Overview of New VFD Rule

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Agenda

- Introduction
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- Overview of the New Rule
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  - Definitions
  - Major Provisions
    - General Requirements
    - Veterinarian Requirements
    - Distributor Requirements
- Important dates
  - October 1, 2015
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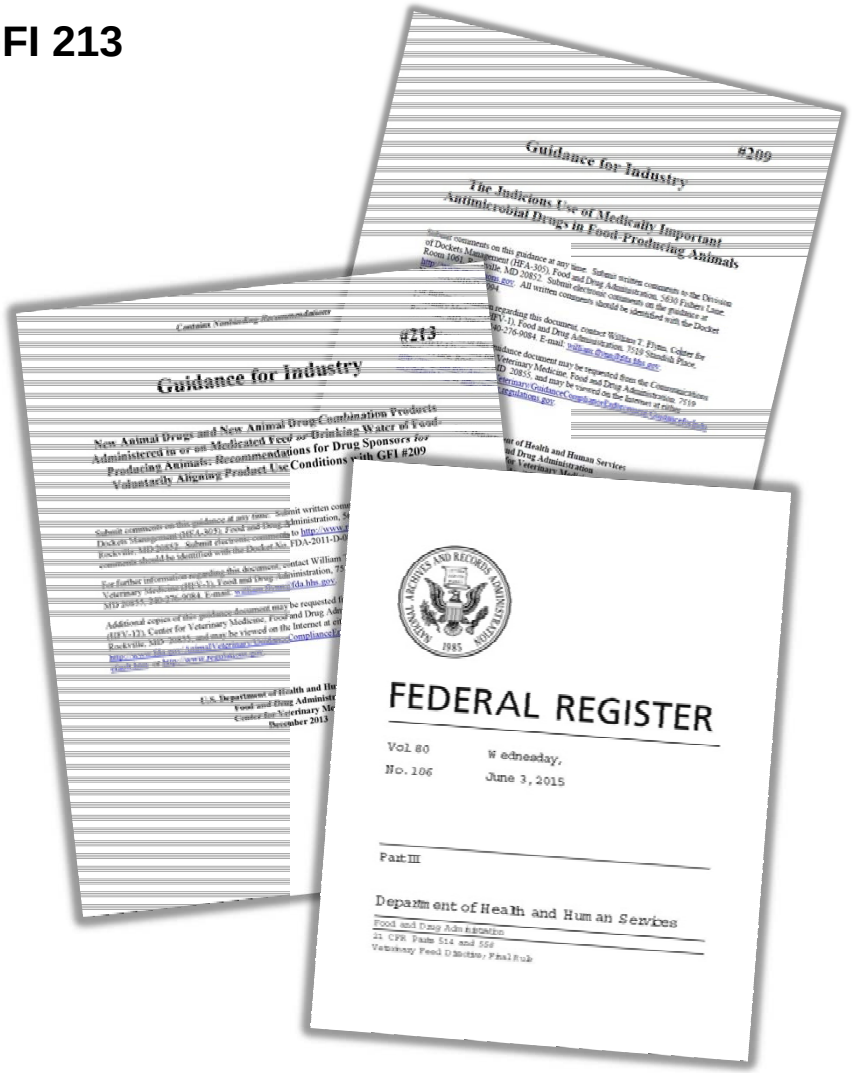
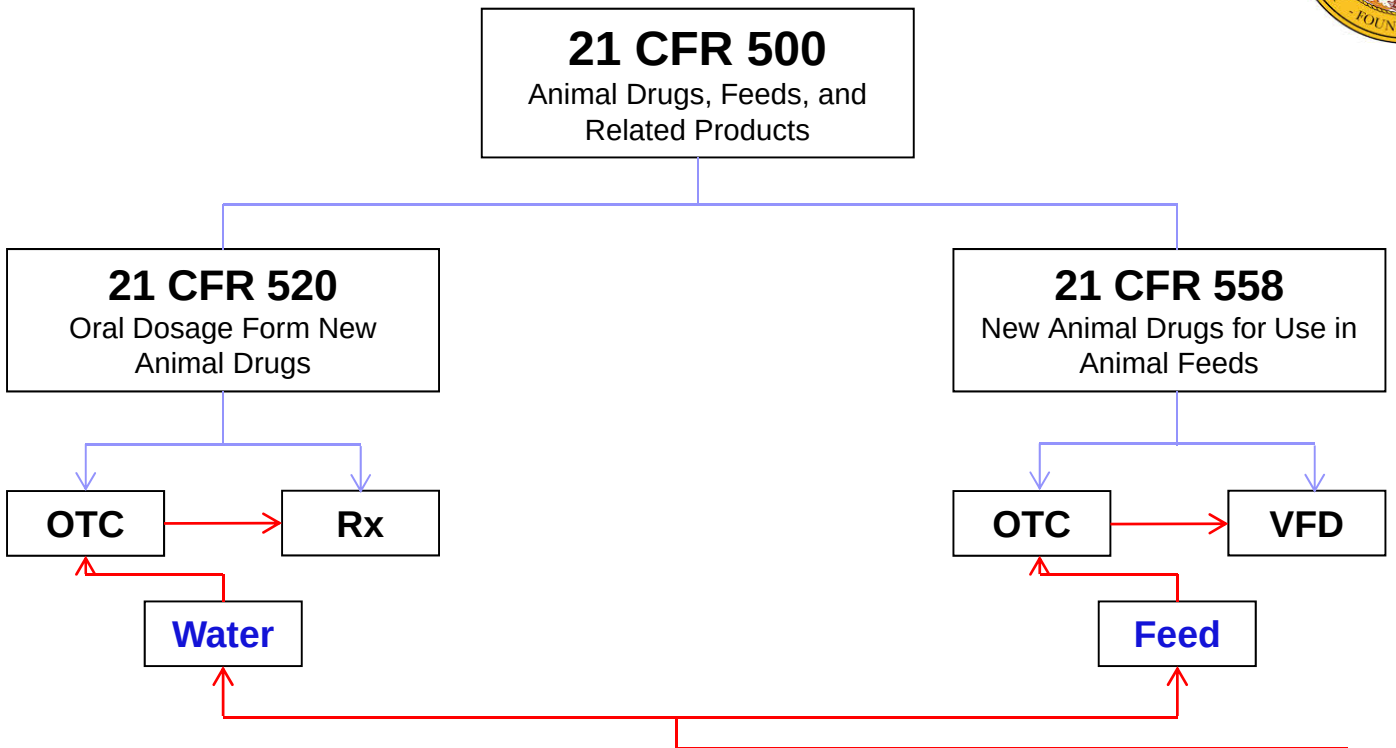
- Conclusions



Introduction



- **Guidance For Industry 209**
  - **Explains Judicious Use of Medically Important Antimicrobial New Animal Drugs**
- **Guidance For Industry 213**
  - **Explains the Timing and Manner of Acting per #209**

Background

- **With passing the ADAA in 1996, Congress created a new regulatory category for certain animal drugs used in animal feed called veterinary feed directive drugs or VFD drugs**

- **FDA has determined that some new animal drugs, vital to animal health, should be approved for use in animal feed but only if such medicated feeds are used under the professional supervision of a licensed veterinarian in the course of the veterinarian's practice**

What is VFD?

- **VFD is a drug**
  - **A ‘‘veterinary feed directive (VFD) drug’’ is a new animal drug intended for use in or on animal feed which is limited by an approved, conditionally approved application, or index and**
  - **for use only under the professional supervision of a licensed veterinarian who authorizes such use by a lawful veterinary feed directive.**

- **VFD is a document**
  - **A ‘‘veterinary feed directive’’ is a written (nonverbal) statement issued by a licensed veterinarian in the course of the veterinarian’s professional practice that orders the use of a VFD drug or combination VFD drug in or on an animal feed, and**
  - **this written statement authorizes the client (the owner of the animal or animals or other caretaker) to obtain and use animal feed bearing or containing a VFD drug or combination VFD drug to treat the client’s animals only in accordance with the approved, conditionally approved application, or index.**

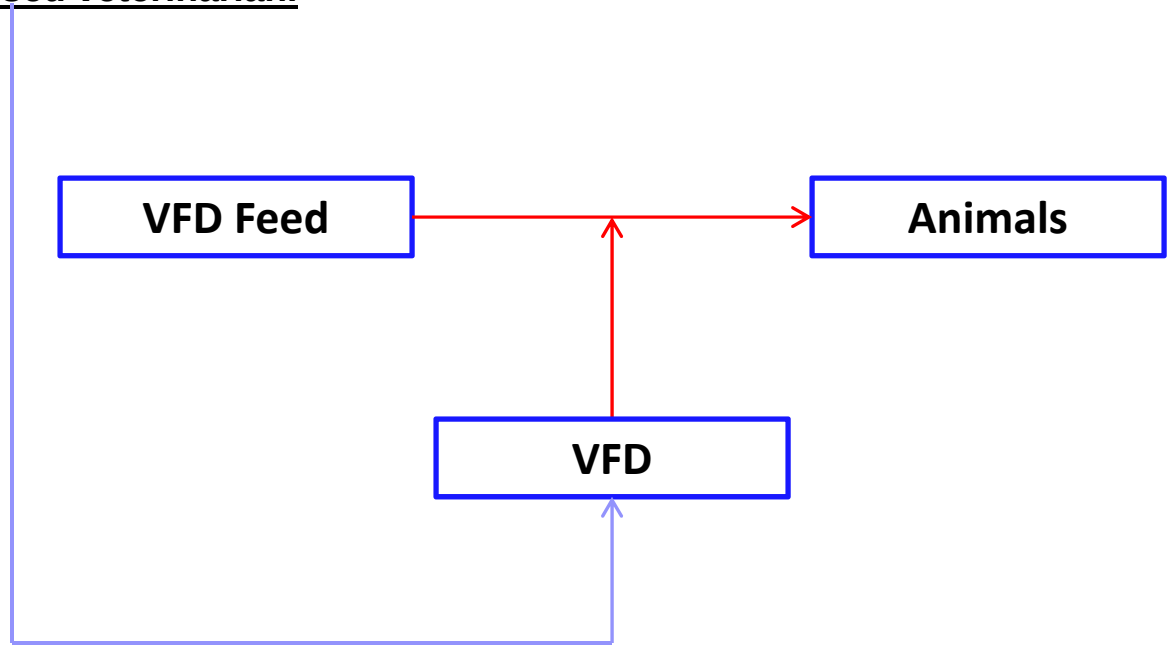
Other Relevant Definitions

- **A “distributor”**
  - **A ‘‘distributor’’ means any person who distributes a medicated feed containing a VFD drug to:**
    - **another distributor, or**
    - **the client-recipient of a VFD.**

- **A “combination VFD drug”**
  - **A ‘‘combination veterinary feed directive (VFD) drug’’ means a combination new animal drug intended for use in or on animal feed which is limited by an approved, conditionally approved, or indexed application**
  - **at least one of the new animal drugs in the combination is a VFD drug, and**
  - **it can only be used under the professional supervision of a licensed veterinarian who authorizes its use with a lawful VFD.**

New Rule - General Requirements
(21 CFR 558.6(a))

- **Animal feed bearing or containing a VFD drug or a combination VFD drug (a VFD feed or combination VFD feed) may be fed to animals only by or upon a lawful VFD issued by <u>a licensed veterinarian.</u>**



