Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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Center for Drug Evaluation and Research (CDER)
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Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 is intended to assist sponsors planning to use minimal residual disease (MRD) as a biomarker in clinical trials conducted under an investigational new drug application (IND) or to support marketing approval of drugs and biological products[2] for the treatment of specific hematologic malignancies.

The use of MRD as a biomarker in drug development is distinct from the FDA requirement for investigation, clearance, or approval of an in vitro diagnostic device for clinical use in measuring MRD. Manufacturers interested in pursuing the development of a specific MRD assay for clinical use should consult the Office of In Vitro Diagnostics and Radiological Health in the Center for Devices and Radiological Health.

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.

[1] 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.

[2] For the purposes of this guidance, all references to *drug products* include both human drugs and biological drug products regulated by CDER and CBER unless otherwise specified.

II. BACKGROUND

Despite the development of treatments that eliminate morphologically detectable malignant cells, some patients with hematologic malignancies who have achieved complete remission or complete response (CR), even of considerable durations, will experience relapses of their diseases. Conventional morphologic detection for hematologic malignancies has a threshold limit of 1 tumor cell in 100 cells. Technology exists that can detect the persistence of malignancy at orders of magnitude below the limit of conventional morphologic detection, a level of disease burden known as MRD. These technologies can measure cell characteristics such as genetic mutations or cell surface markers.

MRD as a general measure of tumor burden has multiple potential regulatory and clinical uses as a biomarker. Depending upon the clinical setting, MRD may reflect a patient's response to treatment or it may be used as a prognostic tool to assess the patient's risk of future relapse. As such, MRD can be used to enrich clinical trial populations or to guide allocation into specific treatment arms in clinical trials. There are challenges within each context of use that need to be addressed, such as underlying disease, patient heterogeneity, therapeutic context, target of therapy, or a combination of disease parameters, to allow effective use of MRD in regulatory decision-making.

MRD assessments can vary among laboratories and technologies, which can cause discrepant results. Many clinical laboratories develop their own protocols that can affect MRD measurements. Technologies can have different performance characteristics. Sample collection procedures can also differ. However, standardized methodologies can ensure that results obtained between technologies and laboratories are consistent. This includes standardized posttreatment timing for when a bone marrow (BM) or blood sample is collected, standardized sample processing, predetermined MRD thresholds, and accurate reporting of the performance characteristics of the test (e.g., accuracy, precision, specificity, sensitivity). For example, reporting MRD negative results without information regarding limit of detection is not meaningful.

The evidence to support the clinical validity of MRD as a biomarker varies across hematologic cancer types and patient populations. To gain a better understanding of the state of the science of MRD, FDA cosponsored public workshops on MRD in acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), and acute myeloid leukemia (AML) as well as a symposium on MRD in multiple myeloma (MM) in 2012–2014. In addition, a public workshop on Minimal Residual Disease as a Surrogate Endpoint in Hematologic Cancer Trials[3] was held on September 7, 2016, under a cooperative agreement with FDA to discuss the clinical, statistical, and technical barriers to implementing use of MRD in clinical trials. As a result of these workshops and an analysis[4] of marketing applications showing inconsistent quality of

[3] The workshop meeting description is available at https://healthpolicy.duke.edu/events/minimal-residual-disease-surrogate-endpoint-hematologic-cancer-trials.

[4] Gormley N et al., 2017, FDA Analysis of MRD Data in Hematologic Malignancy Applications, J Clin Oncol, 35:2541.

MRD data, FDA identified a need to provide sponsors with guidance on use of MRD as a biomarker in regulatory submissions.

III. DEVELOPMENT OF MRD AS A BIOMARKER FOR REGULATORY USE

A. Regulatory Uses of Biomarkers

The term *biomarker* is commonly understood as referring to a characteristic that is measured as an indicator of normal biologic processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.[5] MRD can be used as a biomarker. The terminology listed below is derived from the BEST Resource[6] definitions and the guidance for industry and FDA staff *Qualification Process for Drug Development Tools*,[7] but slightly modified to reflect applicability to MRD. Sponsors can potentially use MRD status as any of the following types of biomarkers:

- **Diagnostic biomarker:** a biomarker used to detect or confirm presence of a disease or condition of interest or to identify individuals with a subtype of the disease.

