for FDA Staff

DRAFT

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Center for Biologics Evaluation and Research (CBER)**

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1 **Table of Contents**

2	1. Executive Summary	3
3	2. Introduction.....	3
4	2.1. Regulatory History.....	3
5	2.2. Scope and Goals of This Document.....	4
6	2.3. Related Documents	5
7	2.4. Terms Referenced Throughout Document.....	5
8	3. FDA’s Adverse Event Reporting Systems	6
9	4. Risk-based Approach to Drug Safety Surveillance.....	7
10	5. Special Topics in Drug and Biological Product Safety Surveillance.....	8
11	5.1. Biological Products.....	8
12	5.1.1. Biosimilar Products.....	10
13	5.2. Generic Drugs	10
14	5.3. Over-the-Counter Drugs	12
15	5.4. Orphan Drugs and Drugs for Rare Diseases or Conditions	12
16	5.5. Compounded Drugs	13
17	5.6. Homeopathic Drug Products.....	13
18	5.7. Combination Products.....	14
19	5.8. Medication Errors	14
20	5.9. Specific Patient Populations.....	16
21	5.9.1. Pregnant population	16
22	5.9.2. Pediatric Populations.....	18
23	5.9.3. Geriatric Population	19
24	5.10. Misuse, Abuse, Addiction, and Overdose.....	20
25	5.11. Product Quality Issues	21
26	6. Safety Signal Identification.....	21
27	6.1. Data Sources	21
28	6.1.1. FAERS and VAERS	22
29	6.1.2. Data Mining	23
30	6.1.3. Medical Literature.....	23
31	6.1.4. Other Information Sources.....	24
32	6.2. Frequency and Extent of Screening	25

33	6.3. Signal Prioritization	26
34	7. Signal Evaluation and Documentation.....	27
35	7.1. FAERS, VAERS, and the Medical Literature.....	27
36	7.1.1. ICSR Retrieval	27
37	7.1.2. Case Definition	27
38	7.1.3. Assessment of ICSRs for Causal Association.....	28
39	7.1.4. Case Series	28
40	7.2. Product Utilization	29
41	7.3. Reporting Ratios	29
42	7.4. Epidemiologic Assessments.....	30
43	8. Causal Association Between Product and AE	30
44	9. Actions	31
45	9.1. Product Labeling Changes	31
46	9.2. Safety Communications	32
47	9.3. Postmarketing Studies and Trials.....	32
48	9.4. Enhanced Pharmacovigilance	33
49	9.5. Web Posting of Potential Safety Signals.....	33
50	9.6. Risk Evaluation and Mitigation Strategies.....	34
51	10. Exploring New Approaches	35
52	11. Acronyms Used.....	35
53		

54 **1. Executive Summary**

55 This document,¹ *Best Practices in Drug and Biological Product Postmarket Safety Surveillance for FDA*
56 *Staff*, sets forth risk-based principles by which the Food and Drug Administration (FDA or Agency)
57 conducts ongoing postmarketing safety surveillance for human drug and biological products (biologics).
58 The main topics this document addresses include:

- 59 • A multidisciplinary, life-cycle approach to the management of drug and biologic safety.
- 60 • General considerations that inform the frequency and extent of systematic drug and biologic
61 safety monitoring (section 4).
- 62 • Additional considerations based on specific product types and patient populations (section 5).
- 63 • Safety signal identification based on screening and data mining of the adverse event (AE)
64 reporting system and other data sources, including general practices for the frequency and extent
65 of screening these data sources, as well as prioritizing identified signals (section 6).
- 66 • A multidisciplinary, comprehensive evaluation of the identified safety signal that integrates the
67 cumulative data gathered from all available sources (section 7).
- 68 • An assessment of the causal association between the identified AE and the product (section 8).
- 69 • An overview of regulatory and other actions that can be taken in response to identified safety
70 signals (section 9).

71 **2. Introduction**

72 **2.1. Regulatory History**

73 Title IX, section 915 of The Food and Drug Administration Amendments Act (FDAAA) of 2007 added a
74 new section 505(r) to the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(r)),²
75 requiring FDA to prepare—

76 . . . by 18 months after approval of a drug or after use of the drug by 10,000 individuals,
77 whichever is later, a summary analysis of the adverse drug reaction reports received for the drug,
78 including identification of any new risks not previously identified, potential new risks, or known
79 risks reported in unusual number.³

80 FDAAA also added a new subsection (k)(5) to section 505, which required FDA to—

81 conduct regular, bi-weekly screening of the Adverse Event Reporting System database and post a quarterly
82 report on the Adverse Event Reporting System Web site of any new safety information or potential signal
83 of a serious risk identified by Adverse Event Reporting System within the last quarter.⁴

¹ This document was prepared by the Office of Surveillance and Epidemiology, in collaboration with other offices in the Center for Drug Evaluation and Research and with the Center for Biologics Evaluation and Research, at the Food and Drug Administration.

² <http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/html/USCODE-2010-title21-chap9-subchapV-partA-sec355.htm>.

³ Ibid.

⁴ Ibid.

84 The 21st Century Cures Act⁵ (Cures Act) was enacted on December 13, 2016, and has the goal of
85 advancing medical product innovation, as well as ensuring patient access to safe and effective treatments
86 as soon as possible. Section 3075 of the Cures Act amended section 505(r)(2)(D) of the FD&C Act to
87 eliminate the requirement for summary analyses for drugs as required by FDAAA. In place of the
88 summary analyses, section 3075 amended section 505(r)(2)(D) of the FD&C Act to include the
89 requirement that FDA make publicly available on its internet website “. . . best practices for drug safety
90 surveillance activities for drugs approved under this section or section 351 of the Public Health Service
91 Act.”

92 Section 3075 of the Cures Act also amended section 505(k)(5) of the FD&C Act to strike “bi-weekly
93 screening,” as required by FDAAA, and insert “screenings”; it also added the requirement that FDA make
94 publicly available on its internet website the following:

95 (i) guidelines, developed with input from experts qualified by scientific training and experience to
96 evaluate the safety and effectiveness of drugs, that detail best practices for drug safety surveillance
97 using the Adverse Event Reporting System; and

98 (ii) criteria for public posting of adverse event signals.

99 2.2. Scope and Goals of This Document

100 As its primary focus, this document sets forth risk-based principles by which FDA conducts ongoing
101 postmarketing safety surveillance for drug and biological products to address the Cures Act requirements
102 to develop and make publicly available best practices and guidelines related to drug safety surveillance.
103 Although section 3075 of the Cures Act only references drugs approved under section 505 of the FD&C
104 Act or section 351 of the Public Health Service Act (PHS Act), this document additionally discusses other
105 products, including over-the-counter (OTC) monograph, compounded, and homeopathic products.⁶ It
106 also includes a high-level overview of other data sources, tools, and methods, as well as drug safety
107 surveillance activities that extend beyond use of the Adverse Event Reporting System (and its
108 successors). These additional topics are included to provide context and a general overview of FDA’s
109 safety surveillance process.

110 The drug safety surveillance principles and best practices detailed in this document build upon lessons
111 learned in preparing and publicly posting the summary analyses of adverse drug reaction reports
112 previously required under section 505(r) of the FD&C Act. FDA conducted a study to assess the impact
113 of these summary analyses on regulatory actions.⁷ In interpreting the study findings, FDA determined
114 these summary analyses were largely redundant to the surveillance practices in place at the time FDAAA

⁵ <https://www.congress.gov/114/bills/hr34/BILLS-114hr34enr.pdf>.

⁶ Biological products discussed in this document are limited to those with approved BLAs for which manufacturers are required to submit adverse experience reports under 21 CFR 600.80. Pharmacovigilance considerations for other biological products (e.g., whole blood and blood components, which are exempt from 21 CFR 600.80) are not discussed in this document.

⁷ Sekine S, Pinnow EE, Wu E, et al. Assessment of the impact of scheduled postmarketing safety summary analyses on regulatory actions. *Clin Pharmacol Ther.* 2016;100(1):102-108.

115 took effect and were not an efficient use of FDA resources. Furthermore, many drugs and biological
116 products for rare diseases never met the 10,000-individual use threshold.

117 2.3. Related Documents

118 The Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and
119 Research (CBER) maintain procedural documentation for various internal practices for evaluation of
120 drugs (i.e., CDER's Manual of Policies and Procedures⁸ (MAPP), CDER's Standard Operating
121 Procedures,⁹ and CBER's Standard Operating Procedures and Policies¹⁰ (SOPPs)). FDA also issues
122 many guidance documents to industry, all of which are posted on the FDA website; FDA maintains a web
123 page of those that relate specifically to drugs.¹¹

124 FDA is also developing internal, supporting technical documents to guide the implementation of the
125 principles articulated in this best practice document.

126 2.4. Terms Referenced Throughout Document

127 An *adverse drug experience* is any *adverse event* (AE) associated with the use of a drug in humans,
128 whether or not considered drug related, and includes the following: an AE occurring in the course of the
129 use of a drug product in professional practice; an AE occurring from drug overdose whether accidental or
130 intentional; an AE occurring from drug abuse; an AE occurring from drug withdrawal; and any failure of
131 expected pharmacological action.

132 FDA also monitors AE reports to detect cases of medication errors. The strategies for AE surveillance are
133 generally the same for medication error pharmacovigilance, with some exceptions noted as applicable in
134 this document. Excluding these exceptions, all references to *adverse event* include *medication error*.

135 The term *AE of interest* is used to describe an AE that reviewers would closely monitor during
136 surveillance based upon biological plausibility or known class effect, as well as signals identified from
137 any source that upon evaluation warrant close monitoring.

138 FDA uses the term *signal* to mean information that arises from one or multiple sources (including
139 observations and experiments), that suggests a new potentially causal association, or a new aspect of a
140 known association, between an intervention and an event or set of related events, either adverse or
141 beneficial, that is judged to be of sufficient likelihood to justify further action to verify.¹² Because this

⁸ A listing of CDER MAPPs is available at <https://www.fda.gov/about-fda/center-drug-evaluation-and-research/cder-manual-policies-procedures-mapp>.

⁹ MAPP 4001.1, describing the policy for developing, issuing, and maintaining SOPs for CDER is available at <https://www.fda.gov/media/90280/download>.

¹⁰ A listing of CBER SOPPs is available at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/default.htm>.

¹¹ <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs>.

¹² The guidance for industry *E2C(R2) Periodic Benefit-Risk Evaluation Report (PBRER)* is available at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

142 document focuses on safety surveillance, the term *signal* is used herein to describe adverse (and not
143 beneficial) events.

144 Acronyms used in this document are defined at first use and are listed in section 11.

145 3. FDA’s Adverse Event Reporting Systems

146 FDA’s adverse event reporting systems are designed to support postmarketing safety surveillance
147 programs for drug and biological products.

148 The FDA Adverse Event Reporting System¹³ (FAERS) is a database that contains individual case safety
149 reports (ICSRs) of AEs. ICSRs in the FAERS database provide critical information to FDA during
150 ongoing product safety surveillance in the postmarketing period.

151 The Vaccine Adverse Event Reporting System¹⁴ (VAERS) is an analogous database that underpins the
152 national program jointly managed by the U.S. Centers for Disease Control and Prevention (CDC) and
153 FDA to monitor the safety of vaccines licensed in the United States. VAERS accepts and CDC and FDA
154 analyze information from reported AEs that occur after vaccination. The National Childhood Vaccine
155 Injury Act (NCVIA) (42 U.S.C. 300aa-25) mandates that health care providers and vaccine manufacturers
156 report certain specified vaccine events, as well as any event that is listed in the manufacturer’s package
157 insert as a contraindication to the vaccine.^{15,16}

158 FDA receives ICSRs from two main sources: the regulated industry and the public. ICSR from industry
159 are sent to FDA on a mandatory basis by applicants, licensed manufacturers, packers, distributors, and
160 responsible persons¹⁷ subject to FDA’s requirements for postmarketing safety reporting.^{18,19} Members of
161 the general public, including health care providers, patients, consumers, and family members, have two
162 avenues to voluntarily report an AE—they may report it to the applicant or they may report directly to

¹³ More information about FAERS is available at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

¹⁴ More information about VAERS is available at <https://vaers.hhs.gov/index>.

