Pharmacokinetic-Based Criteria for Supporting Alternative Dosing Regimens of Programmed Cell Death Receptor-1 (PD-1) or Programmed Cell Death-Ligand 1 (PD-L1) Blocking Antibodies for Treatment of Patients with Cancer
Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact Brian Booth at 301-796-1508.

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

August 2021
Clinical Pharmacology/Clinical

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Pharmacokinetic-Based Criteria for Supporting Alternative Dosing Regimens of Programmed Cell Death Receptor-1 (PD-1) or Programmed Cell Death-Ligand 1 (PD-L1) Blocking Antibodies Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

I. INTRODUCTION AND BACKGROUND

This document provides recommendations for sponsors of investigational new drug applications (INDs) and biologics license applications (BLAs) under 42 U.S.C. § 262 and 21 CFR Parts 312 and 601 on the use of pharmacokinetic (PK)-based criteria to support the approval of alternative dosing regimens for programmed cell death receptor-1 (PD-1) or programmed cell death-ligand 1 (PD-L1) blocking antibodies. This guidance is based on accumulated scientific and regulatory experience for PD-1 and PD-L1 drugs, and as such, does not address development of alternative dosing regimens for other drugs or biologics, changes in route of administration, or novel formulations of previously-approved PD-1/PD-L1 products.

PD-1 and PD-L1 blocking antibody products have been developed for various cancer indications. These antibodies are usually administered intravenously. Sponsors may seek approval of alternative intravenous (IV) dosing regimens that are different from those tested in clinical efficacy and safety trials. These alternative IV dosing regimens are typically designed to change doses (e.g., body weight adjusted doses to flat doses) and/or dosing intervals (e.g., once every 3 weeks to once every 6 weeks). Longer dosing interval periods can minimize patient burden and reduce risks associated with more frequent administration (e.g., infusion reactions), as well as exposure to communicable diseases (e.g., SARS-CoV-2) associated with visits to hospitals or infusion centers. This guidance provides a PK-based approach to support approval of alternative dosing regimens for intravenously administered PD-1/PD-L1 blocking antibody products.

The contents of this guidance 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. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless

[1] This guidance has been prepared by the Office of Clinical Pharmacology in Center for Drug Evaluation (CDER) and the Oncology Center of Excellence (OCE) at the Food and Drug Administration (FDA).

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. PK-BASED APPROACH

A PK-based approach relying on population-PK (Pop-PK) modeling and simulation can be applied to support the approval of alternative dosing regimens for a PD-1 or PD-L1 blocking antibody that is already approved based on clinical efficacy and safety trials. The Pop-PK model should be established with sufficient PK data from all indicated patient populations over a wide range of dosing regimens (i.e., different from the alternative dosing regimens). The model itself should be well validated and determined to be fit for the purpose. Refer to the FDA Pop-PK draft guidance for recommendations about Pop-PK models.[2] Simulation can be performed to derive the PK profiles and parameters following the alternative dosing regimens.

An application for an alternative dosing regimen of a PD-1 or PD-L1 blocking antibody based on modeling and simulation should have the following features:

- The reference dosing regimen used for the comparison is the one used to establish efficacy in clinical trials.

- Both average AUC and C_{trough} following the alternative dosing regimen at steady state and/or in the first dosing cycle are no more than 20% lower compared to those of the reference dosing regimen.

- Average steady state C_{max} following the alternative dosing regimen does not increase more than 20% compared to that of the reference dosing regimen unless there is adequate clinical evidence that the average steady state C_{max} for the new regimen is unlikely to be associated with an unacceptable safety profile (e.g., safety already demonstrated at higher doses; flat or shallow exposure (dose)-safety relationship).

If the features described above are not present, additional clinical data to support the efficacy and safety with the new regimen may be needed. The nature of such clinical data may depend on the specific product under development, patient population and pre-existing clinical and clinical pharmacology data. The sponsor should discuss alternative pathways of development with the appropriate review division.

III. REGULATORY INTERACTION AND SUBMISSION

A sponsor who plans to apply the PK-based criteria to support an alternative dosing regimen is encouraged to interact with Agency early in the development program. The sponsor can seek

[2] See the draft guidance for industry: *Population Pharmacokinetics* (July 2019). When final, this guidance will represent the FDA's current thinking on this topic. We update 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.

regulatory input through regular IND meetings. If a more detailed discussion on modeling and simulation strategies is necessary, the sponsor may request specific meetings through the model-informed drug development (MIDD) paired meeting pilot program.[3] To facilitate the discussion, the sponsor should include the following information in the meeting package:

- Background information for the product including all supporting data (such as receptor occupancy status, response biomarkers, etc.) to support the intended change in the dosing regimens, and summary of the planned strategies and approaches.

- Summary information for the exposure-response relationships for safety and efficacy, and the population PK model building, validation, and performance.

- Simulation strategy and plan.

- Specific questions related to the modeling and simulation strategy.

The following documents are expected in BLA or supplemental BLA submissions seeking approval for alternative dosing regimens:

- A summary document illustrating the objectives of the submission, proposed changes in the label, relevant information on exposure-response relationship for target engagement (if available), efficacy and safety, summary of findings, and links to the relevant reports and supporting documents.

- A population PK report that includes the up-to-date model which is built upon all available PK data in all indicated patient populations over all available dosing regimens. The report should provide adequate information on model validation and performance check in different indicated patient populations and dosing levels.

- A PK study report, if applicable, summarizing the observed PK findings of the reference dosing regimen.

- A simulation report that provides the simulation strategy and outcomes related to the alternative dosing regimens. A direct comparison of PK profiles and parameters from alternative and reference dosing regimens should also be provided.

- Supporting documents in the appropriate format, including original data, relevant codes, and modeling and simulation outcomes.

Please refer to the Draft Guidance for Industry *Population Pharmacokinetics* (July 2019) regarding the format, content, and location of each document.[4]

[3] Model-Informed Drug Development Pilot Program: https://www.fda.gov/drugs/development-resources/model-informed-drug-development-pilot-program

[4] See footnote 2.