Minimal Residual Disease and Complete Response in Multiple Myeloma: Use as Endpoints to Support Accelerated Approval

Guidance for Industry

DRAFT GUIDANCE

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TABLE OF CONTENTS

Minimal Residual Disease and Complete Response in Multiple Myeloma: Use as Endpoints to Support Accelerated Approval 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

This guidance provides recommendations to sponsors about using minimal residual disease (MRD) and complete response (CR) in multiple myeloma as primary endpoints in trials evaluating drug and biological products intended to treat patients with multiple myeloma (MM) to support approval under accelerated approval.[2] For the purpose of this guidance, the MRD endpoint refers to MRD negativity rate as assessed in the bone marrow by either flow cytometry- or sequencing-based methods in patients who have achieved a CR.[3] The definition of CR includes patients who achieved CR or stringent CR.[4]

This guidance does not address the use of MRD or CR for patient selection, enrichment, stratification in clinical trials or to guide treatment decisions. This guidance also does not address the use of MRD or CR in disease settings other than MM. General recommendations on the use of MRD as a biomarker to support marketing approval of drug and biological products for treating specific hematologic malignancies have been discussed in the guidance for industry *Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment* (January 2020). In addition, this guidance does not address the statutory or regulatory standards for accelerated approval. The draft guidance *Accelerated Approval-Expedited Program for Serious Conditions* (December 2024) and the guidance *Expedited Programs for Serious Conditions—Drugs and Biologics* (May 2014) discuss these topics.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.

[1] This guidance has been prepared by the Oncology Center of Excellence in cooperation with the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, and the Center for Devices and Radiological Health at the Food and Drug Administration.

[2] Section 506(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356(c)) and 21 CFR part 314 subpart H, for new drug applications and 21 CFR part 601, subpart E, for biologics license applications.

[3] Kumar S, et al. Lancet Oncol 2016;17: e328-46.

[4] *See id.*

The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

MM is a plasma cell malignancy and accounts for 18% of all hematologic malignancies in the United States.[5] Since 2003, there have been more than 20 new drug or biological products approved for the treatment of multiple myeloma. These new therapeutics combined with advancements in supportive care have significantly improved outcomes for patients with multiple myeloma. As of 2022, the median overall survival (OS) is anticipated to be 7-10 years for patients with newly diagnosed multiple myeloma.[6] In multiple myeloma, accelerated approval based on an endpoint of overall response rate (ORR, defined as a partial response or better) supported by duration of response has expedited access to new therapies. However, the overall response rates observed with new therapeutics have surpassed 60-70% in the relapsed or refractory setting[7,8,9] and 90% in the newly diagnosed setting.[10] With the improved outcomes observed in this disease area, demonstrating statistically significant difference in overall response rates may require infeasibly large clinical trials. Additionally, more sensitive response assessments will allow for continued expeditious drug development.

MRD, which is generally assessed in the bone marrow by either flow cytometry- or sequencing-based methods with a minimum sensitivity to detect one tumor cell in 100,000 normal cells, can further quantify the depth of response to treatment beyond ORR or CR. MRD is a recognized prognostic biomarker in MM; patients who attain MRD-negativity[11] have improved long-term outcomes. The 2016 International Myeloma Working Group (IMWG) response criteria incorporated standardized definitions of MRD-negative response, which has resulted in greater inclusion of these assessments in clinical trials.[12,13] MRD has been assessed in numerous MM trials, often as an exploratory endpoint or as a secondary endpoint with control of Type I error.[14]

In this treatment landscape, there has been interest in the use of MRD as a primary endpoint for clinical trials intended to support regulatory decision-making.

Multiple groups have performed pooled analyses of clinical trial data to assess the relationship between MRD and long-term outcomes (i.e., Progression-Free Survival (PFS) and Overall Survival (OS)). FDA also performed a pooled analysis of data submitted to the Agency to evaluate this relationship. These analyses were discussed at an Oncology Drug Advisory

[5] Seigel R.L, et al. Cancer Statistics, 2023. CA Cancer J Clin.2023;73(1):17-48.
[6] Rajkumar SV. Multiple myeloma: 2022 update on diagnosis, risk stratification, and management. Am J Hematol. 2022 Aug;97(8):1086-1107.
[7]Lesokhin A.L, et al. Nature Medicine 29, 2259-2267 (2023)
[8] Chari A, et al. N Engl J Med 2022;387:2232-2244
[9] Moreau P, et al. N Engl J Med 2022; 387:495-505.
[10] Moreau P, et al. Lancet. 2019 Jul 6;394(10192):29-38.
[11] Munshi NC, et al. JAMA Oncol. 2017 Jan 1;3(1):28-35.
[12] See Kumar, *supra* note 3.
[13] Baines A, et al. Clin Cancer Res 2023; 29:2748-52.
[14] See Guidance for Industry "*Multiple Endpoints in Clinical Trials"* (October 2022).

