
Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Office of New Drug Policy, Eithu Lwin, 301-796-0728, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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

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Clinical/Medical**

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1 **Demonstrating Substantial Evidence of Effectiveness With One**
2 **Adequate and Well-Controlled Clinical Investigation and**
3 **Confirmatory Evidence**
4 **Guidance for Industry¹**
5
6

7
8 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
9 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
10 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
11 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
12 for this guidance as listed on the title page.
13

14
15
16 **I. INTRODUCTION**
17

18 This guidance (the Confirmatory Evidence guidance) complements the draft guidance for
19 industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological*
20 *Products* (December 2019) (the 2019 Effectiveness draft guidance)² and the guidance for
21 industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*
22 (May 1998) (the 1998 Effectiveness guidance). This guidance provides recommendations for
23 sponsors to consider when planning a drug³ development program.
24

25 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
26 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
27 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
28 the word *should* in Agency guidances means that something is suggested or recommended, but
29 not required.
30

31
32 **II. BACKGROUND AND SCOPE**
33

34 In 1962, Congress required for the first time that drugs be shown to be effective as well as safe.
35 A drug’s effectiveness must be established by *substantial evidence*, which is defined as

¹ This guidance has been prepared by the Office of New Drug Policy in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

² When final, this guidance will represent the FDA’s current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

³ For the purposes of this guidance, all references to *drugs* include both human drugs and biological products, unless otherwise specified.

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36 [E]vidence consisting of adequate and well-controlled investigations, including clinical
37 investigations, by experts qualified by scientific training and experience to evaluate the
38 effectiveness of the drug involved, on the basis of which it could fairly and responsibly be
39 concluded by such experts that the drug will have the effect it purports or is represented to have
40 under the conditions of use prescribed, recommended, or suggested in the labeling or proposed
41 labeling thereof.⁴

42
43 FDA has interpreted this substantial evidence requirement as generally requiring two adequate
44 and well-controlled clinical investigations, each convincing on its own, to establish effectiveness.
45 Nevertheless, as noted in the 1998 Effectiveness guidance, FDA has also been flexible within the
46 limits imposed by the statute where data on a particular drug were convincing. In 1997, Congress
47 amended section 505(d) to confirm FDA’s interpretation of the statutory requirements, making
48 clear that FDA may consider data from one adequate and well-controlled clinical investigation
49 and confirmatory evidence to constitute substantial evidence if FDA determines that such data
50 are sufficient to establish effectiveness.⁵ Specifically, Congress added to section 505(d) that

51
52 If [FDA] determines, based on relevant science, that data from one adequate and well-
53 controlled clinical investigation and confirmatory evidence (obtained prior to or after
54 such investigation) are sufficient to establish effectiveness, [FDA] may consider such
55 data and evidence to constitute substantial evidence.

56
57 FDA issued the 1998 Effectiveness guidance in response to this legislative change. The 1998
58 guidance provides examples of the types of evidence that could be considered confirmatory
59 evidence, with a specific focus on adequate and well-controlled trials of the test agent in related
60 populations or indications, as well as a number of illustrations of a single adequate and well-
61 controlled trial supported by convincing evidence of the drug’s mechanism of action in treating a
62 disease or condition.

63
64 Although FDA’s evidentiary standard for effectiveness has not changed since 1998, drug
65 development and science have continued to evolve, leading to changes in the nature of drug
66 development programs submitted to the Agency. In 2019, the Agency concluded that more
67 guidance was needed on the flexibility in the amount and type of evidence needed to meet the
68 substantial evidence standard. The 2019 Effectiveness draft guidance discusses a number of
69 approaches that can yield evidence that meets the statutory standard for substantial evidence, and
70 in particular addresses the agency’s consideration of various trial designs, trial endpoints, and
71 statistical methodologies, reflecting the Agency’s long-standing flexibility when considering the
72 types of data and evidence that can meet the substantial evidence requirement.

73
74 Given the range of topics addressed by the 2019 Effectiveness draft guidance, its discussion of
75 meeting the substantial evidence standard based on one adequate and well-controlled clinical

⁴ Under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262), licenses for biologics have been issued only upon a showing that the products are “safe, pure, and potent.” Potency has long been interpreted to include effectiveness (21 CFR 600.3(s)). FDA has also generally considered *substantial evidence* of effectiveness to be necessary to support licensure of a biological product under section 351 of the PHS Act.

