
Tissue Agnostic Drug Development in Oncology Guidance for Industry

DRAFT GUIDANCE

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

**October 2022
Clinical/Medical**

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Tissue Agnostic Drug Development in Oncology Guidance for Industry¹

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I. INTRODUCTION

This guidance provides recommendations to sponsors regarding considerations for tissue agnostic drug² development in oncology. For the purpose of this guidance, the term *tissue agnostic oncology drug* refers to a drug that targets a specific molecular alteration(s)³ (a kind of biomarker) across multiple cancer types as defined, for example by organ, tissue, or tumor type. A tissue agnostic oncology drug can therefore be used to treat multiple types of cancer (e.g., colorectal, thyroid, and breast cancers) with the targeted molecular alteration (e.g., either the same targeted molecular alteration or targeted molecular alterations affecting a single pathway). Although applications for a tissue agnostic oncology drug are reviewed for safety and effectiveness under the same legal and regulatory standard as drugs indicated for a tissue specific cancer, the development of a tissue agnostic oncology drug raises issues that generally do not arise in more traditional development approaches. This guidance describes the development of tissue agnostic drugs, scientific considerations in determining when tissue agnostic oncology drug development may be appropriate, and, if appropriate, issues to be addressed during such development.

This guidance does not address the development of drugs intended to prevent or decrease the incidence of cancer and does not address the treatment of cancer in the adjuvant or neoadjuvant setting.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law.

¹ This guidance has been prepared by the Oncology Center of Excellence, Center for Drug Evaluation and Research, and Center for Biologics Evaluation and Research in consultation with the Center for Devices and Radiological Health.

² For purposes of this guidance, references to drugs include drugs approved under section 505 of the Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262).

³ For the purpose of this guidance, *molecular alteration* refers to a broad array of molecular changes in DNA, RNA, or proteins, including point mutations, gene fusions, mutational load, antigen or neoantigen burden, epigenetic changes, and over-or-under-expression.

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38 FDA guidance documents, including this guidance, should be viewed only as recommendations,
39 unless specific regulatory or statutory requirements are cited. The use of the word *should* in
40 Agency guidances means that something is suggested or recommended, but not required.

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43 **II. BACKGROUND ON TISSUE AGNOSTIC DRUG DEVELOPMENT**

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45 When drugs are developed for disease indications, the disease has been traditionally defined by
46 pathologic processes, signs or symptoms, or histologic findings in affected organs or specific
47 sites of the body. In oncology, drugs are also developed for subtypes of organ- or tissue-specific
48 cancers defined by molecular alterations (e.g., tumor markers, hormone-receptor status). Based
49 on advancements in the knowledge of disease pathways in oncology, it may be possible, and
50 more efficient, to develop certain oncology drugs for the treatment of cancer for tissue agnostic
51 indications. Tissue agnostic drug development represents a change in approach to oncology drug
52 development in which a drug is developed for an indication defined by a specific molecular
53 alteration across cancer types.

54

55 Tissue agnostic drug development may be possible both for intrinsic alterations (or receptors)
56 (e.g., neurotrophic receptor tyrosine kinase (NTRK) gene fusions) and for factors extrinsic to the
57 cancer (e.g., the tumor microenvironment or surrounding immunologic milieu).

58

59 A key difference between tissue agnostic oncology drug development and traditional oncology
60 drug development is the inherent need in tissue agnostic drug development to generalize⁴
61 treatment effects based on data observed in some cancer types to other cancer types with the
62 same targeted molecular alteration, when no subjects (or a limited number of subjects) with the
63 other cancer types were included in the clinical trial(s). As described further in this guidance,
64 such generalization may be justified, in appropriate cases, by a strong scientific rationale and
65 clinical circumstances, and may expedite or enable the development of new therapies for patients
66 with rare cancer types when it may not be feasible to test the drug in an adequate number of
67 subjects for every cancer type.

68

69 Generalization of treatment effects in tissue agnostic drug development can introduce some
70 uncertainty about a drug's effectiveness across all individual cancer types. In some clinical
71 circumstances, this uncertainty may be acceptable. This is consistent with FDA's longstanding
72 approach to evaluation of data supporting effectiveness.⁵ Therefore, when justified by strong
73 scientific rationale, clinical data demonstrating effectiveness across different cancer types with
74 the same molecular alteration, plus specific clinical circumstances (e.g., unmet medical need),
75 may support generalization of efficacy across cancer types.