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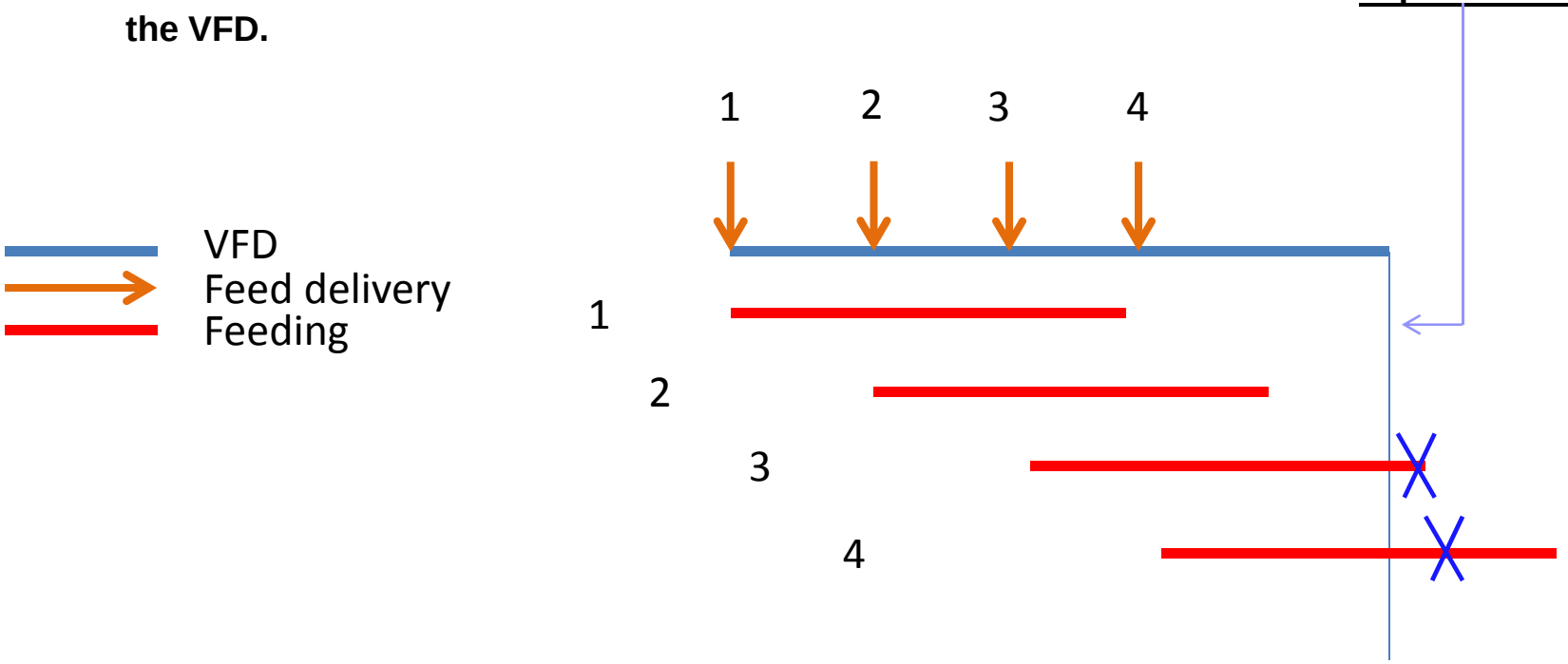
- **A VFD feed or combination VFD feed must not be fed to animals after the <u>expiration date</u> on the VFD.**



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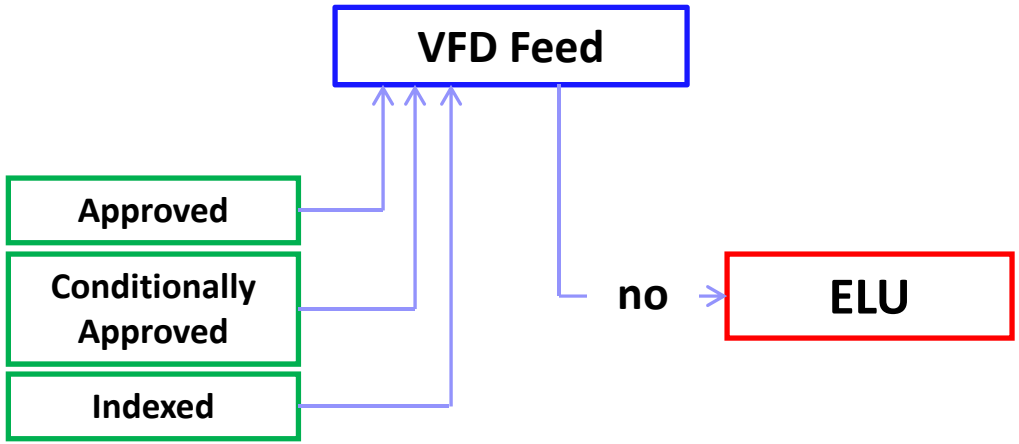
- A VFD feed or combination VFD feed must not be fed to animals after the expiration date on the VFD.

- **Use and labeling of a VFD drug or a combination VFD drug in feed is limited to the approved, conditionally approved, or indexed conditions of use. Use of feed containing this veterinary feed directive (VFD) drug in a manner other than as directed on the labeling (extralabel use) is not permitted.**



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- **All involved parties (the veterinarian, the distributor, and the client) must retain a copy of the VFD for 2 years. The veterinarian must retain the original VFD in its original form (electronic or hardcopy). The distributor and client copies may be kept as an electronic copy or hardcopy.**

VFD Records	2 years

New Rule - General Requirements
(21 CFR 558.6(a))

- **All involved parties must make the VFD and any other records specified in this section available for inspection and copying by FDA upon request.**

- **All labeling and advertising for VFD drugs, combination VFD drugs, and feeds containing VFD drugs or combination VFD drugs must prominently and conspicuously display the following cautionary statement:**

VFD Feed

"Caution: Federal law restricts medicated feed containing this veterinary feed directive (VFD) drug to use by or on the order of a licensed veterinarian."

Repository of Blue Bird labels at:
http://www.fda.gov/AnimalVeterinary/Products/AnimalFoodFeeds/MedicatedFeed/BlueBirdLabels/default.htm

Information Required on VFD

1. Vet's and client's names/addresses/telephone
2. The premises at which the animals specified in the VFD are located
3. Date of VFD issuance
4. VFD expiration date
5. The name of the VFD drug(s)
6. Species and production class of the animals to be fed the VFD feed
7. The approximate number of animals to be fed by the expiration date of the VFD
8. The indication for which the VFD is issued
9. Drug level and duration of use
10. Withdrawal time/any special instructions/cautions
11. Number of reorders (refills) authorized - if permitted by the drug approval
12. The statement: "Use of feed containing this veterinary feed directive (VFD) drug in a manner other than as directed on the labeling (extralabel use) is not permitted"
13. An affirmation of intent for combination VFD drugs
14. Veterinarian's electronic or written signature

Information Optional on VFD

1. More specific description of the location of treated animals (e.g., pen…)

2. The approximate age/weight range of the animals

3. Any other information the veterinarian deems appropriate to identify the animals specified in the VFD

VFD example

Veterinary Feed Directive

Veterinarian: _____ **Client:** _____

Address: _____ **Address:** _____

_____ _____

Phone: _____ **Phone:** _____

Fax or email (optional): _____ **Fax or email** (optional): _____

Drug(s) Name: _____ **Drug(s) Level:** _____ **g/ton** **Duration of use:** _____

Species and Production class: _____ **Number of reorders (refills) authorized** (if permitted by the drug approval): _____

Indications for use (as approved): _____

Caution (related to this medicated feed, if any): _____

USE OF FEED CONTAINING THIS VETERINARY FEED DIRECTIVE (VFD) DRUG IN A MANNER OTHER THAN AS DIRECTED ON THE LABELING (EXTRALABEL USE) IS NOT PERMITTED

VFD Date of Issuance: _____ **(Month/Day/Year)** **VFD Expiration Date:** _____ **(Month/Day/Year)** (As specified in the approval; cannot exceed 6 months after issuance)

Approximate Number of Animals: _____

Premises: _____

Other Identification (e.g., age, weight) (optional): _____

Special Instructions (if any): _____

Affirmation of intent (for combination VFD Drugs) (check one box):

☐ This VFD only authorizes the use of the VFD drug(s) cited in this order and is not intended to authorize the use of such drug(s) in combination with any other animal drugs.

☐ This VFD authorizes the use of the VFD drug(s) cited in this order in the following FDA-approved, conditionally approved, or indexed combination(s) in medicated feed that contains the VFD drug(s) as a component:

Drug(s)	Drug Level(s) and any Special Instructions

☐ This VFD authorizes the use of the VFD drug(s) cited in this order in any FDA-approved, conditionally approved, or indexed combination(s) in medicated feed that contains the VFD drug(s) as a component.

Withdrawal Time (if any): This VFD Feed must be withdrawn ____days prior to slaughter

Veterinarian's Signature: _____

White Copy- Supplier Canary Copy- Client Pink Copy- Veterinarian

All parties must retain a copy of this VFD for 2 years since the date of issuance

Affirms his/her intent on VFD

(i) ‘‘This VFD only authorizes the use of the VFD drug(s) cited in this order and is not intended to authorize the use of such drug(s) in combination with any other animal drugs.’’ ☐

(ii) ‘‘This VFD authorizes the use of the VFD drug(s) cited in this order in the following FDA-approved, conditionally approved, or indexed combination(s) in medicated feed that contains the VFD drug(s) as a component.’’ [List specific approved, conditionally approved, or indexed combination medicated feeds following this statement.] ☐

(iii) ‘‘This VFD authorizes the use of the VFD drug(s) cited in this order in any FDA-approved, conditionally approved, or indexed combination(s) in medicated feed that contains the VFD drug(s) as a component.’’ ☐

Affirms his/her intent on VFD

(i) ‘‘This VFD only authorizes the use of the VFD drug(s) cited in this order and is not intended to authorize the use of such drug(s) in combination with any other animal drugs.’’ ☐

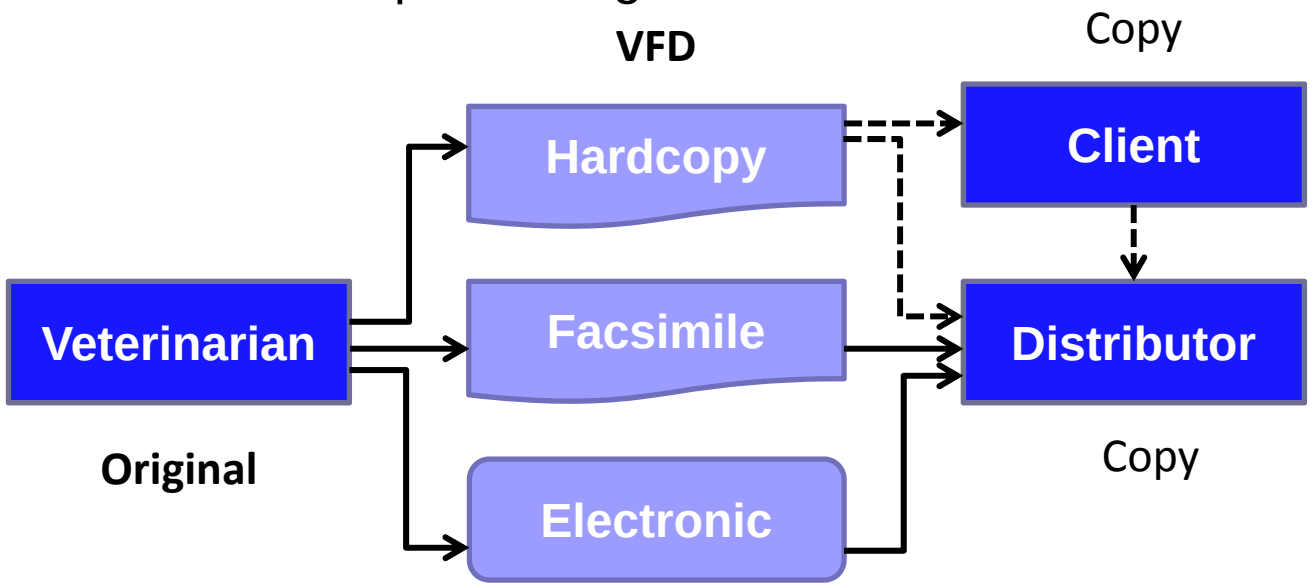
If a VFD drug is not approved in a combination, only first of the three statements is required on the VFD order