⁵ The Food and Drug Administration Modernization Act of 1997 (FDAMA) (Pub. L. 105–115),

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76 investigation plus confirmatory evidence was necessarily brief. This guidance supplements the
77 discussion in the 2019 Effectiveness draft guidance by providing further detail on the use of data
78 drawn from one or more sources (e.g., clinical data, mechanistic data, animal data) to
79 substantiate the results of one adequate and well-controlled clinical investigation.
80

81 This guidance describes factors to consider when assessing whether a single adequate and well-
82 controlled clinical investigation and confirmatory evidence are sufficient to demonstrate
83 substantial evidence of effectiveness. It also provides examples of types of data that could be
84 considered confirmatory evidence. This guidance also emphasizes the importance of early
85 engagement with the Agency for sponsors that intend to establish substantial evidence of
86 effectiveness with one adequate and well-controlled clinical investigation and confirmatory
87 evidence.
88

89 This guidance does not discuss the development paradigm in which, under certain circumstances,
90 a single multicenter trial can satisfy the legal requirement for substantial evidence of
91 effectiveness; that scenario is discussed in the 2019 Effectiveness draft guidance. This guidance
92 also does not discuss approval of a different dose, regimen, or dosage form based on a previous
93 finding of effectiveness of an approved drug, or other regulatory considerations beyond the scope
94 of the substantial evidence determination under section 505(d) of the Act. In addition, in some
95 situations, a sponsor may intend to rely on data submitted in other applications to support a new
96 drug application. This guidance does not address certain regulatory considerations that apply to
97 reliance on certain types of information in certain applications (e.g., reliance on a previous
98 finding of safety and effectiveness for a drug the applicant does not own or to which it has no
99 right of reference in a 505(b)(2) application).⁶
100

101 The finding of substantial evidence of effectiveness is necessary but not sufficient for FDA
102 approval. An approval decision, among other things, also requires a determination that a drug is
103 safe for its intended use.⁷ As all drugs can have adverse effects, evaluating whether a drug is
104 “safe” involves weighing whether the benefits of the drug outweigh its risks. In some cases, one
105 adequate and well-controlled clinical investigation and confirmatory evidence may demonstrate
106 effectiveness, but the clinical trial may not have enrolled a sufficient number of participants or
107 have treated them for a sufficient duration to conclude that the drug is safe. A second clinical
108 trial may be needed to ensure a safety database of adequate size and duration to support an
109 appropriate benefit-risk assessment. Considerations for a safety evaluation, a benefit-risk
110 analysis, and their impact on the acceptability of one trial with confirmatory evidence to support
111 approval are beyond the scope of this guidance.
112
113

⁶ For discussion of this topic, see the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999). When final, this guidance will represent the FDA’s current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>. Note, also, that use of certain sources of information may not be permitted under certain regulatory pathways, but that discussion is beyond the scope of this guidance.

⁷ Section 505(d) of the FD&C Act.

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114 **II. GENERAL CONSIDERATIONS REGARDING CONFIRMATORY EVIDENCE** 115 **AND THE DEMONSTRATION OF SUBSTANTIAL EVIDENCE OF** 116 **EFFECTIVENESS**

117
118 The substantial evidence of effectiveness standard in the FD&C Act (see section II) refers to
119 both the quantity and quality of the evidence. As noted above, the number of trials required to
120 demonstrate substantial evidence of effectiveness can vary across development programs. The
121 2019 Effectiveness draft guidance discusses, in part, the features of adequate and well-controlled
122 clinical investigations,⁸ with a focus on trial design, endpoints, and statistical considerations. A
123 clinical investigation's particular set of features will result in a greater or lesser degree of
124 certainty about effectiveness.

125
126 When one adequate and well-controlled clinical investigation and confirmatory evidence are
127 considered together to assess effectiveness, the quality and quantity of confirmatory evidence are
128 also important considerations. Confirmatory evidence should be evidence generated from
129 quality data derived from an appropriate source (see section III).

130
131 The quantity (e.g., number of sources) of confirmatory evidence necessary to support
132 effectiveness may vary across development programs. Importantly, the quantity of confirmatory
133 evidence needed in a development program will be impacted by the features of, and results from,
134 the single adequate and well-controlled clinical investigation that the confirmatory evidence is
135 intended to substantiate. It may be possible for a highly persuasive adequate and well-controlled
136 clinical investigation to be supported by a lesser quantity of confirmatory evidence, whereas a
137 less-persuasive adequate and well-controlled clinical investigation may require a greater quantity
138 of compelling confirmatory evidence to allow for a conclusion of substantial evidence of
139 effectiveness.

