BCG-Unresponsive Nonmuscle Invasive Bladder Cancer: Developing Drug and Biological Products for Treatment

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact Sundeep Agrawal (CDER/OCE) sundeep.agrawal@fda.hhs.gov , or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
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BCG-Unresponsive Nonmuscle Invasive Bladder Cancer: Developing 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 provides recommendations for the development of drug and biological products[2] for the treatment of patients with bacillus Calmette-Guérin (BCG)-unresponsive nonmuscle invasive bladder cancer (NMIBC) and is intended for pharmaceutical sponsors, the academic community, and other interested parties.[3] This guidance discusses pathological diagnosis and staging, risk stratification, and trial design, including assessment of appropriate clinical endpoints.

The specific recommendations for trial design and endpoints contained herein focus on BCG-unresponsive NMIBC. While some general principles may apply across bladder cancer contexts, sponsors should discuss with the FDA their development plans for drugs intended to treat other forms of NMIBC or muscle invasive, locally advanced, or metastatic bladder cancer.

This guidance addresses select statistical and clinical trial design issues specific to BCG-unresponsive NIMBC. These topics are further addressed in the ICH guidances for industry *E9*

[1] This guidance has been prepared by the Division of Oncology 1 in the Center for Drug Evaluation and Research (CDER) and the Oncology Center of Excellence (OCE) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

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

[3] In addition to consulting guidances, sponsors should contact the division to discuss specific issues that arise during the development of drugs for the treatment of BCG-unresponsive NMIBC.

Statistical Principles for Clinical Trials (September 1998) and *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001), respectively.[4]

This guidance, when finalized, will replace the final guidance titled *BCG-Unresponsive Nonmuscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment* published in February 2018.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. DEVELOPMENT PROGRAM

A. Early Product Development

Sponsors should conduct nonclinical studies to assess toxicity in animal models (see section II.C.2., Nonclinical Safety Considerations).[5] We also recommend that sponsors conduct nonclinical studies to demonstrate antitumor activity in NMIBC and to select the dose and schedule of the investigational drug to be evaluated in the first-in-human (FIH) trial. For intravesical therapy, six weekly installations have become a standard dosing regimen for patients with NMIBC, but few data are available to support this approach; therefore, alternative schedules may be appropriate. Once sponsors complete nonclinical studies, we recommend that sponsors design a FIH trial to evaluate safety, tolerability, pharmacokinetics, and antitumor activity and also explore the dose- and exposure-response relationships, if feasible, to select the dosage(s) to be evaluated in subsequent trials. One option to assess antitumor activity is in patients with marker lesions that can be safely left in place after resection of other areas of NMIBC.

Sponsors developing investigational drugs for BCG-unresponsive NMIBC should also consider assessing antitumor activity in a small number of patients who are awaiting radical cystectomy for BCG-unresponsive NMIBC. With this approach, only a limited window of time is available for observation of antitumor activity because surgery should not be delayed. In addition, these trials should not interfere with the use of any planned neoadjuvant systemic chemotherapy.

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

[5] We support the principles of the "3Rs" to reduce, refine and replace animal use in testing when feasible. We encourage sponsors to consult with us if it they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

B. Late Phase Development

1. Dosage Selection

Dosage selection is critical to an optimal benefit-risk balance and to the success of a late phase trial. Sponsors should consider the nonclinical data and clinical data, such as safety, tolerability, activity, and pharmacokinetics, to obtain an understanding of the dose- and exposure-response relationships of intravesically and systemically administered investigational drugs when selecting dosages to be evaluated in late phase trials. The acceptability of toxicities may be different in an earlier disease setting, such as NMIBC, compared to a later line setting; therefore different and/or lower dosages may be appropriate. A strong rationale for the choice of the dosage(s) to be evaluated should be provided before initiating late phase trials. Dosage optimization is further addressed in the draft guidance for industry *Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases* (January 2023).[6]

2. Trial Population and Entry Criteria

Given the importance of defining a homogenous population of patients with BCG-unresponsive disease for the purposes of determining available therapy and interpreting clinical trial results, sponsors should specifically define the trial entry criteria in the trial protocol and document in detail the NMIBC treatment history in the case report forms.

