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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**

## ***DRAFT GUIDANCE***

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For questions regarding this draft document contact (CDER) Nicole Gormley at 240-402-0210 or (CBER) Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)**

**October 2018  
Clinical/Medical**

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1                   **Hematologic Malignancies: Regulatory Considerations**  
2                   **for Use of Minimal Residual Disease in Development**  
3                   **of Drug and Biological Products for Treatment**  
4                   **Guidance for Industry<sup>1</sup>**  
5  
6

7  
8 This draft guidance, when finalized, will represent the current thinking of the Food and Drug  
9 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not  
10 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the  
11 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible  
12 for this guidance as listed on the title page.  
13

14  
15  
16 **I. INTRODUCTION**  
17

18 This guidance is intended to assist sponsors planning to use minimal residual disease (MRD) as a  
19 biomarker in clinical trials conducted under an investigational new drug application (IND) or to  
20 support marketing approval of drugs and biological products<sup>2</sup> for the treatment of specific  
21 hematologic malignancies.  
22

23 The use of MRD as a biomarker in drug development is distinct from the FDA requirement for  
24 investigation, clearance, or approval of an in vitro diagnostic device for clinical use in measuring  
25 MRD. Manufacturers interested in pursuing the development of a specific MRD assay for  
26 clinical use should consult the Office of In Vitro Diagnostics and Radiological Health in the  
27 Center for Devices and Radiological Health.  
28

29 In general, FDA's guidance documents do not establish legally enforceable responsibilities.  
30 Instead, guidances describe the Agency's current thinking on a topic and should be viewed only  
31 as recommendations, unless specific regulatory or statutory requirements are cited. The use of  
32 the word *should* in Agency guidances means that something is suggested or recommended, but  
33 not required.  
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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, all references to *drug products* include both human drugs and biological drug products regulated by CDER and CBER unless otherwise specified.

## *Contains Nonbinding Recommendations*

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### 36 **II. BACKGROUND**

37  
38 Despite the development of treatments that eliminate morphologically detectable malignant cells,  
39 some patients with hematologic malignancies who have achieved complete remission or  
40 complete response (CR), even of considerable durations, will experience relapses of their  
41 diseases. Conventional morphologic detection for hematologic malignancies has a threshold  
42 limit of 1 tumor cell in 100 cells. Technology exists that can detect the persistence of  
43 malignancy at orders of magnitude below the limit of conventional morphologic detection, a  
44 level of disease burden known as MRD. These technologies can measure cell characteristics  
45 such as genetic mutations or cell surface markers.

46  
47 MRD as a general measure of tumor burden has multiple potential regulatory and clinical uses as  
48 a biomarker. Depending upon the clinical setting, MRD may reflect a patient's response to  
49 treatment or it may be used as a prognostic tool to assess the patient's risk of future relapse. As  
50 such, MRD can be used to enrich clinical trial populations or to guide allocation into specific  
51 treatment arms in clinical trials. There are challenges within each context of use that need to be  
52 addressed, such as underlying disease, patient heterogeneity, therapeutic context, target of  
53 therapy, or a combination of disease parameters, to allow effective use of MRD in regulatory  
54 decision-making.

55  
56 MRD assessments can vary among laboratories and technologies, which can cause discrepant  
57 results. Many clinical laboratories develop their own protocols that can affect MRD  
58 measurements. Technologies can have different performance characteristics. Sample collection  
59 procedures can also differ. However, standardized methodologies can ensure that results  
60 obtained between technologies and laboratories are consistent. This includes standardized  
61 posttreatment timing for when a bone marrow (BM) or blood sample is collected, standardized  
62 sample processing, predetermined MRD thresholds, and accurate reporting of the performance  
63 characteristics of the test (e.g., accuracy, precision, specificity, sensitivity). For example,  
64 reporting MRD negative results without information regarding limit of detection is not  
65 meaningful.

