Tissue Agnostic Drug Development in Oncology

Guidance for Industry

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Tissue Agnostic Drug Development in Oncology
Guidance for Industry[1]

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I. INTRODUCTION

This guidance provides recommendations to sponsors regarding considerations for tissue agnostic drug[2] 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.

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

II. BACKGROUND ON TISSUE AGNOSTIC DRUG DEVELOPMENT

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

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

A key difference between tissue agnostic oncology drug development and traditional oncology drug development is the inherent need in tissue agnostic drug development to generalize[4] treatment effects based on data observed in some cancer types to other cancer types with the same targeted molecular alteration, when no subjects (or a limited number of subjects) with the other cancer types were included in the clinical trial(s). As described further in this guidance, such generalization may be justified, in appropriate cases, by a strong scientific rationale and clinical circumstances, and may expedite or enable the development of new therapies for patients with rare cancer types when it may not be feasible to test the drug in an adequate number of subjects for every cancer type.

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

[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.

FDA has relied on the generalization of efficacy in other settings such as treatment effects across sex (e.g., in certain circumstances, seeing a response to a drug in female breast cancer and permitting labeling for use in male breast cancer)[6] and across age groups[7] when supported by the biology of the disease and the pharmacology of the drug. The Agency also notes in the guidance on developing targeted therapies in low-frequency molecular subsets of a disease that when sponsors follow the principles for grouping subjects, "extrapolation of efficacy findings across multiple subsets may be possible despite the low frequency or absence of patients in some subsets."[8] As that guidance acknowledges, different types of evidence can support a grouping strategy, the strongest of which is clinical evidence – i.e., preliminary clinical studies showing that subjects with the proposed group of specific molecular alterations exhibit similar responses to the drug.[9]

III. DETERMINING WHETHER TISSUE AGNOSTIC DEVELOPMENT MAY BE APPROPRIATE

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

A. Biology

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

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

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

B. Subject Population

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

C. Clinical Pharmacology and Clinical Safety and Efficacy

1. Clinical pharmacology

- Generally, sponsors should collect blood samples to assess pharmacokinetics (PK) and pharmacodynamics (PD). Collection of blood for sparse PK assessment in clinical trials may be sufficient if PK (and PD if appropriate) have been extensively characterized in other clinical trials.

- Sponsors should consider whether there might be meaningful PK or PD differences across cancer types, for example due to patient factors, tumor burden, or tumor location. Exposure-response models should be developed to determine, for example, if drug clearance varies among cancer types resulting in a wide variation in exposure. Sponsors should address whether such differences are clinically relevant resulting in differential safety or effectiveness across cancer types such that a tissue agnostic indication may not be appropriate.

- Sponsors should consider whether the same dose is appropriate across cancer types. For example, hepatic impairment may increase or decrease exposure of a drug and may be more common in certain tumor types (e.g., hepatocellular carcinoma). Sponsors should provide justification for dose selection in subjects across tumor types and should consider whether certain tumor types should be excluded from a tissue agnostic development program due to PK factors.

2. Clinical safety and efficacy

- 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 identity[12], 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.

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

- Sponsors should provide justification regarding prior therapies and the intended patient population prior to initiating studies intending to support a tissue agnostic indication. Sponsors should collect information on disease characteristics and prior therapies in all subjects enrolled intrials supportive of a tissue agnostic indication to support the new drug application (NDA) / biologics license application (BLA) review. Sponsors pursuing accelerated approval should consider whether data will be collected in subjects for which the tissue agnostic indication will be sought with respect to unmet medical need.[14]

IV. ISSUES TO ADDRESS IN TISSUE AGNOSTIC DRUG DEVELOPMENT PROGRAMS

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

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

A. Nonclinical Assessment

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

[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.

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

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

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

B. Clinical Development – Subject Selection

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

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

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

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

C. Clinical Development - Study Designs

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

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

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

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

Codevelopment of more than one drug for a tissue agnostic indication should be supported by nonclinical data (see ICH S9 and ICH S9 Questions and Answers), or clinical data, or both, to 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).

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

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

D. Statistical Considerations

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

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

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

F. Pediatrics

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

- 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*.

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

- Whether a different formulation (e.g., liquid formulation) or dosing regimens are necessary to address the needs of children.[29] Additional data will likely be needed to support the use of a new formulation.[30]
- Whether information is available to inform a dose in children of all ages based on safety and PK information from adult studies as well as any data from completed pediatric dose-finding studies.[31]

- Whether extrapolation (e.g., of data from adult cancers to pediatric cancers) is appropriate based on similarity of disease and the mechanism of action of the drug.

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

G. Diagnostic Considerations

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

There are unique challenges regarding the development of a companion diagnostic in the tissue 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*.

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

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

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

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

[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.

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

H. Postapproval Data and Information

Additional information about tissue agnostic oncology drugs is likely to be obtained in the post approval setting. In particular, for drugs granted tissue agnostic indications, postmarket information may provide additional effectiveness data in cancer types not studied or studied only in a small number of subjects prior to approval. Postmarketing studies may be required for drugs granted accelerated approval[35] or they may be requested to assess effectiveness issues for certain cancer types, including any resistance mechanism(s) and whether there is a lack of effect in a tumor type(s).

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

I. Labeling

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

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