For the purposes of this guidance, BCG-unresponsive disease is defined as being at least one of the following:

- Persistent or recurrent Carcinoma in Situ (CIS) alone or with recurrent Ta/T1 (noninvasive papillary disease/tumor invades the subepithelial connective tissue) disease within 12 months of completion of adequate BCG therapy

- Recurrent high-grade Ta/T1 disease within 6 months of completion of adequate BCG therapy

- T1 high-grade disease at the first evaluation following an induction BCG course[7]

For the purposes of this guidance, adequate BCG therapy is defined as at least one of the following:

- At least five of six doses of an initial induction course plus at least two of three doses of

[6] When final, this guidance will represent the FDA's current thinking on this topic.

[7] Steinberg RL, Thomas LJ, Mott SL, and O'Donnell MA, 2016, Bacillus Calmette-Guérin (BCG) Treatment Failures with Non-Muscle Invasive Bladder Cancer: A Data-Driven Definition of BCG Unresponsive Disease, Bladder Cancer, 2:215–224.

maintenance therapy

- At least five of six doses of an initial induction course plus at least two of six doses of a second induction course

For patients who received partial doses or less than adequate doses of BCG therapy as prior treatment, or who received different substrains of BCG therapy not approved in the United States, see Section IIC3 for additional considerations.

Patients with BCG-unresponsive NMIBC are unlikely to benefit from further therapy with BCG and represent a unique population for the study of new therapies. The standard of care for these patients has been radical cystectomy; however, many of these patients prefer to avoid cystectomy despite the potential risk of progression to muscle-invasive or metastatic disease. Patients who elect not to undergo cystectomy can enter into trials of investigational therapies. Informed consent documents should clearly communicate the risk of tumor progression and/or recurrence, including progression to metastatic disease. Further, sponsors should evaluate these patients at defined intervals to identify persistent or recurrent disease with adequate time to allow patients to discontinue investigational drugs and proceed to other therapies.

Patients with BCG-unresponsive NMIBC include those who experienced recurrence with either papillary disease or CIS or both and who have completely resected disease, resected disease with CIS, or CIS alone at trial entry. The 2004 World Health Organization/International Society of Urologic Pathology classification system is the preferred system for tumor grading. This system categorizes tumors as papillary urothelial neoplasm of low malignant potential, low-grade, or high-grade.[8] Before initiating the trial, sponsors should assess and discuss with the FDA the need for central pathology review of tissue and urine cytology to determine patient eligibility and patient outcomes.

Because the methods of a urologist performing the cystoscopy can affect both patient eligibility and outcome, sponsors should ensure that all participating urologists perform and document their bladder examinations according to the protocol. Investigators should fully characterize a patient's disease status at or before trial entry, for example through mandatory templated biopsies in patients with CIS. Sponsors should also obtain urine cytology. The FDA considers use of biomarkers for further risk stratification exploratory at this time. To fully define the extent of disease at trial entry, sponsors should have patients with T1 disease undergo resection of the base of the lesion (the biopsy should contain muscle fibers) before trial entry to ensure the absence of muscle-invasive disease. Furthermore, for patients with high-risk disease undergoing transurethral resection of their bladder tumors, we recommend pelvic examination under anesthesia to rule out the presence of locally advanced disease. Sponsors should use imaging by computerized tomography or magnetic resonance to further evaluate patients for the presence of locally advanced disease.

[8] Miyamoto H, Miller JS, Fajardo DA, Lee TK, Netto GJ, and Epstein JL, 2010, Non-Invasive Papillary Urothelial Neoplasms: The 2004 WHO/ISUP Classification System, Pathol Int, 60(1):1–8.

Sponsors should collect data on the patient's previous anticancer therapies, the dose and timing of administrations, and the patient's responses to each therapy. If a patient has met criteria for BCG-unresponsive disease at any time during their treatment course, sponsors can consider that patient to have BCG-unresponsive NMIBC regardless of whether BCG was the most recent therapy to which the patient was exposed (i.e., not newly BCG-unresponsive). Duration of the disease-free interval following the most recent therapy prior to recurrence should be recorded, as a prolonged versus a short disease-free interval may reflect different underlying biology. Sponsors are responsible for providing evidence to demonstrate that the patient met "BCG unresponsive" criteria, even if this occurred substantially prior to enrollment. Sponsors should attempt to enroll patients who reflect the clinically relevant patient population that will take the drug if it is approved.