- **Prognostic biomarker:** a biomarker used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest. A prognostic biomarker informs about the natural history of the disease in that particular patient in the absence of a therapeutic intervention.

- **Predictive biomarker:** a biomarker used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a drug product.

- **Efficacy-response biomarker:** a biomarker that is used to show that a response has occurred in an individual who has been exposed to a drug product.

- **Monitoring biomarker:** a biomarker measured serially and used to detect a change in the degree or extent of the disease.

[5] FDA-NIH Biomarker Working Group, 2018, BEST (Biomarkers, EndpointS, and other Tools) Resource, Silver Spring, MD: FDA; Bethesda, MD: National Institutes of Health, accessed May 25, 2018, https://www.ncbi.nlm.nih.gov/books/NBK338448/. See also section 507 of the Federal Food, Drug, and Cosmetic Act, which defines *biomarker* for purposes of that section, in relevant part, as "a characteristic (such as a physiologic, pathologic, or anatomic characteristic or measurement) that is objectively measured and evaluated as an indicator of normal biologic processes, pathologic processes, or biological responses to a therapeutic intervention."

[6] FDA-NIH Biomarker Working Group, 2018, BEST (Biomarkers, EndpointS, and other Tools) Resource.

[7] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

An efficacy-response biomarker could be a surrogate endpoint. However, more specifically, a surrogate endpoint predicts a specific clinical outcome of the patient at some later time and can be used as the basis of marketing application approval decisions. A surrogate endpoint does not measure the clinical benefit of primary interest but instead predicts the clinical benefit based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.

Understanding which of these biomarker attributes applies to the proposed use of MRD is important to consider when validating MRD for that proposed use and for the trial design. There are challenges within each MRD context of use that should be adequately justified such as underlying disease, patient heterogeneity, therapeutic context, target of therapy, or a combination of disease parameters.

B. Mechanisms for Novel Surrogate Endpoint Acceptance or Qualification

Two mechanisms exist to obtain the Agency's feedback on the use of a novel surrogate endpoint to support approval. One mechanism is through the formal drug development tool (DDT) qualification process, specifically the biomarker qualification process. The DDT qualification process is an initiative undertaken in response to the FDA's Critical Path Initiative and updated under the 21st Century Cures Act, adding section 507 to the Federal Food, Drug, and Cosmetic Act. The purpose of the DDT qualification process is to qualify a DDT for a specific context of use, such that a sponsor and FDA can rely on the DDT to have a specific interpretation and application in drug development and regulatory review. Information about a DDT that has been formally qualified for a specific context of use will be made publicly available to expedite drug development and review of regulatory applications. A qualified DDT can be included in IND, new drug application (NDA), or biologics license application (BLA) submissions without the need for FDA to reconsider and reconfirm the suitability of the DDT. The qualification of a biomarker requires robust scientific evidence, and there is a higher evidentiary standard if the biomarker is to be used as a surrogate endpoint.[8]

A second mechanism to obtain the Agency's feedback on the use of a novel surrogate endpoint to support approval is through discussions with the specific Center for Drug Evaluation and Research (CDER) or Center for Biologics Evaluation and Research (CBER) review division. In this setting, the pharmaceutical sponsor or interested group meets with the FDA review division to present scientific data in support of the proposed surrogate endpoint. These data may be from previous clinical trials conducted by the sponsor, a meta-analysis of several trials conducted in the disease area, or other data that support the use of the proposed surrogate endpoint. An example of this mechanism for a surrogate endpoint reasonably likely to predict clinical benefit is pathologic complete response in neoadjuvant treatment of breast cancer.[9] An example of a validated surrogate endpoint that used this mechanism is the surrogate of complete response at

[8] For additional information on the DDT qualification process, see the guidance for industry and FDA staff *Qualification Process for Drug Development Tools* and the DDT Qualification Programs web page at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/default.htm.

[9] See the guidance for industry *Pathological Complete Response on Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval*.

30 months in follicular lymphoma. A surrogate endpoint that is reasonably likely to predict clinical benefit can be used to support accelerated approval, and a validated surrogate endpoint can support traditional approval.[10] To explore this approach further, sponsors should request a meeting with the relevant review division.