¹⁵ Although most AE reporting is voluntary for health care providers, health care providers are required to report some AEs for vaccines. Vaccine Safety Questions and Answers are available at <https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/vaccine-safety-questions-and-answers>.

¹⁶ The VAERS Reportable Events Table lists the events that are reportable by law under NCVIA and is available at https://vaers.hhs.gov/docs/VAERS_Table_of_Reportable_Events_Following_Vaccination.pdf.

¹⁷ “Responsible persons” is the term used for the manufacturer, packer, or distributor whose name appears on the label of an OTC drug marketed in the United States without an approved application and who has AE reporting responsibilities under section 760 of the FD&C Act.

¹⁸ Reporting regulations for products addressed in this document are found in 21 CFR 310.305 (prescription drugs marketed for human use without an approved application); 21 CFR 314.80 (human drugs with approved NDAs); 21 CFR 314.98 (human drugs with approved ANDAs); 21 CFR 600.80 (human biological products with approved BLAs), and section 760 of the FD&C Act (nonprescription human drug products marketed without an approved application).

¹⁹ For the purposes of this document, applicants, licensed manufacturers, packers, distributors, etc., are hereafter referred to as *applicants* except when referring to unapproved products, in which case *manufacturer* is used.

163 FDA (or the VAERS program in the case of vaccines). If a member of the public reports an AE to the
164 applicant, then the applicant must report the AE to FDA in accordance with regulatory requirements.

165 **4. Risk-based Approach to Drug Safety Surveillance**

166 Consistent with the mission to protect and advance the public health, FDA monitors the benefit-risk
167 balance of products over their life cycle and takes regulatory action(s) when appropriate. FDA's safety
168 surveillance begins early in the product's life cycle as part of the review process that may lead up to FDA
169 approval. Once a marketing application for a product is filed, a multidisciplinary team is formed to
170 evaluate the application, including considering appropriate measures to continue to assess the safety of
171 the product if and when it gains FDA approval. Members of the multidisciplinary team have expertise in
172 medicine, pharmacology, epidemiology, safety surveillance, medication error prevention, risk
173 management, product quality, and statistical analysis.

174 It is not possible to identify all risks of a product during the clinical trials conducted as part of that
175 product's development. Once a product is approved and marketed, new information about the safety of
176 the product may be learned. For example, after approval and marketing, many more patients will be
177 exposed to the product, including more patients with comorbid conditions and on concomitant medical
178 products, providing more information. Together, the FDA multidisciplinary team determines the
179 postmarketing surveillance strategy and activities on a product-specific basis using a risk-based approach.
180 The team also provides expert input to identify what additional activities, if any, an applicant must
181 perform in the postmarketing period.

182 Once FDA approves a product, a risk-based postmarketing safety surveillance phase begins and continues
183 for the life of the product. The principles of risk-based safety surveillance include considerations of the
184 product's characteristics and use in a manner that informs the frequency and extent of systematic
185 monitoring. Products that generally are subject to more extensive monitoring include:

- 186 • NDAs that are new molecular entities.
- 187 • Original biological license applications (BLAs).
- 188 • Biosimilar biological products.
- 189 • First in class approvals.
- 190 • Newly approved formulation(s).
- 191 • Newly approved indication(s).
- 192 • Extension into new patient populations.
- 193 • Products with complex pharmacokinetic (PK) or pharmacodynamic (PD) characteristics.
- 194 • Products with complex compositions or manufacturing processes.

195 Reviewers also monitor the safety of compounded products, even though they are not subject to FDA
196 premarket review and approval, as well as homeopathic products.

197 When conducting surveillance, reviewers focus on information that suggests a safety signal or broadly
198 describes safety concerns (i.e., important identified risk(s), important potential risk(s), and important

199 missing information)²⁰ for the product under evaluation. Safety information of interest to reviewers
200 during surveillance includes the following:²¹

- 201 • Important potential risks of the product recognized at the time of or after approval.
- 202 • Apparent increase in the severity or frequency of reporting of a labeled AE.
- 203 • Deaths, particularly in populations or in patients using the product for indications for which there
204 would not be the expectation of death.
- 205 • AEs for which causal attribution to the product is biologically plausible, based on the product's
206 known pharmacological action.
- 207 • Reports of unlabeled, serious AEs.²²
- 208 • Serious AEs thought to be rare in the general population and associated with a high product-
209 attributable risk.
- 210 • Interactions among different products (e.g., drug-drug, drug-device, drug-food, or drug-dietary
211 supplement).
- 212 • Reports of reduced effectiveness or efficacy.
- 213 • Medication errors²³ resulting from confusion about a product's name, labeling, packaging, or use.
- 214 • Off-label use, misuse, abuse, and other intentional uses of a product in a manner that is
215 inconsistent with the FDA-approved labeling.
- 216 • AEs reported or observed in a specific patient population.
- 217 • AEs for which a Risk Evaluation and Mitigation Strategy (REMS) is intended to mitigate the risk.

218 5. Special Topics in Drug and Biological Product Safety Surveillance

219 5.1. Biological Products

220 Biological products (also called “biologics”) include products that are isolated from a variety of natural
221 sources including humans, animals, and microorganisms. Examples of biologics include vaccines, gene
222 therapies, allergenic extracts, cellular therapies, and blood-derived and recombinant therapeutic biologics,
223 such as monoclonal antibodies, immune globulins, clotting factors, and enzyme replacement proteins.
224 Biologics that are demonstrated to be biosimilar to or interchangeable with FDA-approved biologics are
225 discussed in subsection 5.1.1, below.

²⁰ The ICH E2E Guidance describes a method for summarizing important risks and is available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073107.pdf>.

²¹ For additional information, see the guidance for industry *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

²² FDA applies the definition of serious in 21 CFR 314.80(a) and 600.80(a). A serious adverse drug experience results in any of the following five outcomes: death, a life-threatening adverse drug experience, hospitalization (inpatient or prolonged), persistent or significant disability/incapacity, or congenital anomaly/birth defect. Other important medical events may be considered to be serious adverse experiences when they may jeopardize a patient and required intervention to prevent one of the listed outcomes.

²³ Special considerations regarding medication errors are discussed in section 5.8 of this document, including the definition used by FDA.

226 AE reporting practices and regulations for biological products licensed under section 351 of the Public
227 Health Service Act, including vaccines, are similar to those for drugs approved under section 505 of the
228 FD&C Act, and the pharmacovigilance practices discussed in this document generally apply to biologics
229 as well. However, there are issues specific to biologics that need to be addressed when monitoring
230 postmarketing safety. These issues include immunogenicity, product manufacturing variability, and risk
231 of product contamination with infectious agents.

232 **Immunogenicity as a safety concern in therapeutic biological products**

233 Most biologics elicit immunological responses to some extent following human administration,²⁴ which
234 may result in specific AEs generally not seen with small molecule drugs. The following immunological
235 issues are specifically monitored during the safety surveillance of biologics:

- 236 • Anaphylaxis and other hypersensitivity reactions—allergic reactions can occur with therapeutic
237 biologics, although the frequency may be insufficient to allow detection during premarket
238 development. All routine and aggregate analyses of each product’s postmarketing safety
239 evaluation generally include monitoring of AE terms that indicate anaphylaxis or other allergic
240 reactions.
- 241 • Immune complex disease—the immunogenicity of a therapeutic biologic may result in large
242 complexes of the therapeutic biologic in combination with antibodies, resulting in what is known
243 as immune complex disease. Such complexes may accumulate in organs, resulting in organ
244 dysfunction.
- 245 • Loss of efficacy—therapeutic biologics can stimulate an immune response against the biologic
246 itself through the production of anti-drug antibodies; this immune response can lead to a decrease
247 in effectiveness of the therapy over time.
- 248 • Human protein analogs—administration of therapeutic biologics that are similar to human
249 proteins can, in rare cases, lead to breakage in immune tolerance. That is, some patients who
250 receive such products can develop an immune response to the natural human protein, which may
251 result in sustained loss of function of the protein, even after discontinuation of the therapeutic
252 biologic.
- 253 • Off-target binding—in addition to the intended site of action, therapeutic biologics may rarely
254 bind to other tissues, which may cause an AE due to stimulation of an inappropriate immune
255 response.

256 **Product manufacturing variability**

257 The structure of biologics is typically larger and more complex than that of other drugs, and the
258 manufacturing process is generally more complex. Additionally, because some source materials are
259 derived from biological materials, there can be naturally occurring variabilities in the characteristics of
260 these materials with each batch of product. While manufacturers control the process to manage the risks
261 and minimize product variability, product quality issues (PQIs) may still occur. Therefore, when lot
262 information is available during postmarketing surveillance, it can be useful in identifying potential
263 manufacturing issues and in analyzing AEs by lot number.

²⁴ Wadhwa M, Thorpe R. Unwanted immunogenicity: lessons learned and future challenges. *Bioanalysis*. 2010;2(6):1073-1084.

264 **Product contamination**

265 Another complexity of biological products is that manufacturing may include biological systems. In
266 certain cases, there is a potential for source material to be contaminated with infectious agents, and
267 surveillance for infections may be appropriate as part of routine monitoring. Therefore, safety monitoring
268 for these products should routinely include surveillance for infections.

269 **5.1.1. Biosimilar Products**

270 The Biologics Price Competition and Innovation Act of 2009 amended the PHS Act and other statutes to
271 create an abbreviated licensure pathway in section 351(k) of the PHS Act for biologics shown to be
272 biosimilar to or interchangeable with an FDA-licensed biological reference product.²⁵ FDA applies the
273 same surveillance principles for biosimilar products as for NMEs and for originator biological products
274 licensed in a “stand-alone” biologics license application (BLA) under section 351(a) of the PHS Act. On
275 a product-specific basis, reviewers consider the biosimilar product’s safety profile, product
276 characteristics, manufacturing process, and licensed conditions of use, as is the case for NMEs and
277 biological products licensed under section 351(a) of the PHS Act.

278 A newly identified, serious AE may be specific to the particular biosimilar product or it may be associated
279 with the class of biologics that has a common biological target or effect. Therefore, reviewers include a
280 review of data on the reference product as part of the evaluation of the AE to help determine whether the
281 AE is associated with the specific biosimilar product, as opposed to the class of products. Report-level
282 analysis is carried out to identify unusual or unique clinical presentations of labeled AEs. A high index of
283 suspicion is maintained for clinical events reported for the biosimilar product that are not consistent with
284 the safety profile of the reference product. Data mining of FAERS reports for the biosimilar product and
285 the reference product is another approach to identify potential signals and AEs reported
286 disproportionately for the biosimilar product.

287 AEs pertaining to biosimilar products may be reported to FDA by proprietary name or nonproprietary
288 name. The reporter may inadvertently use the reference product’s proprietary name or nonproprietary
289 name to identify the biosimilar product. Reviewers keep these potential reporting limitations in mind to
290 avoid misattributing the reported AE(s). Reviewers are encouraged to review the narrative report, as it
291 may contain more information about the identity of the reported product.

292 **5.2. Generic Drugs**

293 FDA follows a rigorous review process to make sure that, compared to the reference listed drug (i.e.,
294 brand name or innovator), a generic drug, with limited permissible exceptions, has the same active
295 ingredient(s), strength, dosage form (e.g., a tablet, capsule, or liquid), route of administration (e.g., oral,
296 topical, or injectable), labeling, and conditions of use.²⁶ Generic drug surveillance follows a
297 multidisciplinary process built upon continuous collaboration in monitoring and analyzing all available
298 postmarketing AE safety data.