3. Single-Arm versus Randomized, Controlled Trial Design

Whether the patient has active disease at the time of trial enrollment is a key consideration for the recommended trial design and endpoints used to evaluate the effectiveness of an investigational drug treating BCG-unresponsive NMIBC. For patients without active disease (disease was resected at or before trial entry), the FDA recommends a randomized, controlled trial design using a time-to-event primary endpoint such as recurrence-free survival.

In contrast, patients with CIS at trial entry can be studied in either a randomized, controlled trial or a single-arm trial. In the absence of pharmacologic intervention or cystectomy, BCG-unresponsive CIS (a type of NMIBC), with or without resected disease, will persist and progress, making complete response (CR) an interpretable endpoint in the single arm setting. In BCG-unresponsive NMIBC with CIS at trial entry, a single-arm clinical trial with CR rate as the primary endpoint, supported by duration of response, can provide primary evidence of effectiveness to support a marketing application. Sponsors can include patients with completely resected lesions and no evidence of CIS in these single-arm trials but should not include them in the evaluation of the primary efficacy endpoint (e.g., CR rate). However, sponsors should include these patients in the safety analysis.

Single-arm trials are appropriate in clinical settings where a randomized, controlled trial (RCT) is either unethical or not feasible. Randomizing patients with BCG-unresponsive NMIBC to a placebo as a concurrent control raises ethical concerns. Currently, single-arm trials may be appropriate for assessment of therapies for patients with BCG-unresponsive disease (CIS with or without resected papillary disease) because the standard of care has been radical cystectomy and attainment of a durable CR may represent clinical benefit by allowing some patients to delay or forgo radical cystectomy. Sponsors should use randomized trials in clinical settings in which a control arm is feasible and/or a time-to-event endpoint is appropriate.

When deciding between a single-arm versus randomized, controlled trial design in patients with BCG-unresponsive CIS (with or without resected papillary disease), sponsors should consider the following:

- Standard of care intravesicular and systemic treatments exist for patients with BCG-unresponsive NMIBC allowing for an RCT design. An RCT is preferrable and can provide stronger evidence of effectiveness, allow for evaluation of both CIS and papillary disease, and generate comparative safety data.

- Lack of a comparator arm can make differentiating drug-related adverse events from those due to the underlying disease or other causes challenging. An inability to adequately characterize toxicity in a single-arm trial can have important implications on the assessment of overall risk-benefit.

- When the investigational therapy consists of more than one drug, assessing the contribution of effect of each drug to the combination therapy is not possible in a single-arm study. Sponsors should adequately assess the need for each drug to a combination therapy, as ineffective drugs may introduce excess toxicity without improving efficacy outcomes. Sponsors should discuss considerations around contribution of each drug of a combination therapy with the FDA.

- Time-to-event endpoints are uninterpretable in a single-arm trial. Evaluating clinically relevant long-term outcomes assessed as time-to-event endpoints (e.g., cystectomy-free interval time to progression) in a randomized trial allows for characterization of these endpoints that assess clinical benefit that is important to patients.

- Variability in key aspects of trial conduct at screening and follow up (e.g., use of advanced cystoscopy techniques, use of mandatory templated versus directed biopsies, operator-dependent conclusions on cystoscopy findings, frequency of focal CIS being completely resected by screening transurethral resection of bladder tumor (TURBT) alone) can result in challenges in assessment of disease status, evaluation of the primary endpoint, and interpretation of trial results.

Randomization allows for the balancing of known and unknown prognostic and other clinical factors and may mitigate issues related to variability that may occur in the conduct of a single-arm trial, allowing for better interpretation of trial results. Additional considerations for designing a randomized clinical trial in patients with BCG-unresponsive CIS (with or without resected papillary disease) include:

- Sponsors should consider use of a superiority design.

- Control arms should be selected from best available therapy applicable to a U.S. patient population.

- Sponsors should stratify the randomization and analysis of trials that include patients with CIS based on the type of disease (CIS alone or CIS with resected papillary disease) at trial enrollment.