With either approach, the strength of evidence to support surrogacy depends on 1) the biological plausibility of the relationship, 2) the demonstration in epidemiological studies of the prognostic value of the surrogate endpoint for the clinical outcome, and 3) evidence from clinical trials that treatment effects on the surrogate endpoint correspond to effects on the clinical outcome.[11]

C. Meta-Analyses for Validation of MRD as a Surrogate Endpoint

Various statistical criteria have been proposed for validating a surrogate endpoint; often, meta-analytical approaches have been used. The issues pertinent to meta-analyses have been discussed in FDA public meetings.[12]

Sponsors should discuss with the Agency and provide details of the meta-analysis plan. The meta-analysis plan should include, but should not be limited to, consideration of the following aspects:

1) Details of the trial designs, inclusion and exclusion criteria, and disease setting. The sponsor should justify the poolability of data.

2) Inclusion of trials that include a patient population representative of the population in which the surrogate endpoint will ultimately be used.

3) Inclusion of an adequate number of randomized trials with sufficient follow-up time. The sponsor should justify the number of trials to be included in the meta-analysis.

4) Inclusion of trials that demonstrated both positive and negative results.

5) Analysis based on individual patient-level data to allow an assessment of individual-level surrogacy.

6) Prespecified criteria established based on trial-level and patient-level surrogacy measures.

[10] For additional information on expedited programs, see the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*.

[11] See the ICH guidance for industry *E9 Statistical Principles for Clinical Trials*.

[12] See the notice for the public meeting on Meta-Analyses of Randomized Controlled Clinical Trials (RCTs) for the Evaluation of Risk to Support Regulatory Decisions available at https://www.federalregister.gov/documents/2013/10/24/2013-24939/meta-analyses-of-randomized-controlled-clinical-trials-rcts-for-the-evaluation-of-risk-to-support.

7) Prespecified timing and window of the MRD assessment. If a fixed time point is not feasible, the MRD assessments in a window of the trial should be prespecified. The sponsor should explore sensitivity analyses based on different time windows. The sponsor should discuss with the Agency the time window chosen. For example, the sponsor can prespecify for patients with newly diagnosed ALL, to define the MRD assessment at the time of the first complete response (CR1), 28 days plus or minus a window of a specific number of days.

8) Inclusion of long term clinical endpoints, such as event-free survival/progression-free survival (EFS/PFS) and overall survival (OS) that have been clearly and consistently defined across studies. The sponsor should explore alternative event definitions for EFS/PFS or alternative censoring schemes for EFS/PFS/OS as sensitivity analyses.

9) Discussion of missing MRD assessments and reasons for missing data (e.g., caused by sample collection issues, lost to follow-up). The sponsor should explore the effects on the results.

10) Consideration of the statistical handling of unevaluable samples.

11) Potential confounding factors, which the sponsor should incorporate into the planned validation analyses.

12) Sensitivity analyses to demonstrate the robustness of the surrogacy (e.g., alternative statistical methods for evaluation of association,[13] cross validation) and subgroup analyses.

13) Discussion of different assay cutoffs (e.g., 10^{-4}, 10^{-5}). For assisting in the interpretation of the results, the sponsor can present analyses such as surrogate threshold effect.[14]

Even if a meta-analysis supports validation of MRD as a surrogate endpoint, applying these results to a new trial requires a certain amount of extrapolation. Some caveats regarding the use of MRD as a surrogate endpoint include the following:

- Even if MRD can be validated as a surrogate endpoint, the use of MRD may not be applicable to subgroups of the patient population or future trial populations if there are important differences (e.g., prior therapy, disease status, line of treatment) between the population evaluated in the meta-analysis and the to-be-enrolled population. This may represent a different context of use, and as such, any differences should be justified. Sensitivity and subgroup analyses should be performed to evaluate the strength of the surrogate endpoint in different disease settings or patient characteristics.

[13] Shi Q et. al., 2017, Thirty-Month Complete Response as a Surrogate End Point in First-Line Follicular Lymphoma Therapy: An Individual Patient-Level Analysis of Multiple Randomized Trials, J Clin Oncol, 35(5):552.

[14] Burzykowski T and Buyse M, 2006, Surrogate Threshold Effect: An Alternative Measure for Meta-Analytic Surrogate Endpoint Validation, Pharm Stat, 5(3):173.