²⁵Additional information is available at

<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm215089.htm>.

²⁶ 21 CFR 314.92(a)(1).

299 Although innovator and generic drugs have the same active ingredients, there may be permissible
300 differences in formulations, excipients, release technologies, or device components between innovator
301 and generic drugs that pose unique challenges for pharmacovigilance activities. As such, safety
302 surveillance for generics includes processes for detecting AEs possibly related to excipients and other
303 product quality differences between innovator and generic drugs, as well as other unexpected or rare
304 events that become apparent with increasing exposure to an active ingredient (of innovator and generic
305 products) in a larger and potentially more diverse patient population.

306 Due to familiarity with drug brand names, when members of the public report an AE associated with use
307 of a generic drug, they often submit a report to FDA that lists the brand-name drug, or they report the
308 event directly to the innovator manufacturer. In addition, when there are multiple generics on the market,
309 the reporter may not know which specific generic drug is involved and thus list the innovator product.
310 Based on the reported information, reviewers may have great difficulty determining whether the drug
311 used was the innovator drug or a generic. These shortcomings in ICSR quality can lead to misattribution
312 of generic-associated AEs to brand-name drugs, which can limit the reviewer's ability to accurately trace
313 the reported AEs to the associated drug.²⁷

314 One concern for all products is therapeutic failure. In addition, reports that a generic product is not
315 therapeutically equivalent to its reference product are of concern for generic drugs. A potential absence
316 of therapeutic equivalence may present as a perceived increase or decrease in the therapeutic effect when
317 a patient is switched from an innovator to a generic drug, or from one generic drug to another. Reviewers
318 screen for persistent or increasing reports that suggest that a single generic product may not be
319 therapeutically equivalent to its reference listed drug, excessive numbers of reports in proportion to the
320 distribution of a particular generic, or evidence that a generic does not have a significant clinical impact,
321 including medication use errors.

322 Other concerns relate to the complexity of the generic drug or risks associated with differences in the user
323 interface of a generic drug compared to the innovator. Reviewers may focus their surveillance of generic
324 products on solid oral products with modified-release mechanisms, drug-device combination products
325 (e.g., injectables, depot formulations, and transdermal formulations), products with a narrow therapeutic
326 index, and products with active ingredients that have highly correlated PK-PD relationships. Signals that
327 are suggestive of a potential quality issue with a generic product are evaluated in a collaborative process
328 with other FDA offices and in the context of other available data streams including, but not limited to,
329 product distribution data and Field Alert Reports.

330 Reviewers also evaluate serious AEs from expedited safety reports from bioavailability/bioequivalence
331 studies.^{28,29} These important expedited safety reports could reflect a problem with the generic drug
332 formulation, subject inclusion/exclusion criteria, or other aspects of the study design. Reviewers evaluate
333 these initial and follow-up expedited safety reports, request additional information from submitters when

²⁷ Bohn J, Kortepeter C, Muñoz M, et al. Patterns in spontaneous adverse event reporting among branded and generic antiepileptic drugs. *Clin Pharmacol Ther.* 2015;97:508–517.

²⁸ 21 CFR 320.31(d)(3).

²⁹ The guidance for industry and investigators *Safety Reporting Requirements for INDs and BA/BE Studies* is available at <https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/default.htm>.

334 needed, determine probable study-related risks to subjects, and formulate appropriate recommended
335 actions.

336 5.3. Over-the-Counter Drugs

337 In general, OTC drugs are marketed in the United States under either the monograph system, a new drug
338 application (NDA), or an abbreviated new drug application (ANDA). For those OTC drugs marketed
339 under an NDA or ANDA, there is a regulatory requirement for manufacturers to submit AE reports,
340 including periodic safety reports (PSRs)³⁰ to FDA. PSRs can provide a useful source of information for
341 estimating exposure data for an OTC drug and for identifying trends in AE reporting. Unapproved OTC
342 drugs, including those marketed under the monograph system do not have a corresponding requirement
343 for periodic reporting, although they are subject to certain reporting requirements for serious AEs.

344 Surveillance of OTC products containing active ingredients that are also included in prescription drug
345 products necessitates the involvement of other offices that have regulatory oversight for these products.
346 Once a safety signal is identified for any OTC product, a multidisciplinary process is followed to consider
347 changes to the OTC product labeling and other regulatory actions as appropriate.

348 5.4. Orphan Drugs and Drugs for Rare Diseases or Conditions

349 The Orphan Drug Act provides for granting orphan designation to a drug or biologic that is intended for
350 use in a rare disease or condition, which is defined as a disease or condition that affects fewer than
351 200,000 people in the United States or that affects more than 200,000 people in the United States, but
352 there is no reasonable expectation to recover the costs of developing and marketing a treatment drug.³¹
353 While approval for all drugs and biologics—for both rare and common conditions—must be based on
354 demonstration of substantial evidence of effectiveness and a favorable benefit risk balance, FDA
355 recognizes that certain aspects of product development that are feasible for common diseases may not be
356 feasible for rare diseases. Many rare disorders are serious conditions with no approved treatments,
357 leaving substantial unmet medical needs for patients.³² FDA regulations provide flexibility in applying
358 regulatory standards for drug approval because of the many types and intended uses of drugs.³³ This
359 flexibility extends from the early phases of development to the design of adequate and well-controlled
360 clinical studies that are required to demonstrate safety and effectiveness to support marketing approval.

361 The goal of safety evaluation during drug development is to characterize the drug’s safety profile in a
362 reasonable number of patients over a reasonable duration of time, consistent with the intended use of the
363 drug. “Reasonable” in the context of rare diseases requires consideration of feasibility challenges posed
364 by the limited number of patients with the disease. The amount of safety information at the time of

³⁰ Periodic Safety Reports include periodic adverse drug experience reports (21 CFR 314.80) and periodic adverse experience reports (21 CFR 600.80) and, under an approved waiver, International Council for Harmonisation reporting formats (periodic safety update report and periodic benefit risk evaluation report).

³¹ Section 526 of the FD&C Act provides for the designation of drugs for rare diseases or conditions. Available at <https://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/html/USCODE-2010-title21-chap9-subchapV-partB-sec360bb.htm>.

³² The draft guidance for industry *Rare Diseases: Common Issues in Drug Development* is available at <https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/default.htm>. When final, this guidance will represent the FDA’s current thinking on this topic.

³³ 21 CFR 314.105.

365 approval may be less for drugs developed for rare diseases when compared to those for common diseases,
366 given the limited study population. The postmarketing period frequently provides additional safety
367 information, as the number of patients exposed slowly increases over time, or through a specific
368 postmarketing requirement or commitment. Once a safety signal is identified, a multidisciplinary process
369 is followed to consider changes to the product labeling and other regulatory actions as appropriate.

370 5.5. Compounded Drugs

371 Compounding is generally a practice in which a licensed pharmacist, a licensed physician, or, in the case
372 of an outsourcing facility, a person under the supervision of a licensed pharmacist combines, mixes, or
373 alters ingredients of a drug to create a medication tailored to the needs of an individual patient.³⁴
374 Compounded drugs are not approved by FDA.

375 Under section 503A of the FD&C Act, compounded drugs that meet certain conditions are exempt from
376 FD&C Act sections on premarket approval, current good manufacturing practice (CGMP) requirements,
377 and labeling with adequate directions for use if the drug is compounded for an identified individual
378 patient based on a valid prescription. This practice is sometimes referred to as traditional compounding.
379 State boards of pharmacy have primary responsibility for the day-to-day oversight of State-licensed
380 pharmacies that compound drugs in accordance with the conditions of section 503A, although FDA does
381 conduct surveillance and for-cause inspections of state-licensed pharmacies. Section 503A does not
382 contain specific AE reporting requirements.

383 In 2013, Congress enacted new compounding legislation. This legislation, known as the Drug Quality
384 and Security Act³⁵ (DQSA), added a new section 503B to the FD&C Act, which established a new
385 category of compounders known as outsourcing facilities. Outsourcing facilities can compound and
386 distribute drugs without receiving prescriptions for individually identified patients, but they are subject to,
387 among other things, CGMP requirements, inspection by FDA according to a risk-based schedule, and
388 reporting requirements for AEs associated with their products. Under section 503B(b)(5) of the FD&C
389 Act, outsourcing facilities are required to submit reports of adverse drug experiences associated with the
390 use of their compounded drug products. FDA receives AE reports associated with compounded products
391 that are required to be submitted by outsourcing facilities, in addition to reports submitted voluntarily.
392 FDA screens FAERS reports associated with compounded products to identify potential emerging safety
393 and quality concerns. FDA staff collaborate across offices in the review of and follow up on the received
394 reports.

395 5.6. Homeopathic Drug Products

396 Homeopathy is an alternative medical practice generally based on two main principles: (1) that a
397 substance that causes symptoms in a healthy person can be used in diluted form to treat symptoms and
398 illnesses (known as “like-cures-like”); and (2) the more diluted the substance, the more potent it is
399 (known as the “law of infinitesimals”).³⁶ There is a broad misconception that all homeopathic products

³⁴ <https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/default.htm>.

³⁵ <https://www.congress.gov/bill/113th-congress/house-bill/3204>.

³⁶ The revised draft guidance for FDA staff and industry Drug Products Labeled as Homeopathic (October 2019) is available at <https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/default.htm>. When final, this guidance will represent the FDA’s current thinking on this topic.

400 are highly diluted and generally composed of “natural” ingredients, and that they are therefore incapable
401 of causing harm. However, as with all drugs, the safety of homeopathic drugs depends upon many factors,
402 such as the product’s intended use, dosage form, frequency of use, manufacturing quality, intended
403 patient population, and the quantity and combination of ingredients.

404 The definition of drug contained in the FD&C Act includes articles recognized in the official United
405 States Pharmacopeia, the official Homeopathic Pharmacopeia of the United States,³⁷ the official National
406 Formulary, or any supplement to them. There are currently no homeopathic drug products approved by
407 FDA. Unlike FDA-approved drugs, which have a known active ingredient that is readily identifiable, the
408 active ingredients in a homeopathic product often exist as extracts from botanical sources, including those
409 that pose potentially toxic effects such as belladonna and nux vomica. In addition, although the label of
410 many homeopathic products indicates the strength of the active ingredient(s), expressed as a dilution,
411 some do not.

412 Spontaneous reporting is the primary tool for the surveillance of homeopathic drugs. It is sometimes
413 difficult for reporters to know that the subject of their report is a homeopathic drug. In addition, even
414 when the ingredients of homeopathic products are labeled, details regarding product ingredients are often
415 lacking in spontaneous reports, which limits the reviewer’s ability to properly identify the product. For
416 these reasons, it may be difficult for FDA to identify cases attributable to the homeopathic product. Any
417 safety finding is particularly important and could warrant significant and prompt regulatory action against
418 the manufacturer. In a revised draft guidance,³⁶ FDA describes how the Agency intends to prioritize
419 enforcement and regulatory actions for homeopathic drug products, using a risk-based approach.

420 5.7. Combination Products

421 As set forth in 21 CFR Part 3, a combination product is a product composed of two or more different
422 types of medical products (i.e., a combination of a drug, device, and/or biologic with one another).³⁸ The
423 drugs, devices, and biologics included in combination products are referred to as *constituent parts* of the
424 combination product. There are three potential modes of action for a combination product: drug, device,
425 and biologic. Combination products typically have more than one identifiable mode of action. Reviewers
426 consider each constituent part and the product as a whole when evaluating AE reports for combination
427 products. A multidisciplinary process is followed to address identified safety issues.

