CONTAINS NONBINDING RECOMMENDATIONS

 # 137

Guidance for Industry
Analytical Methods Description for Type C Medicated Feeds
Draft Guidance

This draft guidance is being distributed for comment purposes only.

Comments and suggestions regarding this draft guidance should be sent to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. All comments should be identified with the Docket No. 2006D-0254. Comments may also be submitted electronically on the Internet at http://www.fda.gov/dockets/ecomments.

For questions regarding this draft guidance document, contact Rebecca L. Owen, Center for Veterinary Medicine (HFV-141), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 240-276-9842, E-mail: rebecca.owen@fda.hhs.gov.

Additional copies of this draft guidance document may be requested from the Communications Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at http://www.fda.gov/cvm.

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Guidance for Industry
Analytical Methods Description for Type C Medicated Feeds
Draft Guidance[1]

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the telephone number listed on the title page of this guidance.

I. Introduction

This draft guidance provides our (the Office of New Animal Drug Evaluation, Center for Veterinary Medicine) recommendations for describing methods for analyzing new animal drugs in Type C medicated feeds. This draft guidance applies to instrumental methods only (e.g., High Pressure Liquid Chromatography (HPLC), Gas Chromatography (GC)). For information on other methods (e.g., microbiological methods) you should contact us.

Section 512 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 360b) establishes the requirements for new animal drug approval. FDA regulations specify the information you must submit as part of your new animal drug application (NADA) and the proper format for the NADA submission. 21 CFR Part 514. As part of your NADA submission, you must include a "detailed description of the collection of samples and the analytical procedures to which they are subjected." 21 CFR § 514.1(b)(5)(vii). This should include a description of practicable methods of analysis that have adequate sensitivity to determine the amount of the new animal drug in the final dosage form. 21 CFR § 514.1(b)(5)(vii)(*a*).

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

[1] This guidance has been prepared by the Office of New Animal Drug Evaluation in the Center for Veterinary Medicine at the Food and Drug Administration.

II. Discussion

This draft guidance includes recommendations to help you describe the methods used to analyze drug(s) in Type C medicated feeds manufactured with Type A medicated articles. Throughout this draft guidance, we have included examples of items we recommend you include in your method description.

You should include sufficient detail in your description to ensure a clear understanding of the operational procedures. We encourage you to include notes in your description to elaborate upon specific procedures or steps, or to provide recommendations about what to do when an unexpected circumstance occurs. We recommend that you highlight these notes in your description document (e.g., capitalized, bolded, italicized) to emphasize this information. Your description should enable an analyst to perform the test method in its entirety.

The following represent the most common sections of a method used to analyze drugs. We recommend that you organize your description, when possible, under the categories listed. However, not all of the sections we have listed will apply to every method description. Thus, you should include only the appropriate sections in your method description. In general, these sections are:

A. Title of the Method
B. Scope and Field of Application
C. Principle
D. Definitions
E. Warning and Safety Precautions
F. Reagents and Chemicals
G. Equipment and Apparatus
H. Solutions
I. Standards/Reference Materials
J. Sampling and Sample Handling
K. Preparing Samples for Analysis
L. Instrument Analysis of Samples
M. Calculating and Expressing Results
N. Data Acceptability Criteria
O. Figures and Tables
P. References
Q. Appendices

We recommend that you include a header with appropriate identification information such as a brief title, method version number, and company/sponsor name on each page of your method description.

A. TITLE OF THE METHOD

This section of the method description should include the drug, feed type (e.g., mash, pellets), and type of analysis.

B. SCOPE AND FIELD OF APPLICATION

This section should describe the type of analytical techniques (e.g., gas chromatography with flame ionization detector, high pressure liquid chromatography with UV or fluorescence detection) for each drug of interest. If the specific analytical procedure measures multiple chemical entities or forms of a drug, you should clearly describe the range of validated concentrations for the drug and what entity or entities were used to validate the method for each drug form (e.g., free acid, free base, sulfate salt, hydrochloride salt). If applicable, you should describe the multiple forms of the drug as different optical or structural isomers. If the product is a mixture, you should describe the different drug components that the method can determine. We encourage you to develop and refer to a figure with structures of these chemical entities to provide a clear and unequivocal understanding about the drugs in the feed that the method can determine.