- When a new drug product is under investigation, it may not be reasonable to assume that the quantitative relationship between the drug product's effects on the surrogate endpoint and the clinical benefit endpoint will be the same as previously studied drug products' effects. This is especially true for drug products that have a markedly different mechanism of action (e.g., cytotoxic therapy versus immunotherapy). While this extrapolation will be primarily based on biological considerations, the meta-analyses mentioned above can provide supportive evidence. To obtain best estimates of the relationship between the surrogate and clinical benefit endpoints, the meta-analysis should include drug products with varying mechanisms of action.

D. MRD as an Endpoint in Clinical Trials

The MRD evaluable population is a subset of all patients whose disease state is in CR. The MRD evaluable population has been proposed as the analysis population for the MRD endpoint, as MRD is often only tested in patients whose disease state is in CR. The results based on this subset may be biased. Analyses based on the MRD evaluable population may not be adequate to support a regulatory submission. In general, MRD analyses should be based on the intent-to-treat (ITT) population. A patient may not have an MRD assessment because of a missed assessment, test failure, or not meeting clinical criteria for assessment (i.e., lack of CR). For ITT-based analyses, sponsors should consider any patient without an MRD assessment as not responsive to treatment. Analyses based on the MRD evaluable population are appropriate for sensitivity analyses.

Missing and unevaluable assessments of MRD should be kept to a minimum. Sponsors should collect and summarize reasons for missing MRD assessments. Sponsors should seek the Agency's advice before finalizing the statistical analysis plan. Sponsors should also perform further exploratory or sensitivity analyses to evaluate comparability of the results using different evaluation populations.

E. MRD for Patient Selection or Enrichment

Many clinical risk classifications may not be able to accurately predict relapse in patients with hematologic malignancies, which may result in inappropriate use or timing of treatments. To improve risk classification, MRD has been regarded as an important prognostic factor for predicting disease recurrence.

The sponsor can use MRD level to serve as a stratification factor, to select patients at high risk, or to enrich the trial population.[15]

[15] See the draft guidance for industry *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biologic Products.* When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

IV. TECHNOLOGY CONSIDERATIONS

A. Assay Considerations

Currently, four general technologies are used for MRD assessment in hematologic malignancies: multiparametric flow cytometry (MPFC), next generation sequencing (NGS), quantitative reverse transcription polymerase chain reaction (RT-qPCR) of specific gene fusions, and allele-specific oligonucleotide polymerase chain reaction (ASO-PCR). These cellular (MPFC) and molecular (NGS, RT-qPCR, and ASO-PCR) technology platforms have different advantages and limitations in terms of sample input, cost, robustness, and reproducibility. FDA is agnostic to which technology platform is used in clinical trials assessing MRD. However, the sponsor should fully prespecify the selected platform (in terms of assay procedure, reagents, and analysis) and analytically validate the platform for its context of use. Also, in the context of a clinical trial, ideally the sponsor should use a single technology to assess MRD to be able to compare results directly. If the sponsor includes multiple technologies in the trial and plans for the primary analysis to be based on data from multiple technologies, the sponsor should prespecify the methodology for combining these technologies into a single MRD determination and discuss this with the Agency.

Analytical validation ensures that the assay measures the analyte(s) that it is intended to measure in the intended tissue type. The process of analytical validation is defined as establishing that the performance characteristics of the assay are acceptable in terms of its sensitivity, specificity, accuracy, precision, and other relevant performance characteristics using a specified technical protocol (which may include specimen collection, handling, and storage procedures). Analytical validation is concerned with the assay's technical performance and does not address clinical utility.

MRD assay validation should encompass the entire assay system from sample collection (e.g., BM aspirate versus blood) to system output (e.g., decision-making threshold for MRD positive versus negative), and use relevant clinical samples. Additionally, the sensitivity of the MRD assay should be at least 10-fold below the clinical decision-making threshold (the definition of MRD). For example, if MRD positive or negative is defined as detection of greater or less than $1x10^{-5}$ cells, respectively, then the assay should be optimized and validated to have an analytical sensitivity of at least $1x10^{-6}$. Additionally, to ensure that the assay performance achieved in validation testing is replicated in the clinical trial, the assay protocol should be strictly adhered to in all clinical trial laboratory sites. The following sections are specific considerations for the different technology platforms.