New Rule – Veterinarian Responsibilities (21 CFR 558.6(b))

- (1) In order for a VFD to be lawful, the veterinarian issuing the VFD must:
  - be licensed to practice veterinary medicine
  - be operating in the course of the veterinarian's professional practice and in compliance with all applicable veterinary licensing requirements, and in the context of a VCPR (State or Federal)
- (2) Issues a VFD in compliance with the conditions for use approved, conditionally approved, or indexed for the VFD drug or combination VFD drug
- (3) Includes fully and accurately all required information
- (4) Includes the following optional information
- (5) Includes the drug-specific information for each VFD drug used in the combination
- (6) Affirms whether the VFD drug(s) may be used alone or in an approved combination with over-the-counter drug(s)
- (7) Issues VFD in writing (nonverbally)
- (8) VFD could be hardcopy or electronic and must be sent to the distributor
- **(9) Provides a copy to the client**

Transmittal of VFD

- VFD is a written (non verbal) statement and can be hardcopy or electronic
- If the VFD is transmitted electronically, the veterinarian is not required to send the original in hardcopy to the distributor
- The veterinarian keeps the original VFD



New Rule – Distributors Responsibilities (21 CFR 558.6(c))

- is permitted to fill a VFD only if the VFD contains all the required information
- is permitted to distribute an animal feed containing a VFD drug or combination VFD drug only if it complies with the terms of the VFD and is manufactured and labeled in conformity with the approved, conditionally approved, or indexed conditions of use for such drug
- must keep records of the receipt and distribution of all medicated animal feed containing a VFD drug for 2 years
- **In addition to other applicable recordkeeping requirements found in this section, if the distributor manufactures the animal feed bearing or containing the VFD drug, the distributor must also keep VFD feed manufacturing records for 1 year in accordance with part 225 of this chapter. Such records must be made available for inspection and copying by FDA upon request.**

Distributors Record Keeping

Distributor

Only distributes VFD feed

If VFD feed is shipped to	Record	
	Required	Retained for
Clients only	VFD (order)	2 years
Other distributors only	Acknowledgement letter(s)	2 years
Both clients and other distributors	VFD (order) and acknowledgement letter(s)	2 years

Manufactures and distributes VFD feed

If VFD feed is shipped to	Record	
	Required	Retained for
Clients only	VFD (order)	2 years
Other distributors only	Acknowledgement letter(s)	2 years
Both clients and other distributors	VFD (order) and acknowledgement letter(s)	2 years

+

Manufacturing Record	
Required per	Retained for
21 CFR 225 (cGMP)	1 year

New Rule – Distributors Responsibilities (21 CFR 558.6(c))

- must notify FDA prior to the first time it distributes animal feed containing a VFD drug. The notification is required <u>one time</u> per distributor and must include the following information:
  - (i) The distributor's complete name and business address;
  - (ii) The distributor's signature or the signature of the distributor's authorized agent; and
  - (iii) The date the notification was signed.

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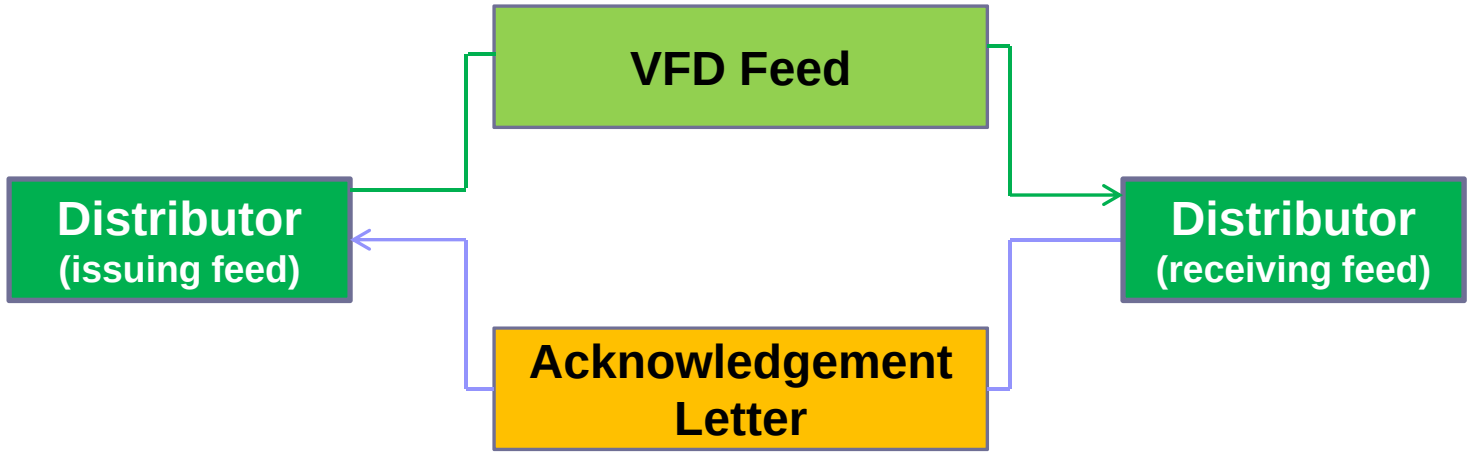
  - (i) The distributor's complete name and business address;
  - (ii) The distributor's signature or the signature of the distributor's authorized agent; and
  - (iii) The date the notification was signed.

- **must also notify FDA within 30 days of any change in ownership, business name, or business address. The notifications must be submitted to:**

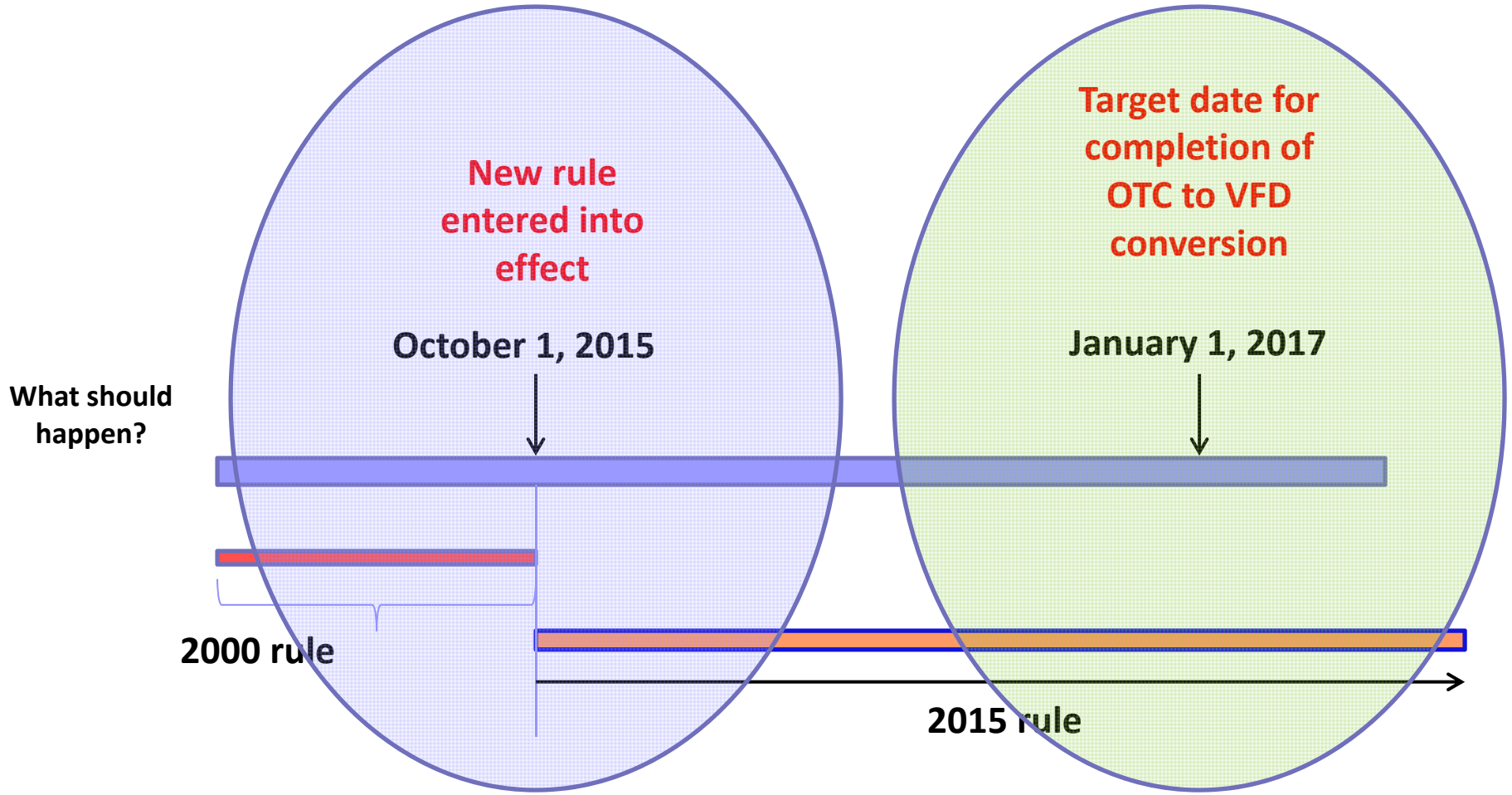
Food and Drug Administration,
Center for Veterinary Medicine,
Division of Animal Feeds (HFV–220),
7519 Standish Pl.
Rockville, MD 20855
FAX: 240–402–7077

New Rule – Distributors Responsibilities (21 CFR 558.6(c))

- **A distributor is permitted to distribute a VFD feed to another distributor only if the originating distributor (consignor) first obtains a written (nonverbal) acknowledgment letter, as defined in § 558.3(b)(11), from the receiving distributor (consignee) before the feed is shipped. Consignor distributors must retain a copy of each consignee distributor's acknowledgment letter for 2 years**



Important Dates



Important Dates – bottom line

What should happen?

- *The new VFD rule became effective*
- *The changes at this time apply only to the drugs that are already approved as VFD (avilamycin, florfenicol, and tilmicosin)*
- *The veterinarian issues VFD according to the new rule*

- *The new VFD rule in effect*
- *The OTC to VFD conversion has completed resulting in an influx of new VFD drugs*
- *The veterinarian continues to issue VFD according to the new rule*

Conclusions

- **Veterinary Feed Directive is an invaluable tool in ensuring proper use of antimicrobial drugs in animal feed**
- **Veterinarians are key in minimizing the potential for rise in antimicrobial resistance**
- **New rule clarifies and updates the old rule**
- **VFD – where the veterinary practice meets medicated feed**

Drugs Transitioning from Over-the-Counter (OTC) to Veterinary Feed Directive (VFD) Status

Upon completion of their voluntary transition from OTC to VFD, all feed uses of the following drugs, alone and in a combination, will require a VFD as of January 1, 2017, except in cases where a sponsor chooses to voluntarily withdraw the drug application:

Drugs Transitioning From OTC to VFD Status

Established drug name	Examples of proprietary drug name(s)[$]
chlortetracycline (CTC)	Aureomycin, CLTC, CTC, Chloratet, Chlorachel, ChlorMax, Chlortetracycline, Deracin, Inchlor, Pennchlor, Pfichlor
chlortetracycline/sulfamethazine*	Aureo S, Aureomix S, Pennchlor S
chlortetracycline/sulfamethazine/penicillin*	Aureomix 500, Chlorachel/Pficlor SP, Pennchlor SP, ChlorMax SP
hygromycin B	Hygromix
lincomycin	Lincomix
oxytetracycline (OTC)	TM, OXTC, Oxytetracycline, Pennox, Terramycin
oxytetracycline/neomycin*	Neo-Oxy, Neo-Terramycin
penicillin[+]	Penicillin, Penicillin G Procaine
sulfadimethoxine/ormetoprim*	Rofenaid, Romet
tylosin	Tylan, Tylosin, Tylovet
tylosin/sulfamethazine*	Tylan Sulfa G, Tylan Plus Sulfa G, Tylosin Plus Sulfamethazine
virginiamycin	Stafac, Virginiamycin, V-Max

Note: apramycin, erythromycin, neomycin (alone), oleandomycin[+], sulfamerazine, and sulfaquinoxaline are also approved for use in feed and are expected to transition to VFD status, but are not marketed at this time. If they return to the market after January 1, 2017, they will require a VFD.