76

⁴ Although we use the term *generalize* here, we acknowledge that the term *extrapolate* may also have been used in other similar contexts. See, for example, the guidance for industry *Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease* (October 2018). FDA updates guidances periodically. 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>.

⁵ See section 505 of the FD&C Act; see also the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When final, this guidance will represent the FDA's current thinking on this topic.

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77 FDA has relied on the generalization of efficacy in other settings such as treatment effects across
78 sex (e.g., in certain circumstances, seeing a response to a drug in female breast cancer and
79 permitting labeling for use in male breast cancer)⁶ and across age groups⁷ when supported by the
80 biology of the disease and the pharmacology of the drug. The Agency also notes in the guidance
81 on developing targeted therapies in low-frequency molecular subsets of a disease that when
82 sponsors follow the principles for grouping subjects, “extrapolation of efficacy findings across
83 multiple subsets may be possible despite the low frequency or absence of patients in some
84 subsets.”⁸ As that guidance acknowledges, different types of evidence can support a grouping
85 strategy, the strongest of which is clinical evidence – i.e., preliminary clinical studies showing
86 that subjects with the proposed group of specific molecular alterations exhibit similar responses
87 to the drug.⁹

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90 **III. DETERMINING WHETHER TISSUE AGNOSTIC DEVELOPMENT MAY BE** 91 **APPROPRIATE**

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93 Sponsors should consider the following factors when determining whether a tissue agnostic
94 oncology drug development program may be scientifically and clinically appropriate.

95

96 **A. Biology**

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98 A robust understanding of the biology (e.g., molecular pathophysiology of the cancer, molecular
99 alteration(s), drug’s mechanism of action, and response to the drug) across cancer types is
100 essential, because it will form the basis for the scientific rationale for tissue agnostic
101 development of a specific drug and may provide support for a conclusion that the drug’s effect
102 across cancer types would be expected to be similar. Nonclinical models and existing scientific
103 data may provide support for a drug’s mechanism of action in different cancer types.¹⁰ See
104 section IV.A, Nonclinical Assessment, for additional information.

105

106 Sponsors should have an appropriate understanding of the molecular alteration(s), such as an
107 understanding of the pathophysiology of the molecular alteration across cancers, including how
108 the molecular alteration influences the natural history of the underlying cancers. In some cases,
109 natural history studies may provide supportive information regarding the prognosis of subjects
110 with a particular molecular alteration as compared to those with the same cancer who do not
111 harbor the same alteration.¹¹ The sponsor should also have an appropriate understanding of the

⁶ See the guidance for industry *Male Breast Cancer: Developing Drugs for Treatment* (August 2020).

⁷ See the draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products* (December 2014). When final, this guidance will represent the FDA’s current thinking on this topic.

⁸ See the guidance for industry *Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease*.

⁹ Section II.A of the guidance for industry *Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease*.

¹⁰ We support the principles of the “3Rs,” to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

¹¹ See the draft guidance for industry *Rare Diseases: Natural History Studies for Drug Development* (March 2019). When final, this guidance will represent the FDA’s current thinking on this topic.

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112 distribution of the molecular alteration(s) across cancer types prior to determining the optimal
113 drug development approach. Certain molecular alterations may not be appropriate for inclusion
114 in a tissue agnostic oncology drug development program. For example, de novo or acquired
115 resistance mechanisms within a subset of cancer types with the molecular alteration may result in
116 heterogeneity of treatment effect (e.g., non-response) across cancer types. Sponsors should
117 develop, if possible, an understanding of potential resistance mechanisms within and across
118 different cancer types.

B. Subject Population

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122 If a molecular alteration across tumor types is extremely rare (e.g., NTRK fusions), tissue
123 agnostic oncology drug development may represent a more feasible developmental strategy. In
124 some cases, if a particular alteration is more frequently present in a specific, common cancer
125 type (e.g., RET-positive lung or thyroid cancer), a sponsor should first assess whether a drug
126 could be developed more efficiently in that cancer type rather than in a tissue agnostic setting. It
127 may be acceptable for a sponsor to seek a tissue agnostic indication in a supplemental application
128 following initial drug approval in one or more specific cancer type(s). The supplemental
129 application for a tissue agnostic drug indication should include data in subjects with cancer types
130 not studied in the initial tissue specific indication(s).