Committee (ODAC) meeting on April 12, 2024.[15] The ODAC members unanimously agreed that it is acceptable to use MRD as an endpoint to support accelerated approval of drug or biological products intended to treat patients with MM. The ODAC meeting included discussion of appropriate time points for assessment of MRD, appropriate trial designs, and disease settings and types of therapeutics[16] where it is most appropriate to use MRD as a primary endpoint in future trials.

III. MRD AS AN ENDPOINT FOR ACCELERATED APPROVAL

A. General Drug Development Considerations

- MRD can be used as an endpoint to support accelerated approval in MM based on single-arm trials or randomized trials. Randomized trials are preferred, as they provide robust assessments for comparative safety. Given that time-to-event endpoints such as PFS and OS are also interpretable in randomized trials, sponsors can conduct one trial evaluating MRD for accelerated approval, with the trial continuing to evaluate later time-to-event endpoints (e.g., PFS/OS) to support traditional approval. Randomized trials are recommended for evaluating combination regimens.

- The control arm should ensure equipoise and be consistent with standard of care in the United States.

- The randomized trial should be designed to adequately assess long-term clinical endpoints such as PFS or ORR as key objectives. Additionally, even if not a key objective, OS should be evaluated as a secondary endpoint or as a safety endpoint.

- In a randomized trial, prior to conducting an analysis of the response endpoint used to support accelerated approval, the trial should be completely enrolled to prevent circumstances that may jeopardize the trial results or trial integrity. For example, there may be excessive drop outs in the control arm(s) if results are inadvertently unblinded at the time of the response endpoint analysis.

- Sponsors should adequately justify the assumed magnitude of treatment difference for MRD negativity rate between the arms in randomized trials. This justification can be based on data derived from a meta-analytic approach or data from the literature and should also consider the toxicity of the therapy to inform benefit-risk.

- Cross-trial comparisons to historical controls to assess whether the observed treatment effect represents an improvement over available therapy is

[15] https://www.fda.gov/advisory-committees/advisory-committee-calendar/april-12-2024-meeting-oncologic-drugs-advisory-committee-meeting-announcement-04122024.

[16] The meta-analyses discussed at the ODAC did not include trials of Chimeric Antigen Receptor (CAR) T-cell therapies in MM. The applicability of the results of these analyses to this therapeutic class is unknown.

challenging.[17] The target MRD negativity rate proposed in a single arm trial should be adequately justified. The justification should also consider the toxicity of the therapy to inform benefit-risk. This may include an assessment of the comparability of the patient populations, MRD threshold, and assay considerations, if applicable.

- If the trial is intended to evaluate a combination regimen, sponsors should specify the approach for demonstrating the contribution of each component to the effect of the combination on MRD negativity rate. Randomized trials are an appropriate design for evaluating combination regimens.

- Similarly, if the trial evaluates multiple phases of treatment (e.g., induction, consolidation, maintenance, etc.), the trial design should allow for evaluation of the contribution of each phase.

B. Trial Design and Statistical Considerations

1. Patient Population

- Use of MRD as an endpoint should be appropriately justified in the specific MM patient population/disease setting. Currently, there are insufficient data to consider the use of MRD as an endpoint to support accelerated approval in the maintenance setting and in populations such as smoldering MM, monoclonal gammopathy of undetermined significance [MGUS], extramedullary disease.

- If the sponsor plans to use MRD as an endpoint to support accelerated approval in MM trials based on a biomarker-selected population, whether to select patients with a higher risk of recurrence (i.e., prognostic biomarker) or to select patients more likely to favorably respond (i.e., predictive biomarker), additional information may be needed regarding the natural history, anticipated outcomes, etc., in that patient population, to aid in determination of the appropriateness of using MRD as an endpoint.

2. Assessments

- Trials designed with MRD as a primary endpoint should enroll patients with measurable disease as per standard criteria.

- The protocol should clearly indicate the assessment schedule for MRD endpoints and include justification for the proposed schedule.

[17] See 21 CFR 314.126(b)(2)(v).

- The protocol should ensure robust data collection for the MRD endpoints with minimal missing data.