428 5.8. Medication Errors

429 The surveillance of medication errors is challenging because of the lack of (1) regulations for applicants
430 to report medication errors,³⁹ (2) a universally accepted definition for medication error,⁴⁰ and (3) detailed
431 information in the ICSR to determine the cause of the error (or that an error occurred). FDA considers a
432 medication error as any preventable event that may cause or lead to inappropriate medication use or
433 patient harm while the medication is in the control of a health care provider, patient, or consumer. This is

³⁷ <http://www.hpus.com/>.

³⁸ The guidance for industry and FDA staff *Current Good Manufacturing Practice Requirements for Combination Products* is available at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

³⁹ Medication errors may be reported in association with an AE.

⁴⁰ Wilmer A, Louie K, Dodek P, Wong H, Ayas N. Incidence of medication errors and adverse drug events in the ICU: a systematic review. *Qual Saf Health Care*. 2010;19:1.

434 based on the definition stated by the National Coordinating Council for Medication Error Reporting and
435 Prevention.⁴¹ The off-label use, misuse, abuse, and other deliberate or intentional uses of a drug product
436 in a manner that is inconsistent with the FDA-required labeling is not generally considered a medication
437 error.

438 FDA has multidisciplinary staff dedicated to minimizing medication errors related to the naming,
439 labeling, packaging, and design for drugs and biologics. The Agency follows a rigorous preapproval
440 review process for drugs and biologics that includes specific review activities to prevent medication
441 errors. FDA reviews and accepts proposed proprietary names to minimize medication errors associated
442 with product name confusion.^{42,43} The Agency also reviews and provides feedback on proposed container
443 labels, carton labeling, packaging, product design, prescribing information, Instructions For Use, and
444 human factor studies to minimize or eliminate hazards contributing to medication errors. Review
445 activities conducted in the preapproval period inform the approach for medication error monitoring once
446 the product is approved for marketing. Similarly, the information learned from monitoring and analyzing
447 medication errors reported postapproval is used to improve the preapproval review processes.

448 Throughout the postapproval period, FDA conducts systematic monitoring of medication errors. There
449 are several reasons for this approach. First, the complete medication error safety profile of a product may
450 be uncertain when the product is approved. Clinical studies performed in the preapproval phases involve
451 a limited number of patients and health care providers. The studies may not use the labeling and
452 packaging approved for marketing. Also, the studies may not involve the entire medication-use system,
453 such as electronic prescribing, storage conditions, or barcode-assisted administration systems typically
454 used in a real-world setting. Second, medication errors are associated with a significant public health
455 burden.⁴⁴ Early detection through monitoring allows FDA to address a medication error before the
456 product is more widely distributed. Third, prescribing practices and the marketplace are continually
457 changing, due to advancements in technology, new therapeutic uses, approval of novel drugs and
458 biologics, and the market entry of generic drugs and biosimilar products. Fourth, some products, such as
459 OTC monograph products, may not undergo the product-specific preapproval review process, that
460 prescription drugs and biologics are subject to prior to marketing.

461 FDA uses several sources of information for monitoring medication errors, including: FAERS and
462 VAERS; partners and patient safety organizations; and PSR submissions. Reviewers routinely review
463 ICSRs, carefully considering those that describe the potential for a medication error. All reports of
464 medication error are examined, regardless of whether they result in an adverse event or whether the

⁴¹ National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) definition and taxonomy for medication errors. Available at <https://www.nccmerp.org/about-medication-errors>.

⁴² The guidance for industry *Contents of a Complete Submission for the Evaluation of Proprietary Names* is available at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁴³ The draft guidance for industry *Best Practices in Developing Proprietary Names for Drugs* is available at <https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/default.htm>. When final, this guidance will represent the FDA's current thinking on this topic.

⁴⁴ In 2011, the Network for Excellence in Health Innovation reported that outpatient and inpatient preventable medication errors cost approximately \$20 billion each year.

465 outcome is serious or nonserious. This approach is used to detect emerging safety issues in naming,
466 labeling, packaging, and design.

467 FDA has established collaborative agreements with Federal and non-Federal partners and patient safety
468 organizations to share medication error information. Under these collaborative agreements, FDA is
469 alerted to possible emerging medication error issues. Medication errors are notably underreported, and
470 collaborative agreements have proved to be an effective way to help monitor and address medication
471 errors.

472 PSRs⁴⁵ submitted by applicants, particularly those in the Periodic Benefit-Risk Evaluation Report
473 (PBRER)⁴⁶ format, are valuable in the overall monitoring of medication errors. The PBRER includes a
474 cumulative tabulation of medication errors and a specific section that summarizes information on patterns
475 of medication errors and potential medication errors, even when not associated with AEs. The
476 availability of the PBRER for review by reviewers can be quite informative to medication error
477 monitoring.

478 5.9. Specific Patient Populations

479 5.9.1. *Pregnant population*

480 During clinical development of most products, pregnant women have historically been excluded from
481 clinical trials. Thus, prior to marketing there is limited information about a product's safety profile when
482 used during pregnancy. FDA conducts drug safety surveillance on the use of products in the pregnant
483 population much as it does for the use of products in the general population but has a specific focus on
484 detecting product-induced fetal effects. The identification of a product's potential for adverse
485 developmental outcomes, including teratogenicity,⁴⁷ is particularly important because product-induced
486 adverse developmental outcomes are potentially preventable.

487 To optimize the detection and characterization of any adverse effects related to prenatal product exposure,
488 FDA staff work collaboratively across the Agency and use all available postmarketing surveillance data
489 sources. Data may be collected from a prospective pregnancy registry study as a postmarketing
490 requirement or commitment. Data may also become available through AE reports submitted by patients
491 or providers or through other pharmacovigilance strategies, including epidemiologic studies. Reviewers
492 consider the strengths and limitations of each data source throughout the review to inform the assessment
493 of adverse drug effects to the pregnant woman and the fetus.

494 A pregnancy exposure registry is a prospective observational study that actively collects information on
495 medical product exposure during pregnancy and associated pregnancy outcomes. One advantage of
496 registries is that they avoid bias that is inherent in studies relying on retrospective reporting. The

⁴⁵ See section 6.1.4, *Other information sources*.

⁴⁶ The guidance for industry *E2C(R2) Periodic Benefit Risk Evaluation Report (PBRER)* is available at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁴⁷ In FDA reviewer guidance *Evaluating the Risks of Drug Exposure in Human Pregnancies*, the term *teratogen* is used to designate products with teratogenic potential at clinical doses used in humans; it is available at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

497 prospective collection of data from exposed women who enroll in the registry prior to the occurrence of
498 an adverse outcome allows investigators to estimate the risks of a variety of adverse outcomes.⁴⁸ When
499 well-conducted and sufficiently powered, findings from a registry-based study may inform whether a drug
500 is a teratogen. However, because registries may enroll limited numbers of pregnant women, it may not be
501 possible to detect a small increased risk of a birth defect that is frequently seen in the background
502 populations. Moreover, while pregnancy registries are still the most common method used to collect
503 pregnancy-related information in the postmarketing setting, registries are also subject to selection bias,
504 confounding, and low enrollment, any of which can complicate the interpretation of the registry results.

505 Additional potential data sources for evaluating a specific drug safety signal associated with the use of a
506 drug during pregnancy include observational studies, such as case-control studies, population-based
507 surveillance and national registries, as well as electronic claims and health record databases. Such
508 sources are often retrospective and usually designed to examine a specific hypothesis. These studies are
509 typically larger than registry studies, particularly those that use electronic health care databases or
510 national register data. Such studies often take advantage of linkages between multiple types of
511 information sources including demographic, clinical, pharmacy, and vital statistics data. However,
512 retrospective studies have limitations. They may rely on unvalidated diagnostic or procedure codes to
513 identify study outcomes, or they may rely on electronic pharmacy data that cannot confirm whether the
514 pregnant women who were dispensed the product actually took the product. Other potential limitations
515 include errors in estimating gestational age and confounding due to the condition for which the pregnant
516 woman received the treatment. Finally, many sources for retrospective studies limit study populations to
517 only live birth populations. If the safety issue relates to an outcome incompatible with live birth (e.g.,
518 stillbirth, severe malformation not commonly resulting in live birth), results from these studies may lack
519 generalizability at the very least, or potentially suffer from selection bias.

520 ICSRs provide yet another source of information that may be used to evaluate specific drug safety
521 concerns in pregnancy. Although in rare circumstances a single ICSR can provide sufficient information
522 necessary for making a reasonable inference about causality in the assessment of teratogenicity, a series
523 of similar reports of a distinct abnormality or group of similar abnormalities can establish a strong
524 association or signal the need for follow-up evaluations to assess the potential risk. Several well-
525 established teratogens were first identified by a case report or case series.^{49,50,51} There are several factors
526 to consider when evaluating ICSRs reporting potential congenital anomalies. These include (1) the
527 physical and chemical nature of the product; (2) the dose, duration, frequency, and route of exposure; (3)
528 gestational timing; (4) concurrent products and comorbidities; (5) background prevalence of adverse
529 pregnancy outcomes; (6) combined versus individual rates of birth defects; and (7) major versus minor
530 birth defects. It is well known that data collected retrospectively may be subject to bias. When analyzing
531 data on adverse outcomes following in utero exposure, it is important that reviewers evaluate prospective

⁴⁸ The guidance for industry *Establishing Pregnancy Exposure Registries* is available at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁴⁹ Mitchell AA. Adverse drug reactions in utero: perspectives on teratogens and strategies for the future. *Clin Pharmacol Ther.* 2011;89(6):781-783.

⁵⁰ Shepard TH. Agents that cause birth defects. *Yonsei Med J.* 1995;36(5):393-396.

⁵¹ Goldberg JD, Golbus MS. The value of case reports in human teratology. *Am J Obstet Gynecol.* 1986;154(3):479-482.

532 reports, those in which information on the patient was collected after exposure but prior to knowledge of
533 the pregnancy outcome, separately from retrospective reports, those in which the pregnancy outcome was
534 known at the time of reporting.

535 5.9.2. *Pediatric Populations*

536 Safety information from adult human studies and animal models may provide preliminary information
537 regarding the expected safety profile of a drug in pediatric populations, but safety information from
538 administration of the drug to children is generally needed to evaluate fully the safety profile of a drug in
539 children. It is well-recognized that there are age-specific changes in drug absorption, distribution,
540 metabolism, and excretion that can affect both the dosing and safety of a drug in children. In addition,
541 long-term follow-up studies, particularly for drugs used in infants or young children, may be needed to
542 assess fully the long-term safety of a drug when used in children.

543 Congress passed legislation that has improved the availability of drugs and biological products approved
544 for use in children. The Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research
545 Equity Act (PREA)⁵² provide both incentives and requirements (respectively) for the collection of
546 pediatric-specific safety and efficacy information. Under BPCA, FDA may issue a Written Request for
547 pediatric studies for a drug that may provide health benefits in children. A Written Request may be
548 issued for both approved and unapproved indications. Sponsors may decline to conduct the requested
549 studies. Under PREA, a pediatric study can be required under certain circumstances. Product labeling is
550 updated to reflect studies conducted under PREA (section 505B(g)) and BPCA (section 505A(i) and (j)).

551 Eighteen months after the date of a pediatric labeling change for the product, a cumulative safety
552 summary analysis⁵³ of pediatric AE reports is conducted by a multidisciplinary team and referred to the
553 Pediatric Advisory Committee (PAC) for external expert input. Members of the PAC review the analysis
554 and can recommend additional actions for FDA consideration.

555 Importantly, BPCA and PREA do not apply to all products or applications for products used in the
556 pediatric population, and the pediatric use of drugs that have not been studied in pediatric populations
557 continues to occur. Reviewers conducting pharmacovigilance for products not studied in the pediatric
558 population include an evaluation of use and considerations for unintentional overdose manifesting in
559 exaggerated physiological effects.

