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# Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies 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## *DRAFT GUIDANCE*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  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)**

**March 2019  
Clinical/Medical**

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1                                   **Cancer Clinical Trial Eligibility Criteria:**  
2                                   **Patients with Organ Dysfunction or Prior or Concurrent**  
3                                   **Malignancies**  
4                                   **Guidance for Industry<sup>1</sup>**  
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9   This draft guidance, when finalized, will represent the current thinking of the Food and Drug  
10 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not  
11 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the  
12 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible  
13 for this guidance as listed on the title page.  
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18   **I.       INTRODUCTION**  
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20   This guidance is one in a series of guidances that provide recommendations regarding eligibility  
21 criteria for clinical trials of drugs or biological products<sup>2</sup> regulated by CDER and CBER for the  
22 treatment of cancer.<sup>3</sup> Specifically, this guidance includes recommendations regarding the  
23 inclusion of patients with organ dysfunction or with prior or concurrent malignancies. This  
24 guidance is intended to assist stakeholders, including sponsors and institutional review boards,  
25 responsible for the development and oversight of clinical trials.  
26

27   A clinical trial's eligibility criteria (for inclusion and exclusion) are essential components of the  
28 trial, defining the characteristics of the study population. Because there is variability in  
29 investigational drugs and trial objectives, eligibility criteria should be developed taking into  
30 consideration the mechanism of action of the drug, the targeted disease or patient population, the  
31 anticipated safety of the investigational drug, and the ability to recruit trial participants from the  
32 patient population to meet the objectives of the clinical trial. However, some eligibility criteria  
33 have become commonly accepted over time or used as a template across trials without clear  
34 scientific or clinical rationale. Unnecessarily restrictive eligibility criteria may slow patient

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<sup>1</sup> This guidance has been prepared by the Oncology Center of Excellence, Center for Drug Evaluation and Research (CDER), and Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

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

<sup>3</sup> Topics of the other three guidances are related to eligibility criteria for patients with human immunodeficiency virus, hepatitis B virus, and hepatitis C virus infections; with brain metastases; and minimum age for pediatric patients.

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

35 accrual, limit patients' access to clinical trials, and lead to trial results that do not fully represent  
36 treatment effects in the patient population that will ultimately use the drug.<sup>4,5</sup>

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38 Broadening cancer trial eligibility criteria can maximize the generalizability of trial results and  
39 the ability to understand the therapy's benefit-risk profile across the patient population likely to  
40 use the drug in clinical practice without jeopardizing patient safety.

41  
42 In general, FDA's guidance documents do not establish legally enforceable responsibilities.  
43 Instead, guidances describe the Agency's current thinking on a topic and should be viewed only  
44 as recommendations, unless specific regulatory or statutory requirements are cited. The use of  
45 the word *should* in Agency guidances means that something is suggested or recommended, but  
46 not required.

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### **II. BACKGROUND**

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51 Patients with organ dysfunction are often excluded from clinical trials, regardless of knowledge  
52 of the metabolic pathways and excretory routes of the investigational drug. The life-span of the  
53 general population is increasing and thus includes increasing numbers of patients with co-morbid  
54 renal disease, cardiac disease, and hepatic dysfunction. Additionally, with the life-span of the  
55 general population increasing, an increasing number of patients with prior or concurrent  
56 malignancies is anticipated. By excluding individuals from cancer clinical trials who have major  
57 organ dysfunction or previous or concurrent cancers, trial recruitment favors younger patients,  
58 which may not be fully representative of the population for whom the drug will be indicated.  
59 Designing cancer clinical trials that include patients with organ dysfunction and prior or  
60 concurrent malignancies and then including this information in the labeling promotes the safe  
61 and effective use of these products across a broader patient population likely to use the drug in  
62 clinical practice.

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### **III. RECOMMENDATIONS**

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67 Thoughtful consideration should be given to the potential inclusion of patients with organ  
68 dysfunction or prior or concurrent malignancies in cancer clinical trials. The following  
69 recommendations for eligibility criteria for patients with organ dysfunction in cancer clinical  
70 trials focus on renal function, cardiac function, and hepatic function. This guidance also includes  
71 recommendations for eligibility criteria for patients with cancer who have a history of prior or  
72 concurrent second primary malignancies.

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<sup>4</sup> Beaver JA, Ison G, Pazdur R, 2017, Reevaluating Eligibility Criteria- Balancing Patient Protection and Participation in Oncology Trials, NEJM, 376:1504-1505.

<sup>5</sup> Kim E, Bruinooge S, Roberts S, et al., 2017, Broadening Eligibility Criteria to Make Clinical Trials More Representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement, JCO, 35(33): 3737-3744.

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### **A. Patients with organ dysfunction**

Where pharmacokinetics (PK) and major routes of elimination in humans are not well understood, it is reasonable to enroll only patients with relatively preserved organ function (primarily renal and hepatic) in cancer clinical trials. As data on toxicity including preclinical and clinical toxicity, PK, and/or pharmacodynamics (PD) become available during drug development, protocols should be revised to include patients with compromised organ function where safe parameters regarding dosage adjustments have been determined.<sup>6</sup>

#### *1. Renal function recommendations*

- Eligibility criteria should be based on a contemporary, widely accepted, and clinically applicable equation that estimates glomerular filtration rate rather than an absolute serum creatinine concentration. The equation used should remain consistent throughout the investigational drug development process.
- Sponsors should provide adequate justification for the inclusion/exclusion of patients with various degrees of renal impairment based on the stage of product development, safety profile of the product, and understanding of the effect of renal impairment on the elimination of the drug.
- Patients with renal impairment should be included in trials of investigational drugs when the available nonclinical and clinical data indicate that inclusion of patients with renal impairment would not place patients at unreasonable risk and/or adequate steps can be taken to mitigate potential risks. When there is an expectation that the PK will increase in patients with renal dysfunction, inclusion of such patients may be facilitated by prospective dose adjustment to produce similar systemic exposures to those seen in patients with relatively preserved kidney function.<sup>7</sup>
- Sponsors should address the need for and timing of studies to evaluate the effect of dialysis on drug clearance and the need for dosage adjustment for patients on dialysis.