This section should also describe the applicable feed types that the method can analyze and the species that will consume the feed. If the test method is validated for other types of feed matrices in addition to Type C complete feeds, you should list these other feed products in this section. For example, some methods may also include instructions for the analyses of Type B medicated feeds and organic or mineral based feed matrices. In addition, this section (as well as other relevant sections throughout the document) should describe changes to the method necessary to analyze different types of feed (liquid or solid feeds, organic- or mineral-based feeds) or in the presence or absence of specific inactive components or carriers in the feed sample.

Interference testing: Your should indicate which compounds you tested for possible interference, how you tested them, and what compounds, if any, could potentially cause interference. You should describe any specific compounds you identified that may interfere with the determination of the drug or drug components.

C. PRINCIPLE

This section should describe the basic steps of the test method in terms of extraction, sample clean-up, final instrument-ready steps, etc., and describe salient features. You should describe whether the method requires derivatization. You may also include information on derivatization under a separate sub-heading, such as, "REACTIONS." We recommend that you develop and refer to a diagram, and include it in a Figures and Tables section (see Section O, below).

D. DEFINITIONS

This section should define terms and abbreviations you use in your method description to ensure a complete understanding of the method. For example, we recommend that you include a precise definition of units used in your method because units can have different meanings in different countries.

E. WARNINGS AND SAFETY PRECAUTIONS

This section should describe appropriate WARNING and/or CAUTION statements and specific procedures for the safe handling of hazardous chemicals and reagents. **Note:** We strongly recommend that methods not require particularly hazardous chemicals and reagents, halogenated solvents, etc., unless necessary for successful analyses. If you believe that such materials are necessary for successful analyses, we encourage you to consult CVM during method development to discuss the use of these materials.

F. REAGENTS AND CHEMICALS

This section should describe all of the reagents and chemicals that the method uses, including buffer salts, solvents, derivatizing agents, etc. If critical to the method, you should also describe the grade of the chemical or solvent. We also encourage you to include the suggested supplier and location, catalog number, etc. For example, you may include the following information in your description of reagents and chemicals:

> *Unless otherwise stated, use only reagents and chemicals of analytical grade quality and only deionized water or chromatographic grade water. Reference to a company is for information and identification only and does not imply a recommendation unless so stated.*

Example chemical descriptions follow:

- *Acetonitrile: UV grade, Company/Vendor name and location, or equivalent, Catalog number, etc.*
- *Citric Acid: AR grade, granular, Company/Vendor name and location, or equivalent, Catalog number, etc.*

G. EQUIPMENT AND APPARATUS

This section should include a list of all of the laboratory supplies, equipment and instruments that the method requires. If critical for proper method performance, you should describe specific information about the supplier, company location, catalog number, product (e.g., glassware type, quality or grade), etc. You should describe the

required accuracy and precision for each piece of equipment or apparatus (e.g., pipettes, analytical balances).[2]

You should state in your method description whether the method requires specific supplies and equipment to meet performance criteria. If common equipment and general laboratory supplies will serve equally well, you should include a statement such as "or equivalent" when referring to equipment and laboratory supplies in your description. You may include a description of the acceptability criteria for these materials in this section, but you should also include this information in Section K.

You may include a disclaimer statement in this section such as:

> *References to specific brand (company) names are for information and identification only and do not imply a recommendation unless so stated.*

This section should also clearly describe the configuration of components in an instrument system, identifying each component of the analytical instrumentation individually. You should describe the configuration of unusual, complex, or specialized analytical instrumentation from sample introduction to data system analysis, preferably in a figure in block diagram fashion.

We recommend using a numbering scheme in your written method description for clarity. The numbering scheme we use in the example below is illustrative. A description of equipment and apparatus could include, but is not limited to, the following:

G.1 Equipment

G.1.1 Autosampler vials: 12 × 32 mm Borosilicate glass, crimp top, Company/Vendor name and location, or equivalent, catalog number(s), etc.

G.1.2 Volumetric flask, 10 ml, Class A, Company/Vendor name and location, or equivalent, catalog number(s), etc.

G.1.3 SPE Cartridge: Name/Model, 500 mg, LRC, Company/Vendor name and location, or equivalent, catalog number(s), etc.

G.1.4 HPLC system:

G.1.4.1 HPLC Pump: Quaternary gradient pump, Company/Vendor name and location, model no., or equivalent.

G.1.4.2 Injector: ..., or equivalent.

[2] Accuracy and precision of specific equipment or apparatus may be inherent.

G.1.4.3 Column: ..., or equivalent. Similar columns from other vendors have not been evaluated for performance in this assay. Therefore, no other columns can be recommended. If other columns are tested, they should meet the system suitability criteria as described in Sections K and L.

