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Biomarkers and Surrogate Endpoints in Clinical Studies to Support Effectiveness of New Animal Drugs

Guidance for Industry

Draft Guidance

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Additional copies of this draft guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville MD 20855, and may be viewed on the Internet at either https://www.fda.gov/animal-veterinary or https://www.regulations.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine (CVM)
July 2020

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

FDA is issuing this draft Guidance for Industry (GFI), as required under section 305 of the Animal Drug and Animal Generic Drug User Fee Amendments of 2018 (Pub. L. 115-234), to assist sponsors in incorporating biomarkers and surrogate endpoints into proposed clinical investigation protocols and applications for new animal drugs under the Federal Food, Drug, and Cosmetic Act (FD&C Act). Section 305 of Pub. L. 115-234, among other things, directed FDA to hold a public meeting for interested parties to discuss innovative animal drug investigation designs and to issue guidance addressing the incorporation of the use of such elements of investigations as complex adaptive and other novel investigation designs, data from foreign countries, real-world evidence (including ongoing surveillance activities, observational studies, and registry data), biomarkers, and surrogate endpoints into clinical investigation protocols and applications to support the effectiveness of new animal drugs.

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. Background

In the *Federal Register* of July 9, 2019 (84 FR 32749), FDA's Center for Veterinary Medicine (CVM) published a notice of a public meeting entitled "Incorporating Alternative Approaches in Clinical Investigations for New Animal Drugs" giving interested persons until August 17, 2019, to comment on the topics discussed at the public meeting and the questions published in the meeting notice (84 FR at 32750-32751).[1] On August 13, 2019, we published a notice

[1] https://www.fda.gov/animal-veterinary/workshops-conferences-meetings/public-meeting-incorporating-alternative-approaches-clinical-investigations-new-animal-drugs

announcing the extension of the comment period to September 16, 2019 (84 FR 40071). CVM received numerous comments on the topics discussed at the public meeting and the questions published in the meeting notice and those comments were considered as draft guidance was developed.

This document describes principles for designing, conducting, and reporting the results for investigations or studies including biomarkers and/or surrogate endpoints to demonstrate substantial evidence of effectiveness or a reasonable expectation of effectiveness of drugs intended for use in animals and to support the approval of a new animal drug application (NADA) or an application for conditional approval of a new animal drug (CNADA). This guidance also provides information about obtaining feedback from CVM with respect to incorporating biomarkers and/or surrogate endpoints in investigations and study protocols for new animal drugs. Other centers within FDA, including the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH), have released draft and final guidance documents on the topics of biomarkers and surrogate endpoints. This guidance document provides CVM's recommendations specific to investigations for animal drugs.

Some concepts and language in the recommendations for animal drugs are intended to be similar or the same as those in other guidance documents issued by FDA on the same or similar topics. Because these recommendations are specific to investigations for animal drugs, they have been tailored to the unique aspects of and considerations for animal drug development.

III. Scope

The purpose of this guidance is to describe how CVM intends to evaluate biomarkers, including surrogate endpoints, to determine whether they may be used to support substantial evidence of effectiveness for an NADA or reasonable expectation of effectiveness for a CNADA. In addition, this guidance describes the process by which sponsors may obtain feedback from CVM on technical issues related to the use of biomarkers before the submission of an application. This guidance does not address the use of biomarkers, including surrogate endpoints, to support technical sections of an application other than Effectiveness or Reasonable Expectation of Effectiveness.

CVM considers biomarker and surrogate endpoint evidence from individual drug sponsors in addition to evidence from the broader scientific, veterinary, and human medical communities, as applicable, as part of a development program for a specific new animal drug. CVM does not have, and is not proposing, a formal qualification[2] program to assess and qualify biomarkers, including surrogate endpoints, for use in effectiveness studies for the approval of new animal drugs, independent from their use in a specific new animal drug development program. Animal drug sponsors or other stakeholders considering qualification of a biomarker or surrogate endpoint should refer to the resources available for human drug or device development and

[2] Qualification is "a determination by the Secretary that a drug development tool and its proposed context of use can be relied upon to have a specific interpretation and application in drug development and regulatory review under [the FD&C Act]." FD&C Act § 507(e)(7).

discuss with CVM their applicability to new animal drug development before starting the qualification process.[3,4,5]

IV. Biomarkers and Surrogate Endpoints in Veterinary Medicine

A. Regulatory Framework

An NADA must include, among other things, a "scientific rationale and purpose the new animal drug is to serve: (a) Clinical purpose."[6] In this guidance, clinical purpose is equated with "intended use," which we have described as the disease or condition to be treated, prevented, mitigated, or cured or the structure or function of the body to be affected.[7] Depending on the intended use, the new animal drug's clinical purpose may provide either clinical benefits or biological effects or both. A clinical benefit is defined as a clinically meaningful effect of a drug on how an animal feels, functions, or survives. A biological effect is defined as a meaningful effect on the structure or function of the body or a clinically relevant pathophysiologic manifestation or characteristic of a disease or condition. Sponsors must submit substantial evidence of effectiveness consisting of one or more adequate and well-controlled studies to demonstrate that a new animal drug is effective for each intended use and associated conditions of use.[8] Generally, a sponsor should use endpoints that provide direct evidence of the effectiveness of the intervention with respect to the intended use. This may include the use of biomarkers alone or in conjunction with clinical or biological outcomes as primary variables or, where appropriate, the use of a biomarker as a surrogate endpoint. Surrogate endpoints should predict either the intended clinical benefit or biologic effect.

B. Biomarkers as Drug Development Tools

Sponsors may choose to use biomarkers as a part of early animal drug development or within clinical effectiveness studies. A context of use (COU) is a statement that fully and clearly describes the way the biomarker is to be used and the drug product development-related purpose of the use.[9] Depending on its intended COU, the use of previously accepted biomarkers, including those used as surrogate endpoints, may require limited justification. However, for the use of novel biomarkers, the individual sponsor may be

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[3] https://www.fda.gov/drugs/drug-development-tool-qualification-programs/cder-biomarker-qualification-program

[4] https://www.fda.gov/medical-devices/science-and-research-medical-devices/medical-device-development-tools-mddt

[5] See Draft GFI, "Biomarker Qualification: Evidentiary Framework," dated December 2018. When final, this guidance will represent FDA's current thinking on this topic.

[6] 21 CFR 514.1(b)(2)(ii)

[7] Please see 62 FR 59830 at 59831 (November 5, 1997), which describes the characteristics of substantial evidence of effectiveness.

[8] 21 CFR 514.4(b)(2)

[9] https://www.ncbi.nlm.nih.gov/books/NBK338448/#IX-C

responsible for providing evidence supporting all aspects of the proposed biomarker and its proposed COU.