[$]Type A medicated articles used to manufacture medicated feed, all products may not be marketed at this time

*Fixed-ratio, combination drug

[+]Currently only approved for production uses

Current VFD Drugs

Established drug name	Proprietary drug name(s)[$]
avilamycin	Kavault
florfenicol	Aquaflor, Nuflor
tilmicosin	Pulmotil, Tilmovet
tylvalosin	Aivlosin

[$]Type A medicated articles used to manufacture medicated feed

This information is up-to-date as of August 8, 2016. As the industry transitions, CVM anticipates additional changes during the coming months to this information. Please check the link below for the most recent updates:
http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/ucm071807.htm

Drugs Transitioning from Over-the-Counter (OTC) to Prescription (Rx) Status

Upon completion of their voluntary transition from OTC to Rx, all uses of the following drugs will require a prescription from a veterinarian as of January 1, 2017, except in cases where a sponsor chooses to voluntarily withdraw the drug application:

Water Soluble Drugs Transitioning From OTC to Rx Status

Established drug name	Examples of proprietary drug name(s)
chlortetracycline	Aureomycin, Aureomycyn, Chlora-Cycline, Chloronex, Chlortetracycline, Chlortetracycline Bisulfate, Chlortet-Soluble-O, CTC, Fermycin, Pennchlor
erythromycin	Gallimycin
gentamicin	Garacin, Gen-Gard, GentaMed, Gentocin, Gentoral
lincomycin	Linco, Lincomed, Lincomix, Lincomycin, Lincomycin Hydrochloride, Lincosol, Linxmed-SP
lincomycin/spectinomycin*	Lincomycin S, Lincomycin-Spectinomycin, L-S, SpecLinx
neomycin	Biosol Liquid, Neo, Neomed, Neomix, Neomycin, Neomycin Liquid, Neomycin Sulfate, Neo-Sol, Neosol, Neosol-Oral, Neovet
oxytetracycline	Agrimycin, Citratet, Medamycin, Oxymarine, Oxymycin, Oxy-Sol, Oxytet, Oxytetracycline, Oxytetracycline HCL, Oxy WS, Pennox, Terramycin, Terra-Vet, Tetravet-CA, Tetroxy, Tetroxy Aquatic, Tetroxy HCA
penicillin	Han-Pen, Penaqua Sol-G, Penicillin G Potassium, R-Pen, Solu-Pen
spectinomycin	Spectam
sulfadimethoxine	Agribon, Albon, Di-Methox, SDM, Sulfabiotic, Sulfadimethoxine, Sulfadived, Sulfamed-G, Sulforal, Sulfasol
sulfamethazine	SMZ-Med, Sulfa, Sulmet
sulfaquinoxaline	S.Q. Solution, Sulfa-Nox, Sulfaquinoxaline Sodium, Sulfaquinoxaline Solubilized, Sul-Q-Nox, Sulquin
tetracycline	Duramycin, Polyotic, Solu/Tet, Solu-Tet, Supercycline, Terra-Vet, Tet, Tetra-Bac, Tetracycline, Tetracycline Hydrochloride, Tetramed, Tetra-Sal, Tetrasol, Tet-Sol, TC Vet

Note: apramycin, carbomycin/oxytetracycline*, chlortetracycline/sulfamethazine*, streptomycin, sulfachloropyrazine, sulfachlorpyridazine, and sulfamerazine/sulfamethazine/sulfaquinoxaline* are expected to transition to Rx status, but are not marketed at this time. If they return to the market after January 1, 2017, they will require a prescription from a veterinarian.

*Fixed-ratio, combination drug

Current Rx Water Soluble Drugs

Established drug name	Examples of proprietary drug names
tylosin	Tylan, Tylomed, Tylosin, Tylosin Tartrate, Tylovet

This information is up-to-date as of January 19, 2016. As the industry transitions, CVM anticipates additional changes during the coming months to this information. Please check the link below for the most recent updates: http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/JudiciousUseofAntimicrobials/default.htm

#120

Guidance for Industry

Small Entity Compliance Guide

Veterinary Feed Directive Regulation Questions and Answers

This guidance document makes revisions to the final guidance that was made available in March 2009 to reflect the VFD final rule published in June 2015.

Submit comments on this guidance at any time. Submit electronic comments on the guidance to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the Docket No. FDA-2010-N-0155.

For further information regarding this document, contact Dragan Momcilovic, Center for Veterinary Medicine (HFV-226), Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, 240-402-5944, e-mail: dragan.momcilovic@fda.hhs.gov

Additional copies of this guidance document may be requested from the Policy and Regulations Staff (HFV-6), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at either http://www.fda.gov/AnimalVeterinary/default.htm or http://www.regulations.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
September 2015

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Draft Guidance for Industry

Small Entity Compliance Guide

Veterinary Feed Directive Regulation Questions and Answers

This guidance represents 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

Before 1996, there were only two options for dispensing new animal drugs: (1) over-the-counter (OTC), and (2) prescription. In 1996 Congress enacted the Animal Drug Availability Act (ADAA) to facilitate the approval and marketing of new animal drugs and medicated feeds. As part of the ADAA, Congress recognized that certain new animal drugs intended for use in animal feed should only be administered under a veterinarian's order and professional supervision. For example, veterinarians are needed to control the use of certain antimicrobials. Control is critical to reducing unnecessary use of such drugs in animals and to slowing or preventing any potential for the development of bacterial resistance to antimicrobial drugs. Safety concerns relating to difficulty of diagnosis of disease conditions, high toxicity, or other reasons may also dictate that the use of a medicated feed be limited to use by order and under the supervision of a licensed veterinarian. Therefore, the ADAA created a new category of products called veterinary feed directive drugs (or VFD drugs).

In June 2015, FDA published a final rule that revised the VFD regulations in 21 CFR 558.6 and introduced clarifying changes to the definitions in 21 CFR 558.3 (80 FR 31708). This guidance document includes revisions that are consistent with the requirements in the 2015 VFD final rule.

This guidance also serves as a Small Entity Compliance Guide (SECG), to aid industry in complying with the requirements of the VFD final rule. FDA has prepared this SECG in accordance with section 212 of the Small Business Regulatory Enforcement Fairness Act (Public Law 104-121). This document is intended to provide guidance to small businesses on the requirements of the final rule.

In general, FDA 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 guidance means that something is suggested or recommended, but not required.

II. VETERINARY FEED DIRECTIVE – GENERAL INFORMATION

A. Veterinary Feed Directive (VFD) Drugs

1. What is a Veterinary Feed Directive Drug?

A "veterinary feed directive (VFD) drug" is a drug intended for use in or on animal feed which is limited by an approved new animal drug application filed pursuant to section 512(b) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), a conditionally approved application filed pursuant to section 571 of the FD&C Act, or an index listing pursuant to section 572 of the FD&C Act to use under the professional supervision of a licensed veterinarian (21 CFR 558.3(b)(6)). Use of animal feed bearing or containing a VFD drug (VFD feed) must be authorized by a lawful VFD (21 CFR 558.6(a)(1)).

2. Who determines whether a drug is VFD drug?

When a new animal drug application is submitted to FDA's Center for Veterinary Medicine (CVM) for approval, CVM evaluates the drug for safety and effectiveness, and as part of the review process, determines whether the drug will be an over-the-counter (OTC) drug, a prescription (Rx) drug, or a VFD drug (limited to drugs used in or on animal feed).

3. What is a "combination veterinary feed directive drug"?

A "combination veterinary feed directive (VFD) drug" is a combination new animal drug (as defined in § 514.4(c)(1)(i)) intended for use in or on animal feed which is limited by an approved application filed pursuant to section 512(b) of the FD&C Act, a conditionally approved application filed pursuant to section 571 of the FD&C Act, or an index listing pursuant to section 572 of the FD&C Act to use under the professional supervision of a licensed veterinarian, and at least one of the new animal drugs in the combination is a VFD drug. Use of animal feed bearing or containing a combination VFD drug must be authorized by a lawful veterinary feed directive (21 CFR 558.3(b)(12)). If any component drug in an approved, conditionally approved, or indexed combination drug is a VFD drug, the combination drug is a combination VFD drug and its use must comply with the VFD requirements.

4. What are Category I and Category II drugs and what is their relevance to VFD?

All new animal drugs, including VFD drugs, approved for use in or on animal feed are placed in one of two drug categories, Category I or Category II (21 CFR 558.3(b)(1)). Category I drugs require no withdrawal period at the lowest use level in each species for which they are approved. Category II drugs either require a withdrawal period at the lowest use level for at least one species for which they are approved, or are regulated on a "no-residue" basis or with a zero tolerance because of a carcinogenic concern regardless of whether a withdrawal period is required.

A medicated feed mill license is required if the VFD drug used to manufacture a Type B or Type C medicated feed is a Category II, Type A medicated article (21 CFR 558.4(a)). A license is not required if the VFD drug is Category I with the exception of certain liquid and free-choice medicated feeds.

B. Veterinary Feed Directive (VFD)

1. What is a Veterinary Feed Directive?

A "veterinary feed directive" is a written (nonverbal) statement issued by a licensed veterinarian in the course of the veterinarian's professional practice that orders the use of a VFD drug or combination VFD drug in or on an animal feed. This written statement authorizes the client (the owner of the animal or animals or other caretaker) to obtain and use animal feed bearing or containing a VFD drug or combination VFD drug to treat the client's animals only in accordance with the conditions for use approved, conditionally approved, or indexed by the FDA (21 CFR 558.3(b)(7)). A VFD may also be referred to as a VFD order.

2. What is required for a VFD to be "lawful"?

To be lawful, a VFD must be issued and used in compliance with all applicable requirements in 21 CFR 558.6. This includes the requirement that a VFD must be issued by a veterinarian licensed to practice veterinary medicine operating in the course of his/her professional practice and in compliance with all applicable veterinary licensing and practice requirements, including issuing the VFD in the context of a veterinarian-client-patient relationship (VCPR) as defined by the state (21 CFR 558.6(b)(1)). If applicable VCPR requirements as defined by such state do not include the key elements of a valid VCPR as defined in FDA's regulations at 21 CFR 530.3(i), the veterinarian must issue the VFD in the context of a valid VCPR as defined in 21 CFR 530.3(i).

3. Does the state or federal definition of a veterinarian-client-patient relationship apply?

In those states that require a VCPR that includes the key elements of the federally-defined VCPR in order for a veterinarian to issue a VFD, the veterinarian issuing the VFD must be operating within the context of a VCPR as that term is defined by the state. In all other cases, the veterinarian must be operating within the context of a valid VCPR as defined by FDA in 21 CFR § 530.3(i). (21 CFR § 558.6(b)(1)(ii)). FDA will consider states with VCPR definitions that at least address the concepts that the veterinarian (1) engage with the client to assume responsibility for making clinical judgments about patient health, (2) have sufficient knowledge of the patient by virtue of patient examination and/or visits to the facility where patient is managed, and (3) provide for any necessary follow-up evaluation or care to include the key elements of the federally-defined VCPR as set forth in 21 CFR § 530.3(i).