G.1.4.4 Mixing Tee: ..., or equivalent.

G.1.4.5 Connecting Tubing: ..., or equivalent.

G. 1.4.6 In-Line Filters: ..., or equivalent.

G.1.4.7 Detector: ..., or equivalent.

G.1.4.8 Data System: ..., or equivalent.

H. SOLUTIONS

This section should describe, by name, each solution used in performing the method, the concentration as molarity or percent (by weight or volume), pH range, storage conditions, stability or shelf life of the solutions, and frequency of preparation (e.g., daily, weekly, monthly). This section should also include the amount of the chemical or reagent that is used to prepare a set volume of the solution, along with instructions for preparing the solution. For each solution, the description should state whether it must be prepared with extreme accuracy and precision, or whether approximate concentrations (state range of concentration, if known) will suffice. If extreme precision is needed, you should describe specific details and equipment for preparing the solution and for performing all critical measurements.

I. STANDARDS/REFERENCE MATERIALS

This section of the method description should specify the chemical name (e.g., generic, International Union of Pure and Applied Chemistry (IUPAC), Chemical Abstracts Service (CAS)), ID number (if applicable), source, storage conditions, and duration of storage for a Drug Substance Reference Standard (provided by sponsor) or Certified Reference Standard Material (commercial source). For some compounds, you may list lot number and purity for the compounds. If, however, you expect lot numbers and/or purity to change with time, we recommend that you instead refer to the Certificate of Analysis accompanying a particular compound.

You should provide detailed descriptions including specific steps or equipment for preparing reference standards, test solutions and any test-matrix fortification solution(s), and for performing all critical measurements.

To reduce the possibility of systematic errors that could occur during calculations, this section should clearly describe any corrections to concentrations of standards based on potency or purity. In addition, this section should describe the storage conditions and stability or shelf life of the solutions, as well as the frequency of preparation (e.g., daily, weekly, monthly).

J. SAMPLING AND SAMPLE HANDLING

J.1. Obtaining the laboratory sample (sample size): The quantity of the sub-sample (weight or volume range) of the original bulk feed should provide a feed sample that is representative of the whole feed matrix. This section should describe the sampling procedure for obtaining this test portion.

If a smaller sub-sample of the laboratory sample can be used for the analysis, you should describe the sub-sample weight or volume range here, and in Section K.[3]

J.2. Sample handling procedures: This section should include a description for homogenizing or grinding the sample before analysis, if necessary, and any special equipment needed to prepare the sample.

J.3. Sample stability: This section should include a description of the storage conditions for samples, as well as the expected shelf-life, in the event that the analyst cannot assay the feed samples immediately upon receipt, and precautionary statements about the stability of the drug in frozen matrix and the effect of freeze/thaw cycles, if known.

K. PREPARING SAMPLES FOR ANALYSIS

This section should describe the information the analyst needs to ensure a complete understanding of the method and to enable the analyst to perform each procedure in its entirety. You should describe any specific supplies and equipment required to meet specific performance or suitability criteria for any procedure or overall performance of the method. You should also clearly describe the procedures to perform suitability tests for these materials.

This section should describe the procedures (e.g., liquid extraction, liquid-liquid partitioning, solid phase extraction) in the method, and all operational steps in those procedures, in sequence. We recommend using some type of numbering or lettering sequence.

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[3] In determining the weight or volume of the sub-sample, we recommend that you consider the following parameters, among others: sensitivity of the analytical method, performance data from method development and validation work, feed mixability and uniformity data, particle size heterogeneity in feeds (e.g., complete feeds with intact grains or roughage), drug concentration, sample size for grinding/homogenization procedures, etc.

You should elaborate upon special aspects of the operational steps. You should describe, in the appropriate sections throughout the document, any contingency actions that may apply. Additionally, you should describe appropriate stopping places in each procedure in the event that interruptions occur, or in the event that the analyst cannot complete the entire procedure from start to finish in a given period of time.

This section should describe the critical control points and include special notes such as:

> *Protect from heat and light* -or-
> *Storage at temperatures < 5 °C is required.*

If, as part of the method, a procedure uses chemicals, solvents or equipment that could be toxic, hazardous, or represent a potentially dangerous step, you should provide a specific precautionary statement, such as:

> *SAFETY PRECAUTION: The following procedure uses toxic solvent ABC. Therefore, you should carry out procedure 10.x in an appropriately well ventilated work center. Refer to Section E. (Warnings and Safety Precautions).*

We recommend you prepare and refer to a flow diagram of the method, from sample preparation through analysis, which you include in a Figures and Tables section (see Section O, below). You should also include a description of the efficiency of the method relative to productivity (e.g., number of samples processed in an 8-hour day or a 5-day week, number of samples an experienced analyst can prepare in *x* hours).