C. Biomarkers as Surrogate Endpoints

Sponsors of new animal drugs may propose to use a biomarker as a surrogate endpoint to predict a clinical benefit or biological effect. If a surrogate endpoint is known to predict a clinical benefit or biological effect, it could be used to support substantial evidence of effectiveness. Biomarkers that have not been fully established as surrogate endpoints may be used to demonstrate a reasonable expectation of effectiveness for conditional approval of certain new animal drugs.[10] The animal drug's effectiveness would then be verified in studies using an established outcome to demonstrate substantial evidence of effectiveness. For sponsors seeking to establish a biomarker as a validated surrogate endpoint, see section IX. *Establishing a Biomarker as a Surrogate Endpoint for Effectiveness Studies* below.

V. Explanation of Applicable Terms for Use within this Document

The terms related to biomarkers and study endpoints have been used and understood in different ways in the various contexts of animal drug development. This section of the guidance seeks to provide consistent, clear definitions of terms related to biomarkers and clinical study endpoints for new animal drug approvals.

A. Biomarker

CVM considers a biomarker to be a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. More simply, biomarkers are measures that can help characterize a baseline state, a disease process, or a response to a treatment. Therefore, they can reflect physiological states, disease characteristics or processes, or pharmacological responses in animals. A biomarker does not assess how an individual feels, functions, or survives, (i.e., it does not assess the clinical benefit). In contrast to a biomarker, an assessment of how an individual feels, functions, or survives is referred to as a clinical outcome assessment.[11] Clinical outcome assessments can be made through reports by a clinician, a patient, or a non-clinician observer or through a performance-

[10] The Minor Use and Minor Species Animal Health Act (21 U.S.C. 360ccc) allows for the conditional approval of new animal drugs intended for use in minor species (those other than horses, dogs, cats, cattle, pigs, turkeys, and chickens) or for minor uses in major species (i.e., MUMS drugs). The Animal Drug and Animal Generic Drug User Fee Amendments of 2018 (ADUFA IV) expanded the conditional approval pathway to include new animal drugs that are intended to treat a serious or life-threatening disease or condition or address an unmet animal or human health need and for which it is determined that a demonstration of effectiveness would require a complex or particularly difficult study or studies. The need to develop a biomarker for an effectiveness endpoint, such as a surrogate endpoint, would qualify for expanded conditional approval assuming all other criteria are met. See CVM Draft GFI #261, "Eligibility Criteria for Expanded Conditional Approval of New Animal Drugs" dated September 2019. When final, this guidance will represent FDA's current thinking on this topic.

[11] https://www.fda.gov/about-fda/clinical-outcome-assessments-coa-frequently-asked-questions#COADefinition

based assessment. Therefore, biomarkers are not themselves assessments of a clinical outcome.

Biomarkers are organized by type and category. The biomarker source or material for measurement determines the biomarker type (e.g., molecular, histologic, radiographic, physiologic characteristic, etc.). The biomarker's use determines the biomarker category (e.g., susceptibility/risk, diagnostic, monitoring, prognostic, predictive, pharmacodynamic/response, or safety). For example, a susceptibility/risk biomarker is used to assess an apparently healthy individual's risk of developing a disease or medical condition and may be based on a molecular, histologic, radiographic, or physiologic characteristic. Changes in biomarkers after treatment reflect a biological response to the drug product and may predict or identify safety problems related to a drug candidate (a safety biomarker) or reveal a pharmacological activity expected to predict an eventual desired outcome from treatment (a pharmacodynamic/response biomarker). These also may be based on a molecular, histologic, radiographic, or physiologic characteristic.

A biomarker test is an assessment system used to detect or measure a biomarker and comprises three essential components: (1) source or materials for measurement; (2) an assay for obtaining the measurement; and (3) method and/or criteria for interpreting those measurements. Examples of biomarker tests include an instrument or method for measuring physiologic variables such as blood pressure, heart rate, or body temperature; a test for measuring an enzyme in blood; or a medical imaging tool used to measure tumor size.

B. Validation

Adequate and well-controlled studies must use a method of selecting animals that provides adequate assurances that the animals are suitable for the purposes of the study (21 CFR 514.117(b)(5)) and methods to assess animal response (endpoints/outcomes) that are well-defined and reliable to establish effectiveness relative to the proposed clinical purpose (intended use) of the new animal drug (21 CFR 514.117(b)(8)). Use of fit-for-purpose biomarkers is one way to meet these characteristics of an adequate and well-controlled study. Fit-for-purpose is a conclusion that the level of validation associated with a biomarker is sufficient to support its COU.

Validation is a process to establish that the performance of a test, tool, or instrument is acceptable for its intended purpose. Biomarker test validation (analytical validation) is separate from validation of the biomarker itself (clinical validation). Validation of biomarker tests is important because reliable tests help ensure the quality of the biomarker data obtained. Analytical validation is a process to establish that the performance characteristics of a test, tool, or instrument 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). This is validation of the test's, tool's, or instrument's technical performance but is not validation of the item's usefulness. (See section VI. *Analytical Considerations* for additional discussion on this topic.) In contrast, clinical validation is a process to establish that the test, tool, or instrument acceptably identifies, measures, or

predicts the concept of interest. For biomarkers this means establishing that the biomarker's relationship with the outcome of interest is acceptable for the proposed COU. Analytical validation and clinical validation are distinct processes. However, the two processes are iterative and dependent on one another. A reliable test should be used to measure the biomarker. Through this iterative process, experience with the biomarker and the biomarker test could lead to improvements in the technical performance of the test and the understanding of the biomarker's biological and clinical significance.

C. Endpoint and Outcomes

Within this guidance document, CVM considers a study outcome to be a measurable characteristic (e.g., clinical outcome assessment, biological outcome assessment, or biomarker) that is influenced or affected by an individual's baseline state or an intervention to evaluate what happens to individuals in a clinical trial; whereas endpoints are the analyzed parameter intended to reflect an outcome of interest. Endpoints are defined based on the type of assessments made, the timing of those assessments, the assessment tools used, and possibly other details, as applicable, such as how multiple assessments within an individual are to be combined. For example, for an analgesic drug intended to control post-operative pain, the study outcome may be the pain scale, whereas the endpoint encompasses how the pain scale is assessed, such as the classification of that score into the analyzed parameter of "success" or "failure." The most reliable study outcomes are those that directly measure the clinical benefit or biological effect.

CVM considers a clinical outcome to be an outcome that describes or reflects how an individual (i.e., the animal) feels, functions or survives. Clinical outcomes generally correspond to therapeutic indications for the diagnosis, cure, mitigation, treatment, or prevention of disease. Examples of clinical outcomes are clinical outcome assessments, such as rating scales for pain or clinical scoring systems for bovine respiratory disease. In some cases, biomarkers may be combined with clinical outcome assessments to establish effectiveness of a new animal drug.