- Sponsors should stratify the randomization and analysis of trials that include patients with resected papillary disease by the type of disease (e.g., Ta, T1, and grade) at trial enrollment.

- Sponsors should consider whether blinding is feasible.

- Using a randomized trial design comparing an intravesical agent(s) to systemic therapy may require additional considerations that should be discussed with the FDA prior to trial initiation.

- Sponsors should discuss the plan of formal hypothesis testing for efficacy endpoints and other statistical considerations with the FDA when designing such a trial.

4. Efficacy Endpoints

The primary efficacy endpoint in single-arm trials of patients with BCG-unresponsive NMIBC with CIS should be CR rate. Sponsors should consider the CR rate in the context of the duration of response. The CR rate can only be determined in those patients who have disease at trial entry (patients with CIS) with or without resected papillary disease. Because partial response has not been defined in this disease setting, sponsors should not use it as a response criterion. Sponsors should discuss with the FDA the minimum duration of follow-up (and, thus, the minimum duration of response) before submitting an application.

For single-arm trials of patients with BCG-unresponsive disease, the FDA defines a CR as at least one of the following:

- Negative cystoscopy and negative (including atypical) urine cytology

- Positive cystoscopy with biopsy-proven benign or low-grade NMIBC and negative cytology

For intravesical therapies with limited systemic absorption, the FDA includes, in the definition of a CR, negative cystoscopy with malignant urine cytology if both a) cancer is found in the upper tract or prostatic urethra and b) mandatory templated bladder biopsies are negative.

Intravesical instillation does not deliver the investigational drug to the upper tract or prostatic urethra. Therefore, the development of disease in these areas cannot be attributed to a lack of activity of the investigational drug. Thus, sponsors can consider patients with new malignant lesions of the upper tract or prostatic urethra who have received intravesical therapy to have achieved a CR in the primary analysis. However, sponsors should record these lesions and conduct sensitivity analyses in which these patients are not considered to have achieved a CR. A large proportion of patients with upper tract or prostatic urethral recurrence or progression despite efficacy within the bladder will be considered in the overall risk-benefit assessment.

Systemic therapies are expected to have a treatment effect throughout the urinary tract. Therefore, a patient who received systemic therapy cannot be considered to have a CR if the patient has a malignant lesion(s) in the upper tract or prostatic urethra.

For the purposes of determining the duration of a CR, the FDA defines a recurrence as findings on follow-up that no longer meet the above definition for a CR. The protocol should provide a plan for the evaluation of patients with suspicious urine cytology. Suspicious cytology does not include the presence of atypical cells. This plan should specify how a suspicious urine cytology will affect the initial definition of CR and the duration of CR. For example, the plan may include repeat cytologies or mandatory templated bladder biopsies. Regardless of the prespecified plan, all investigators should evaluate suspicious urine cytology in the same manner.

The method for assigning the dates of response and recurrence should be prespecified and consistently applied. For example, a patient with an ongoing response and suspicious cytology who later meets the criteria for recurrence without an intervening negative biopsy and/or negative or atypical cytology should be considered to have recurred on the date of the initial suspicious cytology.

One of the potential benefits of therapy for patients with BCG-unresponsive NMIBC is to avoid cystectomy. The development of low-risk/low-grade papillary lesions does not affect the decisions regarding cystectomy because these patients can be treated with transurethral resection alone. Therefore, for the purposes of these trials, sponsors should consider patients with low-risk/low-grade lesions to have achieved a CR and to have maintained this response (following resection of these low risk/low-grade papillary lesions) in the primary analysis. However, sponsors should record these lesions and the incidence and timing of TURBT and conduct sensitivity analyses in which these patients are not considered to have achieved a CR.

Although delay in radical cystectomy is considered a direct patient benefit, the variations in patient and health care provider preferences can confound the interpretation of this endpoint in randomized trials and particularly in single-arm trials. Trials should consider defining prespecified objective criteria for recommendation to undergo radical cystectomy. In all cases, sponsors should collect cystectomy as an event, which may provide supportive evidence of effectiveness. In addition, sponsors should document TURBT and disease progression to muscle-invasive and/or metastatic disease.