In states where the veterinary practice requirements do not require that a VFD be issued within the context of a state-defined VCPR that includes the key elements of a valid VCPR as defined in federal regulations at 21 CFR § 530.3(i), FDA is requiring that the VFD be issued within the context of a federally-defined valid VCPR as defined at 21 CFR § 530.3(i). (21 CFR 558.6(b)(1)(ii)).

FDA will work with State regulatory authorities to verify whether their state has VCPR requirements in place that apply to the issuance of a VFD and include the key elements of the federally-defined VCPR. While FDA works with the State regulatory authorities we will provide information about that process online at http://www.fda.gov/animalveterinary/developmentapprovalprocess/ucm071807.htm.

FDA will then compile a list of states that require a VCPR that includes the key elements of the federally-defined VCPR in order for a veterinarian to issue a VFD. This list will be provided online at the time final guidance publishes (http://www.fda.gov/animalveterinary/developmentapprovalprocess/ucm071807.htm), and will be updated periodically as FDA receives and verifies information from states if they change their VCPR definition or its applicability.

C. Information on the VFD

1. What specific information must the veterinarian include on the VFD order and what information is optional?

21 CFR 558.6(b)(3) requires the following information to be fully and accurately included on the VFD order:

- The veterinarian's name, address, and telephone number;
- the client's name, business or home address, and telephone number;
- the premises at which the animals specified in the VFD are located;
- the date of VFD issuance;
- the expiration date of the VFD;
- the name of the VFD drug(s);
- the species and production class of animals to be fed the VFD feed;
- the approximate number of animals to be fed the VFD feed by the expiration date of the VFD;
- the indication for which the VFD is issued;
- the level of VFD drug in the feed and duration of use;
- the withdrawal time, special instructions, and cautionary statements necessary for use of the drug in conformance with the approval;
- the number of reorders (refills) authorized, if permitted by the drug approval, conditional approval, or index listing;
- the statement: "Use of feed containing this veterinary feed directive (VFD) drug in a manner other than as directed on the labeling (extralabel use), is not permitted";
- an affirmation of intent for combination VFD drugs as described in 21 CFR 558.6(b)(6); and
- the veterinarian's electronic or written signature.

In addition to the information described above that must be included on the VFD, the veterinarian also may, at his or her discretion, include on the VFD the following additional information as described in 21 CFR 558.6(b)(4) to more specifically identify the animals he or she is authorizing to be treated using the VFD feed:

- A more specific description of the location of the animals (for example, by site, pen, barn, stall, tank, or other descriptor the veterinarian deems appropriate);
- the approximate age range of the animals;
- the approximate weight range of the animals; and
- any other information the veterinarian deems appropriate to identify the animals at issue.

2. Who is the "client" for the purpose of filling the VFD?

For purposes of the VFD regulations, the term "client" typically refers to the person responsible for the care and feeding of the animals receiving the VFD feed. As described in the definition of the term "veterinary feed directive," the client may be the owner of the animals or other caretaker (see 21 CFR 558.3(b)(7)).

3. What information should be included on the VFD to describe the "premises" at which the animals are located?

We expect that the veterinarian would enter information about the physical location of the animals referred to in the VFD that would be sufficiently descriptive to allow someone to locate the animals. Typically, the street address for the facility would be an appropriate way to identify the animals' location; however, other generally recognized geographical indicators such a global positioning system (GPS) coordinate may be appropriate if a street address does not exist.

We recognize that an address for a facility may not provide enough information to identify the location of animals in a case where the VFD is meant to authorize the VFD feed to be provided to a very specific group of animals. As a result, the veterinarian may use his or her discretion to enter additional information on the VFD that more specifically describes the location of the animals such as the site, pen, barn, stall, tank, or other descriptor (21 CFR 558.6(b)(4)(i)). The veterinarian should consult with the client to determine whether the animals will remain at this more specific location until the expiration date of the VFD.

We also understand that some groups of animals that are of similar age, weight range, etc., are managed in a similar manner, but may be housed in different physical locations. For example, a group of weaned pigs may be moved out of a nursery facility and transferred to multiple grow-out facilities for finishing. If a VFD is intended to authorize the use of a VFD feed in an identified group (approximate number) of animals that are located at more than one physical location, it is acceptable for a veterinarian to include multiple specified locations for that group of animals on the VFD. The veterinarian may write a VFD that covers animals in multiple locations (animal production facilities) to be fed the VFD feed by the expiration date on the VFD, provided he or she can do so in compliance with professional licensing and practice

standards and provided the VFD feed is supplied to such multiple locations by a single feed manufacturer (distributor).

4. What is an "expiration date" on the VFD?

The expiration date on the VFD specifies the last day the VFD feed can be fed. In other words, a VFD feed or combination VFD feed must not be fed to animals after the expiration date on the VFD (21 CFR 558.6(a)(2)).

5. How is the "expiration date" determined by the veterinarian for a VFD?

In certain cases, FDA determines the expiration date of a VFD (the number of days the VFD feed can be fed to the animal before the VFD expires) as part of the approval, conditional approval, or index listing of that drug. The VFD expiration date defines the period of time for which the authorization to feed an animal feed containing a VFD drug is lawful. The expiration date for the VFD must not extend beyond the expiration date specified in that drug's approval, conditional approval, or index listing (21 CFR 558.6(b)(3)(v)).

In cases where the expiration date is not specified in the approval, conditional approval, or index listing, the expiration date of the VFD must not exceed 6 months after the date of issuance (21 CFR 558.6(b)(3)(v)). This provision allows veterinarians, based on their medical judgment and knowledge of the animal production operation, to determine on a case-by-case basis whether the maximum 6-month period is an appropriate expiration date for the VFD, or whether a more limited period is warranted. The veterinarian will use his or her medical judgment to determine what expiration date is appropriate for the VFD, based on many factors including, but not limited to, the type of animal production facility and operation, the VFD drug or combination VFD drug at issue, the intended use of the VFD drug, and the health status, treatment history, and lifecycle of the animals.

The date of expiration should be calculated by the calendar date, not the number of days. For example, using a 6-month expiration date for a VFD, if the VFD is written on July 10, then the expiration date would be January 10 of the following year. Using the same 6-month expiration date example, but having the VFD written on the last day of the month, the VFD expiration date would be the last day of the sixth month even if that month has fewer days. Thus, in this example, if the VFD is written on August 31, the expiration date would be the following February 28 during a regular calendar year, or February 29 during a leap year.

6. What is the "duration of use" and how does it relate to the "expiration date"?

The VFD expiration date defines the period of time for which the authorization to feed an animal feed containing a VFD drug is lawful. This period of time may be specified in the approved labeling of a given VFD drug or, if not specified in the labeling, the veterinarian must specify an expiration date for the VFD that does not exceed 6 months (21 CFR 558.6(b)(3)(v)). The duration of use is a separate concept from the expiration date, and determines the length of time, established as part of the approval, conditional approval, or index listing process, that the animal feed containing the VFD drug is allowed to be fed to the animals. This period of time is

specified in the labeling of the VFD drug. For example, the currently approved VFD drug tilmicosin has an expiration date of 45 days and a duration of use of 21 days. This means that when the VFD is issued, the client has 45 days to obtain the VFD feed and complete the 21 day course of therapy. It is unlawful to feed the VFD feed to animals after the VFD expiration date (21 CFR 558.6(a)(2)).

7. What is the "approximate number of animals" on the VFD?

The approximate number of animals is the potential number of animals of the species and production class identified on the VFD that will be fed the VFD feed or combination VFD feed at the specified premises by the expiration date of the VFD (21 CFR 558.6(b)(3)(viii)).

8. Can a VFD authorize either the approved pioneer or approved generic VFD drug(s)?

The veterinarian is required to write the name of the VFD drug on the VFD (21 CFR 558.6(b)(3)(vi)). The veterinarian may choose to write the trade name of the approved pioneer or an approved generic (if available) VFD drug or the established name of the VFD drug (i.e., active drug ingredient) to complete this requirement.

The veterinarian may choose to specify that a substitution by the feed manufacturer of either the pioneer or generic VFD drug identified on the form is not allowed. If the veterinarian does not specify that a substitution is not allowed, the feed manufacturer may use either the approved pioneer or an approved generic VFD drug to manufacture the VFD feed. However, the feed manufacturer may not substitute a generic VFD drug for a pioneer VFD drug in a combination VFD feed if the generic VFD drug is not part of an approved combination VFD drug.

9. In cases where a VFD drug is approved for use at multiple drug levels, or for use in a range of drug levels, would one or multiple VFD orders have to be issued to cover such drug uses?

In cases where a VFD drug is approved for use at multiple drug concentrations, or levels, the veterinarian may issue a single VFD order covering all those approved drug levels intended to be used, and the approved duration(s) of feeding the VFD feed at the approved drug level(s).

If a VFD drug is approved for use within a range of drug levels, then the veterinarian may specify a particular drug level within that range, or authorize use at any drug level within the range by putting the entire authorized range on the VFD.

10. What additional information is required on a VFD authorizing the use of a combination VFD drug?

A VFD authorizing the use of a combination VFD drug that contains two or more VFD drug(s) is required to include the name of the drugs in the combination, the indication(s) of use, the levels of the drugs in the VFD feed and duration of use, the withdrawal time, special instructions, and cautionary statements necessary for use of the combination VFD drug required by the approval

(21 CFR 558.6(b)(5)) (i.e., the drug-specific information specified in 21 CFR 558.6(b)(3)(vi), (ix), (x), and (xi) for each VFD drug in the combination).

The veterinarian may expand or limit the use of a VFD drug along with one or more OTC animal drugs in an approved, conditionally approved, or indexed combination VFD drug by completing the drug-specific information specified in 21 CFR 558.6(b)(3)(vi), (ix), (x), and (xi) for the use of the VFD drug(s) and by including one of the following affirmation of intent statements (21 CFR 558.6(b)(6):

- "This VFD only authorizes the use of the VFD drug(s) cited in this order and is not intended to authorize the use of such drug(s) in combination with any other animal drugs."

- "This VFD authorizes the use of the VFD drug(s) cited in this order in the following FDA-approved, conditionally approved, or indexed combination(s) in medicated feed that contains the VFD drug(s) as a component." [List specific approved combination medicated feeds following this statement.]

- "This VFD authorizes the use of the VFD drug(s) cited in this order in any FDA-approved, conditionally approved, or indexed combination(s) in medicated feed that contains the VFD drug(s) as a component."

11. Do these regulations allow reorders and refills?

The regulation allows the issuing veterinarian to authorize reorders (refills) of the VFD only if reorders (refills) are explicitly permitted by the drug approval, conditional approval, or index listing. In cases where reorders (refills) are not specified on the labeling for an approved, conditionally approved, or index listed VFD drug, reorders (refills) are not permitted (21 CFR 558.6(b)(3)(xii)).

12. What is an "extralabel use" of a VFD drug and is it allowed?

"Extralabel use" is defined in FDA's regulations as actual or intended use of a drug in an animal in a manner that is not in accordance with the approved labeling (21 CFR 530.3(a)). For example, feeding the animals VFD feed for a duration of time that is different from the duration specified on the label, feeding VFD feed formulated with a drug level that is different from what is specified on the label, or feeding VFD feed to an animal species different than what is specified on the label would all be considered extralabel uses.

Extralabel use of medicated feed, including medicated feed containing a VFD drug or a combination VFD drug, is not permitted (21 U.S.C. 360b(a); 21 CFR 530.11(b) and 558.6(a)(3)). Use of medicated feeds, including those containing a VFD drug or a combination VFD drug, is limited to the approved, conditionally approved, or indexed conditions of use (21 U.S.C. 360b(a); 21 CFR 558.6(a)(3)).

The VFD must include the statement "Use of feed containing this veterinary feed directive (VFD) drug in a manner other than as directed on the labeling (extralabel use) is not permitted." (21 CFR 558.6(b)(3)(xiii)).