1. Cellular Technology Platforms

Sponsors should consider the following when using cellular technology platforms for MRD assessments in clinical trials:

- Prespecify the total number of events to be collected

- Use a consistent panel of antibodies and fluorochromes, as no single antigen is specific for any neoplasm

- Consider sample stability, which may limit the utility of flow cytometry

- Use a consistent analysis template (e.g., gating strategy)

- Determine whether the therapy affects the detectability of the specific antigens targeted by the antibody panels of the flow cytometry assay

- Evaluate the potential for the flow assay to detect normal BM cells that are regenerating after chemotherapy to reduce the likelihood that those cells are misinterpreted as abnormal cells

2. Molecular Technology Platforms

Sponsors should consider the following when using molecular technology platforms for MRD assessments in clinical trials:

- Prespecify nucleic acid quantity and quality

- Consider the need for an internal control when cell number is derived from DNA content calculations because poor DNA quality may output artificially low MRD levels

- Store diagnostic samples used for clone identification in case of assay changes

- Track assay failures (i.e., failures of the assay to identify the relevant clone for a patient) and consider this failure rate for clinical endpoint calculations

3. All Technology Platforms

Sponsors should consider the following when using any technology platform for MRD assessments in clinical trials:

- Prespecify preanalytical procedures and ensure that the sample collection and storage procedures used are appropriate to obtain the desired cell population

- Take hemodilution into account (specifically, the amount of blood needed for the procedure to obtain the required number of events or amount of nucleic acid)

- Standardize all protocols and evaluation to ensure MRD measurements are comparable between laboratories

B. Sampling Considerations

Target levels of MRD for use in a regulatory setting are disease-specific and dependent upon the proposed use of the biomarker. In a clinical trial, the protocol should prespecify the measurement of MRD, which should be conducted at prespecified times, using a consistent and validated assay. The MRD assessment at a prespecified postinduction therapy time point is anticipated to be a sensitive measure of CR to induction therapy in either a frontline or relapsed/refractory setting. Consistent time point specification would provide an opportunity to assess the kinetics of an MRD response and its duration, which may provide supportive evidence of drug activity. The timing of MRD assessment is also important when considering the use of MRD before allogeneic hematopoietic cell transplantation to predict transplant outcomes.

FDA recommends that the sponsor consult the Agency regarding the incorporation of any MRD assay into a trial.

V. DISEASE-SPECIFIC CONSIDERATIONS

A. Acute Lymphoblastic Leukemia

MRD has emerged as one of the most significant prognostic factors in ALL independent of patient age, B- or T-cell origin, or genetic subtype. Additional considerations for use of MRD in ALL treatment trials include the following:

- Marrow is the preferred substrate for measurement of MRD. If blood samples are used for assessment of MRD in the clinical trial, the sponsor should include justification for using blood rather than marrow.

- CR with recovery of blood counts is the preferred time point to assess MRD. For *pediatric-inspired* regimens where the efficacy response evaluation is based on a calendar-driven time point rather than waiting for blood count recovery, at least an M1 marrow (marrow with leukemic blasts less than 5%) should be documented for the patients being assessed for MRD.

- When using MRD as an efficacy endpoint for ALL, the absence of extramedullary disease should be documented concurrently with assessment of marrow and blood counts. Note, however, that the FDA does not expect the conduct of invasive procedures to test for extramedullary disease if the procedures are not within the clinical standard of care at the time of the efficacy evaluation.

- FDA has accepted an MRD level of 0.1% or more to define patients with ALL in first or second CR with high risk of relapse. For trials that use MRD levels of less than 0.1% with CR for patient selection, the submission should include information to justify the use of the lower MRD level.

- For new drugs that have a demonstrated durable CR in patients with relapsed or refractory ALL, FDA has accepted MRD of less than 0.01% as supporting evidence of efficacy. As technologies improve and new clinical findings emerge, the level of MRD needed to support an efficacy claim may change.

B. Acute Myeloid Leukemia

The molecular heterogeneity of AML poses substantial challenges to use of MRD as a biomarker. Additional considerations for use of MRD in AML treatment trials include the following:

- Marrow is the preferred substrate for measurement of MRD. If blood samples are used for response assessment of MRD in the clinical trial, the sponsor should include justification for using blood rather than marrow.

- CR with recovery of blood counts is the preferred time point to assess MRD. If assessments are made at CR without count recovery or at lesser responses, the sponsor should include data to justify the plan.