K.1. Test Portion: This section should describe how to obtain the sub-sample, either by weight or volume, and the equipment you should use for this purpose. It should describe acceptable variance limits to the weight or volume of the sample. For example:

> *Accurately weigh 10±1 g of "thawed" feed (Section J.) to the nearest 0.01 g with an analytical balance using a 50 mL polypropylene test tube ... .*

You may also describe whether the method includes a control/blank feed sample and a fortified control feed sample, as quality control (QC) samples, with each set of test samples or at other defined intervals, and a description of the fortification procedure.[4]

K.2. Operational steps: This section should include a detailed description, numbered for clarity, of the operational steps the analyst should perform, including preparing the processed sample for instrument introduction. Examples include liquid partitioning or solid phase extraction. You should include any precautionary statements. For example:

[4] We recommend that you use a feed matrix similar in composition and intended for the same animal species, if the specific control feed sample matrix is not available.

Critical Control Point: The flow rate should not exceed 2 mL/min at any time. Flow-rates slower than 1 mL/min are acceptable, but do not significantly improve method performance.

You should describe the specific procedure for diluting the sample, if necessary for performing the method. If the sample is sensitive to light, temperature, or requires special handling, you should clearly state this information. You should also describe storage conditions, as well as the expected shelf life, in the event that the analyst cannot assay the final prepared sample immediately.

L. INSTRUMENT ANALYSIS OF SAMPLES

L.1. Instrument System Set-Up: This section should describe the essential operating parameters for the instrument. You should describe all required parameters, specific setup instructions, and specific maintenance steps (e.g., periodic flushing of lines, equilibration time between runs, preconditioning analytical columns) in sufficient detail for the analyst to properly operate the instrument. We recommend that you include subheadings and precautionary notes, as appropriate, in your method description.

For example, for an HPLC method, the description of parameters could include, but is not limited to, information about: pump system, dead volume of pump system, mobile phase, gradient program, flow rate, column pre-equilibration times between runs, chromatographic column, detector type, and all other instrument settings, etc.

L.2. Instrument and Equipment Suitability: This section should describe the suitability test(s) that helps diagnose whether instrument performance is acceptable. You should describe performance criteria that are required for acceptable performance. You should also describe what, if any, corrective action should be taken for unacceptable performance.

If specific supplies and equipment must meet minimum performance criteria before being used in the method (see Section G), you should describe in clear, well defined terms the procedure(s) and criteria to establish the suitability of materials. These parameters may be based upon experience gained during development or validation of the method.

L.3. Sample Analysis Steps: This section should clearly describe any steps that are critical to the proper execution of the method. If specific data collection or processing steps are critical for achieving acceptable performance, or if atypical procedures are needed, you should include this information in your written method description. This section should also describe procedures and parameters for data acquisition, base-line correction, and peak integration. If the drug and interfering compounds potentially have similar retention times, you should describe procedures for peak definition in sufficient detail to identify and quantitate the specific drug peak. An example follows:

- *System Operation: Make the HPLC operational (Section L.1).*

- *Calibration Standards: As applicable, describe the number of standards and whether calibration requires single or multiple injections of each to generate a typical calibration curve or response factor. Describe minimum acceptance criteria as appropriate.*

- *System Suitability Tests: Describe the procedures and criteria that ensure system performance. This description could include, but is not limited to, information on criteria such as: obtaining a linear calibration curve, precision of repeat injections, analyte retention times, analyte peak shape, recovery of analyte from spiked samples or quality assurance samples, lack of chromatographic interference for the analyte, etc.* ***Note:*** *We recommend you include a description of criteria used in the method for accepting or rejecting results from suitability tests, and a description of corrective actions to take for any unacceptable results.*

- *Sample Analysis: This section should describe the steps for performing the sample analyses (sample analyses sequence). For example:*

  Analyze samples and standards by HPLC in random order using the bracketing technique.

In addition, this section could describe the recommendations for an analysis sequence which may include, but is not limited to, analysis of check samples, other types of quality assurance samples, feed controls and blanks, etc.

M. CALCULATING AND EXPRESSING RESULTS

M.1. Calibration Method: This section should provide a description of how to construct a standard response curve, if applicable. In most cases, a linear response function will be sufficient. This section should also describe the instrument data systems or non-system PC software, such as spreadsheets, used to perform the calculations.