C. Clinical Pharmacology and Clinical Safety and Efficacy

1. Clinical pharmacology

- 136 • Generally, sponsors should collect blood samples to assess pharmacokinetics (PK)
137 and pharmacodynamics (PD). Collection of blood for sparse PK assessment in
138 clinical trials may be sufficient if PK (and PD if appropriate) have been extensively
139 characterized in other clinical trials.
- 140
141 • Sponsors should consider whether there might be meaningful PK or PD differences
142 across cancer types, for example due to patient factors, tumor burden, or tumor
143 location. Exposure-response models should be developed to determine, for example,
144 if drug clearance varies among cancer types resulting in a wide variation in exposure.
145 Sponsors should address whether such differences are clinically relevant resulting in
146 differential safety or effectiveness across cancer types such that a tissue agnostic
147 indication may not be appropriate.
- 148
149 • Sponsors should consider whether the same dose is appropriate across cancer types.
150 For example, hepatic impairment may increase or decrease exposure of a drug and
151 may be more common in certain tumor types (e.g., hepatocellular carcinoma).
152 Sponsors should provide justification for dose selection in subjects across tumor types
153 and should consider whether certain tumor types should be excluded from a tissue
154 agnostic development program due to PK factors.

2. Clinical safety and efficacy

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- Sponsors should consider whether early clinical data show generally similar response rates across different cancer types. For example, lack of responses in select cancer types may not provide the scientific rationale necessary to support tissue agnostic oncology drug development and therefore, it may be more appropriate and efficient to focus development on the individual cancer type(s) that met a threshold level of response. While it is possible that observed response rates in individual cancer types as defined by organ, tissue, or tumor type may differ substantively from the mean overall effect across cancer types due to chance (e.g., due to small sample size for certain cancer types), true differences in treatment effect among cancer types may also occur.
 - The number and types of cancers that should be studied prior to determining whether a sponsor should pursue a tissue agnostic indication should be justified based on the biological factors described above and discussed with the appropriate review division. Sponsors should provide justification for their plan to enroll a representative population of subjects with the molecular alteration in different cancer types to support a tissue agnostic indication. Furthermore, cancer types in which the prevalence of a molecular alteration is comparatively high (e.g., colon cancers and endometrial cancers with MSI-H/dMMR) should be studied in adequate numbers sufficient to describe the treatment effects in these subjects in the development program.
 - FDA advises sponsors to seek diversity in clinical trial enrollment, including race, ethnicity, and other underrepresented populations defined by demographics such as sex, gender identity¹², age, socioeconomic status, disability, pregnancy status, lactation status, and co-morbidity. FDA encourages sponsors to also submit diversity plans that help ensure the adequate participation of relevant and underrepresented populations and analyses of data collected from clinically relevant subpopulations.¹³
 - Sponsors should consider whether any unique safety considerations exist for their drug that might limit the drug’s use in a particular population (e.g., a subject with hepatocellular

¹² See National Strategy on Gender Equity and Equality.

<https://www.whitehouse.gov/wpcontent/uploads/2021/10/National-Strategy-on-Gender-Equity-and-Equality.pdf>

¹³ Adequate participation and analyses of data collected from clinically relevant subpopulations may provide important information pertaining to medical product safety and effectiveness for product labeling. Additional patient characteristics such as age, sex, gender, geographic location (e.g., rural), emotional, physical, sensory, and cognitive capabilities can often be important variables when evaluating medical product safety and efficacy. While these additional characteristics are not addressed in this guidance, FDA encourages sponsors to consider broadening their diversity plans to include all clinically relevant populations as appropriate. FDA guidance for industry “*Enhancing the Diversity of Clinical Trial Populations: Eligibility Criteria, Enrollment Practices, and Trial Designs*” (November 2020) encourages the inclusion of persons with disabilities in clinical trials including during the study design phase. For example, FDA guidance recommends that sponsors consider the recruitment challenges that may occur because of the planned visit schedule and difficulties with accessibility. In addition, guidance for industry “*Inclusion of Older Adults in Cancer Clinical Trials*” (March 2022) provides recommended guidance for this demographic.

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189 carcinoma and cirrhosis when the drug under development is hepatotoxic). In such cases,
190 tissue agnostic development may still be appropriate but there may be specific labeling
191 considerations (e.g., limitation of use in patients with hepatic impairment, different dosage
192 regimen for patients with hepatic impairment, or description of risks in Warnings and
193 Precautions).