In the context of this guidance document, CVM considers a biological outcome to be an outcome that describes or reflects an effect on the structure or any function of the body of a target animal; a consumer's response to or evaluation of products, such as meat or milk, derived from the target animal; or a molecular, histologic, radiographic, or physiologic characteristic (i.e., biomarker) of a recognized disease or condition. Biological outcomes may correspond to either production or therapeutic indications, depending on the intended biological effect of the drug. Examples of biological outcomes include the measurement of average daily gain for a production drug, measurement of the carriage or shedding status of a human pathogen, assessment of meat aroma and flavor, or the measure of the infection level of a gastrointestinal nematode using worm counts.

D. Surrogate Endpoints

For new animal drugs, CVM considers a surrogate endpoint to be an endpoint that is used in clinical studies as a substitute for a direct measure of a biological or clinical outcome (Myers et al., 2017). In other words, an effect on the surrogate endpoint predicts a

clinical benefit or biological effect based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence rather than measure the effect directly.

Surrogate endpoints are used when a clinical or biologic endpoint might take a very long time to study, or in cases where the relationship between the change in the clinical or biological outcome and the change in the surrogate endpoint is well understood. Generally, clinical studies are needed to show that surrogate endpoints can be relied upon to predict, or correlate with, a clinical benefit or biological effect. A surrogate endpoint is considered validated after a sponsor demonstrates a clear mechanistic rationale and submits strong evidence that an effect on the surrogate endpoint predicts a clinical benefit or biological effect. When establishing a biomarker as a surrogate endpoint, it is important to have a high level of confidence in the biomarker test's analytical performance when confirming the relationship between a biomarker and the clinical benefit or biological effect of interest, and generally, studies intended to confirm this relationship should be conducted using a validated test.

Validation is especially important when a surrogate endpoint biomarker is the basis for a conclusion about safety or substantial evidence of effectiveness of a new animal drug. A biomarker that fails to represent disease processes or structural or functional changes and the intended effectiveness of the new animal drug may lead to erroneous decisions (either for approval or not) in new animal drug evaluation, even if the test for the biomarker is analytically valid. If the effect of treatment on the biomarker does not adequately reflect the effect on the traditionally accepted clinical or biological outcome, erroneous conclusions might be drawn about the safety or effectiveness of the new animal drug.

A reasonably likely surrogate endpoint is an endpoint supported by strong mechanistic and/or epidemiologic rationale such that an effect on the surrogate endpoint is expected to be correlated with an outcome of primary interest, but without sufficient clinical data to show that it is a validated surrogate endpoint.

VI. Analytical Considerations

Academic researchers, pharmaceutical companies, and diagnostic companies have published white papers and reviews in an effort to establish "best practices" and industry standards for analytical validation of biomarkers. FDA's guidance for industry, "Bioanalytical Method Validation,"[12] incorporates recommendations only pertaining to the validation of assays to measure in vivo biomarker concentrations in biological matrices such as blood or urine. Because biomarkers can be used for a wide variety of purposes during drug development, a fit-for-purpose (FFP) approach should be used when determining the appropriate extent of method validation. The guidance suggests that the approach used for drug assays should be the starting point for validation of biomarker assays, although the FDA realizes that some characteristics may not apply or that different considerations may need to be addressed.

[12] See GFI, "Bioanalytical Method Validation" (May 2018).

Not all biomarkers are evaluated using assays. Some are measured by imaging, rulers, scales, or other measuring devices. Therefore, the analytical validation studies and performance characteristics vary greatly according to the biomarker type (molecular, histologic, radiographic, and physiologic characteristic) and technology of the biomarker test.[13] The specifics of the validation methodology will depend on the measurement technology, the biomarker, and COU. However, in general, the validation of the analytical procedure should determine if the measurement method is able to discriminate the change in the biomarker needed to support clinical validation, and a validation should demonstrate that measured changes, as applicable, are acceptable for the COU.

Specific recommendations for assessing the performance characteristics of biomarker measurements other than assays are beyond the scope of this guidance. However, the analytical validation process of a biomarker measurement method is similar regardless of the biomarker type, technology used for biomarker measurement, or the proposed COU and generally includes the following:

- Description of the biomarker measurand(s) and measurement approach;
- Technical protocols to limit introduction of variability and improve reliability;
- Performance characteristics of the measurement method; and
- Analytical validation to ensure performance under COU conditions is suitable (accurate and reliable).

Unlike the predefined acceptance criteria established for small and large molecule pharmacokinetic assays, determining assay acceptance criteria for biomarker assays is likely the most challenging exercise for a biomarker assay validation (Piccoli and Sauer, 2019). It should be emphasized that the acceptance criteria for biomarker assays will depend heavily on the intended use of the assay and should be based on physiological variability as well (Lee et al., 2006). Analytical validation includes evidence to demonstrate that the test provides accurate and precise measurements, including the determination of a cutoff, if necessary, for the interpretation of the biomarker results. The cutoffs should be defined before the biomarker test is analytically validated. Sufficient data should be provided to adequately describe the performance characteristics of the tool. Commercial availability of a test does not automatically imply that it has sufficient analytical validation for its proposed COU.

As stated above, the FFP approach with validation criteria that are appropriate for the intended use of the resulting data should be used. Whenever appropriate, recommendations and acceptance criteria in FDA's 2018 Bioanalytical Method Validation GFI should generally be considered during method validation. Accordingly, analytical method validation for biomarker assays should include the following analytical parameters.

[13] See Draft GFI, "Biomarker Qualification: Evidentiary Framework," dated December 2018. When final, this guidance will represent FDA's current thinking on this topic.

Accuracy

The accuracy, sometimes termed "trueness," of an analytical procedure expresses the closeness of the determined value to the value that is accepted either as a conventional true value or an accepted reference value. It is calculated as (the determined value/the true value) x 100%. Accuracy should be established using at least three independent chromatographic assay runs or six ligand binding assay (LBA) runs; four to five quality control (QC) levels per run (lower limit of quantification (LLOQ), low (L), middle (M), high (H), upper limit of quantification (ULOQ)); and three chromatographic assay replicates or five LBA replicates per QC level.

Precision

The precision of an analytical procedure expresses the closeness of agreement (i.e., degree of scatter) among a series of measurements obtained from multiple sampling of the same homogenous sample under the prescribed conditions. Precision encompasses repeatability and reproducibility and is expressed as the percent coefficient of variation of a series of measurements.

- Repeatability is the closeness of agreement between results of successive measurements of the same samples carried out in the same laboratory under the same operating conditions within short intervals of time (Lee et al., 2006).