140
141 Sponsors must include in their marketing submissions a description and analysis of all data or
142 information relevant to an evaluation of the safety and effectiveness of the drug product, from
143 any source, foreign or domestic, to avoid selecting only those sources that favor a conclusion of
144 effectiveness.⁹ The results of a clinical investigation or confirmatory evidence can be called into
145 question by conflicting evidence unless there is a sufficient scientific justification that may
146 explain the disparate findings.

147
148 When evaluating whether to approach establishing substantial evidence of effectiveness with one
149 adequate and well-controlled clinical investigation and confirmatory evidence, sponsors should
150 consider the clinical context for the proposed therapy. Disease- or condition-specific
151 considerations (e.g., unmet need, size of the patient population) may be relevant to whether such
152 an approach is appropriate. Furthermore, although safety considerations are beyond the scope of
153 this guidance, decision making about a drug development program should also take into account
154 the data necessary to demonstrate that a drug is safe for the intended use.

155

⁸ See 21 CFR 314.126(b) for additional information on the features of adequate and well-controlled investigations.

⁹ See 21 CFR 314.50(d)(5)(iv).

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156 Sponsors who plan to establish substantial evidence of effectiveness with a single adequate and
157 well-controlled clinical investigation and confirmatory evidence should discuss their proposed
158 approach with FDA early in development, such as at a pre-IND meeting and no later than when
159 the sponsor is seeking feedback regarding the clinical investigation (e.g., at the end-of-phase 2
160 meeting; see section IV).¹⁰ When meeting with FDA, sponsors should be prepared to provide a
161 rationale for their chosen approach to development, along with descriptions of the planned single
162 adequate and well-controlled clinical investigation and planned confirmatory evidence. The goal
163 of such engagement is to allow the sponsor and Agency an opportunity to evaluate whether a
164 development program consisting of a single adequate and well-controlled clinical investigation
165 and confirmatory evidence could demonstrate substantial evidence of effectiveness. Ultimately,
166 whether a single adequate and well-controlled clinical investigation and confirmatory evidence
167 are sufficient to demonstrate substantial evidence of effectiveness will depend on the results
168 generated by the development program.

169
170

171 III. TYPES OF CONFIRMATORY EVIDENCE

172

173 This section provides examples of types of confirmatory evidence that can, in appropriate
174 circumstances, be used to substantiate one adequate and well-controlled clinical investigation to
175 demonstrate substantial evidence of effectiveness. This section is not intended to provide an
176 exhaustive list. We note that some of these examples involve data that are frequently generated
177 during a conventional drug development program, and that such data may or may not be
178 appropriate as confirmatory evidence depending on the specific development program under
179 consideration. Whether confirmatory evidence and the adequate and well-controlled clinical
180 investigation provide substantial evidence of effectiveness is determined case by case, for each
181 application, in the context of the application as a whole.

182

183 A. Clinical Evidence from a Related Indication

184

185 Under certain circumstances, evidence of effectiveness of a drug from a clinical investigation for
186 a particular indication can provide confirmatory evidence of effectiveness to support approval of
187 the drug in a different but closely related indication.

188

189 A common example of this approach is the submission of a new drug application or a biologics
190 license application for a new indication for an already approved therapy, where one adequate and
191 well-controlled clinical investigation of the drug for the new indication is supported by the
192 results from the clinical investigation or investigations that formed the basis of the previous
193 approval (for a different but closely related indication). In another example, one adequate and
194 well-controlled clinical investigation in each of two related, unapproved indications can serve as
195 confirmatory evidence for the other indication, thereby supporting concurrent approval of the
196 drug for both indications.

197

198 Among the factors critical to determining whether an indication is closely related, and whether a
199 drug's effectiveness for that indication can provide confirmatory evidence for a trial that studied

¹⁰ See the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (December 2017). When final, this guidance will represent the FDA's current thinking on this topic.

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200 the drug for a different indication, are the degree of similarity between the indications, the degree
201 of similarity in the drug's mechanism of action in the diseases, and the degree of similarity
202 between the efficacy endpoints in the two diseases.