194
195 • Sponsors should provide justification regarding prior therapies and the intended
196 patient population prior to initiating studies intending to support a tissue agnostic
197 indication. Sponsors should collect information on disease characteristics and prior
198 therapies in all subjects enrolled in trials supportive of a tissue agnostic indication to
199 support the new drug application (NDA) / biologics license application (BLA)
200 review. Sponsors pursuing accelerated approval should consider whether data will be
201 collected in subjects for which the tissue agnostic indication will be sought with
202 respect to unmet medical need.¹⁴
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IV. ISSUES TO ADDRESS IN TISSUE AGNOSTIC DRUG DEVELOPMENT PROGRAMS

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207 Sponsors should have early and frequent discussions with FDA to discuss development
208 approaches that are critical to tissue agnostic oncology drug development, including the
209 nonclinical data, justification for the sample sizes for the overall population and for subgroups of
210 specific cancer types, and approval pathway (traditional or accelerated approval).
211

212
213 Additional considerations to be addressed in a tissue agnostic drug development program
214 include:

A. Nonclinical Assessment

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216
217 In general, the nonclinical development program for drugs seeking tissue agnostic indications
218 should follow recommendations in the ICH guidance for industry *S9 Nonclinical Evaluation for*
219 *Anticancer Pharmaceuticals*¹⁵ (ICH S9) and the ICH guidance for industry *S9 Nonclinical*
220 *Evaluation for Anticancer Pharmaceuticals Questions and Answers* (ICH S9 Questions and
221 Answers).¹⁶ Nonclinical pharmacology studies should include cell lines from multiple cancer
222 origins, harboring the molecular target(s) of interest. Nonclinical pharmacology studies
223 conducted in support of first-in-human trials may also be supplemented with nonclinical or
224 clinical results from other drugs with the same mechanism of action showing similar effects in
225 tumor types with the targeted molecular alteration(s).¹⁷ Confidence in the relevance of findings
226 from one drug to another in the same class depends on their similarity in structure, binding sites,
227

¹⁴ For additional information on accelerated approval, see 21 CFR parts 314, subpart H and 601, subpart E; section 506(c) of the FD&C Act, as amended by section 901 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA); and the guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014).

¹⁵ March 2010.

¹⁶ June 2018.

¹⁷ See footnote 8.

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228 and other drug properties. Although nonclinical data supporting the biological rationale for a
229 drug's effect across molecular alteration-positive cancer types can provide support for a tissue
230 agnostic indication, FDA does not expect a sponsor to conduct a nonclinical study in every
231 potential cancer type where the molecular alteration might exist in humans.
232

233 In some cases, clinical data might direct a sponsor to conduct additional nonclinical studies to fill
234 in gaps to support a tissue agnostic indication. Ultimately, a sponsor should provide justification
235 within an NDA or BLA regarding the nonclinical approach used to support development of a
236 tissue agnostic oncology drug.
237

238 For cellular or gene therapy products being developed for tissue agnostic indications, sponsors
239 should consult the guidance for industry *Preclinical Assessment of Investigational Cellular and*
240 *Gene Therapy Products*,¹⁸ and should discuss their nonclinical development program with the
241 appropriate division within CBER.
242

B. Clinical Development – Subject Selection

243
244
245 Tissue agnostic oncology drug development will be informed by the disease, patient population,
246 presence or absence of unmet medical need, and characteristics of the drug determined from
247 nonclinical or early clinical information. For example, it may be appropriate to begin studying
248 the drug: (1) in one or a small number of subgroup populations, (2) across a larger number of
249 subpopulations, or (3) by excluding a certain subgroup population(s). Information from earlier
250 clinical testing can inform the approach taken to continue developing the drug in a tissue
251 agnostic versus tissue specific setting(s).
252

253 If a sponsor intends to develop a drug for a tissue agnostic indication targeting a specific
254 molecular alteration *and* contemporaneously develop the drug separately in a specific cancer
255 type(s), sponsors should address how inclusion of molecular alteration-positive subjects in tumor
256 specific studies would impact the efficacy results. This may require some understanding of a
257 drug's effect on cancers without the targeted molecular alteration. The appropriate study
258 population and design of a cancer specific study will depend upon a drug's effect in molecular
259 alteration-positive and -negative populations and the incidence rate of the molecular alteration in
260 the specific cancer type. At a minimum, the presence of the alteration should be assessed in any
261 cancer specific study. In some cases, FDA may recommend separate analyses in the molecular
262 alteration-negative subject populations.
263