- Reproducibility is the closeness of agreement of results measured under significantly changed conditions (e.g., inter-laboratory or alternate vendor of a critical reagent) (Lee et al., 2006).

Precision should be established using at least three independent chromatographic assay runs or six LBA runs; four to five quality control (QC) levels per run (LLOQ, L, M, H, ULOQ); and three chromatographic assay replicates or five LBA replicates per QC level.

Sensitivity

Sensitivity is defined as the lowest analyte concentration in the matrix that can be measured with acceptable accuracy and precision (i.e., LLOQ).

Specificity

Specificity is the ability of the method to unequivocally assess the analyte in the presence of other components that are expected to be present (e.g., impurities, degradation products, matrix components, etc.). The method specificity should be assessed for interference by cross-reacting molecules, concomitant medications, bio-transformed species, etc. Sponsors should make a scientific judgment about the need to assess these (and any other) potential interferences during method development.

Selectivity

Selectivity is the extent to which the method can determine a particular compound in the analyzed matrices without interference from matrix components. Selectivity should be

established by analyzing blank samples of the appropriate biological matrix from at least six individual sources in chromatographic assays, or at least 10 individual sources in LBAs. For LBAs, it is important to investigate any interference originating from structurally or physiologically similar analytes (i.e., exogenous interference) or matrix effects (i.e., endogenous interference). Matrix effects evaluation involves comparing calibration curves in multiple sources of the biological matrix against a calibration curve in the matrix for parallelism (serial dilution of incurred samples) and nonspecific binding.[14]

Parallelism

Parallelism is the extent to which the dose-response relationship between two materials (i.e., calibrator versus unknown specimens) is constant for the examined range of concentrations (Piccoli and Sauer, 2019). The absence of suitable blank matrices means that many biomarker assays use calibrators prepared in a substitute matrix that differs from the test sample matrix (Lee et al., 2006). If study samples are available, parallelism between the calibration standard curve and serially diluted study samples should be assessed to detect possible matrix effect or differing affinities for metabolites (EMA, 2011). A minimum of four serial dilutions of each sample should be performed (Piccoli and Sauer, 2019). Parallelism between dilution curves, where dilution of test samples in the range of the calibration curve does not result in substantially different extrapolated analyte concentrations, validates the use of the substitute matrix for calibrator preparation. Results of these experiments may also define suitable dilution ranges should dilution be necessary to alleviate matrix effects (Lee et al., 2006).

Quantification (Calibration) Range

Quantification (Calibration) Range is the range of concentrations, including the ULOQ and the LLOQ that can be reliably and reproducibly quantified with accuracy and precision with a concentration-response relationship.

The choice of a curve fitting model for calibration curves should be tailored to each analytical method because of the wide variety of assay formats and analytes in biomarker applications (Lee et al., 2006). The simplest regression model for chromatographic methods and a four- or five-parameter logistic model for LBAs are usually used, but other models may be acceptable with justification.[15] The appropriate calibration model should be confirmed with at least six validation runs, with a blank and at least six, non-zero calibrator levels analyzed per each validation run.

Stability

During method development, the sponsor should determine the chemical stability of an analyte in a given matrix under specific conditions for given time intervals, including the effects of sample collection, handling, and storage of the analyte. The sponsor should assess autosampler, benchtop, processed or extracted sample, freeze-thaw, stock solution, and long-term stability of

[14] See footnote 11.

[15] See footnote 11.

the analyte. The sponsor should assess the stability in the same matrix as that intended for in-study samples; however, when the matrix is rare, the sponsor may explore the use of suitable surrogate matrices. Stability determinations should be performed using at least three replicates at L and H QC concentrations.

Sample Integrity

Results from biomarker assays are valid only if sample integrity is maintained from sample collection through analysis. Early, consistent application of predefined sample collection and handling techniques is especially important when such manipulations might affect sample and/or biomarker integrity. Provision of a detailed sample collection and storage protocol and adequate training of clinical trial site personnel are especially important when extraordinary measures are necessary to assure analyte integrity (Lee et al., 2006).

In-study Use of Validated Biomarker Assays

The sponsor should ensure that the assay continues to perform as per predefined specifications in each study run (i.e., to ensure the assay remains in control) (Lee et al., 2006), by use of appropriate QC samples (typically L, M, and H QCs, in duplicate at each level); using the same curve fitting method, weighting, and goodness-of-fit test determined during the validation stage; by performing incurred sample reanalysis; and reanalysis of samples based on reasons described in a preexisting standard operating procedure.[16] The specific recommendations and acceptance criteria for in-study use of bioanalytical methods in GFI, "Bioanalytical Method Validation," could be used as a general guidance. However as in the validation stage, these recommendations may be modified with justification, depending on the specific type of bioanalytical method.

VII. Biomarker Use in Effectiveness Studies

A. Context of Use

The information and level of evidence needed to support the use of a biomarker as part of the development plan to establish the effectiveness of a new animal drug will depend on its COU. For a new animal drug, the COU includes two components: (1) the biomarker category; and (2) the biomarker's proposed use in drug development. The biomarker may have multiple COUs in a drug development plan. If a sponsor is considering the use of a biomarker in an effectiveness study, CVM encourages sponsors to discuss their proposed COU with CVM early in the development process. Early communication with CVM is especially important if the biomarker is to be an outcome used as the basis of a decision regarding substantial evidence of effectiveness.

1. Biomarker category:

Biomarkers can be disease-related or treatment-related and should be classified according to the following list:

[16] See footnote 11.

- diagnostic biomarker: a biomarker used to detect or confirm presence of a disease or condition of interest to identify individuals with a subtype of a disease;

- monitoring biomarker: a biomarker measured serially for assessing the status of a disease or medical condition or for evidence of exposure to (or the effect of) a medical product or an environmental agent;

- pharmacodynamic/response biomarker: a biomarker used to show that a biological response has occurred in an individual exposed to a medical product or an environmental agent;

- predictive biomarker: a biomarker used to identify individuals more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a medical product or an environmental agent;

- prognostic biomarker: a biomarker used to identify the likelihood of a clinical event or disease recurrence or progression in individuals having the disease or medical condition of interest;

- safety biomarker: a biomarker measured before or after an exposure to a medical product or an environmental agent to indicate the likelihood, presence, or extent of toxicity as an adverse event; and

- susceptibility/risk biomarker: a biomarker that indicates the potential for developing a disease or medical condition in an individual not currently having clinically apparent disease or the medical condition.