203

204 Examples of when clinical trial data from a related indication may be appropriate for use as
205 confirmatory evidence include when the new indication is:

206

207 • A different stage of the same disease (e.g., for initial treatment of a particular type of
208 cancer, where the previously approved indication was for a treatment-refractory form of
209 that cancer)

210

211 • A different but closely related disease, for example:

212

213 – Infections at different anatomical sites caused by similar pathogens against which the
214 drug is active (e.g., bone/joint infections and acute bacterial skin and skin structure
215 infections)

216

217 – Diseases with a common precursor targeted by the product (e.g., genital warts and
218 cervical cancer both prevented by human papillomavirus vaccine through prevention
219 of infection)

220

221 – Diseases with similarities in their underlying pathophysiology (e.g., rheumatoid
222 arthritis and psoriatic arthritis)

223

B. Mechanistic or Pharmacodynamic Evidence

224

225
226 Under certain circumstances, strong mechanistic evidence of the drug's treatment effect in a
227 particular disease may be appropriate to use as confirmatory evidence. In such cases, (1) the
228 pathophysiology of the disease should be well understood and (2) the drug's mechanism of
229 action should be both clearly understood and shown to directly target the major driver or drivers
230 of the disease pathophysiology. When the drug's mechanism of action affects several
231 pathophysiologic pathways and it is not clear which pathway is important to disease occurrence
232 and/or progression, mechanistic data may not provide sufficient confirmatory evidence to
233 support approval, and additional evidence from other sources may be needed. Similarly, when a
234 disease has multiple causal pathways that lead directly to disease occurrence or progression and
235 the drug only impacts one causal pathway, mechanistic data may not provide sufficient
236 confirmatory evidence.

237

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240 Mechanistic evidence is generally obtained from clinical testing using a relevant and well-
241 understood pharmacodynamic endpoint¹¹ not accepted by itself as an endpoint to establish
242 evidence of effectiveness. Mechanistic evidence can also be obtained from *in vitro* testing (e.g.,
243 if the disease is caused by a genetic defect that results in defective function of an anion
244 transporter on epithelial cells, *in vitro* evidence in a relevant cell line and at relevant
245 concentrations demonstrating that the drug directly augments transporter function). The quality
246 and strength of mechanistic data exist on a spectrum, ranging from exploratory in nature to
247 results that demonstrate clear evidence for a particular pathophysiological mechanism of disease
248 and the drug's effect on the established mechanism.

249
250 Examples of when mechanistic data may be appropriate for use as confirmatory evidence include
251 the following:

- 252
- 253 • When the disease is caused by a single gene and/or enzyme defect and the drug's
254 mechanism of action corrects the enzymatic or genetic defect or its sequelae. For
255 example:
256
 - 257 – An enzyme replacement therapy that corrects the underlying enzymatic deficiency in
258 a lysosomal storage disease at the affected target tissues or organs (e.g., laronidase in
259 mucopolysaccharidosis type I)
 - 260
 - 261 – A small-molecule drug that increases a metabolite, or decreases a precursor, in a
262 disease caused by an enzymatic block in its biosynthetic pathway, resulting in
263 absence or reduced levels of that metabolite (e.g., uridine replacement in hereditary
264 orotic aciduria), and/or elevation of the precursor chemical
 - 265
 - 266 – An antisense oligonucleotide directed at a specific gene variant or molecular genetic
267 mechanism causing an inborn error of metabolism or genetic disease (e.g.,
268 overexpression of a gene leading to overexpression of an enzyme), where
269 biochemical data in the target organ shows expected changes in gene expression (e.g.,
270 knockdown of the gene expression in the tissue and decreased enzyme activity)
 - 271
 - 272 – Nonclinical data demonstrating concentration-dependent inhibition of cell
273 proliferation or signaling correlating with inhibition of an oncogene-dependent
274 pathway (e.g., single driver mutation) in a specific cancer type
 - 275
 - 276 • When the therapy is a chelating or binding agent, where there is a body of evidence
277 describing the clinical consequences of excessive amounts of a substrate (e.g., iron,

¹¹ In some settings where the pathophysiology of a disease is not well understood, a pharmacodynamic biomarker might not elucidate a drug's mechanism of action but could still provide information about a clinical outcome. In an appropriate case, the results of a single adequate and well-controlled clinical investigation could be substantiated by the confirmatory evidence provided by the pharmacodynamic data. Demonstration of a well-characterized exposure-response relationship for the pharmacodynamic biomarker may be particularly persuasive as confirmatory evidence when such data suggest that the effect observed in a successful adequate and well controlled clinical investigation is more likely attributable to the pharmacological action of the drug than to chance.