66  
67 The evidence to support the clinical validity of MRD as a biomarker varies across hematologic  
68 cancer types and patient populations. To gain a better understanding of the state of the science of  
69 MRD, FDA cosponsored public workshops on MRD in acute lymphoblastic leukemia (ALL),  
70 chronic lymphocytic leukemia (CLL), and acute myeloid leukemia (AML) as well as a  
71 symposium on MRD in multiple myeloma (MM) in 2012–2014. In addition, a public workshop  
72 on Minimal Residual Disease as a Surrogate Endpoint in Hematologic Cancer Trials<sup>3</sup> was held  
73 on September 7, 2016, under a cooperative agreement with FDA to discuss the clinical,  
74 statistical, and technical barriers to implementing use of MRD in clinical trials. As a result of  
75 these workshops and an analysis<sup>4</sup> of marketing applications showing inconsistent quality of

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

<sup>4</sup> Gormley N et al., 2017, FDA Analysis of MRD Data in Hematologic Malignancy Applications, *J Clin Oncol*, 35:2541.

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

78

79

### 80 III. DEVELOPMENT OF MRD AS A BIOMARKER FOR REGULATORY USE

81

#### 82 A. Regulatory Uses of Biomarkers

83

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

91

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

94

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

99

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

103

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

106

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

109

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<sup>5</sup> 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.”

<sup>6</sup> FDA-NIH Biomarker Working Group, 2018, BEST (Biomarkers, EndpointS, and other Tools) Resource.

<sup>7</sup> 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>.

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

115  
116 Understanding which of these biomarker attributes applies to the proposed use of MRD is  
117 important to consider when validating MRD for that proposed use and for the trial design. There  
118 are challenges within each MRD context of use that should be adequately justified such as  
119 underlying disease, patient heterogeneity, therapeutic context, target of therapy, or a combination  
120 of disease parameters.

### **B. Mechanisms for Novel Surrogate Endpoint Acceptance or Qualification**

121  
122  
123  
124 Two mechanisms exist to obtain the Agency’s feedback on the use of a novel surrogate endpoint  
125 to support approval. One mechanism is through the formal drug development tool (DDT)  
126 qualification process, specifically the biomarker qualification process. The DDT qualification  
127 process is an initiative undertaken in response to the FDA’s Critical Path Initiative and updated  
128 under the 21st Century Cures Act, adding section 507 to the Federal Food, Drug, and Cosmetic  
129 Act. The purpose of the DDT qualification process is to qualify a DDT for a specific context of  
130 use, such that a sponsor and FDA can rely on the DDT to have a specific interpretation and  
131 application in drug development and regulatory review. Information about a DDT that has been  
132 formally qualified for a specific context of use will be made publicly available to expedite drug  
133 development and review of regulatory applications. A qualified DDT can be included in IND,  
134 new drug application (NDA), or biologics license application (BLA) submissions without the  
135 need for FDA to reconsider and reconfirm the suitability of the DDT. The qualification of a  
136 biomarker requires robust scientific evidence, and there is a higher evidentiary standard if the  
137 biomarker is to be used as a surrogate endpoint.<sup>8</sup>

138  
139 A second mechanism to obtain the Agency’s feedback on the use of a novel surrogate endpoint  
140 to support approval is through discussions with the specific Center for Drug Evaluation and  
141 Research (CDER) or Center for Biologics Evaluation and Research (CBER) review division. In  
142 this setting, the pharmaceutical sponsor or interested group meets with the FDA review division  
143 to present scientific data in support of the proposed surrogate endpoint. These data may be from  
144 previous clinical trials conducted by the sponsor, a meta-analysis of several trials conducted in  
145 the disease area, or other data that support the use of the proposed surrogate endpoint. An  
146 example of this mechanism for a surrogate endpoint reasonably likely to predict clinical benefit  
147 is pathologic complete response in neoadjuvant treatment of breast cancer.<sup>9</sup> An example of a  
148 validated surrogate endpoint that used this mechanism is the surrogate of complete response at

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<sup>8</sup> 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>.

<sup>9</sup> 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*.

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149 30 months in follicular lymphoma. A surrogate endpoint that is reasonably likely to predict  
150 clinical benefit can be used to support accelerated approval, and a validated surrogate endpoint  
151 can support traditional approval.<sup>10</sup> To explore this approach further, sponsors should request a  
152 meeting with the relevant review division.