- In randomized trials, the assessment schedule and frequency should be similar across the arms to minimize bias.

- Bone marrow aspirate assessment is required to assess achievement of CR to determine MRD negativity. The protocol should include clear instructions to ensure adequate collection of bone marrow aspirate samples to permit a robust assessment of MRD.

- In general, we recommend an independent review committee for assessment of CR.

- MRD-negative response should be assessed at the time of CR or within a specific time window of CR response (e.g., achievement of MRD negativity within +/- 3 months of CR).

- The timepoint for the analysis of the primary endpoint for MRD negativity should be prespecified and justified (e.g., 9-month or 12-month timepoint, or best MRD).

- MRD negativity should be assessed at a threshold of at least 1 in 10^5 residual tumor cells; alternate thresholds for assessing MRD negativity should be appropriately justified.

- Using bone marrow MRD-based definitions to identify relapse can be challenging since it would require frequent marrow sampling. It may be more practical to monitor for progressive disease based on standard disease response criteria.

- Currently, there are limited data on the use of imaging based MRD response endpoints or sustained MRD negativity rate to support their use as a primary MRD endpoint. Sponsors may consider including imaging based MRD response or sustained MRD negativity rate as secondary or exploratory endpoints.

3. Statistical Considerations

- The primary analysis of MRD should be based on the stated study objectives and should be detailed in a study protocol and the statistical analysis plan (SAP) to define the primary metric for decision-making based on this endpoint.

    - The primary analysis should be based on a prespecified threshold (e.g., ≤1 in 10^5)
    - The summary measure to be used for the primary analysis should be prespecified. Generally, the point estimate of the MRD negativity rate at a prespecified timepoint should be calculated, along with its exact 95% confidence interval, for the pre-specified cohort or treatment arm.
    - In a randomized trial, the difference in rates between treatment arms should be assessed, along with the 95% confidence interval. Any other measures to quantify

the treatment effect (e.g., odds ratio or other measurements) should be prespecified, and methods for analyzing these treatment effect measures should be described and justified.

  - Appropriate Type I error control should be prespecified, to include all statistical tests for MRD or any additional endpoints in the trial for which claims are intended. The use of one- or two-sided tests of statistical significance should also be clarified.
  - The primary analysis may be based on the Cochran-Mantel-Haenszel test or an exact version with stratification factors used at randomization.

- Key assumptions and justification should be detailed in the SAP, as well as any other key considerations for statistical analyses, such as the following:

  - The hypotheses that are to be tested and/or the treatment effects that are to be estimated.
  - The denominator used for the rate calculations. The denominator for the analysis of MRD response should be all treated patients (single-arm trial) or the intent-to-treat (ITT) population (randomized trial), and the numerator should be all patients who achieved the required level of MRD negativity.
  - The timepoint of the primary MRD analysis and any other key analyses.
  - Strategies for handling of missing data and any intercurrent events.
  - Known subgroups should be prospectively identified in a study, and a plan for adequate data collection within the subgroups should be specified. These subgroups should be justified, and assumptions about MRD within these subgroups should be included.
  - In a randomized trial, analyses of PFS and OS should be pre-specified. If MRD is to be assessed at an earlier timepoint, OS and PFS data at that time point may be immature; however, an evaluation of PFS to assess futility (with prespecified stopping boundaries) and OS to assess safety, may be appropriate at the time of the primary MRD assessment. Justification should be provided for appropriate timing of the PFS and OS analyses, which may occur at later timepoints.

- Provide multiple supplementary and/or sensitivity analyses of MRD based on different methods and/or assumptions to evaluate the robustness of the primary analysis results as applicable. For example:

  - Alternate thresholds for negativity (e.g., ≤ 1 in 10^4, ≤ 1 in 10^6).
  - Patients in CR or better as the denominator for MRD negativity instead of ITT
  - MRD negativity regardless of attaining CR

- Patients with missing MRD information should be considered as missing in the primary analysis and included in the denominator for assessment of MRD response.

  - Imputation methods may be used to address missing MRD data for exploratory purposes, but these methods should be prespecified and justified in the SAP.

C. Assay Considerations for MRD Evaluation

- The assay used to assess MRD (e.g., Next Generation Sequencing (NGS), Next Generation Flow (NGF)) should be appropriately validated to support regulatory decisions.

- When including an MRD assay in a clinical study protocol for the purposes of using MRD as an endpoint, sponsors should consider the MRD assay methodology and validation data supporting the assay. Sponsors should also consider the proposed context of use of the MRD assay in the study and the analytical performance information supportive of such use such as accuracy, precision, limit of detection, limit of blank, limit of quantitation, linearity, reagent and sample stability, analytical specificity, and as applicable, appropriate DNA input.