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278 potassium, phosphate), and in vitro or in vivo data convincingly demonstrate the ability
279 of the drug to bind a meaningful percentage of the substrate
280

- 281 • When the therapy is an antimicrobial drug, proposed for use in combination with a novel
282 inhibitor of a bacterial-resistance mechanism (e.g., beta-lactam antibacterial drug with a
283 novel beta-lactamase inhibitor), and in vitro and animal data demonstrate increased
284 activity of the combination compared with the antimicrobial alone against organisms
285 resistant to the antimicrobial alone
286

C. Evidence from a Relevant Animal Model

287
288
289 Animal data (e.g., proof-of-concept data, pharmacological studies, toxicology studies) are used
290 in drug development for a number of purposes, including to help characterize a therapy's
291 pharmacodynamic effects (which may be done either in healthy animals or in animal models of
292 disease, as appropriate); provide evidence of efficacy in an animal model of disease, using an
293 endpoint that is intended to reflect or translate to a similar outcome in humans with disease; or
294 profile drug toxicity.¹² Typically, results of studies conducted in an animal model of disease are
295 intended to support progressing a drug candidate forward from preclinical to clinical
296 development, rather than to support a finding of substantial evidence. Infrequently, however,
297 sponsors can use data from an established animal model of disease as confirmatory evidence of
298 effectiveness; in such cases, sponsors should discuss in advance these planned nonclinical
299 studies with the appropriate FDA review division.
300

301 Whether data from an established animal model of disease would be suitable as confirmatory
302 evidence depends on several factors, including similarity of pathophysiology and manifestations
303 of the disease in the animal model and in humans, elucidation of the drug's mechanism of action
304 with evidence of similar pharmacology and pharmacodynamics in the animal model and humans
305 with disease, and evidence that the results of efficacy studies conducted in the animal model
306 reasonably support clinical benefits and outcomes in humans with disease (e.g., if the disease in
307 humans leads to renal failure and the drug is intended to preserve renal function, showing that
308 the animal model of disease also is characterized by renal failure and the drug reduces
309 progression of renal failure when tested in the animal model). Although animal models are
310 useful in the preclinical stages of drug development, only a few such models may accurately
311 predict human responses quantitatively or even qualitatively. Only models that have proved to
312 be translational (i.e., prior drugs with the same intended clinical effect have been shown to have
313 this effect observed in the animal model, with similar exposure-response) are likely to be
314 considered as confirmatory evidence.
315

316 Examples of when animal data may be appropriate for use as confirmatory evidence include the
317 following:
318

¹² FDA supports the principles of the 3Rs (reduce/refine/replace) for animal use in testing when feasible. FDA encourages sponsors to consult with review divisions when considering a nonanimal testing method believed to be suitable, adequate, validated, and feasible. FDA will consider if the alternative method could be assessed for equivalency to an animal test method.

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- 319 • When the drug is an antimicrobial agent, and there is a well-established model of
320 infection for a relevant infectious disease, and use of the therapy in the animal model
321 demonstrates antimicrobial activity
322
- 323 • When the product is a preventive vaccine, and there is a well-established model of
324 infection for a relevant infectious disease, and use of the vaccine in the animal model
325 demonstrates prevention of disease
326

327
328 Using animal model data as confirmatory evidence of effectiveness in the setting of one adequate
329 and well-controlled clinical investigation is distinct from the approval pathway established in
330 FDA regulations collectively known as the *animal rule*,¹³ although some of the considerations
331 that are relevant to approval under the animal rule (e.g., the need for a well-understood
332 underlying pathophysiology, the predictiveness of the animal model, and the relatedness of the
333 animal efficacy to the desired benefit in humans)¹⁴ may also be relevant where results of studies
334 conducted in an animal model are used as confirmatory evidence of effectiveness.
335