560 When analyzing ICSRs for the pediatric population, it is often necessary to analyze reports in specific age
561 groups. Chronic conditions may require long-term treatment and latent adverse drug effects may be
562 different based on the age and stage of growth and development of the patient when the drug was
563 initiated. Therefore, reviewers monitor reports for all latent adverse drug effects, including those

⁵² BPCA, which amended the FD&C Act to add section 505A (21 U.S.C. 355a), was originally enacted in 2002 (Public Law 107-109, 115 Stat. 1408 (Jan 4, 2002)). PREA, which amended the FD&C Act to add section 505B (21 U.S.C. 355c), was originally enacted in 2003 (Public Law 108-155, 117 Stat. 1936 (Dec 3, 2003)). Both were permanently reauthorized in 2012 as part of the Food and Drug Administration Safety and Innovation Act (FDASIA).

⁵³ The analyses are prepared for the Pediatric Advisory Committee (PAC) according to internal standard procedures for pharmacovigilance review.

564 describing endocrine dysfunction and reproduction effects, neurodevelopmental outcomes, delayed
565 growth, and delayed or accelerated puberty.

566 Reviewers are vigilant in screening for AE reports that describe accidental exposures of various etiologies
567 (e.g., defeated or defective child-resistant packaging or improperly discarded products). They also screen
568 for reports of overdose related to unique aspects of drug delivery and potential errors in preparing specific
569 formulations (e.g., dilution error) for this population.

570 5.9.3. Geriatric Population

571 ICSRs that describe AEs in the geriatric patient population warrant special consideration by reviewers,
572 because at the time of a product's approval, there is typically limited data on its effects in the geriatric
573 population, and thus postmarketing experience is important.

574 Aging is associated with well-described changes in organ function (e.g., renal function) that affect the
575 pharmacokinetics and therefore the safety profile of pharmaceuticals. In addition, the geriatric population
576 experiences not only an increased frequency of chronic disease, but also an increased concurrent
577 utilization of multiple medications (*polypharmacy*). This contributes to the potential for serious AEs,
578 which are reported to occur in 5 to 10 percent of the general elderly population. When hospitalized due to
579 a drug AE, this population experiences in-hospital mortality rates as high as 10 percent.^{54,55,56}

580 Impaired renal function can contribute to drug toxicity, due to accumulation of parent drugs and of certain
581 metabolites that preserve variable levels of activity despite biotransformation. With aging, the prevalence
582 of chronic kidney disease increases because of both age-related natural loss of renal function and incident
583 disease. In this context, serum creatinine may underestimate renal function primarily because of age-
584 related loss of muscle mass, which is the site of origin of creatinine.

585 Estimation of glomerular filtration rate (GFR) using standardized formulas is a better way to define renal
586 function, although most of the current formulas were originally validated in younger populations and can
587 be relatively unprecise in the elderly.^{57,58} This can lead some clinicians to assume “normal” renal
588 function in older patients, when in fact the actual GFR reflects a substantial decline from normal adult
589 levels. The most accurate method of measuring GFR is the 24-hour creatinine clearance, but the
590 difficulty of collecting an accurate 24-hour urine sample is a major limitation in older persons. In

⁵⁴ Kongkaew C, Noyce PR, Ashcroft DM. Hospital admissions associated with adverse drug reactions: a systematic review of prospective observational studies. *Ann Pharmacother.* 2008;42(7):1017-1025.

⁵⁵ Bouvy JC, De Bruin ML, Koopmanschap MA. Epidemiology of adverse drug reactions in Europe: a review of recent observational studies. *Drug Saf.* 2015;38(5):437-453.

⁵⁶ van der Hooft CS, Dieleman JP, Siemes C, et al. Adverse drug reaction-related hospitalisations: a population-based cohort study. *Pharmacoepidemiol Drug Saf.* 2008;17(4):365-371.

⁵⁷ Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150(9):604-612.

⁵⁸The draft guidance for industry *Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling* is available at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>. When final, this guidance will represent the FDA's current thinking on this topic.

591 reviewing AE reports for products that are eliminated renally, it is prudent to consider the potential for
592 unrecognized renal dysfunction in the setting of an exaggerated pharmacodynamic effect.

593 Polypharmacy and the potential for drug-drug interactions represent another important concern for the
594 geriatric population. It has been reported that 40 percent of patients over age 65 take 5 or more drugs on a
595 chronic basis.⁵⁹ The likelihood for hospital admission due to an AE is much higher for older individuals.
596 In addition, some drug-drug interactions result in predictable changes in PD effects, PK effects, or
597 unforeseen effects due to the appearance of a novel active metabolite. It follows that good
598 pharmacovigilance for the geriatric population includes considerations for previously unrecognized drug-
599 drug interactions leading to both predictable and novel AEs.

600 5.10. Misuse, Abuse, Addiction, and Overdose

601 Many products are subject to misuse, abuse, addiction, and overdose, including fatal overdose. For
602 purposes of this document, the term *abuse* is defined as the intentional, non-therapeutic use of a drug
603 product or substance, even once, to achieve a desirable psychological or physiological effect.⁶⁰ Abuse is
604 not the same as *misuse*, which refers to the intentional therapeutic use of a drug product in an
605 inappropriate way and specifically excludes the definition of abuse.⁶¹ FDA reviewers consider *overdose*
606 to be the administration of a quantity of product above the maximum recommended dose.

607 In evaluating reports of misuse and overdose, reviewers stratify them by intentionality wherever possible.
608 Reviewers examine specific product information to better understand the role of specific product
609 characteristics as risk factors for misuse and abuse, as appropriate. Products found to be associated with
610 misuse or overdose are evaluated for the need for changes to the labeling (indications, instructions for
611 administration, packaging).

612 Information used to evaluate drug product abuse can come from a variety of sources, including FAERS
613 reports, national surveys, calls to poison control centers, surveys of individuals entering treatment or
614 under assessment for substance use disorders, and national mortality data. Reviewers utilize all of these
615 data sources, because each has its own unique strengths and limitations. In evaluating AE reports,
616 reviewers may not have information describing how the person experiencing an event obtained the
617 product. The most obvious way to obtain a product, whether for legitimate use or intended abuse, is for a
618 person to be dispensed a prescription. However, AEs from abuse commonly occur in individuals who
619 may *not* have been prescribed the product.

620 The evaluation of AEs that result from product misuse and abuse is challenging because (1) AEs related
621 to misuse and abuse may occur outside the health care system and may not be reported to FDA; (2) there
622 is substantial geographic variation in levels, trends, and routes of abuse for any given product; (3) key
623 information (e.g., product, frequency, and route of abuse) can only be gathered from the individual
624 abusing the drug and generally cannot be verified; and (4) many health professionals do not accurately

⁵⁹ Kantor ED, Rehm CD, Haas JS, et al. Trends in Prescription Drug Use Among Adults in the United States From 1999-2012. *JAMA*. 2015;314(17):1818–1830.

⁶⁰ The guidance for industry *Assessment of Abuse Potential of Drugs* is available at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁶¹ Ibid.

625 record or are unaware of misuse and/or abuse-related behavior. Despite these challenges, reviewers
626 assess trends and potential harm from misuse and abuse during the screening process.

627 It is well known that prescription opioid analgesic drugs are associated with overdose, addiction, and
628 death that can result from problems of inappropriate prescribing, misuse, and abuse. The recent HHS
629 report, *Addressing Prescription Drug Abuse in the United States: Current Activities and Future*
630 *Opportunities*,⁶² discusses both the public health crisis and actions that can be taken to help address this
631 serious epidemic. It is important to note that products other than opioids, including some not requiring a
632 prescription, are also subject to the same problems highlighted in the HHS report. Although problems
633 related to non-opioid products don't receive the same attention from academia or the media, reviewers
634 need to keep them in mind when conducting drug safety surveillance.

635 5.11. Product Quality Issues

636 For purposes of this document, FDA considers product quality issues (PQIs) to be deviations from the
637 established A/NDA or BLA specifications for the drug product such as identity, strength, purity, and
638 other characteristics designed to ensure the required levels of product quality, safety, and effectiveness.
639

640 Reviewers monitor for PQIs, which may be reported to FDA when there is a concern about the product's
641 quality, authenticity, performance, or safety. PQIs may be reported as physical product issues (e.g.,
642 friable tablet, discoloration) or manifestations of PQIs (e.g., product ineffective, disease progression).
643 Reports describing PQIs are reviewed by FDA product quality experts. Considerations for the assessment
644 of PQIs in FAERS include the assessments of trends over time by manufacturer, lot number, or national
645 drug code (NDC).

646
647 Signals identified from FAERS suggestive of a PQI are evaluated by multiple FDA offices and in the
648 context of other available data streams (e.g., Field Alert Reports; Biological Product Deviation Reports;
649 manufacturing facility inspection data; product distribution; bioequivalence data; and recent chemistry,
650 manufacturing, or control changes). These signals may lead to further investigation including inspections
651 and product evaluations (e.g., chemical and microbial sample analysis).

652 6. Safety Signal Identification

653 For the purposes of this document, the term *signal identification* is broad in scope. It includes the
654 activities of screening FAERS, VAERS, and the medical literature, as well as accessing other information
655 sources, to identify potential safety signals. Identified signals are prioritized for more extensive
656 evaluation.

657 6.1. Data Sources

658 Multiple strategies and tools are used to identify safety signals in both the FAERS and VAERS databases.
659 Reviewers routinely screen ICSRs at the report level and also screen ICSRs in a cumulative manner. In
660 addition, systematic, automated techniques are used routinely, which lend efficiency to screening the
661 database. These approaches complement each other and are described in the sections that follow. The

⁶² https://www.cdc.gov/drugoverdose/pdf/hhs_prescription_drug_abuse_report_09.2013.pdf.

662 use of multiple strategies in concert allows FDA to manage the increasing number of ICSRs in both the
663 FAERS and VAERS databases, to efficiently identify potential safety signals, and to facilitate the
664 prioritization of potential safety issues.

665 The typical frequency for screening each of the data sources discussed in the following subsections is
666 presented as a summary table in section 6.2.

667 6.1.1. *FAERS and VAERS*

668 **Individual ICSR screening**

669 Screening of individual ICSRs in the AE database begins with selecting the product or the AE based upon
670 considerations for risk that are discussed in section 4, *Risk-based approach to drug safety surveillance*.
671 By using risk-based principles, reviewers use screening tools first to identify potential signals; a more
672 rigorous review is conducted later in the course of report analysis.

673 The quality of information provided in the ICSRs is highly variable.⁶³ It is critical that an ICSR be of
674 high quality for optimal evaluation of the relationship between the product and AE. The most useful
675 ICSRs contain detailed descriptive information in the narrative section to describe the AE as it occurred in
676 the patient. Using the information in the narrative and other sections of the ICSR, reviewers attempt to
677 establish a temporal relationship between administration of the product and occurrence of the AE to
678 determine if there is sufficient support for further evaluation of the potential safety signal. For further
679 details on assessment of ICSRs for causal association, see section 7.1.3.

680 If an ICSR does not include sufficient information to assess the suspected causal relationship between the
681 product and event, the reviewers may follow up with the applicant or the reporter to obtain additional
682 information necessary for case assessment. Reviewers also seek to learn more information about the
683 event and how it resolved. They attempt to get more information about the circumstances surrounding the
684 AE and other possible contributory or confounding factors (e.g., other concurrent products and pertinent
685 medical history). They may also attempt to obtain autopsy reports and results of any laboratory or
686 diagnostic tests, which are added to the database.

687 **Cumulative screening**

688 Reviewers perform cumulative screening of the AE database to provide an aggregate, high-level summary
689 of the reported postmarketing safety experience (e.g., by clinically relevant AE terms, serious outcomes,
690 year of occurrence, or any demographic variable of interest) for the product under evaluation. Screening
691 of cumulative AE reports from multiple sources (e.g., health care providers, consumers, the medical
692 literature) and of both serious and nonserious outcomes is one approach to better understanding the
693 postmarketing safety profile of products.