D. VFD Transmission and Recordkeeping

1. How can a VFD order be transmitted to the distributor?

A veterinarian must send a copy of the VFD to the distributor in hardcopy by facsimile (fax), or by electronic means. If the veterinarian sends the VFD in hardcopy, he or she must send the copy of the VFD to the distributor either directly or through the client (21 CFR 558.6(b)(8)).

2. Is the veterinarian required to send the original VFD order to the distributor?

No, the veterinarian is not required to send the original paper copy to the distributor. The veterinarian must retain the original VFD in its original form (electronic or hardcopy). The distributor and client copies may be kept either as an electronic copy or hardcopy (21 CFR 558.6(a)(4)).

3. Can a VFD order be transmitted by telephone?

The veterinarian is required to issue a written (nonverbal) VFD (21 CFR 558.6(b)(7)). Therefore, a VFD order may not be issued verbally, including verbal transmission by telephone. A VFD order may be sent by facsimile (fax).

4. Can a VFD order be transmitted to the distributor by the Internet?

Yes. According to 21 CFR 558.6(b)(8), a VFD order must be sent to the distributor "via hardcopy, facsimile (fax), or electronically." The term "electronically" includes sending via the Internet. For example, transmitting the VFD "electronically" includes using the Internet to transmit the image of a paper VFD order (e.g., emailing a scanned VFD document) or using the Internet to transmit an electronic VFD order generated in a system that is shown to be in compliance with FDA's regulations at 21 CFR part 11. For additional information about how part 11 applies to the VFD process, see discussion at question 8, "What is 21 CFR part 11 and how does it apply to the issuance of electronic VFDs?" below.

5. Who is responsible for distributing the VFD order?

The veterinarian must retain the original VFD order in its original form (electronic or hardcopy) (21 CFR 558.6(a)(4)). In addition, the veterinarian is required to send a copy to the distributor directly or, if sending the VFD order in hardcopy, either directly or through the client (21 CFR 558.6(b)(8)), and the veterinarian is also required to give a copy of the VFD to the client (21 CFR 558.6(b)(9)). Thus, it is the veterinarian's obligation to ensure that the VFD order is distributed to the client and the distributor.

6. How long must VFD orders be kept and who must keep them?

All involved parties (veterinarian, client, distributor) must retain a copy of the VFD for 2 years. The veterinarian is required to keep the VFD in its original format. The distributor and client copies may be kept as an electronic copy or hardcopy (21 CFR 558.6(a)(4)).

7. In what format can the "original VFD" order be kept?

The veterinarian must retain the original VFD in its original form (electronic or hardcopy) (21 CFR 558.6(a)(4)).

8. What is 21 CFR part 11 and how does it apply to the issuance of electronic VFDs?

21 CFR part 11 sets out the criteria under which the agency considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be generally equivalent to paper records and handwritten signatures executed on paper.

21 CFR part 11 applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any FDA records requirements. Therefore, electronic VFD orders issued by veterinarians must be compliant with 21 CFR part 11, and electronic VFD orders received and electronically stored by distributors and clients must also be compliant with 21 CFR part 11. 21 CFR part 11 does not apply to paper records that are, or have been, transmitted by electronic means (such as facsimile, email attachments, etc.).

9. Can a third-party server company require testing of its clients' computers before starting to transmit VFD orders?

Whether or not third-party server companies require testing of their clients' computers for compatibility with their systems before starting to provide the clients with their service is a business decision between third-party server companies and their clients and not an FDA requirement.

III. QUESTIONS AND ANSWERS SPECIFIC TO INVOLVED PARTIES

A. Veterinarian

1. What are my responsibilities as a veterinarian?

In order for a VFD to be lawful, the veterinarian issuing the VFD:

- must be licensed to practice veterinary medicine (21 CFR 558.6(b)(1)(i));
- must be operating in the course of the veterinarian's professional practice and in compliance with all applicable veterinary licensing and practice requirements (21 CFR 558.6(b)(1)(ii));
- must write VFD orders in the context of a veterinarian-client-patient relationship (VCPR) (21 CFR 558.6(b)(1)(ii));
- must only issue a VFD that is in compliance with the conditions for use approved, conditionally approved, or indexed for the VFD drug or combination VFD drug (21 CFR 558.6(b)(2));
- must prepare a written (nonverbal) VFD (21 CFR 558.6(b)(7)) that includes the veterinarian's electronic or written signature (21 CFR 558.6(b)(3)(xv));
- must ensure the VFD includes all required information specified in the VFD regulation (21 CFR 558.6(b)(3));
- may enter additional discretionary information to more specifically identify the animals to be treated/fed the VFD feed (21 CFR 558.6(b)(4));
- must include certain drug-specific information for each VFD drug when the veterinarian is authorizing the use of a drug combination that includes more than one VFD drug (21 CFR 558.6(b)(5));
- for VFD drugs approved for use alone or in combination with one or more OTC drugs, must include on the VFD order an affirmation of intent either to restrict authorized use only to the VFD drug cited on the VFD or to allow the use of the cited VFD drug in an approved combination with one or more OTC drug(s) (21 CFR 558.6(b)(6));
- must provide the distributor with a copy of the VFD order (21 CFR 558.6(b)(8));
- must provide the client with a copy of the VFD order (21 CFR 558.6(b)(9));
- must retain the original VFD for 2 years (21 CFR 558.6(a)(4)); and
- must provide VFD orders for inspection and copying by FDA upon request (21 CFR 558.6(a)(5)).

2. Can I write a VFD order for an OTC drug?

No. A practicing veterinarian may not write a VFD order for an OTC drug. A veterinarian may only write a VFD order for drugs approved, conditionally approved, or indexed as VFD drugs by the FDA (21 U.S.C. 354); nor may he or she write a VFD order to be used other than as specified on the labeling for that drug (i.e., extralabel use is not permitted). (21 CFR 558.6(a)(3)).

3. How do I authorize or limit the use of a VFD drug that is approved to be used in combination with OTC drugs?

Some VFD drugs are approved for use alone or in a combination with one or more OTC drug(s). In those circumstances, the issuing veterinarian would specify on the VFD whether he or she authorizes the VFD drug to be used alone or in an approved drug combination with one or more OTC drug(s). In accordance with 21 CFR 558.6(b)(6), the veterinarian is required to affirm his or her intent by including one of the following three statements on the VFD:

- "This VFD only authorizes the use of the VFD drug(s) cited in this order and is not intended to authorize the use of such drug(s) in combination with any other animal drugs."

    - This statement is used if the veterinarian does **not** authorize the VFD drug to be used in combination with any other animal drug in the medicated feed. For those VFD drugs that are only approved as a single ingredient Type A medicated article, i.e., there are no approved combinations that contain the VFD drug as a component, this statement is the only one of the three statements that can be selected and must be included in the VFD.

- "This VFD authorizes the use of the VFD drug(s) cited in this order in the following FDA-approved, conditionally approved, or indexed combination(s) in medicated feed that contains the VFD drug(s) as a component." [List specific approved combination medicated feeds following this statement.]

    - This statement is used if the veterinarian chooses to authorize the use of the VFD drug(s) only in **specific** combination(s); the veterinarian may only list approved, conditionally approved, or indexed combination(s) that contain the VFD drug. The client is authorized to use the VFD drug(s) in medicated feed either alone or in those specific combinations that the veterinarian has specified on the VFD.

- "This VFD authorizes the use of the VFD drug(s) cited in this order in any FDA-approved, conditionally approved, or indexed combination(s) in medicated feed that contains the VFD drug(s) as a component."

    - This statement is used if the veterinarian authorizes the use of the VFD drug(s) in **any** approved combination that contains the VFD drug. The client is authorized to use the VFD drug(s) either alone or in any approved, conditionally approved, or indexed combination with the OTC drug(s) in the medicated feed.

4. Other than the required information, what other information may I include in the VFD?

As also noted in II.C.1 above, the veterinarian may, at his or her discretion, more specifically identify the animals authorized to be treated/fed the VFD feed (21 CFR 558.6(b)(4)). Specifically, the veterinarian can further specify the location of the animals (e.g., site, pen, barn, stall, or tank), the approximate age or weight range of the animals, or any other information the veterinarian deems appropriate to identify the animals subject to the VFD.

5. How can I transmit an electronic VFD order to the distributor immediately if my third-party computer server holds all VFD orders and only transmits them once per day (e.g., midnight)?

For an immediate delivery of an electronic VFD order, we recommend that the veterinarian print a copy of the VFD and have it hand delivered, transmitted by facsimile, or transmitted electronically to the distributor.

6. How do I cancel my VFD order?

To cancel a paper VFD order we recommend that the veterinarian promptly contact the client and distributor in possession of a copy of the VFD order.

To cancel an electronic VFD order that involves a third-party server, we recommend that the veterinarian contact the server and request that the VFD order not be transmitted. If the veterinarian wants to cancel the VFD order after the order has been electronically transmitted, we recommend that he or she contact the distributor and client who received a copy of the VFD order and request that the VFD order be cancelled.

We recommend that the involved parties document the cancellation request and make the records available at the time of an inspection. In a situation where the distributor is contacted regarding cancellation of the VFD order, we recommend that the distributor document the final outcome of the cancellation request (e.g., state that the VFD feed was neither prepared nor distributed to the client).

7. In the past, I issued paper VFD orders. Do I have to issue electronic VFD orders now?

No. Issuing VFD orders electronically is entirely optional. Paper VFD orders remain an acceptable means of authorizing the use of a VFD drug.

8. How do I obtain a VFD form for a VFD drug?

Although it is not mandatory for VFD drug sponsors to provide copies of a VFD form for use by veterinarians, sponsors may make the VFD forms available to veterinarians in triplicate to ensure efficiency and completeness of VFD order transmission. Regardless of whether or not a drug sponsor makes VFD forms available to veterinarians, a veterinarian may create his/her own VFD form for a VFD drug. Any VFD form, whether provided by the drug sponsor or created by a veterinarian, must include the information specified in 21 CFR 558.6(b)(3).

9. Can I make my own VFD form to authorize the use of a VFD drug?

Although many companies distribute for use by veterinarians a VFD form that is specific to their products, a veterinarian may also create or use a different VFD form, as long as it contains all of the required information specified in 21 CFR 558.6(b)(3).

B. Distributor

1. What are my responsibilities as a distributor?

If you distribute an animal feed containing a VFD drug or a combination VFD drug, you must:

- File a one-time notice with FDA of intent to distribute VFD drugs (21 CFR 558.6(c)(5)). The notice should be sent to FDA, Center for Veterinary Medicine, Division of Animal Feeds (HFV-220), 7519 Standish Pl., Rockville, MD 20855 (21 CFR 558.6(c)(7));
- notify FDA within 30 days of any change in ownership, business name, or business address (558.6(c)(6));
- fill a VFD order only if the VFD contains all required information (21 CFR 558.6(c)(1));
- ensure that the distributed animal feed containing the VFD drug or combination VFD drug complies with the terms of the VFD and is manufactured and labeled in conformity with the approved, conditionally approved, or indexed conditions of use for such drug (21 CFR 558.6(c)(2));
- ensure all labeling and advertising prominently and conspicuously displays the following cautionary statement: "Caution: Federal law restricts medicated feed containing this veterinary feed directive (VFD) drug to use by or on the order of a licensed veterinarian." (21 CFR 558.6(a)(6));
- retain VFD orders for two years from date of issuance (21 CFR 558.6(a)(4));
- retain records of the receipt and distribution of all medicated animal feed containing a VFD drug for 2 years (21 CFR 558.6(c)(3));
- provide VFD orders for inspection and copying by FDA upon request (21CFR 558.6(a)(5));

- retain records of VFD manufacturing for 1 year in accordance with 21 CFR part 225 and make such records available for inspection and copying by FDA upon request (21 CFR 558.6(c)(4)); and
- if you are the originating distributor (consignor), you must obtain an acknowledgement letter from the receiving distributor (consignee) before the feed is shipped (21 CFR 558.6(c)(8)); and
- if you are a consignor distributor, you are required to retain a copy of each consignee distributor's acknowledgement letter for 2 years (21 CFR 558.6(c)(8)).