264 Consistent with the statutory standard for safety and effectiveness,¹⁹ a tissue agnostic indication
265 will require an assessment of efficacy of the drug in subjects with an appropriate spectrum of
266 different cancer types and an adequate assessment of safety. Furthermore, if the molecular
267 alteration is complex (e.g., a fusion with multiple partners or a continuous biomarker), sponsors
268 should provide justification that an appropriate spectrum of specific cancer types and an
269 appropriate spectrum of biomarker-defined cancers (e.g., based on the different fusion partners)
270 is included in clinical trials and that the efficacy results are not heavily weighted towards a
271 specific cancer type or specific biomarker-defined tumor.

¹⁸ November 2013.

¹⁹ See section 505(d) of the FD&C Act and section 351 of the PHS Act.

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273 Additional information regarding the evidence supporting the appropriateness of grouping
274 subjects together based on a molecular alteration can be found in the guidance for industry
275 *Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease*.

276 277 **C. Clinical Development - Study Designs**

278
279 The choice of the study design depends on multiple factors, including available therapies, unmet
280 medical need, observed magnitude and duration of benefit, and size of the patient population.
281 Early in development, sponsors of oncology drugs frequently conduct smaller single arm trials to
282 assess the activity of a drug in one or more cancer types. Early trials of a drug agnostic of tumor
283 type or in multiple cohorts of patients with different tumor types may provide information to
284 determine whether tissue agnostic development is appropriate.

285
286 Single arm trials using response rate and duration as a primary efficacy endpoint to support
287 further development or where appropriate, to support an approval, may be acceptable if the
288 investigational drug is intended for patients with refractory, advanced, or metastatic cancers and
289 the results are clinically meaningful.²⁰ Response rates can be assessed in nonrandomized trials
290 in oncology because, in general, tumors do not decrease in size in the absence of therapy. The
291 acceptability of whether one or more single arm trials will support an approval will depend on
292 multiple factors including available therapy (e.g., for an accelerated approval), magnitude and
293 duration of effect, clinical context, and clinical trial and patient population sizes. Sponsors
294 should also consider whether the safety profile of the drug can be adequately assessed using a
295 single arm design.

296
297 Randomized controlled trials in rare molecular alteration-positive tumor types with known
298 unprecedented effects on endpoints such as response may not be feasible or may not be
299 appropriate in a refractory setting. Furthermore, because standard of care and prognosis is
300 different across cancer types, ensuring baseline balance (i.e., comparability) across two or more
301 treatment arms may be difficult in a clinical trial that allows for the enrollment of subjects with
302 different cancer types. Due to the challenges of such trials, sponsors should seek FDA's advice
303 prior to conducting any randomized trial that intends to enroll subjects across multiple cancer
304 types selected by a particular molecular alteration.

305
306 In some cases, however, a randomized trial of a drug in one or more cancer types might provide
307 data to inform a separate tissue agnostic program of the drug. Randomized trials in specific
308 cancer type(s) may also be necessary if the drug is intended for use in early stages of the disease
309 or when there is satisfactory available therapy.

310
311 Codevelopment of more than one drug for a tissue agnostic indication should be supported by
312 nonclinical data (see ICH S9 and ICH S9 Questions and Answers), or clinical data, or both, to
313 demonstrate the contribution of each drug to the overall safety and effectiveness of the

²⁰ See the guidance for industry *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* (December 2018).

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314 combination for the tissue agnostic oncology drug indication.²¹ When a development program
315 involves codevelopment of more than one drug, randomized trials in one or more cancer types
316 may be necessary to demonstrate that each drug contributes to effectiveness.

317
318 Various types of master protocol designs that use a single infrastructure, trial design, and
319 protocol to simultaneously evaluate multiple disease populations may facilitate efficient drug
320 development and may be appropriate for tissue agnostic oncology drug development. The design
321 and conduct of clinical trials intended to simultaneously evaluate more than one cancer type are
322 addressed in the guidance for industry *Master Protocols: Efficient Clinical Trial Design*
323 *Strategies to Expedite Development of Oncology Drugs and Biologics*.²² The guidance discusses
324 biomarker development, specific design considerations including adding and stopping treatment
325 arms, and content of a master protocol. In some cases, master protocols will investigate the
326 effects of different drugs that target different molecular alterations. Sponsors should discuss
327 with FDA how subjects will be grouped for the purposes of analysis and such plans should be
328 prespecified prior to conducting any analyses. The guidance for industry *Adaptive Designs for*
329 *Clinical Trials of Drugs and Biologics*²³ includes recommendations that may facilitate tissue
330 agnostic drug development.