- For the marker (e.g., cell surface or genetic mutation) selected to assess MRD, the sponsor should provide data showing that the marker reflects the leukemia and not underlying clonal hematopoiesis (false positive result). The sponsor should also describe the false-negative rate that might result from relapse from a marker-negative clone. If multiple markers and/or multiple platforms are used, the sponsor should provide an analysis of the risk of false-positive and false-negative results for each marker individually and for the panel as a whole.

- For studies of targeted therapies where the MRD marker is the target of the therapy, the sponsor can use nonclinical data to identify the mutations in the marker that are known to be sensitive to the therapy and those that are known to be resistant to the therapy. If using only the target of therapy as the MRD marker, the sponsor should provide justification for not using other MRD markers to avoid false-negative results.

C. Acute Promyelocytic Leukemia

The standard-of-care use of MRD testing and monitoring is established for the initial treatment of patients with acute promyelocytic leukemia (APL) using tretinoin with arsenic and/or anthracycline. Whether the same guidelines for use of MRD apply to other drug classes needs to be confirmed as new drugs are evaluated for initial or salvage therapy. Additional specific considerations include the following:

- Marrow is the preferred substrate for measurement of MRD. If blood samples are used for response assessment in the clinical trial, the sponsor should include justification for using blood rather than marrow.

- CR following recovery of blood counts is the preferred time point to assess MRD. If assessments are to be made at CR without count recovery or at lesser responses, the sponsor should include data to justify the plan.

- To avoid false-positive results, assessment of MRD at end of consolidation is preferred over end of induction when differentiating agents are used. For new drug products for treatment of APL, the sponsor should use data from early phase trials to establish the optimal timing for MRD assessment in the pivotal trials.

- Patients with low-risk APL who achieve confirmed MRD negativity after arsenic/tretinoin-based therapy are generally considered cured and require no further monitoring. For new drug products for treatment of APL, long-term monitoring may be required in the pivotal trial if data from early phase trials are not sufficient to confirm that MRD negativity is also durable with the new drug product.

- An MRD level less than 0.01% is generally considered negative after first-line arsenic/tretinoin- or idarubicin/tretinoin-based induction. For new drug products for treatment of APL, the sponsor should use data from early phase trials to confirm this threshold for defining MRD negativity for the new drug product.

- Although an MRD level less than 0.01% is generally considered negative after first-line treatment, marketing applications for treatment of molecular relapse may need clinical outcomes (i.e., event-free survival) if data are not available to support a proposed MRD threshold as the sole criterion for response to salvage therapy.

D. Chronic Lymphocytic Leukemia

Current literature suggests that attaining MRD negativity in CLL patients is associated with prolonged PFS and OS in patients treated with chemoimmunotherapy, independent of clinical remission status and pretreatment patient characteristics. The therapeutic paradigm with small molecule inhibitors of the B-cell receptor signaling pathway is different, and the achievement of MRD negativity and association with PFS or OS with these drug products has not yet been established. Additional specific considerations include the following:

- MRD status should be measured by a standardized method with a quantitative lower limit of detection sufficient to evaluate the prospective cutoff in the trial and at least less than 10^{-4} (0.01%). Currently, MRD is most commonly assessed using RT-qPCR and flow cytometric methods.

- A challenge in MRD testing is that CLL is a multicompartmental disease involving the BM, blood, lymph nodes, liver, and spleen; after treatment, one or more of these sites may serve as a reservoir for residual disease.

- Currently in patients with CLL, MRD is assessed in either the peripheral blood (PB) or BM. The sponsor should carefully consider for assessment the sample source, which ideally should be the same throughout the trial. This is especially important if the

therapeutic intervention differentially effects MRD measurement in PB and BM, as has been demonstrated with certain therapeutics (e.g., anti-CD20 monoclonal antibodies, alemtuzumab). With consideration of the therapy administered and the timing of assessment in relation to the therapy, it may be acceptable to use the PB as a screening assessment with confirmation in the BM if the PB suggests MRD negativity, provided the assay has adequate performance characteristics in both sources.

- MRD should be assessed in patients that are in CR. If MRD assessments are to be made in patients in other response categories (e.g., partial response (PR)), the sponsors should include data to justify the plan.

- Measurement of MRD should be conducted at the end-of treatment response assessment to fully capture the treatment effect.