2. Proposed use in drug development

The proposed use in drug development (pertinent to the effectiveness plan) should include a consideration of the following points, as appropriate.

a) Purpose of use in drug development (e.g., a diagnostic biomarker to define enrollment criteria in a clinical study; a prognostic biomarker to support enrichment of a field study for a particular disease; a safety biomarker to evaluate drug-induced liver injury within a field effectiveness study; or a pharmacodynamic/response biomarker as an outcome to demonstrate drug effectiveness). Sponsors should discuss the biomarker's purpose of use in drug development in the context of the proposed clinical purpose for the new animal drug (e.g., indication for use). If a biomarker is being used as a primary endpoint in an effectiveness study, the biomarker's proposed use should include whether the biomarker will be used alone or together with other biomarkers or clinical endpoints or if the biomarker is being proposed as a surrogate endpoint.

b) Proposed stage of drug development (e.g., exploratory/discovery phase, dosage characterization, reasonable expectation of effectiveness, and/or substantial evidence of effectiveness).

c) Clinical study population or model system (e.g., healthy animals; animals undergoing surgery or diagnosed with a particular disease; cultured white blood cells; etc.).

d) Mechanism of action (MOA) of the new animal drug for which the biomarker is intended to have value, provided that the MOA is relevant to the biomarker's biology and the intended effect of the new animal drug (e.g., both the MOA and the biomarker are within the same biologic pathway or process) (Fleming and Powers, 2012).

Sponsors should consider, and in some cases submit to CVM for comment, an assessment of the benefits and risks[17] of the use of the biomarker for the proposed COU, as well as any potential risk mitigation strategies. The overall balance of benefits, risks, and risk mitigation efforts are important to determine the level of evidence needed to support the use of the biomarker.

The potential benefits of a biomarker for use in drug development depend on the biomarker's proposed COU. Biomarker use could benefit study animals participating in clinical trials (e.g., earlier identification of toxicity with a safety biomarker) or general drug development and regulatory decision making (e.g., a prognostic or predictive biomarker used to enrich a patient population might reduce the sample size needed to achieve statistical significance).

The potential risks of using a biomarker in the effectiveness assessment of a new animal drug should address the consequences of incorrect decision making or harm to study animals if the biomarker does not perform as expected and should consider factors that might mitigate harm. For example, if a pharmacodynamic/response biomarker fails to accurately establish the effectiveness of a new animal drug, study animals may be unnecessarily used in a clinical study and an effective drug may not actually be approved. Alternatively, if a pharmacodynamic/response biomarker without sufficient validation is used in a clinical study and appears to demonstrate effectiveness, where effectiveness does not exist, there is the risk of approving an ineffective new animal drug. These risks (e.g., inaccurately establishing effectiveness) could be mitigated, in part, by using the proposed biomarker along with clinical outcomes or other biological outcomes as part of a multi-component endpoint, rather than as a stand-alone assessment for the establishment of effectiveness. In another example, a prognostic biomarker intended for clinical study enrichment might fail to identify study animals with more rapid disease progression. In this case, the mitigation strategies might include incorporating an interim analysis for sample size re-estimation.

[17] The terms "benefit," "risk," and "risk mitigation" that are used in the context of biomarker evaluation for new animal drugs have specific meanings that are relevant to biomarker development and evaluation, and these meanings are separate and distinct from how these terms are used in the context of evaluating the safety and effectiveness of medical products.

Evidence to support biomarker use consists of data to support analytical validation and clinical validation. The level of evidence needed to use a biomarker in the generation of data to demonstrate the effectiveness of a new animal drug will depend on how the biomarker is used. Ultimately, whether there is sufficient evidence to support the use of a biomarker in the effectiveness evaluation for a new animal drug depends on the selection of the appropriate biomarker for the proposed COU, the quality of the biomarker measurement, and if necessary, the correlation of the biomarker with the outcome of interest.

B. Considerations for Different Stages of Drug Development

Exploratory/discovery phase

During early drug development, sponsors may use biomarkers to identify reasons for differences between responders and non-responders to a drug (e.g., using certain genetic markers), which is important to inform later study designs, such as enrichment strategies, and potentially the development of companion diagnostic tests; development of prognostic information to understand the natural history of a disease; or to identify potential disease targets for therapy.

Dosage characterization

For the purposes of dosage characterization, sponsors should submit a justification of the dosage (dose or dose range, dosing frequency, and the dosing duration) and a characterization of the critical aspects of the dose response relationship related to each intended use and associated conditions of use. Dosage characterization information may be derived from dose titration studies, pilot studies, foreign studies, or scientific literature. A biomarker, such as a pharmacodynamic marker, may also be used to select the dosage to be used in studies to demonstrate reasonable expectation of effectiveness or substantial evidence of effectiveness. Although CVM does not expect the sponsor to submit a discussion of the COU, or an assessment of the benefits and risks of the use of a biomarker for the purposes of dosage characterization, sponsors should consider the quality of the analytical and clinical validation, the reliability of the biomarker(s) used for dosage characterization, and the impact of the biomarker use on the drug development plan and on the confidence in the dosage selection for use in studies to demonstrate reasonable expectation or substantial evidence of effectiveness.

Reasonable expectations of effectiveness

CVM would not expect biomarkers used in studies to demonstrate reasonable expectation of effectiveness (for conditional approval, as described in Section IV of this guidance) to have the same level of analytical and/or clinical validation as biomarkers used as primary endpoints in studies used to demonstrate substantial evidence of effectiveness. However, insufficient analytical and/or clinical validation could lead to a failure to accurately predict effectiveness in studies used to generate substantial evidence of effectiveness.

A need to develop and "qualify" effectiveness endpoints such as biomarkers to conduct the clinical study to demonstrate substantial evidence of effectiveness may qualify a

project for the expanded conditional approval pathway if all other requirements for conditional approval are met.[18]

Substantial evidence of effectiveness

Biomarkers may be used in a variety of ways in studies designed to demonstrate substantial evidence of effectiveness including providing information to inform the design of the study or serving as a primary endpoint, including their use as a validated surrogate endpoint.

1. Use of biomarkers in the design of clinical effectiveness studies

Biomarkers may be used to determine whether an animal meets enrollment criteria (e.g., to confirm a diagnosis of disease in enrolled animals), to refine the population to enroll (e.g., to enrich for specific study population), or to establish appropriate randomization factors (e.g., appropriate allocation of animals at various disease stages across treatment groups). For example, a threshold fecal egg count value may be used to include or exclude animals in an anthelmintic dose confirmation study; radiography may be used to confirm a diagnosis of osteoarthritis in dogs for an analgesic study; and special stains used at the time of histopathology may be used to enrich for a specific study population (e.g., proliferative index of mast cell tumors).

2. Biomarkers as primary endpoints in clinical effectiveness studies

Any method used to assess an animal's response to treatment in a clinical study, including biomarkers, must be well-defined and reliable (21 CFR 514.117(b)(8)) and be used in such a way to allow for a conclusion that the measured parameters and responses reliably reflect the effectiveness of the new animal drug.