694 The strategy for cumulative ICSR screening of a product under evaluation can include analyses of the AE
695 terms most frequently reported in (1) all reports, (2) reports with a serious outcome, (3) reports with AEs
696 of interest, and (4) reports for a specific population (e.g., pregnancy or pediatric exposure and outcome).
697 This screening strategy also includes a review of PSRs for new safety signals or concerns. The goal of

⁶³ Information on FAERS data limitations is available at
<https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugs/effects/>.

698 this risk-based surveillance process is to generate an overview of serious unlabeled AEs, known AEs
699 reported in an unusual number, or other new potential safety concerns with the product. In the course of
700 cumulative screening, the reviewer may identify one or more AE(s) that may cause the reviewer to read in
701 detail all ICSRs for the AE(s).

702 Periodic, cumulative screening of ICSRs complements ongoing screening at the individual report level.

703 6.1.2. *Data Mining*

704 Data mining in the context of drug safety surveillance refers to the use of statistical or mathematical tools
705 to discover patterns of associations or unexpected occurrences in large databases, such as FAERS and
706 VAERS. It involves the systematic examination of reported AEs to provide information about the
707 existence of an excess of AEs reported for a product relative to other products in the database
708 (disproportionality). Results from data mining are considered hypothesis generating and do not, by
709 themselves, demonstrate causal associations.

710 By applying data mining techniques, FDA may be able to identify unusual or unexpected product-event
711 combinations that warrant further investigation. FDA reviewers use data mining to assess patterns, as
712 well as identify particular AEs associated with drug-drug interactions.⁶⁴ Reviewers consider both
713 sensitivity and precision in the chosen approach. Unexpectedly high reporting associations (e.g., the
714 doubling of a particular product-event combination over a specified time interval) may generate a
715 hypothesis that there may be an association between the particular AE and the product. However, the
716 absence of disproportionality does not confirm the absence of a safety signal or negate a signal detected
717 by other methods.

718 It is necessary to adjust signal thresholds to account for the severity of the AE, severity of the condition
719 for which the product is being used, and a product's established safety profile. For example, a lower
720 signaling threshold may be considered for serious AEs (e.g., progressive multifocal leukoencephalopathy)
721 or for products for which less may be known about the safety profile. The products and AEs that may be
722 appropriate for a lower signaling threshold are discussed in section 4, *Risk-based approach to drug safety*
723 *surveillance*. Additionally, the database can be filtered by various characteristics (e.g., pediatric reports
724 or serious outcomes) to identify potential signals.

725 6.1.3. *Medical Literature*

726 FDA reviewers routinely screen the medical literature in an effort to identify emerging safety signals that
727 are not submitted as ICSRs to FDA. Screening is accomplished by searching the medical literature by
728 product or by AE. The principles underlying how reviewers select products and AEs for screening are
729 discussed in section 4, *Risk-based approach to drug safety surveillance*.

730 Reviewers supplement their screening of published AE case reports with additional data sources, such as
731 studies completed by academic institutions or other researchers outside of FDA, studies performed by

⁶⁴ The guidance for industry *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* discusses and provides recommendations on the use of data mining and is available at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

732 other Government agencies and referred to FDA for comment, and other studies that FDA becomes aware
733 of. These may be presented in peer-reviewed or online journals or as abstracts at conferences. The
734 information is made available in a variety of forms, including case reports of clinical AEs and health care
735 professionals' interpretations of postmarketing safety data. Reviewers also have access to findings from
736 patient registry studies, observational and pharmacoepidemiologic studies, meta-analyses, and
737 randomized controlled clinical trials.

738 6.1.4. *Other Information Sources*

739 In addition to systematically screening and data mining the FAERS and VAERS databases and
740 monitoring the medical literature, reviewers make use of other sources of information that can give rise to
741 signals. Safety signals can arise during studies conducted as part of product development, such as animal
742 studies, in vitro studies, or an imbalance in safety findings in clinical trials that was not considered an
743 adverse drug reaction at the time of approval. During the preapproval review process, potential signals
744 that are identified by the clinical reviewer, especially those arising in Phase II and Phase III clinical trials,
745 lead to multidisciplinary discussions to determine what, if any, postmarketing activities are needed.

746 Application holders submit required PSRs to FDA on a recurring basis for review.⁶⁵ PSRs provide
747 summary information directly from the applicant, which may include clinical and nonclinical study
748 reports and the applicant's assessment of the marketed product's benefit-risk profile. PSRs may
749 supplement the spontaneous reports available to reviewers for identifying potential safety signals and
750 learning about potential changes in the benefit-risk profile for marketed products. In addition to the PSRs
751 specified in FDA regulation, FDA accepts PSRs prepared in accordance with ICH E2C guidelines.⁶⁶ The
752 PSRs submitted using an ICH format provide additional data and information to that required by FDA
753 regulation, which can materially inform the safety review process. In reviewing PSRs, reviewers pay
754 particular attention to products with recently approved new indications or worldwide safety data with
755 concerning findings that might indicate an emerging safety signal.

756 REMS assessments can contain useful information regarding important identified risk(s). FDA can
757 require a REMS when FDA determines that a risk evaluation and mitigation strategy beyond approved
758 professional labeling is necessary to ensure that the benefits of the drug outweigh its risks. REMS
759 generally must include a timetable for submission of assessments of the REMS.⁶⁷ The timetable must
760 include an assessment by the dates that are 18 months and 3 years after the REMS is initially approved

⁶⁵ FDA's postmarketing safety reporting regulations require applicants to submit PSRs in the form of a periodic adverse drug experience report (PADER) (for drugs) or a periodic adverse experience report (PAER) (for biologics) (21 CFR 314.80(c)(2) and 600.80(c)(2)).

⁶⁶ With an approved waiver (under 21 CFR 314.90(b) and 600.90(b)), the Periodic Safety Update Report (PSUR) and the PBREER are accepted PSR formats.

⁶⁷ New Drug Applications (NDAs) and Biologics License Applications (BLAs) must include a timetable for submission of assessments. Abbreviated new Drug Applications (ANDAs) are not subject to the requirement for a timetable for submission of assessments (Section 505-1(i)), but FDA can require any application holder, including ANDA applicants, to submit REMS assessments under Section 505-1(g)(2)(C). The draft guidance for industry *Format and Content of a REMS Document* is available at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>. When final, this guidance will represent the FDA's current thinking on this topic.

761 and an assessment in the 7th year after the REMS is approved or at another frequency specified in the
762 REMS. REMS are discussed in greater detail in a subsection of section 9, *Actions*.

763 A risk management plan (RMP) is a document prepared by the applicant that describes the product's
764 safety profile (e.g., important identified risks, important potential risks, and important missing
765 information), planned pharmacovigilance and studies for these safety concerns, and how known risks
766 associated with the product will be managed. U.S. regulations do not require submission of RMPs as a
767 condition of approval; however, some other regulatory authorities do. Applicants may submit an RMP
768 prepared for another authority to FDA, in which case it may serve as an additional source of safety
769 information.

770 A variety of additional information sources for signals are generally received on an ad hoc basis. They
771 include applicant submissions of supplements to make a postapproval safety-related labeling change(s).
772 Signals may also be identified following receipt of a citizen petition⁶⁸ requesting that FDA take action
773 based on factual or legal grounds. FDA has ongoing communications with international regulators, which
774 may lead to identification of signals. In addition, FDA may become aware of drug safety issues through
775 media inquiries or reports.

776 6.2. Frequency and Extent of Screening

777 The extent and frequency for screening the FDA AE databases and the medical literature varies with the
778 product type. Products are grouped into three categories⁶⁹ for ease of reference; a summary for screening
779 the FDA AE databases by product category appears below in the Table and is described in some detail in
780 the paragraphs that follow.

781 Category A

782 Generally, on a weekly basis, reviewers screen newly received ICSRs⁷⁰ for products in the first 3 years
783 following approval. These products include (1) NMEs; (2) originator biological products; (3) biosimilars;
784 and (4) products without NME designation but having newly approved dosage form(s), newly approved
785 indication(s), extension into new patient populations, complex PK or PD characteristics, or complex
786 compositions or manufacturing processes.

787 Additionally, reviewers perform screening on a periodic basis of cumulative data in the FDA AE
788 databases for these products, including data mining. In many cases, these screenings are scheduled to
789 coincide with PSR receipt to leverage resources and optimize efficiencies. PSR submissions, which
790 contain the manufacturer's analysis on a cumulative basis, inform the overall review. Products in this
791 category that are beyond 3 years postapproval are screened as described for category C.

792 Category B

⁶⁸ 21 CFR 10.30, accessible at: <https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=1&SID=bd7d8fe119073e6a690a878c505a1af2&ty=HTML&h=L&mc=true&n=pt21.1.10&r=PART>.

⁶⁹ The description here describes CDER's grouping of products into categories. CBER follows similar principles but does not group products into categories.

⁷⁰ Reviewers, generally, additionally screen the medical literature on a weekly basis.

793 Reviewers generally screen on a weekly basis newly received ICSRs and the medical literature for
 794 homeopathic and compounded products.

795 **Category C**

796 Reviewers generally screen the database weekly for newly received ICSRs that report AEs of interest for
 797 (1) any product in category A that is beyond 3 years postapproval, (2) OTC products, and (3) any product
 798 not in category A or B. In addition, reviewers generally perform data mining at least yearly for category
 799 C products.

Table: General Screening Frequency	
Screening Category	FDA Adverse Event databases
A	Weekly for newly received ICSRs
	At intervals coinciding with PSR receipt for all ICSRs since approval, including data mining
B	Weekly for newly received ICSRs
C	Weekly for newly received ICSRs reporting AEs of interest
	Yearly (at minimum) data mining of all ICSRs since approval
<p>A - <u>Up to 3 years postapproval</u>: NMEs; originator biological products; biosimilars; and products without NME designation but having newly approved dosage form(s), newly approved indication(s), extension into new patient populations, complex PK or PD characteristics, or complex compositions or manufacturing processes.</p> <p>B - Homeopathic and compounded products.</p> <p>C - Products in category A beyond 3 years postapproval. OTC products. Any product not in category A or B.</p>	

800

801 **6.3. Signal Prioritization**

802 Identified signals are prioritized both within and across products. Prioritization is made based upon the
 803 nature of the AE, the seriousness of the outcome, the impact on the individual, and the impact on public
 804 health. When new information becomes available that may change the benefit-risk profile of a product,
 805 the signals are reevaluated and reprioritized.

806 In examining the AE, reviewers determine whether the signal is a serious AE (i.e., one that involves
 807 patient outcomes of death, life-threatening AEs, inpatient or prolonged hospitalization, persistent or
 808 significant disability/incapacity, congenital anomaly, or other serious important medical events).
 809 Reviewers also consider the severity of the AE relative to the disease being treated in the individual
 810 patient, as well as the effects of the AE on the individual patient in the absence of intervention. In

811 addition, reviewers consider the impact of the AE on the health of the overall treatment patient population
812 and the broader impact on public health. Signal prioritization allows for effective signal management,
813 including evaluation, timelines, decisions, and regulatory actions and plans.

814 **7. Signal Evaluation and Documentation**

815 A multidisciplinary team conducts an integrated, comprehensive evaluation of the prioritized signal to
816 determine whether and what regulatory action(s) are indicated. The team integrates the cumulative data
817 gathered from all available sources, which includes ICSRs submitted to FAERS and VAERS, medical
818 literature case reports, product utilization data, reporting ratios, and epidemiologic assessments.