The trial design should prespecify whether patients with CIS who do not achieve a CR at their 3-month assessments should discontinue the investigational drug(s) because of the risk of progression. Sponsors should consider the patient's disease history, type of disease present at 3 months (e.g., T1), and the mechanism of action of the investigational drug(s). At 3 months, patients with BCG-unresponsive CIS at study entry who are at a particularly high risk of progression (e.g., new, T1 high-grade disease with or without CIS at first assessment) should discontinue the investigational drug(s). Sponsors should discuss these issues with the FDA during the development of the trial design.

In addition to durable CR in patients with CIS, time-to-event endpoints, such as event-free survival (EFS), may be appropriate as the primary endpoint in a randomized trial. Patients with persistent CIS at the first evaluation (e.g., 3 months), or after a re-induction if permitted, should be considered to have an event at the time of randomization.

For patients with papillary-only disease that was resected at or before trial entry, FDA recommends a randomized, controlled trial design using a time-to-event endpoint such as recurrence-free survival.

Given the differences in event definition and timing between patients with CIS and those with papillary-only disease, the FDA strongly recommends that efficacy be evaluated in separate cohorts. If both patients with persistent disease (i.e., CIS) and those without active disease (i.e. resected papillary disease) are enrolled in the same cohort in a randomized, controlled trial evaluating a time-to-event endpoint (e.g., EFS), differences in event definition and timing and potential disproportionate contribution of one subgroup (patients with CIS or papillary disease) to the observed efficacy results of the combined cohort may cause challenges in determination of whether substantial evidence of effectiveness has been demonstrated for both populations.

5. Trial Procedures and Timing of Assessments

During the conduct of a clinical trial, patients with BCG-unresponsive NMIBC should be followed every 3 months for 2 years, then every 6 months for 2 years, and then annually with cystoscopy, directed biopsies, and urine cytology. In addition to directed biopsies, the FDA recommends mandatory bladder biopsies based on a pre-specified template at a specific time point(s) (e.g., at the time of assessment of the primary endpoint) in single-arm trials.[9] The protocol should address the number of biopsies and the biopsy sites.

If advanced (e.g., fluorescence-guided) cystoscopy is used at baseline, the same method of assessment should be used at any visit(s) to document initial response, and during any directed or mandatory biopsies to maintain consistency in evaluation of disease status. For cystoscopy with multiple modalities (e.g., white light and fluorescence-guided), the investigator should record whether a lesion is visualized on either or both modalities.

Sponsors should use central pathology review of biopsy specimens and/or cytology for all patients in single-arm trials. For randomized trial designs, sponsors should consult with the FDA regarding the need for central pathology review.

6. Statistical Considerations

For single-arm trials of patients with BCG-unresponsive NMIBC with CIS that use CR rate as the primary endpoint, the lower bound of the 95 percent confidence interval around the observed response rate should rule out a clinically unimportant CR rate. The median duration of CR is also

[9] Gudjonsson S, Blackberg M, Chebil G, Jahnson S, Olsson H, Bendahl PO, Mansson W, and Liedberg F, 2012, The Value of Bladder Mapping and Prostatic Urethra Biopsies for Detection of Carcinoma in Situ, BJU Int, 110(2 Pt 2):E41–45.

important. A high CR rate is not meaningful if the response duration is short. The sponsor should discuss with the appropriate review division the minimum duration of response prior to the time of NDA or BLA submission. Patients participating in the trial should continue to be followed for the development of a CR and for duration of CR.

For randomized, controlled trials of patients with BCG-unresponsive CIS that use CR rate as the primary endpoint, sponsors should conduct formal hypothesis testing to compare CR rates and should meet with the FDA when planning these analyses. A statistically significant and clinically meaningful difference in CR rates should be supported by a clinically meaningful duration of response. Sponsors should also meet with the FDA to discuss statistical considerations for any endpoints other than CR rate.

7. Risk-Benefit Considerations

The approval of a marketing application is based, in part, on a favorable risk-benefit assessment. For therapies that have greater toxicity (e.g., systemic therapies), substantially greater efficacy might be needed to achieve an overall favorable risk-benefit assessment. Sponsors of clinical trials using either intravesical or systemic therapy should meet with the FDA to discuss trial design details.