D. Statistical Considerations

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334 Sponsors should prospectively provide adequate justification for the number of subjects and
335 cancer types (sample size) in each trial that might provide support for approval of a tissue
336 agnostic oncology drug as well as for the number of subjects and cancer types across trials (if
337 applicable). This is generally accomplished after developing a hypothesis based on a meaningful
338 treatment effect while controlling for Type I error or to ensure adequate precision of the
339 treatment effect. Bayesian approaches can also be considered; however, sponsors should discuss
340 such approaches with the Agency prior to initiation of clinical studies. The appropriate number
341 of subjects and cancer types may differ for each drug development program because the
342 distribution of the molecular alteration across different cancer types may differ across different
343 programs. In some cases, a separate statistical analysis document may be necessary to analyze
344 information across multiple randomized trials.

345
346 Although FDA recommends that sponsors prespecify their statistical analysis plan(s), FDA may
347 not be able to determine if a tissue agnostic oncology drug indication (versus a more limited
348 indication) will be appropriate until FDA assesses the data from the clinical trials in the
349 development program. For example, although a trial may allow for enrollment of any number of
350 cancer types, if a sponsor only enrolls subjects with lung cancer, the indication may be limited to
351 alteration-positive lung cancer.

E. Endpoints

²¹ See the guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination* (June 2013).

²² March 2022.

²³ November 2019.

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355 Sponsors considering the development of drugs in the tissue agnostic oncology drug setting
356 should review the guidance for industry *Clinical Trial Endpoints for the Approval of Cancer*
357 *Drugs and Biologics*.²⁴ Any tumor specific response criteria should be predefined with adequate
358 justification.

359

360 F. Pediatrics

361

362 A tissue agnostic oncology drug indication should address the needs of patients of all ages;
363 therefore, sponsors should consider in their development plan how they will develop a drug to
364 address the needs of children with the targeted molecular alteration.^{25, 26, 27} Consultation with
365 the Agency regarding pediatric studies is recommended as early as possible in drug development.
366 In general, FDA recommends enrollment of children as early as safely possible in clinical trials
367 to support a tissue agnostic oncology drug indication. Sponsors should consider enrolling
368 children age 12 years or older in adult trials.²⁸ Sponsors should consider the following factors to
369 determine the appropriate pediatric development plan for a tissue agnostic oncology drug
370 indication:

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- The spectrum of the molecular alteration across pediatric cancers and the expected distribution of patient ages in the pediatric setting.
- The incidence of molecular alteration-positive disease in the pediatric population and the expected rate of the molecular alteration across different cancer types. Even if a disease is rare, it may be easier to identify subjects if most or all of a cancer type is expected to be molecular alteration-positive (compared to a setting where the alteration rarely occurs in a more common cancer).
- The age groups and any safety considerations arising from the intended use of the drug. For example, if patients receiving the drug are anticipated to survive long-term

²⁴ December 2018.

²⁵ For additional information on oncology drug development in children, see the guidance for industry *Cancer Clinical Trial Eligibility Criteria: Minimum Age Considerations for Inclusion of Pediatric Patients* (July 2020) and the guidance for industry *Considerations for the Inclusion of Adolescents in Adult Oncology Trials* (March 2019).

²⁶ Section 505B(a)(1)(B) of the FD&C Act requires that all original new drug applications (NDAs) or biologics license applications (BLAs) for a new active ingredient, must submit reports on the molecularly targeted pediatric cancer investigation required under section 505B(a)(3) with the application, “if the drug or biological product that is the subject of the application is (i) intended for the treatment of an adult cancer; and (ii) directed at a molecular target that the [FDA] determines to be substantially relevant to the growth or progression of a pediatric cancer”, unless the requirement is waived or deferred. Section 505B(a)(1) of the FD&C Act also requires NDAs and BLAs (or supplements to applications) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment unless the requirement is waived or deferred. For information on marketing applications for certain drugs that are directed at a molecular target FDA determines to be substantially relevant to the growth or progression of a pediatric cancer, see the guidance for industry *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act* (May 2021).