153  
154 With either approach, the strength of evidence to support surrogacy depends on 1) the biological  
155 plausibility of the relationship, 2) the demonstration in epidemiological studies of the prognostic  
156 value of the surrogate endpoint for the clinical outcome, and 3) evidence from clinical trials that  
157 treatment effects on the surrogate endpoint correspond to effects on the clinical outcome.<sup>11</sup>

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

160  
161 Various statistical criteria have been proposed for validating a surrogate endpoint; often, meta-  
162 analytical approaches have been used. The issues pertinent to meta-analyses have been  
163 discussed in FDA public meetings.<sup>12</sup>

164  
165 Sponsors should discuss with the Agency and provide details of the meta-analysis plan. The  
166 meta-analysis plan should include, but should not be limited to, consideration of the following  
167 aspects:

- 168  
169 1) Details of the trial designs, inclusion and exclusion criteria, and disease setting. The  
170 sponsor should justify the poolability of data.
- 171  
172 2) Inclusion of trials that include a patient population representative of the population in  
173 which the surrogate endpoint will ultimately be used.
- 174  
175 3) Inclusion of an adequate number of randomized trials with sufficient follow-up time. The  
176 sponsor should justify the number of trials to be included in the meta-analysis.
- 177  
178 4) Inclusion of trials that demonstrated both positive and negative results.
- 179  
180 5) Analysis based on individual patient-level data to allow an assessment of individual-level  
181 surrogacy.
- 182  
183 6) Prespecified criteria established based on trial-level and patient-level surrogacy measures.
- 184

---

<sup>10</sup> For additional information on expedited programs, see the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*.

<sup>11</sup> See the ICH guidance for industry *E9 Statistical Principles for Clinical Trials*.

<sup>12</sup> 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>.



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- 185 7) Prespecified timing and window of the MRD assessment. If a fixed time point is not  
186 feasible, the MRD assessments in a window of the trial should be prespecified. The  
187 sponsor should explore sensitivity analyses based on different time windows. The  
188 sponsor should discuss with the Agency the time window chosen. For example, the  
189 sponsor can prespecify for patients with newly diagnosed ALL, to define the MRD  
190 assessment at the time of the first complete response (CR1), 28 days plus or minus a  
191 window of a specific number of days.  
192
- 193 8) Inclusion of long term clinical endpoints, such as event-free survival/progression-free  
194 survival (EFS/PFS) and overall survival (OS) that have been clearly and consistently  
195 defined across studies. The sponsor should explore alternative event definitions for  
196 EFS/PFS or alternative censoring schemes for EFS/PFS/OS as sensitivity analyses.  
197
- 198 9) Discussion of missing MRD assessments and reasons for missing data (e.g., caused by  
199 sample collection issues, lost to follow-up). The sponsor should explore the effects on  
200 the results.  
201
- 202 10) Consideration of the statistical handling of unevaluable samples.  
203
- 204 11) Potential confounding factors, which the sponsor should incorporate into the planned  
205 validation analyses.  
206
- 207 12) Sensitivity analyses to demonstrate the robustness of the surrogacy (e.g., alternative  
208 statistical methods for evaluation of association,<sup>13</sup> cross validation) and subgroup  
209 analyses.  
210
- 211 13) Discussion of different assay cutoffs (e.g.,  $10^{-4}$ ,  $10^{-5}$ ). For assisting in the interpretation  
212 of the results, the sponsor can present analyses such as surrogate threshold effect.<sup>14</sup>  
213

214 Even if a meta-analysis supports validation of MRD as a surrogate endpoint, applying these  
215 results to a new trial requires a certain amount of extrapolation. Some caveats regarding the use  
216 of MRD as a surrogate endpoint include the following:  
217

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

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<sup>13</sup> 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.

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

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- 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.<sup>15</sup>

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<sup>15</sup> 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>.

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### 266 **IV. TECHNOLOGY CONSIDERATIONS**

267

#### 268 **A. Assay Considerations**

269

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

284

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

292

293 MRD assay validation should encompass the entire assay system from sample collection (e.g.,  
294 BM aspirate versus blood) to system output (e.g., decision-making threshold for MRD positive  
295 versus negative), and use relevant clinical samples. Additionally, the sensitivity of the MRD  
296 assay should be at least 10-fold below the clinical decision-making threshold (the definition of  
297 MRD). For example, if MRD positive or negative is defined as detection of greater or less than  
298  $1 \times 10^{-5}$  cells, respectively, then the assay should be optimized and validated to have an analytical  
299 sensitivity of at least  $1 \times 10^{-6}$ . Additionally, to ensure that the assay performance achieved in  
300 validation testing is replicated in the clinical trial, the assay protocol should be strictly adhered to  
301 in all clinical trial laboratory sites. The following sections are specific considerations for the  
302 different technology platforms.