819 **7.1. FAERS, VAERS, and the Medical Literature**

820 *7.1.1. ICSR Retrieval*

821 In preparing to retrieve ICSRs, the reviewer considers the signal to be evaluated and determines whether
822 to cast a broad search (sensitivity) or a narrow search (specificity). For example, a broad search can
823 retrieve all ICSRs for a specific product or product class, while a narrow search can be constructed to
824 retrieve ICSRs for a specific product by a specific manufacturer and for a particular time period. A broad
825 search is most useful for exploratory searches of the database or for evaluating a signal with novel
826 features. A narrower search is more appropriate for examining a particular aspect of a known risk. Best
827 practices for reviewers in searching FAERS are covered in an internal document and include
828 considerations for selecting product and AE terms to optimize the sensitivity and specificity of search
829 results.

830 *7.1.2. Case Definition*

831 A case definition is a set of uniformly applied criteria for determining whether a person should be
832 identified as having a particular disease, injury, or other health condition. It is developed by a
833 multidisciplinary team based on information from the medical literature and current expert clinical
834 practice guidelines. A case definition comprises a specific combination of signs, symptoms, and test
835 results. As a conservative approach, a report that has been corroborated by a physician or other health
836 care provider with relevant training is generally deemed to meet the case definition even if all of the
837 diagnostic criteria are not explicitly included. Depending on the complexity of the diagnosis and the
838 setting in which it was made, reviewers should discuss in their review their rationale for including or
839 excluding such reports in a case series.

840 The use of a case definition in the comprehensive evaluation of a postmarketing safety signal is often
841 necessary when the signal is generated from spontaneous AE reports. Reviewers evaluate individual
842 ICSRs for potential inclusion in a set of similar cases (section 7.1.4, *Case series*) by using, as a point of
843 reference, a case definition for the event. A case definition consists of pre-specified criteria for
844 determining whether an individual report belongs in the case series. When available, it is preferable that
845 reviewers use an existing case definition. However, the combined characteristics of the particular AE and
846 the particular product may require modification of the existing case definition. It is important to note that
847 the use of a case definition does not involve a causality assessment or establish criteria for the
848 management of patients, nor does it require evidence of exposure to the product.

849 7.1.3. *Assessment of ICSRs for Causal Association*

850 Postmarketing AEs are reported from a variety of sources, including commercial marketing experience,
851 postmarketing clinical studies, medical literature, and direct reports from health care professionals and
852 consumers. The process of assessing potential causal associations between an AE and a product presents
853 many challenges to reviewers and other staff involved in safety surveillance. Although a variety of
854 methods has been developed to standardize the causal association assessment process, none has been
855 validated.^{71,72,73} Causal association assessments are conducted at the ICSR (report) level as well as the
856 overall product-AE level. Considerations for causal assessment at the ICSR level are described below,
857 while section 8 describes considerations at the product-AE level.

858 When assessing an ICSR for causal association, reviewers are focused on evaluating the relatedness of the
859 AE to the product taken by the individual patient described in the ICSR. They evaluate a number of
860 features, which can be divided into five broad categories: (1) chronologic data (e.g., plausible temporal
861 sequence, dechallenge, rechallenge),⁷⁴ (2) precedents (e.g., similar AEs with the same product or related
862 products), (3) biological or pharmacological plausibility (e.g., toxic drug concentration in body fluid,
863 occurrence of a recognized pharmacodynamic phenomenon), (4) information quality, and (5) alternative
864 etiologies (e.g., concurrent diseases or conditions, concomitant medications). Some of those features are
865 also considered during the causal assessment at the product-AE level (e.g., precedents, biological or
866 pharmacological plausibility), as outlined in section 8.

867 Once the aforementioned ICSR features have been evaluated, reviewers categorize the ICSR using a
868 binary categorical system (i.e., related or unrelated). For example, a case with a plausible temporal
869 relationship and an absence of factors with a contributory role would be considered a related case. On the
870 other hand, cases without a temporal relationship and describing alternative etiologies with a contributory
871 or confounding role would be considered unrelated.

872 Information from spontaneous reporting systems generally cannot provide definitive answers regarding
873 causal associations between a product and an AE. However, a well-documented case of a rare AE,⁷⁵ one
874 that is usually drug-related, or a well-documented report of positive rechallenge can be sufficient to
875 strongly suggest or even establish a causal association.

876 7.1.4. *Case Series*

877 After retrieving the cases, applying the case definition, and accounting for duplicate reports, reviewers
878 assess the ICSRs for causality and assemble a case series built upon those meeting all criteria. The

⁷¹ Meyboom R, Hekster Y, Egberts A, et al. Causal or casual? The role of causality assessment in pharmacovigilance. *Drug Saf.* 1997;17(6):374-389.

⁷² Agbabiaka T, Savovic J, Ernst E. Methods for causality assessment of adverse drug reactions: a systematic review. *Drug Saf.* 2008;31(1):21-37.

⁷³ The guidance for industry *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* is available at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁷⁴ *Dechallenge* is the withdrawal of a suspect product from a patient's therapeutic regimen; *rechallenge* is the reintroduction of a product suspected of having caused an AE following partial or complete disappearance of the AE after withdrawal of the suspect product.

⁷⁵ For example, cases of progressive multifocal leukoencephalopathy in psoriasis patients treated with efalizumab. Kothary N, Diak IL, Brinker A, et al. Progressive multifocal leukoencephalopathy associated with efalizumab use in psoriasis patients. *J Am Acad Dermatol.* 2011;65(3):546-551.

879 review document includes a summary of the considerations or rationale for inclusion of the ICSRs in the
880 case series, as well as descriptive clinical information that characterizes the case series, such as patterns
881 and trends of the AE across the cases. In addition, summaries for select ICSRs that are the most
882 informative or that otherwise best represent the cases in the series are discussed in some detail.

883 7.2. Product Utilization

884 Product utilization analyses are conducted to quantify and evaluate the use of medical products in the U.S.
885 population. These analyses inform FDA's regulatory decision making about how to address a drug safety
886 signal. Depending on the data sources used, these analyses can provide important information about
887 patient demographics, prescriber specialty, diagnoses and procedures associated with the patient visit,
888 directions for use, prescribed dosing, dosage form or route of administration, duration of product use,
889 products taken concurrently, and use during pregnancy.

890 Principles of pharmacy practice, health care delivery, and pharmacoepidemiology are used to evaluate
891 and interpret these data alongside electronic health care data to describe and characterize product
892 utilization and treatment patterns in the United States. Several types of proprietary product utilization
893 data are available to FDA, including sales distribution data, outpatient prescription- and patient-level data,
894 hospital discharge billing data, office physician survey data, and longitudinal health care claims-level
895 data. Data obtained from product manufacturers may also be used in the assessment.

896 The particular data source(s) and methods to be used for each product utilization analysis are selected
897 based upon the characteristics of the signal (e.g., AE, specific patient populations, setting of care) as well
898 as utilization patterns. Because U.S. national utilization data across all settings of care is not available,⁷⁶
899 multiple data streams are often necessary to project national estimates of product usage. Patient- and
900 prescription-level product utilization analyses are often conducted for the primary setting(s) of care in
901 which the product is dispensed or administered to characterize the patient population of interest or the
902 primary setting of care associated with the AE or other safety issue. These analyses provide information
903 on the extent of patient exposure, as well as a description of patient characteristics and patterns of use.
904 Overall, product utilization analyses can provide context for pharmacovigilance activities and define the
905 landscape of real-world use.

906 7.3. Reporting Ratios

907 When a signal is identified from FAERS or VAERS, examining the reporting ratio (sometimes called a
908 reporting rate) informs signal evaluation. Reporting ratios, although not incidence rates, can be used to
909 provide context and generate hypotheses. Reporting ratios are based on drug utilization, which may be
910 measured in units of patients exposed, prescriptions dispensed, or amount of drug sold at wholesale. The
911 numerator is derived from counts of ICSRs associated with the drug of interest that were reported to
912 FAERS or VAERS during a specified time period. In calculating the reporting ratio, FDA typically uses
913 the number of dispensed prescriptions as the denominator, where it serves as a surrogate measure of drug
914 exposure in the population over a specific time period. The number of dispensed prescriptions is

⁷⁶ Although national utilization data across all settings of care is available in countries with a single-payer system, those data are not generalizable to the U.S. population.

915 estimated from proprietary drug utilization databases, which are described above in section 7.2, *Product*
916 *utilization*.

917 Although reporting ratios are useful in informing signal evaluation, they have limitations. The numerator
918 (representing the number of ICSRs) and the denominator (derived from product use data) are obtained
919 from different data sources. There are additional factors that introduce uncertainty. For example,
920 underreporting of AEs is common, and product use data are based on national estimates, not actual
921 counts. If indicated and feasible, these calculations are followed by formal inferential analyses using
922 rigorous postmarketing studies in population- or disease-based data sources. Reporting ratios are not
923 considered in isolation; reviewers must take into account all available data and the strength of such data.

924 Reporting ratios can be calculated prior to building a case series (i.e., prior to applying the case definition
925 and assessing causality); in this situation the reporting ratio is based on total report counts for the drug-
926 AE pair of interest. The reporting ratio can also be calculated after building the case series, in which case
927 duplicate reports and other factors are accounted for (section 7.1.4, *Case series*). Whether calculated
928 before or after building the case series, reporting ratios are only crude estimates. They are useful for
929 providing context and generating hypotheses to the extent that inherent limitations from each data source
930 are addressed appropriately (e.g., both numerator and denominator are aligned by date, time period,
931 indication for use, setting of care, and reporting rule considerations).

932 7.4. Epidemiologic Assessments

933 Epidemiologic assessments are often an integral part of the signal evaluation process. Preliminarily, a
934 thorough review of the medical literature is performed to determine whether the signal has been
935 previously identified or evaluated by other researchers and what unanswered questions might remain. In
936 addition, the applicant, a multidisciplinary FDA team, or both may reassess the available clinical trial data
937 for the drug (or drug class) during the postmarketing period.

938 Through the Sentinel Initiative,⁷⁷ FDA accesses information from large electronic health care databases,
939 such as electronic health records, insurance claims data, and registries. These health care databases are
940 made available by a diverse group of data partners through a distributed data system that enables FDA to
941 actively gather information (active surveillance) about the safety of marketed products. Exploratory
942 analyses are conducted to characterize health outcomes, examine medical product use, and explore the
943 feasibility of conducting more detailed evaluations. Using automated design tools, as well as statistical
944 methods that control for confounding, FDA may conduct additional analyses to build on prior work and
945 formally evaluate medical product-outcome associations.

946 8. Causal Association Between Product and AE

947 The determination of whether there is a causal association between a product and an AE is based on the
948 strength of evidence from the totality of data for the product under review. Causal association
949 assessments made at the ICSR level (section 7.1.3) reflect the individual patient who experienced the AE.
950 Aggregate data evaluation takes into account several different considerations, such as the number of well-

⁷⁷ In-depth information about the Sentinel program is available at <https://www.fda.gov/safety/fdas-sentinel-initiative/fdas-sentinel-initiative-background>.

951 documented cases in the case series, the consistency of the data, and the presence of features used for
952 causal association assessment, especially biological and pharmacological plausibility. In addition,
953 precedents of similar AEs with the same product or related products (e.g., drug class) are taken into
954 consideration.

955 The evaluation of biological and pharmacologic plausibility is an important element of causal association
956 assessment, and it is necessary to perform further evaluation when the plausibility is unclear or lacking.
957 FDA performs such assessments to gain a better understanding of the mechanisms underlying drug or
958 biological product toxicity, as well as insights into the links between a drug's chemical structure and its
959 potential to induce AEs. Computational tools and predictive modeling related to a drug's mechanism of
960 action or chemical structure-activity relationships can be used to bolster the causal association evidence
961 between a drug and an AE, particularly when the number of reported cases is limited. PK or PD
962 modeling and other pharmacologic or toxicologic evaluations may provide additional insight into
963 plausibility, including class effect.