D. Evidence from Other Members of the Same Pharmacological Class

336
337
338 In certain circumstances, FDA has accepted one adequate and well-controlled clinical
339 investigation as the basis to demonstrate effectiveness, when the single trial is supported by
340 confirmatory evidence of effectiveness from adequate and well-controlled trials of other drugs in
341 the same pharmacological class approved for the same indication.¹⁵ The ability to use
342 information about drugs in a pharmacological class as confirmatory evidence generally depends
343 on all of the following:
344

- 345 • The mechanism of action of the new drug, which should be the same as that of approved
346 members of the class.
347
- 348 • The extent to which similar endpoints were measured across the class, and the
349 homogeneity of each drug's effect on clinical outcomes. Relevant considerations
350 generally include whether the new drug has similar effects on the same endpoints
351 assessed for approved drugs, or whether the new drug demonstrates positive effects on
352 some endpoints and no effect or adverse effects on others.
353
- 354 • The consistency and predictability of the measured effect among drug class members.
355

¹³ 21 CFR part 314, subpart I (drugs) and 21 CFR part 601, subpart H (biological products). The animal rule only applies when it is not ethical or feasible to conduct clinical studies. In such situations FDA can allow the use of adequate and well-controlled efficacy studies in appropriate animal models to generate evidence to establish effectiveness of products intended to treat or prevent serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances.

¹⁴ See 21 CFR 314.610(a).

¹⁵ See footnote 6.

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- 356 • The number of drugs approved in the class. Although it is not possible to assign a
357 threshold number, the greater the number of approved drugs in a class that demonstrate
358 the same general effects, the greater the confidence is likely to be that these effects are
359 related to a common pharmacological effect.

360

E. Natural History Evidence

362

363 In certain circumstances, natural history data can provide confirmatory evidence to substantiate
364 the results of a single adequate and well-controlled investigation. Such an approach can be
365 useful when there is uncertainty about whether the outcomes observed in the control group
366 accurately reflect those that would have been expected in the absence of the intervention.
367 Natural history data being used as confirmatory evidence should be distinct from any data used
368 as a control for the single adequate and well-controlled clinical investigation.

369

370 Examples of when natural history data may be appropriate for use as confirmatory evidence
371 include the following:

372

- 373 • A novel drug to treat patients with an acquired blood enzyme deficiency, where patients
374 had high levels of the abnormal blood protein at baseline with deficient oxygen-carrying
375 capacity. In the double-blind, placebo-controlled crossover design clinical trial, each
376 participant served as his or her own control, with demonstration of nonmeasurable
377 abnormal blood protein levels and improvement in oxygenation after drug administration
378 but not after administration of placebo, and complete resolution of this disorder. The
379 evidence from the one adequate and well-controlled clinical investigation could be
380 supported by confirmatory evidence, from natural history data, which demonstrates
381 failure of this disorder to spontaneously resolve with subsequent high morbidity and
382 mortality.

383

- 384 • A drug for a progressive disease, for which the adequate and well-controlled clinical
385 investigation demonstrates stability of a clinically important outcome in the experimental
386 group compared with deterioration in the control group, and for which natural history
387 data are available to confirm the amount of deterioration in the control group is an
388 expected outcome for the period of observation.

389

F. Real-World Data/Evidence

391

392 Pursuant to section 3022 of the 21st Century Cures Act¹⁶ FDA developed a program to evaluate
393 the potential use of real-world evidence to help support the approval of a new indication for a
394 drug already approved under section 505(c) of the FD&C Act or to help support or satisfy post-
395 approval study requirements.¹⁷

¹⁶ Public Law 114–255, signed December 13, 2016.

¹⁷ This real-world evidence program also covers biological products licensed under the Public Health Service Act. See Framework for FDA’s Real-World Evidence Program, available at <https://www.fda.gov/media/120060/download>.

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396
397 For the purposes of this guidance, FDA defines real world data (RWD) and real-world evidence
398 (RWE)¹⁸ as follows:

- 399
400
- RWD are data relating to patient health status or the delivery of health care routinely
401 collected from a variety of sources (e.g., electronic health records, medical claims data,
402 registries).
 - RWE is the clinical evidence about the usage and potential benefits or risks of a drug
403 derived from analysis of real-world data.
- 404
405
406

407 As noted above, confirmatory evidence can come from one or a variety of sources, including
408 RWD sources. Whether an RWD source may be appropriate to develop RWE that serves as
409 confirmatory evidence depends on several factors, including but not limited to the reliability and
410 relevance of the RWD source and, when relevant, the quality of the study design and the use of
411 appropriate prespecified statistical methods and analyses.¹⁹ FDA recommends that sponsors
412 discuss with the relevant review divisions any plans to use RWE as confirmatory evidence in a
413 drug development program.