303

#### 304 *1. Cellular Technology Platforms*

305

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

308

- 309 • Prespecify the total number of events to be collected

310

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- 311 • Use a consistent panel of antibodies and fluorochromes, as no single antigen is specific  
312 for any neoplasm
- 313
- 314 • Consider sample stability, which may limit the utility of flow cytometry  
315
- 316 • Use a consistent analysis template (e.g., gating strategy)  
317
- 318 • Determine whether the therapy affects the detectability of the specific antigens targeted  
319 by the antibody panels of the flow cytometry assay  
320
- 321 • Evaluate the potential for the flow assay to detect normal BM cells that are regenerating  
322 after chemotherapy to reduce the likelihood that those cells are misinterpreted as  
323 abnormal cells  
324

### *2. Molecular Technology Platforms*

325  
326  
327 Sponsors should consider the following when using molecular technology platforms for MRD  
328 assessments in clinical trials:  
329

- 330 • Prespecify nucleic acid quantity and quality  
331
- 332 • Consider the need for an internal control when cell number is derived from DNA content  
333 calculations because poor DNA quality may output artificially low MRD levels  
334
- 335 • Store diagnostic samples used for clone identification in case of assay changes  
336
- 337 • Track assay failures (i.e., failures of the assay to identify the relevant clone for a patient)  
338 and consider this failure rate for clinical endpoint calculations  
339

### *3. All Technology Platforms*

340  
341  
342 Sponsors should consider the following when using any technology platform for MRD  
343 assessments in clinical trials:  
344

- 345 • Prespecify preanalytical procedures and ensure that the sample collection and storage  
346 procedures used are appropriate to obtain the desired cell population  
347
- 348 • Take hemodilution into account (specifically, the amount of blood needed for the  
349 procedure to obtain the required number of events or amount of nucleic acid)  
350
- 351 • Standardize all protocols and evaluation to ensure MRD measurements are comparable  
352 between laboratories  
353

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### **B. Sampling Considerations**

354  
355  
356 Target levels of MRD for use in a regulatory setting are disease-specific and dependent upon the  
357 proposed use of the biomarker. In a clinical trial, the protocol should prespecify the  
358 measurement of MRD, which should be conducted at prespecified times, using a consistent and  
359 validated assay. The MRD assessment at a prespecified postinduction therapy time point is  
360 anticipated to be a sensitive measure of CR to induction therapy in either a frontline or  
361 relapsed/refractory setting. Consistent time point specification would provide an opportunity to  
362 assess the kinetics of an MRD response and its duration, which may provide supportive evidence  
363 of drug activity. The timing of MRD assessment is also important when considering the use of  
364 MRD before allogeneic hematopoietic cell transplantation to predict transplant outcomes.

365  
366 FDA recommends that the sponsor consult the Agency regarding the incorporation of any MRD  
367 assay into a trial.

368

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## **V. DISEASE-SPECIFIC CONSIDERATIONS**

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### **A. Acute Lymphoblastic Leukemia**

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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:

378

379

380

381

- 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.

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- 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**

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406 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:

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- 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**

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434 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:

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- 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.

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- 444 • CR following recovery of blood counts is the preferred time point to assess MRD. If  
445 assessments are to be made at CR without count recovery or at lesser responses, the  
446 sponsor should include data to justify the plan.  
447
- 448 • To avoid false-positive results, assessment of MRD at end of consolidation is preferred  
449 over end of induction when differentiating agents are used. For new drug products for  
450 treatment of APL, the sponsor should use data from early phase trials to establish the  
451 optimal timing for MRD assessment in the pivotal trials.  
452
- 453 • Patients with low-risk APL who achieve confirmed MRD negativity after  
454 arsenic/tretinoin-based therapy are generally considered cured and require no further  
455 monitoring. For new drug products for treatment of APL, long-term monitoring may be  
456 required in the pivotal trial if data from early phase trials are not sufficient to confirm that  
457 MRD negativity is also durable with the new drug product.  
458
- 459 • An MRD level less than 0.01% is generally considered negative after first-line  
460 arsenic/tretinoin- or idarubicin/tretinoin-based induction. For new drug products for  
461 treatment of APL, the sponsor should use data from early phase trials to confirm this  
462 threshold for defining MRD negativity for the new drug product.  
463
- 464 • Although an MRD level less than 0.01% is generally considered negative after first-line  
465 treatment, marketing applications for treatment of molecular relapse may need clinical  
466 outcomes (i.e., event-free survival) if data are not available to support a proposed MRD  
467 threshold as the sole criterion for response to salvage therapy.  
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### **D. Chronic Lymphocytic Leukemia**