C. Other Considerations

1. Risk Management Considerations

The FDA cannot make a decision concerning a risk management plan before reviewing the data included in an NDA or BLA. Sponsors should provide a plan to assess the long-term outcomes of patients receiving the investigational drug. For example, a long-term study or trial to assess bladder capacity may be needed if there was a signal in premarketing studies that the investigational drug caused bladder fibrosis.

2. Nonclinical Safety Considerations

Before sponsors initiate clinical trials in patients with BCG-unresponsive NMIBC, sponsors should use nonclinical studies to optimize the dose and schedule of intravesical drugs. A sponsor's choice and use of nonclinical models will vary with the investigational drug. The sponsor should discuss this with the appropriate review division. Sponsors also can use nonclinical studies to ensure that systemic therapies are active at the mucosal surface of the bladder and to justify the potential risks associated with systemic therapies. For drugs intended for intravesical administration, sponsors can use the extent of systemic exposure in nonclinical studies following intravesical administration to determine the need for evaluation of systemic toxicity. If systemic exposure is low, histological evaluation may be limited to locally exposed tissues. Similarly, if systemic exposure of the active substance is equivalent to or less than that of an approved route of administration for the same active substance, histological evaluation also may be limited to locally exposed tissues. The recommendations for and timing of additional nonclinical studies depend upon the available nonclinical and clinical data, the nature of the

toxicities observed, and the patient population (e.g., more advanced NMIBC such as BCG-unresponsive NMIBC). Sponsors should discuss this with the appropriate review division before conducting a clinical trial using either a systemic or intravesicular drug in patients with BCG-unresponsive NMIBC.

For recommendations on the substance and scope of nonclinical information needed to support clinical trials for cell therapy and gene therapy products, see the guidance for industry *Preclinical Assessment of Investigational Cellular and Gene Therapy Products* (November 2013)*, Clinical Considerations for Therapeutic Cancer Vaccines* (October 2013)*, and Recommendations for Microbial Vectors Used for Gene Therapy* (September 2016).

3. BCG Supply Issues

In times of BCG supply issues or when enrollment of sufficient patients who meet the prior BCG criteria in the definition of BCG unresponsive disease is not feasible, sponsors may consider inclusion of patients who received less than adequate prior BCG as defined in Section IIB2, partial doses of BCG, or alternative treatment schedules. Enrolling these patients will create uncertainty in the interpretation of endpoints such as durable CR as assessed in a single arm trial given that the outcomes in response to subsequent therapies is unknown for these patients.

Given this uncertainty, a randomized trial is recommended to allow for interpretation of results if sponsors enroll a heterogenous population with respect to prior BCG received. In a randomized trial, stratification is recommended to control for differences in exposure to prior BCG. Sensitivity analyses should assess the effect of the variability in previous BCG exposure on trial results. Labeling will reflect the enrolled population.

Currently, there are limited prospective, randomized trial data demonstrating equivalence of BCG substrains not approved in the United States to those that are approved, and it is unclear whether BCG substrains vary with respect to efficacy and safety and are applicable to a U.S. BCG-unresponsive patient population. For regulatory purposes, different substrains of BCG are not considered equivalent and each BCG substrain-derived drug product is regulated as a separate product. This has implications for trial designs in the BCG-unresponsive setting for (1) eligibility, as patients may be determined to be BCG-unresponsive based on prior treatment with substrains not approved in the United States, and (2) trial conduct, if BCG substrains not approved in the United States are used as part of combination therapy.

An adequate percentage of patients should be treated with FDA-approved BCG substrains for the results of a trial to be applicable to a U.S. population. Sensitivity analyses should be conducted to explore the effects of different BCG substrains on clinical efficacy and safety. Variation in the safety and activity of different substrains of BCG can pose a challenge in interpreting trial results. If sponsors plan to enroll patients who received prior BCG therapy with substrains not approved by the FDA, they should discuss their proposal with the appropriate FDA review division. Use of alternative control arms (e.g., non-BCG, reduced dose BCG, or alternative BCG schedules) should be supported by a rationale that includes their expected efficacy in this patient population.