Depending on the clinical purpose of the drug, as reflected in the indication (the intended use) and associated conditions of use, effects on a biomarker may be used as a primary endpoint in conjunction with clinical outcomes to demonstrate biological effects or clinical benefit, as the sole primary endpoint to demonstrate certain biological effects, or as a surrogate endpoint to predict biological effects or clinical benefit. For biomarkers used as primary outcome variables, including as surrogate endpoints, appropriate statistical analysis methods should be chosen according to the distribution of the biomarker following the general principles of statistics.

a. Use of biomarkers in conjunction with clinical or biological outcomes

Biomarkers that have not been validated as a biological outcome for a biological effect or as a surrogate endpoint to substitute for a clinical outcome to predict a clinical benefit should not be used as the only outcome for the demonstration of substantial evidence of effectiveness. However, it may be appropriate to use the

[18] See CVM Draft GFI #261, "Eligibility Criteria for Expanded Conditional Approval of New Animal Drugs," dated September 2019. When final, this guidance will represent FDA's current thinking on this topic.

biomarker(s) in conjunction with clinical outcomes or other biological outcomes, depending on the COU. An example is the use of serum total T4 levels in conjunction with improvement in clinical signs to evaluate the effectiveness of antithyroid drugs for the treatment of hyperthyroidism in cats; and the use of the Na^+ and K^+ levels or the Na^+/K^+ ratio along with resolved or reduced clinical signs to evaluate the effectiveness of mineralocorticoid drugs for use as replacement therapy for mineralocorticoid deficiency in dogs with primary hypoadrenocorticism.

b. Use of biomarkers as the sole outcome to demonstrate a biological effect

In some cases, a biomarker that is not validated as a surrogate endpoint may be used as a biological outcome, and effects on the biomarker serve as the primary endpoint for a biological effect indication. In these situations, the purpose of the new animal drug (i.e., the biological effect) should have appropriate utility to the end user.

An example is the measurement of ammonia gas emissions (biomarker/biological outcome) from cattle in chambers to demonstrate the effectiveness of a new animal drug to reduce ammonia gas emissions (the biological endpoint) in cattle in feedlots. Another example is the use of nematode worm counts to demonstrate the effectiveness of a drug to treat and control gastrointestinal parasite infections. In this situation, worm counts are evaluated to demonstrate a biological effect that has utility to the veterinarian and end user (treatment and control of the parasite species), rather than a clinical outcome (such as clinical signs of diarrhea, anemia, or weight loss) to demonstrate a clinical benefit.

c. Use of biomarkers as surrogate endpoints

For some clinical studies, the development and use of a biomarker as a substitute (surrogate) for a clinical outcome or certain types of biological outcomes may be desirable. If a surrogate endpoint biomarker can be measured earlier or more easily than the clinical outcome (such as mortality or a pain score, respectively), it may help avoid studies of excessively long duration or with invasive or difficult-to-obtain endpoints. For example, in veterinary oncology, a consensus framework using the human response evaluation criteria in solid tumors (RECIST v1.1) outlined by the Veterinary Cooperative Oncology Group provides guidelines for the use of response criteria that may be used as surrogate endpoints for survival in the evaluation of treatment effectiveness of solid tumors in dogs (Nguyen et al., 2015). In another example, CVM accepted sperm count as a surrogate endpoint for male sterility as a substitute for an evaluation of the dog's ability to reproduce clinically, for the approval of a drug indicated for chemical sterilization in dogs.[19]

[19] NADA 141-217, available on Animal Drugs @FDA

Biomarkers proposed as surrogate endpoints in studies to demonstrate substantial evidence of effectiveness should be validated, such that they accurately represent and predict clinical effectiveness, are analytically valid, and fit the specific intended context of the proposed indication (i.e., its intended COU). The evidence used to validate a biomarker as a surrogate endpoint for substantial evidence of effectiveness should be generated separately from the data used to determine effectiveness for a specific drug. Use of a surrogate endpoint does not change the requirement for substantial evidence of effectiveness but offers an alternate method of measuring effectiveness.

3. Biomarkers as secondary endpoints

Biomarkers used as secondary endpoints (i.e., ancillary information that may be supportive) may not be fully validated but they should always be shown to be fit-for-purpose. Biomarkers that are used as part of a multi-component primary endpoint are not considered secondary endpoints.

C. Statistical Considerations

For surrogate endpoints that need to be established through studies, we recommend that you refer to section IX. *Establishing a Biomarker as a Surrogate Endpoint for Effectiveness Studies* of this guidance for statistical considerations and consult with FDA statisticians regarding the detailed analysis plan you will be undertaking in your study. When biomarkers are used as part of a multi-component primary endpoint to demonstrate substantial evidence of effectiveness, the basis of study conclusion and analysis should be prospectively specified to avoid a problem with multiplicity.[20]

VIII. Labeling Considerations

Determining the indication may be straightforward for many intended uses (e.g., the disease, condition, manifestation, or clinical signs of the disease or condition being treated, prevented, mitigated, cured, or diagnosed; the structural or functional changes; or alterations in clinically relevant pathophysiologic manifestations of a disease or condition). In such circumstances, the indication should convey the clinical benefit or biologic effect. For prescription new animal drugs, the descriptions of specific outcomes and endpoints should be summarized in the effectiveness section of labeling and should not be included in the indication.

When biomarkers and surrogate endpoints are used as primary variables to demonstrate the effectiveness of a drug for an intended use, they are typically not described in the labeling except for within the description of the effectiveness studies. However, there are three circumstances when identifying a biomarker or surrogate endpoint in the indication may be appropriate.

[20] See Draft GFI, "Multiple Endpoints in Clinical Trials," dated January 2017. When final, this guidance will represent FDA's current thinking on this topic.

First, if a drug only affects certain manifestations of a disease or condition or biological outcome and this effect was directly measured using a biomarker, the indication should be worded to reflect the intended outcomes with respect to that biomarker.

Second, it may be appropriate to include additional context about the approval in the indication by identifying the clinical benefit(s) or biological effect(s) that are expected (based on the effect demonstrated on the surrogate endpoint) but not yet established. Such circumstances should be determined on a case-by-case basis and are most common with CNADAs because they are approved based on a reasonable expectation of effectiveness rather than substantial evidence of effectiveness.

Third, in some cases, a broad indication for a disease or biological effect may not be appropriate and an indication identifying an outcome or endpoint, including a biomarker or surrogate endpoint, may be considered. Such cases include when the drug's effect on the overall disease or biological outcome is not well understood; when different drugs have different effects on various manifestations of a disease or aspects of a biologic outcome; when studies evaluated only one or some of the manifestations of the disease or aspects of a biologic outcome; or when the endpoints are different from typical effectiveness measures.