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471 Current literature suggests that attaining MRD negativity in CLL patients is associated with  
472 prolonged PFS and OS in patients treated with chemoimmunotherapy, independent of clinical  
473 remission status and pretreatment patient characteristics. The therapeutic paradigm with small  
474 molecule inhibitors of the B-cell receptor signaling pathway is different, and the achievement of  
475 MRD negativity and association with PFS or OS with these drug products has not yet been  
476 established. Additional specific considerations include the following:  
477

- 478 • MRD status should be measured by a standardized method with a quantitative lower limit  
479 of detection sufficient to evaluate the prospective cutoff in the trial and at least less than  
480  $10^{-4}$  (0.01%). Currently, MRD is most commonly assessed using RT-qPCR and flow  
481 cytometric methods.  
482
- 483 • A challenge in MRD testing is that CLL is a multicompartmental disease involving the  
484 BM, blood, lymph nodes, liver, and spleen; after treatment, one or more of these sites  
485 may serve as a reservoir for residual disease.  
486
- 487 • Currently in patients with CLL, MRD is assessed in either the peripheral blood (PB) or  
488 BM. The sponsor should carefully consider for assessment the sample source, which  
489 ideally should be the same throughout the trial. This is especially important if the

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

- 496
- 497 • MRD should be assessed in patients that are in CR. If MRD assessments are to be made  
498 in patients in other response categories (e.g., partial response (PR)), the sponsors should  
499 include data to justify the plan.
  - 500
  - 501 • Measurement of MRD should be conducted at the end-of treatment response assessment  
502 to fully capture the treatment effect.

### **E. Chronic Myeloid Leukemia**

503

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

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- 509 • Monitoring of MRD in CML should utilize assays with results based on the International  
510 Scale (IS) with the standardized baseline set to 100 percent. Molecular response is  
511 expressed as log reduction from 100 percent.
  - 512 • Currently, qPCR(IS) is the preferred assay to monitor response to therapy. In general,  
513 qPCR assays with a sensitivity of more than 4.5-log reduction from the standardized  
514 baseline are recommended for the measurement of BCR-ABL1 transcripts.
  - 515 • Major molecular response (MMR) is defined as BCR-ABL(IS) of less than 0.1% or more  
516 than 3-log reduction in BCR/ABL1 mRNA from the standardized baseline, if qPCR(IS)  
517 is not available.
  - 518 • There is evidence that achieving an MMR predicts superior long-term clinical outcomes  
519 (PFS/EFS).
  - 520 • The achievement of MMR has become a consensus goal of CML therapy, and durable  
521 MMR can be a measure of clinical benefit.
  - 522 • In addition, MRD can be used to select and monitor patients who are eligible for  
523 treatment discontinuation of tyrosine kinase therapy.

### **F. Multiple Myeloma**

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



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

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- 540 • Most of the published literature to date has evaluated MRD in the newly diagnosed  
541 posttransplant setting. Fewer studies have evaluated MRD in the setting of  
542 relapsed/refractory disease or newly diagnosed patients with myeloma who are not  
543 eligible for transplant. The relationship between MRD and clinical benefit and the test  
544 performance characteristics will need to be demonstrated in each disease setting (e.g.,  
545 relapsed refractory, newly diagnosed, nontransplant eligible, smoldering MM). This is  
546 especially important in disease settings such as smoldering myeloma, where there is a  
547 lower disease burden and the potential for toxicity or other nondisease related factors  
548 influence long-term outcomes.
  - 549
  - 550 • MRD should be assessed only in patients that are in CR. If MRD assessments are to be  
551 made in patients in other response categories (e.g., PR, very good partial response), the  
552 sponsor should include data to justify the plan.
  - 553
  - 554 • MRD is currently assessed using MPFC and NGS methods in the bone marrow. These  
555 methodologies are not able to detect extramedullary disease. There has been interest in  
556 the use of imaging techniques (e.g., positron emission tomography-computed  
557 tomography, magnetic resonance imaging) in combination with MRD to assess response.  
558 When considering using MRD in MM clinical trials, the sponsor should discuss with  
559 FDA how extramedullary disease will be assessed and whether imaging should be  
560 incorporated into the assessment of response.
  - 561
  - 562 • At this time, the relationship between MRD and clinical benefit in patients with different  
563 cytogenetic abnormalities and their associated risks is unclear. When considering using  
564 MRD in clinical trials, it may be prudent to consider the patient's cytogenetic risk. For  
565 example, given the prognostic effect of cytogenetics, the trial may benefit from  
566 stratification to ensure that there is no imbalance between the arms that would affect the  
567 MRD assessment. Alternatively, trials may be designed to intervene in patients who are  
568 MRD positive and have poor risk cytogenetics because this may represent a group at risk  
569 for particularly poor outcomes.