964 In addition to the aforementioned assessments, determination of causal association between product and
965 AE may require a comprehensive review of all other available information, including the medical
966 literature and premarket development programs (e.g., clinical studies, trials, and toxicological data).
967 Other data, such as product utilization, reporting ratios (or rates), results from epidemiologic studies, and
968 postmarketing studies or trials add to the strength of evidence.

969 **9. Actions**

970 Following the comprehensive review, the multidisciplinary team may determine that subsequent actions
971 are necessary. Potential actions include requiring the applicant to change the product labeling, issuing a
972 drug safety communication, gathering additional data through requiring a postmarketing study or trial
973 with the aim of better characterizing the risk, and requiring a new REMS or modifying an approved
974 REMS to better mitigate the risk.

975 If insufficient evidence exists to support a causal association between the drug and AE, the AE can be
976 considered an AE of interest for continued close monitoring. Regardless of regulatory action taken, FDA
977 continues to monitor for new safety information that may change the determination.

978 **9.1. Product Labeling Changes**

979 FDA-approved product labeling for health care professionals is the primary source of information about a
980 product's safety and efficacy; the labeling summarizes the essential scientific information needed for the
981 safe and effective use of the product.

982 FDA is authorized to require drug and biological product application holders to make safety-related
983 labeling changes based on new safety information that becomes available after approval of the drug or

984 biological product.⁷⁸ FDA guidance documents describe the Agency approaches to such labeling
985 changes, including where in the labeling the changes are to appear.^{79,80,81}

986 9.2. Safety Communications

987 FDA develops and disseminates information to the public about important drug safety issues, including
988 emerging drug safety information. Timely communication of important drug safety information provides
989 health care professionals, patients, consumers, and other interested persons with access to the most
990 current information concerning the potential risks and benefits of a marketed drug, helping them to make
991 more informed treatment choices. A Drug Safety Communication (DSC) is a specific tool used by FDA
992 to communicate important new and emerging safety information about marketed products to health care
993 professionals and to patients.⁸²

994 FDA issues DSCs after considering whether the communicated information can aid prescribing decisions,
995 affect a patient's decision to use the drug, or whether actions can be taken to avoid, prevent, or minimize
996 harm. DSCs highlight emerging safety issues that pose potentially serious or life-threatening risks or
997 AEs. They may relate to previously unknown interactions, a potential medication error, or updated
998 information about a known AE. DSCs generally convey information regarding:

- 999 • The safety issue and the nature of the risk being communicated.
- 1000 • The approved indication or use of the product.
- 1001 • The established benefit or benefits of the product being discussed.
- 1002 • Recommended actions for health care professionals and patients, when appropriate.
- 1003 • A summary of the data reviewed or being reviewed by FDA.

1004 In addition to FDA-issued communications, applicants may be requested or required by FDA to issue a
1005 Dear Health Care Provider letter, for example, to disseminate information regarding a significant hazard
1006 to health, to announce important changes in prescribing information, or to emphasize corrections to
1007 prescription drug advertising or prescribing information.

1008 9.3. Postmarketing Studies and Trials

1009 FDA is authorized to require that applicants holding approved NDAs and BLAs conduct additional
1010 studies or clinical trials under certain circumstances.⁸³ Under section 505(o)(3)(D)(i), before requiring a

⁷⁸ Section 505(o)(4) of the FD&C Act.

⁷⁹ The guidance for industry *Safety Labeling Changes — Implementation of Section 505(o)(4) of the FD&C Act* is available at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁸⁰ The guidance for industry *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* is available at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁸¹ The guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format* is available at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁸² The guidance for industry *Drug Safety Information — FDA's Communication to the Public* is available at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁸³ See, e.g., the guidance for industry *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* is available at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

1011 postmarketing study, FDA must find that AE reporting under section 505(k)(1) of the FD&C Act and the
1012 active postmarket risk identification and analysis system⁸⁴ established under section 505(k)(3) of the Act
1013 will not be sufficient to meet the purposes described in section 505(o)(3)(B). Under section
1014 505(o)(3)(D)(ii), before requiring a postmarketing clinical trial, FDA must find that a postmarketing study
1015 will not be sufficient to meet the purposes described in section 505(o)(3)(B).

1016 9.4. Enhanced Pharmacovigilance

1017 In an effort to enhance FDA's ability to perform safety surveillance of AEs of interest, FDA may request
1018 that the applicant:

- 1019 • Use a targeted data collection tool to gather detailed case information specific to the product and
1020 AE of interest.
- 1021 • Expediently submit reports of labeled AEs of interest beyond minimum reporting requirements.
- 1022 • Summarize and assess AEs of interest at a frequency defined by FDA (e.g., in PSRs or in some
1023 other form).

1024 9.5. Web Posting of Potential Safety Signals

1025 In accordance with statutory requirements and established policies and procedures, FDA routinely posts
1026 potential signals identified from available data sources. Potential signals of serious risks or new safety
1027 information that were identified from FAERS, or for which FAERS data were contributory, are posted to
1028 the FDA internet website.^{85,86}

1029 A new report is made available each quarter. Information from previous quarters is updated on the
1030 website and remains available until an FDA regulatory action has been taken or FDA determines that no
1031 regulatory action may be required. FDA may determine, for products that may be associated with the
1032 risk, that one or more of the following actions is required: modifying the product labeling, gathering
1033 additional data to characterize the risk, a REMS or a modification to a REMS is necessary to ensure the
1034 benefits of the drug outweigh the risks, or suspending or withdrawing marketing approval. After FDA
1035 has taken a regulatory action for each issue on a quarterly report or determined that no regulatory action is
1036 required, no further updates are made, and the quarterly report is archived.

1037 In addition to the quarterly posting, a separate website posting includes signals evaluated under the
1038 Sentinel program.⁸⁷ The information posted to the Sentinel website is provided as part of FDA's

⁸⁴ Information about the system, known as ARIA, is available at <https://www.sentinelinitiative.org/active-risk-identification-and-analysis-aria>.

⁸⁵ MAPP available at <https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm248882.pdf>.

⁸⁶ See *Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System (FAERS)* at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082196.htm>.

⁸⁷ In-depth information about the Sentinel program is available at <https://www.sentinelinitiative.org/>.

1039 commitment to make knowledge acquired from the Sentinel system available in the public domain as
1040 soon as possible.

1041 For each of these postings, the appearance of a product on the listing does not mean that FDA has
1042 concluded that the product is causally associated with the AE. It means that FDA has identified a
1043 potential safety signal for further evaluation, unless FDA has specifically stated that it has concluded that
1044 there is a causal association between the product and the AE, by noting, for example, in the posting that a
1045 label update has been made reflecting causality.

1046 **9.6. Risk Evaluation and Mitigation Strategies**

1047 FDAAA amended the FD&C Act to authorize⁸⁸ FDA to require a REMS when FDA determines that a
1048 REMS is necessary to ensure that the benefits of a drug⁸⁹ outweigh its risks. A REMS therefore provides
1049 additional risk mitigation beyond product labeling and can provide safe access for patients to products
1050 (approved under an NDA, BLA, or ANDA) with known serious risks that would otherwise be
1051 unavailable. A guidance for industry clarifies how FDA applies the factors for determining when a
1052 REMS is necessary to ensure the benefits of the drug outweigh the risks.⁹⁰

1053 Once the need for a REMS is determined, FDA considers the intended goal(s) of the REMS and specific
1054 strategies to meet the goals. A REMS can include a Medication Guide,^{91,92} a communication plan,
1055 elements to assure safe use (ETASU), an implementation system, and a timetable for assessment of the
1056 REMS. A communication plan to health care providers may be required if FDA determines that the plan
1057 may support implementation of the REMS, to disseminate information to health care providers regarding
1058 REMS requirements, or to explain certain safety protocols, such as medical monitoring through periodic
1059 laboratory tests.

1060 FDA can require ETASU as part of a REMS to mitigate a specific serious risk listed in the labeling of a
1061 drug if, in the absence of a REMS with ETASU, the drug would otherwise not be approved or would be
1062 withdrawn. A REMS that includes ETASU may comprise, for example, requirements that health care
1063 providers who prescribe the drug have particular training or experience, that patients using the drug be
1064 monitored, or that the drug be dispensed to patients with evidence or other documentation of safe use
1065 conditions.

1066 A REMS may be required as a condition of the approval of a new product or for an approved product
1067 when new safety information becomes available that indicates that such a strategy is necessary to ensure

⁸⁸ The requirements for REMS are found in section 505-1 of the FD&C Act.

⁸⁹ A REMS can be required for prescription drugs, whether brand or generic (i.e., products approved under an NDA, BLA, or ANDA).

⁹⁰ The guidance for industry *REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary* is available at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁹¹ Federal regulations authorize FDA to require a Medication Guide as a part of drug product labeling under certain circumstances (21 CFR 208). Additionally, section 505-1 of the FD&C Act authorizes FDA to require a Medication Guide as an element of a REMS. FDA may decide that the Medication guide should be required as labeling (but not as part of a REMS).

⁹² The guidance for industry *Medication Guides — Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)* is available at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

1068 the drug’s benefits continue to outweigh the risks. New safety information is defined as a serious risk
1069 associated with the use of the product that FDA has become aware of since the product was approved,
1070 since a REMS was required, or since the last assessment of the REMS.⁹³ Applicants are required to
1071 periodically assess their REMS and submit such assessments to FDA as to whether the programs are
1072 meeting their goals or should be modified. Applicants work with FDA to modify their REMS throughout
1073 the life cycle of the product as new information becomes available. FDA reviews all REMS assessments.
1074 Assessments of approved REMS provide a valuable source of information for reviewers as well as a
1075 safety surveillance tool to ensure that a product is used safely.

1076 **10. Exploring New Approaches**

1077 To enhance its capabilities in promoting product safety to protect and improve public health, FDA
1078 continues to explore new approaches to drug safety surveillance. Likewise, through the establishment of
1079 partnerships and contractual arrangements, FDA aims to support and further develop new data systems,
1080 new surveillance infrastructure, and new methodological tools to complement its existing resources.

1081 **11. Acronyms Used**

1082	AE	adverse event
1083	ANDA	abbreviated new drug application
1084	ARIA	active risk identification and analysis system
1085	BLA	biologics license application
1086	BPCA	Best Pharmaceuticals for Children Act
1087	CBER	Center for Biologics Evaluation and Research
1088	CDC	Centers for Disease Control and Prevention
1089	CDER	Center for Drug Evaluation and Research
1090	CGMP	current good manufacturing practice
1091	DQSA	Drug Quality and Security Act
1092	ETASU	element to assure safe use
1093	FAERS	FDA Adverse Event Reporting System
1094	FDA	Food and Drug Administration
1095	FDAAA	Food and Drug Administration Amendments Act

⁹³ Section 505-1(b)(3) of the FD&C Act.

1096	FD&C Act	Federal Food, Drug, and Cosmetic Act
1097	GFR	glomerular filtration rate
1098	ICH	International Council for Harmonisation
1099	ICSR	individual case safety report
1100	MAPP	Manual of Policies and Procedures
1101	NCVIA	National Childhood Vaccine Injury Act
1102	NDA	new drug application
1103	NDC	national drug code
1104	NME	new molecular entity
1105	OTC	over the counter
1106	PAC	Pediatric Advisory Committee
1107	PBRER	Periodic Benefit-Risk Evaluation Report
1108	PD	pharmacodynamic
1109	PHS Act	Public Health Service Act
1110	PK	pharmacokinetic
1111	PMR	postmarketing requirement
1112	PQI	product quality issue
1113	PREA	Pediatric Research Equity Act
1114	PSR	periodic safety report
1115	REMS	Risk Evaluation and Mitigation Strategy
1116	RMP	risk management plan
1117	SOPP	Manual of Standard Operating Procedures and Policies
1118	VAERS	Vaccine Adverse Event Reporting System