²⁷ For information regarding an initial pediatric study plan (iPSP) and any amendments to the iPSP, see the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (July 2020).

²⁸ See the guidance for industry *Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials*.

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383 and clinical or nonclinical safety signals have been identified during development,
384 sponsors should assess the impact of late effects (e.g., growth and development,
385 cognitive functioning, reproductive safety, risk of secondary malignancies).
386 Additionally, in this setting, sponsors should discuss with FDA the need to conduct
387 additional nonclinical or human studies or to obtain long-term follow-up information
388 to further assess drug safety in pediatric patients. Sponsors should discuss with FDA
389 any such considerations before exclusion of any pediatric populations from a tissue
390 agnostic oncology drug indication development program.

- 391
- 392 • Whether a different formulation (e.g., liquid formulation) or dosing regimens are
393 necessary to address the needs of children.²⁹ Additional data will likely be needed to
394 support the use of a new formulation.³⁰
 - 395 • Whether information is available to inform a dose in children of all ages based on
396 safety and PK information from adult studies as well as any data from completed
397 pediatric dose-finding studies.³¹
 - 398
 - 399 • Whether extrapolation (e.g., of data from adult cancers to pediatric cancers) is
400 appropriate based on similarity of disease and the mechanism of action of the drug.
 - 401

402 There are several important ethical considerations specific to including pediatric subjects in
403 clinical trials outlined in the FDA regulations addressing human subject protection at 21 CFR
404 part 50, subpart D, Additional Safeguards for Children in Clinical Investigations.³²

405
406
407
408

G. Diagnostic Considerations

409

410 Tissue agnostic indications are identified by a molecular alteration that can range from simple
411 genetic alterations such as single nucleotide changes, amplifications or fusions, or complex
412 phenotypic alterations such as microsatellite instability or tumor mutation burden that occur
413 broadly across cancers but infrequently in many cancer types. The identification of molecular
414 alteration-defined populations is dependent on the availability of accurate and reliable diagnostic
415 tests that can identify patients irrespective of cancer type. When accurate testing for molecular
416 alterations is essential for the safe and effective use of the drug, an FDA-cleared or -approved
417 companion diagnostic for this intended use should be commercially available at the time of drug
418 approval to identify patients in the health care setting.

419

420 There are unique challenges regarding the development of a companion diagnostic in the tissue
421 agnostic oncology drug setting, for example, variability in specimen collection and handling

²⁹ FD&C Act § 505B(a)(1).

³⁰ See the draft guidance for industry *Bioavailability Studies Submitted in NDAs or INDs – General Considerations* (February 2019). When final, this guidance will represent the FDA’s current thinking on this topic.

³¹ See footnote 7.

³² For additional information regarding these regulations, see section III.A.1 of the guidance for industry *Cancer Clinical Trial Eligibility Criteria: Minimum Age Considerations for Inclusion of Pediatric Patients*.

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422 across tumor types and limited tissue for testing multiple biomarkers.³³ Platforms such as next-
423 generation sequencing may facilitate testing for the presence of multiple alterations at the same
424 time and increase the likelihood that a patient may be eligible for clinical studies of targeted
425 therapies. Nevertheless, subjects will often be identified (or pre-screened) using a different test
426 or platform than the test or platform that a device sponsor may be developing. When subjects are
427 enrolled based on different tests than the device sponsor is developing, the drug sponsor should
428 have a robust plan to acquire and save adequate tissue from subjects to perform a bridging
429 study.³⁴ Information on the performance characteristics of local and central tests used to enroll
430 the patients in the trial should also be collected. FDA recommends that device sponsors discuss
431 with the Agency appropriate pathways for clinical validation of the companion diagnostic.
432

433 For some alterations (e.g., fusions), testing sensitivity may vary from platform to platform. For
434 example, testing sensitivity may depend on the fusion partners tested in the panel. There may be
435 cancer specific factors that influence the sensitivity or specificity of a companion diagnostic that
436 should be considered when developing a companion diagnostic. Identification of patients who
437 will respond to the drug should be ideally achieved by use of a companion diagnostic that has
438 been approved or cleared by FDA to accurately and reliably detect and measure the relevant
439 molecular alteration(s).
440