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## **VI. REGULATORY SUBMISSIONS THAT UTILIZE MRD**

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

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<sup>16</sup> 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.

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

581

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

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

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

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

<b>IND clinical trial submission*</b>	<b>NDA or BLA submission*</b>
<p>1. Justification that MRD as used is clinically valid for the proposed context <b>and</b></p> <p>2. Letter of authorization to cross-reference the investigational device exemption (IDE) or other device-related regulatory submission for information about the assay <b>or</b></p> <ul style="list-style-type: none"> <li>• A statement of intended use;</li> <li>• The specific test method (including instruments, reagents, and specimen handling);</li> <li>• Confirmation that the lab has a process in place for reagent control;</li> <li>• A brief discussion of how the test method was validated analytically for each specimen type; and</li> <li>• A summary of the performance obtained for accuracy, precision, specificity, and sensitivity; <b>and</b></li> </ul> <p>3. Indicate in the clinical trial informed consent document that the MRD assay is investigational.</p>	<p>1. Justification that MRD as used is clinically valid for the context of the proposed claim <b>and</b></p> <p>2. Letter of authorization to cross-reference the IDE or other device-related regulatory submission for information about the assay <b>or</b></p> <ul style="list-style-type: none"> <li>• A statement of intended use;</li> <li>• The specific test method (including instruments, reagents, and specimen handling);</li> <li>• Confirmation that the lab has a process in place for reagent control;</li> <li>• A brief discussion of how the test method was validated analytically for each specimen type; and</li> <li>• A summary of the performance obtained for accuracy, precision, specificity, and sensitivity; <b>AND</b></li> </ul> <p>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.</p>

594 \* MRD – minimal residual disease; IND – investigational new drug application; NDA – new drug application; BLA  
 595 – biologics license application.  
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597 For an IND clinical trial submission, when use of the MRD assay that is not FDA-cleared or -  
 598 approved for the intended use poses a significant risk to trial subjects (e.g., eligibility criterion,  
 599 allocation to a specific treatment, departures from standard of care, etc.), FDA may require an  
 600 investigational device exemption for use of the assay in the clinical trial.<sup>17</sup> When no significant  
 601 risk exists, the sponsor should submit abbreviated information about the assay (see Table 1) to  
 602 the IND for review to allow FDA to confirm that the investigational plan is safe. An NDA or  
 603 BLA submission should include similar information about the assay (see Table 1) in addition to a  
 604 data file with the results of MRD testing.  
 605

<sup>17</sup> 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*.

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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.

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**APPENDIX A: GLOSSARY OF ACRONYMS**

618		
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620	ALL	Acute lymphoblastic leukemia
621	AML	Acute myeloid leukemia
622	APL	Acute promyelocytic leukemia
623	ASO-PCR	Allele-specific oligonucleotide polymerase chain reaction
624	BLA	Biologics license application
625	BM	Bone marrow
626	CBER	Center for Biologics Evaluation and Research
627	CDER	Center for Drug Evaluation and Research
628	CLL	Chronic lymphocytic leukemia
629	CML	Chronic myeloid leukemia
630	CR	Complete response or complete remission
631	CR1	First complete response
632	DDT	Drug development tool
633	EFS	Event-free survival
634	FDA	U.S. Food and Drug Administration
635	IDE	Investigational device exemption
636	IND	Investigational new drug application
637	IS	International Scale
638	ITT	Intent to treat
639	MM	Multiple myeloma
640	MMR	Major molecular response
641	MPFC	Multiparametric flow cytometry
642	MRD	Minimal residual disease
643	NDA	New drug application
644	NGS	Next generation sequencing
645	OS	Overall survival
646	PB	Peripheral blood
647	PFS	Progression-free survival
648	PR	Partial response
649	RT-qPCR	Quantitative reverse transcription polymerase chain reaction
650		