
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

**U.S. Department of Health and Human Services
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Oncology Center of Excellence (OCE)
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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 Industry¹

This guidance represents 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 the original clinical efficacy and safety trials that served as the basis of approval of the current dosing regimen, or in the pre-approval setting, dosing regimens that differ from those tested in earlier PK and efficacy studies conducted during development. These alternative IV dosing regimens are typically designed to change doses and dosing intervals. Longer dosing intervals 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 PD-1/PD-L1 blocking antibody products in both the pre- and post-approval setting. This paradigm may apply to PD-1/PD-L1 monotherapies, as well as combination regimens in which the dose and/or dose schedule of the PD-1/PD-L1 is the only proposed change.

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

Contains Nonbinding Recommendations

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and 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. PK-BASED APPROACH

A PK-based approach that relies on population-PK (Pop-PK) modeling and simulation can be applied to support the approval of alternative dosing regimens for an approved or unapproved PD-1 or PD-L1 blocking antibody. 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 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 include the following features:

- The reference dosing regimen used for the comparison is the dosing regimen (i.e., dose and schedule) used to establish efficacy in the clinical trial(s) that served as the basis for approval of the original BLA. In the preapproval setting, the reference regimen used for comparison is the dosing regimen used in the early clinical development to characterize the PK and efficacy of the product.
- Both geometric means of AUC over the least common time interval³ (or C_{average}) and C_{trough} following the alternative dosing regimen at steady state and/or in the first least common time interval are no more than 20% lower compared to those of the reference dosing regimen.
- Geometric mean of steady state C_{max} following the alternative dosing regimen does not increase more than 25% compared to that of the reference dosing regimen unless there is adequate clinical evidence that the 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).

² See the guidance for industry: *Population Pharmacokinetics* (February 2022). 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>.

³ In a comparison of dosing schedules/regimens, the least common time interval is the smallest multiple of the longer dosing schedule that can be compared to a shorter schedule. For example, in a comparison of a once-every-2-week schedule to a once-every-3-week schedule, the least common time interval is 6 weeks.

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If the features described above are not present, additional clinical data (e.g., clinical study of efficacy and/or safety) 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 the Agency early in the development program. The sponsor can seek 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 program.⁴ 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 a summary of the planned strategies and approaches.
- Summary information for the exposure-response relationships for safety and efficacy; any exposure-response modeling of biomarkers that were used to support approval of the original BLA or early development trials under an IND or in a pre-IND setting; and the population PK model building, validation, and performance.
- Simulation strategy and plan, including simulation objectives, assumptions, target simulated population(s), simulation scenarios, and data analysis plans for the results.
- 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 labeling, relevant information on exposure-response relationships for target engagement or biomarkers (if available), exposure-response relationships for 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 assessment in different indicated patient populations and dosing levels.

⁴ Model-Informed Drug Development Program: <https://www.fda.gov/drugs/development-resources/model-informed-drug-development-pilot-program>.

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- 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.

Refer to the guidance for industry *Population Pharmacokinetics* (February 2022) regarding the format, content, and location of each document.