IX. Establishing a Biomarker as a Surrogate Endpoint for Effectiveness Studies

For a biomarker development effort to be successful, the biomarker should be clearly identified and characterized, including its source material or matrix and its method of measurement. The biomarker should be clearly identified based on the specific analyte (e.g., fibrinogen), anatomic feature (e.g., joint angle), or physiological characteristic (e.g., blood pressure) being measured. For composite biomarkers, it is important to list the individual biomarker components and how these components are interrelated (e.g., a description of an algorithm or scoring system). If individual components have differential weighting, the description should include the biologic rationale to support this decision. Because biomarkers are measured entities, it is important to describe the biomarker source or material for measurement, which determines the biomarker type (e.g., molecular, histologic, radiographic, or physiologic characteristic). For example, a molecular biomarker obtained from a biofluid should state the sample matrix (e.g., plasma, urine, etc.), and a radiographic biomarker should include the organ or tissue imaged (e.g., kidney).

The items that should be considered when determining the type and level of evidence sufficient to support the use of a biomarker as a surrogate endpoint consists of several components. The items include: (1) describing the drug development need; (2) defining the COU; (3) considering potential benefits if the biomarker is accepted for use; and (4) considering potential risks associated with the proposed use of the biomarker in a drug development program.

Ultimately, whether there is sufficient evidence to support acceptance of a biomarker as a surrogate endpoint depends on the selection of the appropriate biomarker for the proposed COU, the quality of the biomarker measurement, and the correlation of the biomarker with the outcome of interest. Evidence to support biomarker acceptance consists of data to support clinical validation and analytical validation. As defined above, clinical validation is the process to establish that the test, tool, or instrument acceptably identifies, measures, or predicts the concept

of interest. Clinical validation establishes that a biomarker's relationship with the outcome of interest is acceptable for the proposed COU.

The sponsor should describe what is known about the biomarker's role in the causal or outcome pathway of interest, as well as describe knowledge gaps about the pathophysiology and molecular underpinnings of the disease, condition, or outcome of interest. Describing the biomarker's position in the physiologic or pathologic pathway, if applicable, helps to support the biological plausibility of the biomarker's role in the proposed COU. The sponsor should provide data supporting the relationship between the biomarker and the outcome of interest. This relationship should be supported by statistical analyses (see section X. *Statistical Considerations* below) and should come from multiple independent data sources, if possible. Together this information can establish the clinical validity of a biomarker for a specified COU.

When assessing whether the association between a biomarker and an outcome of interest is acceptable for the proposed COU, a key consideration is how to define the outcome of interest. In some settings, there might not be a current standard outcome, or a standard outcome with known limitations is used for comparative purposes. For example, changes in serum creatinine are widely used in biomarker development as the current standard for predicting changes in kidney function. However, changes in serum creatinine levels are neither highly sensitive nor highly specific for changes in kidney function. In a setting in which the current standard outcome has significant limitations or a current standard outcome does not exist, it is important to consider the totality of all available data that may provide sufficient information to establish that the biomarker can be acceptably relied upon for the proposed COU.

Sponsors should provide evidence of the prognostic and/or predictive value of the biomarker as a surrogate endpoint. Sponsors also should provide evidence and sufficient justification that the biomarker test is analytically fit-for-purpose within the specific context of the proposed indication. This evidence should be collected separately from the data that will be used to support substantial evidence of effectiveness of a new animal drug. CVM encourages sponsors to establish biomarkers for use as surrogate endpoints as early in the development phase as possible, ideally prior to seeking concurrence on an effectiveness study protocol in which the biomarker is used as a surrogate endpoint.

Sponsors should also provide evidence to support analytical validation of the biomarker for use as a surrogate endpoint (see section VI. *Analytical Validation for Biomarkers*).

Sponsor should consider and address, as appropriate, the following regarding the use of surrogate endpoints.

1. What is the outcome the surrogate endpoint is proposed to predict?

2. What is the rationale for using a surrogate endpoint rather than a clinical outcome or traditionally measured biological outcome (e.g., feasibility, study duration, sample size, etc.)?

3. What evidence exists to support the relationship between the surrogate endpoint and the outcome of interest (e.g., epidemiologic studies, randomized controlled trials, data generated from therapeutic products from the same class, etc.)?

4. If the surrogate endpoint is proposed based on prior publications and general scientific community acceptance, discuss the current body of evidence and the use of the surrogate endpoint in clinical studies.

5. What is the relationship of the surrogate endpoint with the causal pathway for the disease or the predicted biological effect?

6. How much do changes in the surrogate endpoint reflect changes in the outcome of interest or the probability of the outcome occurring?

7. What is the extent and timing of change in the surrogate endpoint that would predict the outcome of interest?

8. Is the change in the surrogate endpoint stable or does it only occur for a short time?

9. If a minimum threshold for change has been selected (both size and duration), how was this value determined (include studies conducted and data generated)? What information is available about the sensitivity and specificity of any measurement tools used?

10. How does the surrogate endpoint predict the outcome across different subgroups of the targeted population (e.g., animal class, disease severity, co-existing conditions, concomitant medications typical of the population, etc.)?

11. Is there data showing that the surrogate endpoint predicts the response similarly across relevant subgroups of the targeted population?

12. What is the evidence that a drug-induced change in the surrogate endpoint will be predictive of a change in the outcome (e.g., the surrogate endpoint is a correlate vs. the surrogate endpoint has actual predictive value)?

X. Statistical Considerations for Studies to Establish a Biomarker as a Surrogate Endpoint

The goal of statistical analyses to establish a biomarker as a surrogate endpoint is to evaluate the degree and certainty of association between a biomarker and the outcome of interest. This subsection describes the general considerations in the study design, sources of data, statistical analysis methods in assessing the biomarker, and the criteria to establish the biomarker as a surrogate endpoint.

Statistical evidence for establishing a biomarker as a surrogate endpoint is usually based on trial-level analysis. Patient-level analysis can be used as secondary supporting evidence. Some of the statistical approaches for assessment of biomarker surrogacy include the following:

- The strongest level of evidence to support the association of a biomarker with an outcome of interest comes from prospective controlled studies that are specifically designed to assess the association. In designing a study to demonstrate the association between a biomarker and an outcome, many of the general statistical principles for clinical trials, such as randomization,

masking, sample size, and multiplicity issues, are relevant and useful. However, special considerations should be taken as follows:

  - The purpose of such studies is to establish the association between a biomarker and an outcome, not to test for significant differences. Therefore, the correlation and its confidence interval may be more useful, and over-reliance on p-values should be avoided, unless the study is designed to test the null hypothesis of no relationship of the biomarker to the outcome of interest.

  - When multiple candidate biomarkers are evaluated in one study, the potential for false positive results is increased; therefore, the analysis plan should control for multiplicity.