E. Chronic Myeloid Leukemia

There have been dramatic improvements in clinical outcomes in patients with chronic myeloid leukemia (CML) by targeting the BCR-ABL1 oncoprotein. The detection and monitoring of MRD has become standard of care in patients with CML. Specific considerations include the following:

- Monitoring of MRD in CML should utilize assays with results based on the International Scale (IS) with the standardized baseline set to 100 percent. Molecular response is expressed as log reduction from 100 percent.

- Currently, qPCR(IS) is the preferred assay to monitor response to therapy. In general, qPCR assays with a sensitivity of more than 4.5-log reduction from the standardized baseline are recommended for the measurement of BCR-ABL1 transcripts.

- Major molecular response (MMR) is defined as BCR-ABL(IS) of less than 0.1% or more than 3-log reduction in BCR/ABL1 mRNA from the standardized baseline, if qPCR(IS) is not available.

- There is evidence that achieving an MMR predicts superior long-term clinical outcomes (PFS/EFS).

- The achievement of MMR has become a consensus goal of CML therapy, and durable MMR can be a measure of clinical benefit.

- In addition, MRD can be used to select and monitor patients who are eligible for treatment discontinuation of tyrosine kinase therapy.

F. Multiple Myeloma

There have been significant improvements in clinical outcomes of MM that have spurred interest in the use of MRD as a potential surrogate endpoint to expedite drug development. Multiple

trials have evaluated the relationship between MRD status and PFS/OS. Additional specific considerations for use of MRD in trials of new drug products for treatment of MM include the following:

- Most of the published literature to date has evaluated MRD in the newly diagnosed posttransplant setting. Fewer studies have evaluated MRD in the setting of relapsed/refractory disease or newly diagnosed patients with myeloma who are not eligible for transplant. The relationship between MRD and clinical benefit and the test performance characteristics will need to be demonstrated in each disease setting (e.g., relapsed refractory, newly diagnosed, nontransplant eligible, smoldering MM). This is especially important in disease settings such as smoldering myeloma, where there is a lower disease burden and the potential for toxicity or other nondisease related factors influence long-term outcomes.

- MRD should be assessed only in patients that are in CR. If MRD assessments are to be made in patients in other response categories (e.g., PR, very good partial response), the sponsor should include data to justify the plan.

- MRD is currently assessed using MPFC and NGS methods in the bone marrow. These methodologies are not able to detect extramedullary disease. There has been interest in the use of imaging techniques (e.g., positron emission tomography-computed tomography, magnetic resonance imaging) in combination with MRD to assess response. When considering using MRD in MM clinical trials, the sponsor should discuss with FDA how extramedullary disease will be assessed and whether imaging should be incorporated into the assessment of response.

- At this time, the relationship between MRD and clinical benefit in patients with different cytogenetic abnormalities and their associated risks is unclear. When considering using MRD in clinical trials, it may be prudent to consider the patient's cytogenetic risk. For example, given the prognostic effect of cytogenetics, the trial may benefit from stratification to ensure that there is no imbalance between the arms that would affect the MRD assessment. Alternatively, trials may be designed to intervene in patients who are MRD positive and have poor risk cytogenetics because this may represent a group at risk for particularly poor outcomes.

VI. REGULATORY SUBMISSIONS THAT UTILIZE MRD

As indicated above, FDA views MRD as a biomarker that is a reliable quantitation of tumor burden, independent of assay. As such, FDA does not foresee the need for codevelopment of an MRD assay with a drug product.[16] However, for FDA to adequately assess the safety of a

[16] A potential exception might be when the MRD marker is the direct target of the drug product under study, such as for selection of patients for treatment in a clinical trial of an Fms-related tyrosine kinase 3 (FLT3) inhibitor when the MRD assay is for a FLT3 mutation. In such a circumstance, sponsors should seek advice from FDA regarding the need for a companion diagnostic early in clinical development.

proposed clinical trial that utilizes MRD or to determine the credibility of a clinical trial outcome based in part on MRD, submissions that utilize MRD for regulatory purposes or for critical treatment purposes should include sufficient information to address the following two main issues:

- Is MRD as assessed (sample, timing, threshold, etc.) a clinically valid biomarker for the context of use (disease, disease status, type of therapy, etc.)?