2. What is the Distributor Notification Process?

A distributor must submit a one-time notification to FDA of its intent to distribute medicated feed containing a VFD drug (21 CFR 558.6(c)(5)). The term "distributor" means any person who distributes a medicated feed containing a VFD drug to another person. Such other person may be another distributor or the client-recipient of a VFD (21 CFR 558.3(b)(9)). The distributor notification must include the distributor's complete name and business address, the distributor's signature or the signature of the distributor's authorized agent, and the date the notification was signed (21 CFR 558.6(c)(5)).

In some cases, an animal producer (the client) may also be a distributor. When a manufacturer of a Type B VFD feed distributes the Type B VFD feed to an animal producer, the animal producer may manufacture a Type C VFD feed to either feed the VFD feed to his or her own animals and/or further distribute the Type C VFD feed to another distributor or client-recipient.

If the VFD feed is being shipped to an animal producer who is a distributor that has sent a one-time notification to FDA, the animal producer must supply either an acknowledgment letter (see also answer to question #5 below "What is an acknowledgement letter and how is it different than a distributor notification?") or a VFD for the receipt of the Type B VFD feed from the distributor. (§ 558.6(c)(2) and (8)) (Note: In order for the animal producer to receive a Type B or Type C VFD feed without a VFD in hand, he or she must have previously notified FDA that he or she is a distributor. (§ 558.6(c)(5)) If the animal producer provides an acknowledgment letter to the distributor from whom the animal producer receives the VFD feed, the animal producer must either receive an acknowledgment letter or a VFD prior to further distributing the VFD feed to another person, or have a VFD on hand prior to feeding the Type C VFD feed to his or her own animals. (§ 558.6(c)(2) and (8)).

3. When is a distributor required to submit an updated notification to the FDA?

An updated notification is required within 30 days of any change in ownership, business name, or business address (21 CFR 558.6(c)(6)).

4. Is there a publicly available VFD distributor notification list?

Yes. The list is available at:
http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/ucm071807.htm#listing.

5. What is an acknowledgment letter and how is it different than a distributor notification?

An acknowledgement letter is a letter that a distributor obtains from a consignee-distributor (the distributor receiving the VFD feed) when the distributor ships an animal feed containing a VFD drug in the absence of a valid VFD. Specifically, an "acknowledgement letter" is a written (nonverbal) communication provided to a distributor (consignor) from another distributor (consignee). An acknowledgement letter must be provided either in hardcopy or through electronic media, and must affirm: (1) that the distributor will not ship such VFD feed to an animal production facility that does not have a VFD; (2) that the distributor will not ship such VFD feed to another distributor without receiving a similar written acknowledgment letter; and (3) that the distributor has complied with the distributor notification requirements in 21 CFR 558.6(c)(5). (21 CFR 558.3(b)(11)) The acknowledgment letter allows a distributor to have VFD feed on hand so that when a client gives them a valid VFD they can fill the VFD immediately.

An acknowledgment letter is different than a distributor notification. A distributor notification is the one-time notice by a distributor to the FDA of its intent to distribute a medicated feed containing a VFD drug (21 CFR 558.6(c)(5)).

6. When is a medicated feed mill license required?

A medicated feed mill license is required to manufacture a Type B or Type C medicated feed from a Category II, Type A medicated article (21 CFR 558.4(a)). A medicated feed mill license is also required to manufacture certain free-choice medicated feeds (21 CFR 510.455(f)) and liquid medicated feeds (21 CFR 558.5(g)). The licensing requirements are the same whether manufacturing medicated feed from OTC or VFD drugs.

7. Is a medicated feed mill license required when a medicated feed containing a VFD drug is manufactured from a Type A medicated article?

It depends. A medicated feed mill license is required if the VFD drug used to manufacture a Type B or Type C medicated feed is a Category II, Type A medicated article (21 CFR 558.4(a)). A license is not required if the VFD drug is Category I with the exception of certain liquid and free-choice medicated feeds.

8. What should the distributor do if the VFD is not completely filled out?

The veterinarian must ensure that all required information is fully and accurately included on the VFD (21 CFR 558.6(b)(3)). The distributor is permitted to fill a VFD only if the VFD contains all required information (21 CFR 558.6(c)(1)). If it does not contain all of the required information, the distributor must not fulfill the VFD and we recommend that the distributor notify the veterinarian that the order cannot be filled until all the necessary information on the VFD is provided.

9. If a VFD authorizes the use of a drug(s) that is not approved as a VFD, can a distributor fill the VFD order?

No.

C. Client

1. What are my responsibilities as a client?

A client recipient of an animal feed containing a VFD drug or a combination VFD drug must:

- Only feed animal feed bearing or containing a VFD drug or a combination VFD drug (a VFD feed or combination VFD feed) to animals based on a VFD issued by a licensed veterinarian (21 CFR 558.6(a)(1));
- feed a VFD feed or combination VFD feed to animals by no later than the expiration date on the VFD (21 CFR 558.6(a)(2));
- provide a copy of the VFD order to the distributor if the issuing veterinarian sends the distributor's copy of the VFD through you, the client (21CFR 558.6(b)(8);
- maintain a copy of the VFD order for a minimum of 2 years (21 CFR 558.6(a)(4)); and
- provide VFD orders for inspection and copying by FDA upon request (21 CFR 558.6(a)(5)).

2. What is my role as a client in the veterinarian-client-patient-relationship (VCPR)?

In order for a VFD to be lawful, the VFD must be issued and used in compliance with all applicable requirements in 21 CFR 558.6. This includes the requirement that the veterinarian must issue the VFD in the context of a state-defined VCPR, or if the VCPR requirements as defined by such state do not include the key elements of the federally-defined valid VCPR or are not applicable to the issuance of a VFD, then the veterinarian must issue the VFD in the context of a valid VCPR as that term is defined in FDA's regulations at 21 CFR 530.3(i). (21 CFR 558.6(b)(1)(ii)). In those cases where the federally-defined VCPR applies, in order for the VFD to be written in the context of a valid VCPR you, as the client, must agree to follow instructions of the veterinarian (21 CFR 530.3(i)(1)). In those cases where a veterinarian is issuing the VFD in the context of a state-defined VCPR, as a client you must follow the client requirements in the state-defined VCPR.

3. Can a client distribute or feed drugs that are not approved as VFD drugs if such distribution or feeding is authorized by a veterinarian on a VFD order?

No.

4. Can a client feed a VFD feed past the VFD expiration date?

No. A VFD feed or combination VFD feed must not be fed to animals after the expiration date on the VFD (21 CFR 558.6(a)(2)).

5. I have a VFD order that I would like to use to feed a VFD feed, but the order will expire before I can complete the duration of use on the order, what should I do?

The client should contact his/her veterinarian to request a new VFD order. A VFD feed or combination VFD feed must not be fed to animals after the expiration date on the VFD (21 CFR 558.6(a)(2)).

Contains Nonbinding Recommendations

#213

Guidance for Industry

New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209

Submit comments on this guidance at any time. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. All written comments should be identified with the Docket No. FDA-2011-D-0889.

For further information regarding this document, contact William T. Flynn, Center for Veterinary Medicine (HFV-1), Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, 240-276-9084. E-mail: william.flynn@fda.hhs.gov.

Additional copies of this 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 either http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm or http://www.regulations.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
December 2013

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Guidance for Industry

New Animal Drugs and New Animal Drug Combination Products, Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209

This guidance represents 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 the 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 number listed on the previous page of this guidance.

I. Introduction

This guidance is intended for sponsors of approved applications for new animal drugs and new animal drug combination products containing medically important antimicrobial new animal drugs for use in or on medicated feed or water of food-producing animals. The guidance contains information for sponsors of such new animal drugs and combination products to facilitate voluntary changes to the conditions of use for such new animal drugs and combination products consistent with FDA's recommendations included in the guidance document entitled "The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals" (Judicious Use Guidance, GFI #209). In particular, the purpose of this guidance is to provide sponsors with specific recommendations on how to supplement their approved new animal drug applications to align with FDA's GFI #209.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA'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 FDA's guidances means that something is suggested or recommended, but not required.

II. Background

On April 11, 2012, FDA finalized a guidance document entitled "The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals" (Judicious Use Guidance, GFI #209). That final guidance represents the Agency's current thinking regarding antimicrobial drugs that are medically important in human medicine and used in food-producing animals. Specifically, the final guidance discusses FDA's concerns regarding the development of antimicrobial resistance in human and animal bacterial pathogens when medically important antimicrobial drugs are used in food-producing animals in an injudicious manner. In addition,

the Judicious Use Guidance provides two recommended principles regarding the appropriate or judicious use of medically important antimicrobial drugs:

> (1) Limit medically important antimicrobial drugs to uses in animals that are considered necessary for assuring animal health, and
> (2) Limit medically important antimicrobial drugs to uses in animals that include veterinary oversight or consultation.

As noted above, the purpose of this guidance is to provide sponsors with specific recommendations on how to voluntarily modify the use conditions of their medically important antimicrobial drug products to align with the above two principles. The voluntary process outlined in this guidance would help to phase out the use of medically important antimicrobial drugs for production purposes and phase in veterinary oversight of therapeutic uses of these drugs.

A. Therapeutic Uses that Help Assure the Health of Animals

As discussed in GFI #209, FDA believes that, in light of the risk that antimicrobial resistance poses to public health, the use of medically important antimicrobial drugs for production purposes in food-producing animals does not represent a judicious use of these drugs. Such uses are typically administered through the feed or water on a herd- or flock-wide basis and are currently approved for such uses as increasing rate of weight gain or improving feed efficiency.

Production uses are not directed at any specifically identified disease, but rather are expressly indicated and used for the purpose of enhancing the production of animal-derived products. FDA believes that production use indications such as "increased rate of weight gain" or "improved feed efficiency" are no longer appropriate for the approved conditions of use for medically important antimicrobial drugs. In contrast, FDA considers uses that are associated with the treatment, control, and prevention of specific diseases to be therapeutic uses that are necessary for assuring the health of food-producing animals.

B. Veterinary Oversight

New animal drugs and new animal drug combination products are approved with one of three types of marketing status: (1) over-the-counter (OTC), (2) veterinary prescription (Rx), or (3) veterinary feed directive (VFD). Products for which adequate directions for use can be written for use by lay persons are labeled for OTC marketing status. When adequate directions can not be written in a manner that enables a layperson to use a drug safely and for the purposes for which it is intended, the drug is restricted to use under veterinary oversight as an Rx or VFD product.

FDA believes it is important to include veterinary oversight in the use of antimicrobial new animal drugs to assure their appropriate and judicious use. Veterinarians play a critical role in the diagnosis of disease and in the decision-making process related to instituting measures to treat, control, or prevent disease. As discussed in more detail below, FDA believes that the

judicious use of medically important antimicrobial new animal drugs in the feed or water of food-producing animals needs the scientific and clinical training of a licensed veterinarian.

III. Medically Important Antimicrobial Drugs

FDA uses the concepts set out in its Guidance for Industry (GFI) #152, "*Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern*," in reviewing the human food safety component of new animal drug applications for medically important antimicrobial new animal drugs for use in food-producing animals. Guidance for Industry #152 includes an appendix that ranks antimicrobial drugs into three tiers, "critically important," "highly important," or "important," in regard to their human medical importance. At this time, FDA considers all antimicrobial drugs listed in Appendix A to GFI #152 (Appendix A) to be "medically important" in the context of implementing the recommendations outlined in GFI #209 and further discussed in this guidance document (GFI #213). We believe that the policy in GFI #209 and GFI #213 applies to all three tiers of medically important antimicrobial drugs at this time because each tier (and thus all of the drugs listed in Appendix A) contains drugs that have been previously assessed through the public processes used to develop GFI#152 and determined to be important for treating bacterial infections in people.