414

G. Evidence from Expanded Access Use of an Investigational Drug

415
416

417 Expanded access generally refers to the use of an investigational drug when the primary purpose
418 is to diagnose, monitor, or treat a patient's or group of patients' disease or condition rather than
419 to obtain the kind of information about the drug that is generally derived from clinical trials.²⁰ It
420 may also refer to use of an approved drug where availability is limited by a risk evaluation and
421 mitigation strategy (REMS) for diagnostic, monitoring, or treatment purposes, by patients who
422 cannot obtain the drug under the REMS.²¹ Expanded access may be permitted where the patient
423 or patients have a serious or immediately life-threatening diseases or conditions where there is no
424 comparable or satisfactory alternative therapy available; where the potential patient benefit
425 justifies the potential risks of treatment; and where the requested use will not interfere with the

¹⁸ See the draft guidance for industry *Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products* (September 2021). When final, this guidance will represent the FDA's current thinking on this topic.

¹⁹ See the draft guidances for industry *Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products*, *Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products* (December 2021), *Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products* (November 2021), and *Data Standards for Drug and Biological Product Submissions Containing Real-World Data* (October 2021). When final, these guidances will represent the FDA's current thinking on these topics. Also refer to FDA's Real-World Evidence web page, available at <https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence>.

²⁰ 21 CFR 312.300(a); see also the guidance for industry *Expanded Access to Investigational Drugs for Treatment Use: Questions and Answers* (June 2016).

²¹ *Id.*

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426 initiation, conduct, or completion of clinical investigations that could support marketing approval
427 of the expanded access use or otherwise compromise the potential development of the therapy
428 for the expanded access.²² Under FDA regulations, expanded access may be authorized if the
429 relevant criteria are met for an individual patient, under either emergency or nonemergency
430 conditions, or for a group of patients.²³

431
432 Although the purpose of expanded access is not primarily for research, if the patient outcome
433 information collected under expanded access use of the drug is of sufficient quantity and quality
434 to be highly persuasive, the information may be considered for use as confirmatory evidence.
435 Typically, however, only limited and inconsistent information is available from expanded access
436 (e.g., source documents are often lacking, diagnostic criteria and stage of disease may vary,
437 monitoring and outcome assessments vary across patients, among other limitations), and such
438 information provides an incomplete picture of the course of events, which may make the
439 information unfit for use as confirmatory evidence.

440
441 The following scenario is an example of how patient outcome information collected under
442 expanded access could be used as confirmatory evidence:

- 443
- 444 • A new drug application for an antidote to treat overdose of a chemotherapy drug, where
445 the application included patient outcome information from a large number of single
446 patient emergency investigational new drug applications for which the sponsor collected
447 detailed medical records, and the documented clinical results were markedly improved
448 compared with the expected serious outcome in the absence of treatment. Such
449 information could then potentially serve as confirmatory evidence supporting the results
450 of one adequate and well-controlled clinical investigation.

451

452

IV. PROCESS CONSIDERATIONS

453

454
455 As discussed above, FDA recommends that sponsors discuss early with the review divisions any
456 plans to use one adequate and well-controlled clinical investigation and confirmatory evidence to
457 establish substantial evidence of effectiveness. During these discussions, sponsors should do the
458 following:

459

- 460 • Provide a strong scientific rationale to support the use of a single clinical investigation
461 and confirmatory evidence for their specific drug development program, taking into
462 account the considerations outlined in section III of this document.
- 463
464 • Describe the anticipated design of one adequate and well-controlled clinical investigation
465 that the confirmatory evidence is intended to support.

466

²² See 21 CFR 312.305(a).

²³ See 21 CFR 312.310; 312.315, and 312.320.

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- 467 • Discuss the confirmatory evidence they intend to use to demonstrate, in conjunction with
468 one adequate and well-controlled clinical investigation, substantial evidence of
469 effectiveness. Sponsors should describe the type (i.e., data source) and quantity of
470 confirmatory evidence that will be included in their application.

471

472 Sponsors should continue to meet with the Agency throughout product development, particularly
473 if changes to the clinical investigation or confirmatory evidence are contemplated.

474