- Systematic review may be used to evaluate the association of a biomarker with an outcome. Systematic review is a process where data from multiple studies, including those published in the scientific literature, are identified and evaluated, with a prospective study design and analysis plan.

- Meta-Analysis based on published data is another approach to evaluate the association of a biomarker with an outcome. The general statistical principles for performing meta-analysis should be followed.

- Other innovative statistical approaches, such as a Bayesian method including prior information and hierarchical models, may be considered to evaluate the association of a biomarker with an outcome. As with any innovative statistical proposal, CVM recommends sponsors discuss with the appropriate CVM review division the approaches to be undertaken in the study.

Data used to assess the relationship between a biomarker and an outcome of interest may come from a variety of sources. Some examples are as follows:

- Randomized, controlled clinical trials;
- Open-label/historical-control clinical trials; and
- Observational studies, such as longitudinal cohort studies, case-control studies, cross-sectional data, and case reports.

The sponsor should develop a detailed plan on how the data will be collected and selected for the intended use. When published data are used, certain limitations and gaps, such as publication bias and data quality assurance, should be considered and specified a priori.

An appropriate statistical analysis method for quantitative evaluation of the relationship between the biomarker and the biological or clinical outcome should be pre-specified in the study protocol. Typically, the analysis plan should include definitions of the biomarker variable and the biological or clinical outcome, as well as the statistical analysis model. The analysis method should be consistent with the study design and the distribution properties of the variables of interest. For example, for continuous measures, results can be evaluated using regression models. For binary variables, results can be evaluated using sensitivity and specificity. When

continuous measurements are categorized, the level cutoff values should be clinically meaningful.

The success criteria to establish the biomarker as a surrogate endpoint should be pre-specified. There are no standard quantitative criteria for determining whether the relationship between the biomarker and the biological or clinical outcome is sufficiently strong to support surrogacy. The evidence of strong association may vary, depending on the characteristics of the biomarker and the biological or clinical outcome. The sponsor should discuss with CVM the criteria before the study is conducted.

XI. Obtaining CVM Feedback on Use of Biomarkers and Surrogate Endpoints

There are various approaches that sponsors may take to open a discussion with CVM on the use of biomarkers and surrogate endpoints as part of their development program to demonstrate effectiveness or a reasonable expectation of effectiveness. The sponsor's decision regarding which approach to select may be affected by where the project is in the development process. Communication about biomarkers and surrogate endpoints may occur at any point in the development process.

The Office of New Animal Drug Evaluation (ONADE) project managers (PMs) serve as a central point of contact for drug sponsors and can provide information about the new animal drug review process and ONADE's regulatory procedures. If you have questions about the approval process and do not have an ONADE PM assigned to your company, you can contact the PMs through the CVM mailbox AskCVM@fda.hhs.gov.

A. When to submit information regarding the use of biomarkers and surrogate endpoints

There are a variety of points in the development process and a variety of submission types that can be used to obtain feedback. CVM encourages sponsors interested in using biomarkers and surrogate endpoints as part of their development program for a new animal drug to inform CVM as early in the product development process as possible.

Sponsors planning to incorporate biomarkers and surrogate endpoints to demonstrate effectiveness or reasonable expectation of effectiveness are encouraged to inform CVM of their intent either as part of their initial request to open a General Correspondence (GC) file or an INAD file (A-0000), or as part of their initial presubmission conference with CVM to discuss the drug product development plan (Z-submission product development meeting). If one or more studies incorporating biomarkers and surrogate endpoints is already complete, sponsors should provide CVM with a summary of the design and conduct of the study during the drug product development meeting or contact their assigned PM for assistance in determining the most appropriate method for obtaining feedback from CVM.

B. How to submit information regarding the use of biomarkers and surrogate endpoints

There are several ways that sponsors may submit detailed information about plans for incorporating biomarkers and surrogate endpoints as part of their development program to demonstrate effectiveness or reasonable expectation of effectiveness. The regulatory pathway selected (CNADA versus NADA), the stage of development, the information available, and the feedback being sought from CVM, among other factors, may influence the submission type selected.

Sponsors may submit information to support use of biomarkers and surrogate endpoints to a GC file prior to opening an INAD file; as part of their initial request to open an

INAD file; as part of a meeting request for a presubmission conference (Z-submission)[21] to discuss the Effectiveness technical section requirements; or as part of an information submission (H-submission) or meeting request (Z-submission) to discuss study protocol design.

The submission of a study protocol utilizing biomarkers and surrogate endpoints should only be considered after the proposed study design has been discussed with CVM. Obtaining CVM input regarding study design will make reaching protocol concurrence more efficient. Sponsors considering incorporating biomarkers and surrogate endpoints into future studies to demonstrate effectiveness or reasonable expectation of effectiveness should, prior to conducting a study, submit a study protocol for review (E-submission).

Sponsors may also open a Veterinary Master File (VMF) to hold detailed information regarding a specific study design if the information will be used in the development of multiple applications.[22] The VMF is confidential and is typically used when a holder wishes the material in the VMF to remain proprietary, although the material may be referenced by multiple third-party products or files (INAD, NADA, or CNADA). Alternatively, if multiple sponsors are cooperating on product development, sponsors may establish a Public Master File (PMF) to allow all cooperators to reference the information. As suggested by the name, the information in a PMF is publicly available.

Regardless of how information is submitted to CVM, sponsors should submit an organized and focused information package. This will allow CVM the best opportunity to provide appropriate recommendations in response. Although full information may not be available in the early stages of the development program, the amount of information provided and the level of detail of the information provided should be commensurate with the submission type. The information should address some or all of the following elements, as appropriate for the submission type:

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[21] See CVM Program Policy and Procedures (P&P) Manual 1243.2200 Submission and Review of Early Information (EI) Prior to Presubmission Conferences and Protocol Review (June 2020) and CVM P&P Manual 1243.3050 Determining Technical Section Requirements for New Animal Drug Product Approval (May 2019)

[22] See CVM P&P Manual 1243.2400 Veterinary Master Files with Manufacturing Information (August 2019)

1. The proposed COU, including the category of biomarker and its proposed use in biomarker development;

2. An assessment of the benefits and risks[23] of the use of the biomarker for the proposed COU;

3. A description of the sponsor's plan for analytical and clinical validation, as appropriate;

4. A discussion of known prior uses of the biomarker (e.g., in clinical practice settings, other countries, etc.); and

5. A statement regarding whether other FDA Centers have qualified the biomarker for the same or similar purposes in the target animal or other species.

Additional questions and considerations specific to surrogate endpoints are presented in section VIII. *Establishing a Biomarker as a Surrogate Endpoint for Effectiveness Studies*.

XII. References

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[23] See footnote 16.