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<sup>6</sup> Lichtman S, Harvey R, Smit M, et al., 2017, Modernizing Clinical Trial Eligibility Criteria: Recommendations of the American Society of Clinical Oncology – Friends of Cancer Research Organ Dysfunction, Prior or Concurrent Malignancy, and Comorbidities Working Group, *JCO*, 35(33): 3753-3759.

<sup>7</sup> Public Workshop: Evaluating Inclusion and Exclusion Criteria in Clinical Trials, Workshop Report, July 2018, workshop date April 16, 2018, available at <https://www.fda.gov/downloads/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCA/t/FDARA/UCM613054.pdf> (accessed February 7, 2019).

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### 2. *Cardiac function recommendations*

- Inclusion of patients with cardiovascular dysfunction may be possible when the totality of the available nonclinical and clinical data, including PK and PD data, indicates that inclusion of these patients does not present an unreasonable risk.
- Patients with significant clinical cardiac abnormalities (e.g., clinical heart failure, unstable angina, or ejection fraction (EF) < 35%) should be excluded, especially in early-phase studies.
- Protocols should call for investigator assessment of a potential participant's risk for heart failure with a validated clinical classification system (e.g., the New York Heart Association Functional Classification).
- Ejection fraction (EF) values:
  - There is no clearly established minimum cardiac EF predictive of development of treatment-related heart failure.
  - EF measured by either echocardiography or multigated acquisition scan is acceptable for determining cardiac EF for evaluating whether patients meet eligibility criteria.
- QTc Prolongation<sup>8</sup>:
  - Baseline clinical evaluation in early-phase studies should be developed in coordination with the FDA review division or office.
  - Requiring a minimum baseline QTc interval for clinical trial eligibility is appropriate for investigational drugs that have exhibited potential risks of QTc prolongation.
  - If QTc prolongation is not identified as a concern in first-in-human and early phase studies, the appropriate QTc interval eligibility criteria in later development trials should be re-evaluated.

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<sup>8</sup> See the ICH guidance for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (October 2005) for additional information regarding QTc prolongation. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

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### 3. *Hepatic function recommendations*

Unlike other organ systems, liver biochemical testing does not provide sufficient evidence of adequate liver function to predict the liver's capacity to effectively handle drug metabolism. While estimates of hepatic function that incorporate clinical variables as well as functional and laboratory values, such as the Child-Pugh and Model for End-Stage Liver Disease scoring systems,<sup>9,10</sup> are adopted as markers of hepatic metabolism in dedicated PK studies, hepatic metabolism may also be influenced by cancer and inflammation, even in the setting of normal scoring. To gauge hepatic drug transformation capacity, pre-existing liver disease, as well as epidemiological, genetic, environmental, and historical variables (e.g., chronic alcohol use and a past history of adverse drug reactions) should be ascertained. Impaired hepatic blood flow, in particular, when portal hypertension is evident, is critical to assessing liver handling of drugs. Therefore, even in the setting of low Child-Pugh or Model for End-Stage Liver Disease scores, normal international normalized ratio/prothrombin time, and normal total bilirubin, more reliable measures to predict biotransformation, conjugation, and drug permeability related to hepatic transformation of xenobiotics are needed.

- **Patients with mild to moderate hepatic impairment<sup>11</sup>**

- Patients with mild and moderate hepatic impairment (defined as the equivalent of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade 1 toxicity), as well as those with aspartate transaminase (AST) and alanine transaminase (ALT) elevations defined as grade 3 by the NCI CTCAE (> 5 to 20 x ULN (upper limit of normal)), may be asymptomatic and able to tolerate doses equivalent to patients with normal hepatic function.
- Inclusion of patients with mild to moderate hepatic impairment may be appropriate when the totality of the available nonclinical and clinical data, including PK and PD data, indicate that inclusion of these patients does not present an unreasonable risk to patients.

- **Patients with asymptomatic elevations in unconjugated bilirubin**

- The eligibility criteria for patients with Gilbert syndrome or stable chronic hemolytic anemia (e.g., hereditary spherocytosis, sickle cell disease, thalassemia intermedia) should be defined in the protocol.

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<sup>9</sup> See the guidance for industry *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling* (May 2003).

<sup>10</sup> See the Protocol Template for Organ Dysfunction Studies, updated February 26, 2018 for the NCI criteria, available at [https://ctep.cancer.gov/protocolDevelopment/templates\\_applications.htm](https://ctep.cancer.gov/protocolDevelopment/templates_applications.htm) (accessed on February 7, 2019).

<sup>11</sup> Talal AH, Venuto CS, Younis I, 2017, Assessment of hepatic impairment and implications for pharmacokinetics of substance use treatment, *Clin Pharmacol Drug Dev*, 6: 206-212.



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192           **B.       Patients with prior or concurrent malignancy**

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194 Patients with a history of prior or concurrent second primary malignancy whose natural history or  
195 treatment does not have the potential to interfere with the safety or efficacy assessment of the  
196 investigational drug should generally be eligible for enrollment in clinical trials. For example, in  
197 initial dose finding or preliminary activity-estimating or proof-of-concept studies, patients with a  
198 history of prior or concurrent second primary malignancies should not be excluded.