M.2. Drug Concentration: You should describe how to calculate the concentration of the drug in feed, and define units and other parameters of the equation. You should describe the specific chemical entity or entities measured, and the form of the drug used in calculations, as appropriate. Additionally, you should describe any corrections to concentrations of the standard solutions based on potency or purity in this section as well as in Section I.

You should include a description of the calculation used to measure the drug concentration in a sample using hypothetical data. For example, you could include a detailed illustration of drug recovery from a fortified control.

We are including example equations, below, for determining the concentration using a linear calibration line and using a single point calibration standard (single response function).

Example 1 *(calibration line):*

$$[(P_{sample} - Y_{intercept}) \div slope] \times [Vol_{sample} \div Wt_{sample}] \times DF$$

Where:

P_{sample} = *Peak Height or Peak Area for the drug,*

$Y_{intercept}$, *obtained from analysis of the standard curve,*

Slope, obtained from analysis of the standard curve.

Vol_{sample} = *Final volume of the sample solution for analysis,*

Wt_{sample} = *Weight of feed sample analyzed or extracted*

DF = Dilution/Conversion Factor, if any, when dilutions were made in the sample preparation that changed the relationship of the final sample relative to the original feed sample or to allow conversion of units of measure.

Example 2 *(single point calibration):*

$$[P_{sample} \div R_{standard}] \times [Vol_{sample} \div Wt_{sample}] \times DF$$

Where:

$R_{standard}$ = *Response factor (peak height of standard per unit concentration).*

N. DATA ACCEPTABILITY CRITERIA

This section should describe criteria for accepting or rejecting feed assay data. Unlike Sections G, K, and L, which describe suitability criteria for the independent performance of equipment, supplies, and instrumentation, this section should describe the cumulative aspects of these factors to interpret whether final data from a sample are acceptable. This section should describe the corrective or contingency actions that should be taken if data are not acceptable.

Data acceptability criteria for samples may include procedures for initiating the method in a new laboratory (qualification) or for routine processes used during regular analyses (quality control). If this section recommends conducting analyses of a blank/control feed or a blank feed spiked with drug, these control feeds should be available or you should provide information that allows the analyst to prepare these samples.

N.1. Sample Analysis Evaluation: This section should describe the criteria to evaluate the acceptability of final results from analyses. You can base these criteria on, among other things, chromatographic performance (peak shape, resolution of drug from interfering substances, etc.), recovery of drug from fortified samples within a specified range, minimum acceptable CVs when $n \geq 3$, etc.

N.2. Calibration difficulties: This section should describe the steps to take if an unknown sample falls above or below the limits of the standard curve. This description should include directions for dilution or concentration of the final sample or re-analysis by specific procedures to bring the amount of drug injected within specified calibration limits.

N.3. System Failures: This section should describe the steps to take, including corrective action, if analytical results are unacceptable or if system failures produce poor results. As appropriate, this section may describe diagnostic procedures for evaluating the cause(s) of analysis failures and procedures for corrective or contingency actions. This section may reference specific system suitability tests that were described in Sections G, K, and L.

N.4. Blank/Control Results: This section should describe criteria to evaluate the acceptability of analysis of control samples. You may base these criteria on, among other things, chromatographic resolution or window of noninterference. We recommend that you include contingency options in case problems arise.

O. FIGURES AND TABLES

This section should include figures and tables to aid in describing features of the method or to illustrate expected behavior of specific assays. Below is an example of figures that may accompany a HPLC method. These figures could include, but are not limited to:

- *Structures of chemical entities measured in the assay.*
- *Proposed chemistry in the derivatization of the drug.*
- *Block diagram of the HPLC analytical system.*
- *Flow diagram of the sample preparation procedure.*

- *Representative HPLC chromatogram for the drug standard.*
- *Standard curve if using multiple point calibration.*
- *Representative HPLC chromatogram(s) for control/blank (nonfortified) feed sample(s) – multiple illustrative chromatograms if you use multiple feed matrices or types of feeds.*
- *HPLC chromatogram for control feed fortified with drug at x g/ton.*
- *HPLC chromatogram for an authentic feed containing drug at a concentration of x ppm (or x g/ton).*

P. REFERENCES

This section should include a list of references, as appropriate.

Q. APPENDICES

This section should include any additional information or documents that improve the understanding of the method. We recommend that you provide a summary of validation data to allow analysts to compare the performance of the method in their laboratories to the originating laboratory.