- Is the MRD assay used (or to be used) in the clinical trial analytically valid for the range of results that are important to the trial?

When the MRD assay used is FDA-cleared or -approved for the context of use, identifying the assay with the required number of cells to be evaluated or the DNA input requirements will be sufficient to address these two issues in most cases. When the MRD assay is not FDA-cleared or -approved, FDA would expect additional information, such as listed in Table 1, to be submitted for review.

Table 1. Information to Assist Review of Regulatory Submissions That Utilize MRD*

IND clinical trial submission*	NDA or BLA submission*
1. Justification that MRD as used is clinically valid for the proposed context **and**	1. Justification that MRD as used is clinically valid for the context of the proposed claim **and**
2. Letter of authorization to cross-reference the investigational device exemption (IDE) or other device-related regulatory submission for information about the assay **or** • A statement of intended use; • The specific test method (including instruments, reagents, and specimen handling); • Confirmation that the lab has a process in place for reagent control; • A brief discussion of how the test method was validated analytically for each specimen type; and • A summary of the performance obtained for accuracy, precision, specificity, and sensitivity; **and**	2. Letter of authorization to cross-reference the IDE or other device-related regulatory submission for information about the assay **or** • A statement of intended use; • The specific test method (including instruments, reagents, and specimen handling); • Confirmation that the lab has a process in place for reagent control; • A brief discussion of how the test method was validated analytically for each specimen type; and • A summary of the performance obtained for accuracy, precision, specificity, and sensitivity; **AND**
3. Indicate in the clinical trial informed consent document that the MRD assay is investigational.	3. A SAS XPORT file (xpt file extension) with results of MRD testing. For each result, specify the sample type, date of sample, assay used, input quantity, assay sensitivity, and assay result.

* MRD – minimal residual disease; IND – investigational new drug application; NDA – new drug application; BLA – biologics license application.

For an IND clinical trial submission, when use of the MRD assay that is not FDA-cleared or -approved for the intended use poses a significant risk to trial subjects (e.g., eligibility criterion, allocation to a specific treatment, departures from standard of care, etc.), FDA may require an investigational device exemption for use of the assay in the clinical trial.[17] When no significant risk exists, the sponsor should submit abbreviated information about the assay (see Table 1) to the IND for review to allow FDA to confirm that the investigational plan is safe. An NDA or BLA submission should include similar information about the assay (see Table 1) in addition to a data file with the results of MRD testing.

[17] 21 CFR 812. For information on the risk determination for investigational use of devices, see the guidance for industry and FDA staff *Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff*.

606 Although general principles outlined in this guidance should help applicants with crucial
607 questions regarding potential MRD use for marketing applications, FDA recommends that
608 applicants meet with FDA before starting a drug development pathway incorporating MRD
609 assessment intended to support NDA or BLA marketing applications. FDA will ensure that
610 these meetings include a multidisciplinary team of review staff from CBER, CDER, and the
611 Center for Devices and Radiological Health as needed. Applicants can then submit protocols
612 utilizing MRD after these meetings and request a special protocol assessment for eligible
613 protocols, if they choose, that provides confirmation of the acceptability of assessments,
614 endpoints, and protocol design to support drug marketing applications. Ultimately, marketing
615 approval depends not only on the design of clinical trials but on FDA review of the results and
616 data from all studies in the drug marketing application.
617

APPENDIX A: GLOSSARY OF ACRONYMS

ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
APL	Acute promyelocytic leukemia
ASO-PCR	Allele-specific oligonucleotide polymerase chain reaction
BLA	Biologics license application
BM	Bone marrow
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CLL	Chronic lymphocytic leukemia
CML	Chronic myeloid leukemia
CR	Complete response or complete remission
CR1	First complete response
DDT	Drug development tool
EFS	Event-free survival
FDA	U.S. Food and Drug Administration
IDE	Investigational device exemption
IND	Investigational new drug application
IS	International Scale
ITT	Intent to treat
MM	Multiple myeloma
MMR	Major molecular response
MPFC	Multiparametric flow cytometry
MRD	Minimal residual disease
NDA	New drug application
NGS	Next generation sequencing
OS	Overall survival
PB	Peripheral blood
PFS	Progression-free survival
PR	Partial response
RT-qPCR	Quantitative reverse transcription polymerase chain reaction