- The assay analytical sensitivity should generally be at least one log below the pre-specified MRD negativity threshold; however, the precision of the assay at the MRD negativity threshold should be considered when determining which MRD negative threshold is acceptable for the assay technology (e.g., NGS). The proposed MRD negativity threshold cutoff should be discussed with FDA.

- With sequencing assays (e.g., NGS), high baseline calibration failure rates can impact data interpretation. Calibration failure may be due to low disease burden, insufficient DNA sample, and hemodilution. Sponsors should ensure robust data collection to reduce calibration failures and missing MRD data.

- Requirements under 21 CFR Part 812 may apply when investigational devices are used to detect MRD in the trial. For additional information regarding investigational device use and requirements under the IDE regulation, see the guidance for industry *In Vitro Diagnostic (IVD) Device Studies – Frequently Asked Questions.*[18]

- FDA encourages sponsors to meet with the therapeutic product center (i.e., CDER or CBER) early in development regarding the MRD assay to ensure adequate data collection and analytical validation.

  For additional information on the use of MRD as an efficacy endpoint, see the guidance for industry *Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment* (January 2020).

[18] See guidance for industry *In Vitro Diagnostic (IVD) Device Studies – Frequently Asked Questions* at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/in-vitro-diagnostic-ivd-device-studies-frequently-asked-questions.

IV. CR AS AN ENDPOINT FOR ACCELERATED APPROVAL

CR allows for a quantification of the depth of response to treatment beyond ORR. CR is a recognized prognostic biomarker; patients who attain CR have improved long-term outcomes.[19] The 2016 International Myeloma Working Group (IMWG) response criteria incorporate standardized definitions of CR[20] and CR rate has been assessed in numerous MM trials, often as a secondary endpoint with control of Type I error.

FDA conducted a pooled analysis of clinical trial data, which demonstrated an association between CR and long-term outcomes (i.e., PFS and OS). Like MRD, CR rate can be used as an endpoint to support accelerated approval in trials evaluating drug and biological products intended to treat patients with multiple myeloma.

The general principles for the design and analysis of clinical trials that use MRD as an endpoint for accelerated approval outlined in Section III A and III B also apply to trials that propose CR rate as an endpoint for accelerated approval.

Below are additional considerations specific to using the CR endpoint:

- The CR endpoint should be assessed as overall CR rate rather than CR rate at a specific timepoint.
- Since the potential utility of CR as an endpoint is similar to that of ORR, adequate follow-up is needed in order to establish that the durability of CR is meaningful.
- Durability for CR should generally be assessed from time to achievement of CR to progression or death.

V. REGULATORY CONSIDERATIONS

For products granted accelerated approval based on MRD or CR endpoints, verification of clinical benefit will generally be required, and timely verification of clinical benefit is critical. Generally, the confirmatory trial(s) to verify the anticipated clinical benefit of a product should be underway prior to accelerated approval.[21] Sponsors may take one of the following approaches to verify clinical benefit:

- Two-trial model for accelerated approval – this approach involves use of a single arm trial using MRD and CR endpoints for accelerated approval, followed by a randomized study using an endpoint that directly measures clinical benefit (e.g., PFS or OS) to verify the anticipated clinical benefit for traditional approval.

[19] Helgi J.K, et al. Haematologica 2007;92(10):1399-1406.

[20] See Kumar, *supra* note 3.

[21] See section 506(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356(c)). We note that section 506(c)(2) of the Federal Food, Drug, and Cosmetic Act was recently amended to provide that FDA "may require, as appropriate, a study or studies to be underway prior to approval, or within a specified time period after the date of approval, of the applicable product." Pub. L. 117-328, Div. FF, § 3210(a)(1).

- Alternatively, a single randomized trial approach, designed to use MRD or CR to support initial accelerated approval, and powered for clinical benefit endpoints such as PFS and OS with follow-up from the same study to support traditional approval can be used. A single trial approach can facilitate timely verification of clinical benefit.

For additional information, refer to the guidance for industry *Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics* (March 2023).

While this guidance outlines important considerations when proposing to include MRD or CR as a primary endpoint to support accelerated approval in MM, this is an evolving area with complex trial/statistical design, drug development, and assay considerations. Therefore, we encourage sponsors to meet with the appropriate review division to discuss MM trials that incorporate MRD or CR assessment as a primary endpoint.