441 The challenges for validation of complex biomarkers such as the extent of tumor mutation
442 burden lie in the uniform definition of the biomarker and the demonstration that a cut off can be
443 established across cancer types for an individual companion diagnostic, to ensure accurate
444 identification of the intended patient population. The companion diagnostic for a tissue agnostic
445 biomarker should provide sufficient evidence that assures that measured test performance (both
446 analytical and clinical) is representative across cancer types and accounts for cancer specific
447 variables that can impact final results.
448

449 If FDA determines that an IVD companion diagnostic device is essential to the safe
450 and effective use of a novel therapeutic product or indication, FDA generally will not
451 approve the therapeutic product or new therapeutic product indication if the IVD companion
452 diagnostic device is not approved or cleared for that indication. In deciding whether to approve
453 in the absence of an approved IVD companion diagnostic device, FDA would consider whether
454 the drug treats a serious or life-threatening condition for which no satisfactory alternative
455 treatment exists and the FDA determines that the benefits from the use of the drug outweigh the
456 risks from the lack of an approved or cleared companion diagnostic. Generally, a postmarketing
457 commitment to develop such a companion diagnostic postapproval will be requested in these
458 situations.
459

³³ For additional information on companion diagnostics see the guidance for industry *Developing and Labeling In vitro Companion Diagnostic Devices for a Specific Group of Oncology Therapeutic Products* (April 2020), the guidance for industry and FDA staff *In Vitro Companion Diagnostic Devices* (August 2014), and the guidances for stakeholders and Food and Drug Administration staff *Considerations for Design, Development, and Analytical Validation of Next Generation Sequencing (NGS)–Based In Vitro Diagnostics (IVDs) Intended to Aid in the Diagnosis of Suspected Germline Diseases* (April 2018) and *Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics* (April 2018).

³⁴ Li, M, *Statistical Methods for Clinical Validation of Follow-On Companion Diagnostic Devices via an External Concordance Study*, 2016, *Statistics in Biopharmaceutical Research*, 8(3): 355-363.

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460 FDA recommends that drug and device sponsors meet with the appropriate Center(s) in the
461 Agency to determine the requirements for approval of a companion diagnostic as soon as the
462 decision to initiate a tissue agnostic development program is made. FDA recommends that
463 device sponsors describe their plan to analytically validate the companion diagnostic across
464 cancer types and discuss this prospectively with FDA.

H. Postapproval Data and Information

466
467
468 Additional information about tissue agnostic oncology drugs is likely to be obtained in the post
469 approval setting. In particular, for drugs granted tissue agnostic indications, postmarket
470 information may provide additional effectiveness data in cancer types not studied or studied only
471 in a small number of subjects prior to approval. Postmarketing studies may be required for drugs
472 granted accelerated approval³⁵ or they may be requested to assess effectiveness issues for certain
473 cancer types, including any resistance mechanism(s) and whether there is a lack of effect in a
474 tumor type(s).

475
476 Sponsors should discuss with FDA what types of data will be required or should be collected in
477 the postmarket setting.³⁶ If substantive data emerge postmarket (e.g., indicating a drug lacks
478 effectiveness in a particular tumor type) FDA would review the emerging data and take action as
479 appropriate.

I. Labeling

480
481
482
483 If an application is approved, efficacy results across cancer types should be described in the
484 CLINICAL STUDIES section of labeling. Pooling of overall response rate and duration of
485 response, if assessed as the primary endpoint, may be included in labeling when adequately
486 justified by sponsors. Such justification should include an assessment of effects across studies or
487 cancers. Efficacy results may also be described by listing response rates by tumor or histologic
488 subtype or based on individual studies if adequately justified; however, if the number of subjects
489 with a specific cancer type is very small, it may be more appropriate to list the response for each
490 subject rather than describe a specific percent and confidence interval.

491
492 In general, studies to support efficacy supplements after initial approval should be based on a
493 prespecified analysis plan(s). However, as described in the previous section, FDA may consider
494 reviewing the status of the indication if there is accumulating data in a sufficient number of
495 patients related to the lack of effectiveness of a drug in a specific cancer type; sponsors should
496 discuss with FDA.

³⁵ See for example, 21 CFR part 314, subpart H and 21 CFR part 601, subpart E, for postmarketing requirements for accelerated approval.

³⁶ See for example, 21 CFR part 314, subpart H and 21 CFR part 601, subpart E, for postmarketing requirements for accelerated approval; see also FD&C Act §505(o)(3).