FDA recognizes that the list of drugs in Appendix A is not static and should be periodically reassessed and updated as necessary. Such reassessment is necessary to take into consideration such factors as the development of new antimicrobials for human therapy, the emergence of diseases in humans, or changes in prescribing practices in the United States. FDA intends to update Appendix A, as necessary, through a separate process that will also be subject to public comment. However, because Appendix A identifies those antimicrobials that have been determined to be medically important to human medicine, FDA believes the existing Appendix A provides adequate clarity for purposes of moving forward with the recommendations outlined in GFI #209. Therefore, the current list of medically important antimicrobial drug classes that are the subject of this guidance includes: aminoglycosides, lincosamides, macrolides, penicillins, streptogramins, sulfonamides, and tetracyclines.

IV. Voluntary Adoption of Judicious Use Principles

As discussed in the following section, FDA intends to work with affected drug sponsors to help them to voluntarily implement the principles described above through modifications to the approved conditions of use of their new animal drug products. FDA believes a voluntary approach, conducted in a cooperative and timely manner, is the most effective approach to achieve the common goal of more judicious use of medically important antimicrobials in animal agriculture.

FDA recognizes that it is equally important that the Agency also work with the veterinary and animal producer communities, the end users of these products, to ensure that their concerns are taken into consideration as these changes are implemented. One issue of concern is the

ability of producers, particularly those with smaller operations in remote locations, to have adequate access to veterinary services. Therefore, as steps are taken to phase in the voluntary changes discussed in this document, FDA is working collaboratively with United States Department of Agriculture (USDA) to engage the veterinary community and other stakeholders to explore strategic approaches (e.g., new models, pilot programs) to address this issue.

A. Voluntarily Phasing out Production Uses

FDA is concerned about the risk that antimicrobial resistance poses to public health from the use of medically important antimicrobial drugs in food-producing animals for production purposes. As a consequence of this concern, FDA will be working with affected drug sponsors who wish to voluntarily withdraw approved production uses of their medically important antimicrobial new animal drugs and combination new animal drug products. This guidance is intended to facilitate the voluntary process by providing useful information for sponsors intending to revise their approved labeling through a supplemental new animal drug application. In addition, as discussed later in this guidance, FDA is asking affected sponsors to notify the Agency within 3 months from the date of publication of this final guidance to inform us of their intentions to make these voluntary changes.

B. Need for Veterinary Oversight of Medically Important Antimicrobial Drugs Used in the Feed or Water of Food-Producing Animals

Prior to 1993, most antimicrobial drugs were approved for over-the-counter use in food-producing animals and many of these were administered through medicated feed or drinking water. At that time, the methods used by FDA to assess the microbial food safety aspects of new animal drug applications for antimicrobials intended for use in food-producing animals were not as rigorous as those used today, in part because less scientific data about the public health ramifications of antimicrobial resistance existed at that time. In addition, FDA's recommended approach for conducting pre-approval microbial food safety assessments has evolved over time as the quantity and quality of epidemiologic and other data bearing on antimicrobial resistance has improved. As a result, all antimicrobial new animal drugs for use in food-producing animals approved by CVM since 1993 have been labeled with Rx or VFD marketing status, with the exception of approvals of generic copies of existing OTC products and approvals of combination medicated feeds using existing OTC antimicrobial Type A medicated articles[1]. This shift to a marketing status requiring veterinary oversight was viewed as an important step to mitigate the microbial food safety risks of antimicrobial new animal drugs, particularly for those drugs considered to be medically important.

Based on the available scientific evidence concerning antimicrobial resistance, including information about resistance trends associated with the use of medically important antimicrobial drugs in food-producing animals, FDA believes that the judicious use of medically important antimicrobial drugs intended for use in food-producing animals should involve the scientific and

[1] A "Type A medicated article" is a concentrated new animal drug product used as a component in the manufacture of (1) another Type A medicated article, (2) an intermediate Type B medicated feed, or (3) a final formulation Type C medicated feed. See definition at 21 CFR 558.3(b)(2).

clinical training of a licensed veterinarian. This is because judicious use involves accurately identifying bacterial disease that is present or likely to be present and selecting the suitable antimicrobial drug.

In the case of prevention, judicious use includes a consideration by the veterinarian of relevant factors for determining the risk of a specific bacterial disease and for determining whether the use of medically important antimicrobials for prevention purposes is appropriate in a particular situation. The decision by the veterinarian to use a specific approved drug or combination drug is based on factors such as the mode of antibacterial action, drug distribution in specific tissues, and the duration of effective drug levels at the site of infection. Other important factors veterinarians consider when determining the appropriateness of a preventive use include whether: (1) there is evidence of effectiveness, (2) such a preventive use is consistent with accepted veterinary practice, (3) the use is linked to a specific etiologic agent, (4) the use is appropriately targeted to animals at risk of developing a specific disease, and (5) no reasonable alternatives for intervention exist. Numerous risk factors have been documented to increase susceptibility to bacterial disease, including environmental factors (such as temperature extremes and inadequate ventilation), host factors (such as age, nutrition, genetics, immune status), and other factors (such as stress of animal transport). From FDA's standpoint, the administration of a drug to animals when a veterinarian determines that there is a risk of a specific disease, based on the presence of such risk factors, could be considered judicious prevention use. For example, if a veterinarian determines, based on the client's production practices and herd health history, that cattle being transported or otherwise stressed are more likely to develop a certain bacterial infection, preventively treating these cattle with an antimicrobial approved for prevention of that bacterial infection would be considered a judicious use. Another example would be the prevention of necrotic enteritis in broiler chickens. In this case, the preventive use of an antimicrobial approved for such use is important to manage this disease in certain flocks in the face of concurrent coccidiosis, a significant parasitic disease in chickens. On the other hand, FDA would not consider the administration of a drug to apparently healthy animals in the absence of any information that such animals were at risk of a specific disease to be judicious. FDA believes that veterinarians are uniquely qualified to determine which specific disease-causing microorganisms are likely to be present in a particular situation and to determine appropriately timed administration to prevent disease based on specific, known risk.

For these reasons, in FDA's 1999 proposed rule on veterinary feed directives (64 FR 35966; July 2, 1999), the Agency gave antimicrobial resistance as a key example of a reason it can be important for medicated feed to be administered under a veterinarian's supervision. FDA stated, "control of the usage of certain antimicrobials is critical to reducing unnecessary use of such drugs in animals and to slowing or preventing the development of bacterial resistance to antimicrobial drugs."

Accordingly, FDA recommends that affected drug sponsors voluntarily revise the conditions of use of their medically important antimicrobial new animal drugs and combination new animal drug products to reflect the need for the professional oversight of a licensed veterinarian. This would mean a change from OTC to VFD status for medicated feed products and from OTC to Rx status for medicated drinking water products. A proposed timeline for making such changes is discussed in more detail below. FDA acknowledges that in order to facilitate the OTC to VFD change in marketing status, existing requirements related to the

distribution and use of VFD drugs must be updated and streamlined. Therefore, concurrent with the development of this guidance, FDA is actively pursuing revisions to the VFD regulations (in 21 CFR part 558) through the rulemaking process. Some of the key changes being considered include better alignment between the criteria for appropriate veterinary supervision or oversight and those established as part of veterinary licensing and practice requirements and streamlining administrative procedures. To facilitate the transition from OTC to VFD status, FDA believes it is critically important that changes such as these be implemented to minimize impacts on veterinarians, the animal feed industry, and animal producers.

While FDA believes that all medically important antimicrobial new animal drug products should be marketed with the appropriate professional oversight restriction, at this time FDA is most concerned with medically important antimicrobial new animal drugs and combination new animal drug products intended for use in or on the feed or water of food-producing animals. As discussed in GFI#209, FDA's current methodology for assessing antimicrobial risks associated with the use of antimicrobial new animal drugs in food-producing animals is premised on the concept that increasing the exposure of bacterial populations to antimicrobial drugs increases the risk of generating resistance to those antimicrobial drugs. Because feed or water use antimicrobial drugs are typically administered to entire herds or flocks of food-producing animals, such uses pose higher risk to public health than the administration of such drugs to individual animals or targeted groups of animals. For that reason, this guidance is focused on those medically important antimicrobial new animal drugs that are approved for use in the feed or water of food-producing animals.

C. Additional Considerations.

It is important to note that any extralabel use of medicated feed is not permitted by law (see sections 512(a)(2) and (a)(4)(A) of the FD&C Act). Neither veterinarians nor their clients may use, or direct the use of, a medicated feed in an extralabel manner. Therefore, when production claims for medically important antimicrobials are voluntarily removed from the approved labeling of these drugs, consistent with the judicious use principles of GFI #209, any further use of a drug without a production claim in medicated feed for production purposes will be considered an extralabel use and, thus, illegal.

V. Timeline for Voluntarily Implementing Changes

The Agency recognizes the significance of the proposed changes and the potential impacts such changes will have on the animal pharmaceutical industry, animal producers, the animal feed industry, and the veterinary profession. For this reason, FDA is currently pursuing a strategy for the voluntary adoption of these changes in an effort to minimize the impacts and provide for an orderly transition. FDA encourages all sponsors of affected new animal drugs and new animal drug combination products to contact the Agency and initiate steps to change product labeling and approved conditions of use through the process outlined in this guidance.

FDA also believes it is critical to see meaningful progress toward eliminating production uses of medically important antimicrobial drugs and bringing the remaining therapeutic uses of such drugs in or on the feed or water of food-producing animals under the oversight of

veterinarians. In order to ensure progress under the cooperative framework outlined in this guidance, FDA will monitor progress to assess whether these changes are being adopted along the timelines discussed below. FDA is confident that the objective of phasing in these changes can be met through the cooperative process discussed in this guidance, which is why we are initially pursuing this voluntary approach. If, after the period of evaluation of the three year phase in, we determine that adequate progress has not been made, we will consider whether further action under the existing provisions of the FD&C Act may be appropriate. To assist FDA in effectively monitoring rates of adoption in the industry, we request that sponsors of affected products (i.e., those products containing antimicrobial new animal drugs of importance to human medicine that are administered in medicated feed or drinking water of food-producing animals) notify the Agency of their intentions to engage in the voluntary process to modify their product labeling within 3 months from the date of publication of this final guidance. FDA anticipates that sponsors of affected products should be able to complete implementation of the changes discussed in this final guidance within 3 years of the date of publication.

FDA intends to keep the public apprised of progress. First, FDA is making public on its website a listing of all antimicrobial products affected by the guidance. Second, FDA intends to notify affected drug sponsors and, following the 3-month notification period, FDA intends to publish summary information to provide an indicator of the level of engagement of affected drug sponsors in the voluntary process. In addition, the public will be notified of completed changes to affected products through publication of approval of supplemental new animal drug applications.

Upon issuance of this final guidance, the Agency will monitor the progress of its strategy for the voluntary adoption of the changes outlined, including the progress of measures intended to facilitate an orderly and minimally disruptive transition. Three years from the date of publication of this final guidance, FDA intends to evaluate the rate of adoption of the proposed changes across affected products. The Agency will then consider further action as warranted in accordance with existing provisions of the FD&C Act for addressing matters related to the safety of approved new animal drugs.

FDA recognizes that the proposed changes in the use of these antimicrobial drugs have significant practical implications for animal producers, veterinary practitioners, animal drug sponsors, and feed mills. In particular, as mentioned previously, implementing changes to streamline existing VFD requirements is pivotal to facilitating the transition to greater veterinary oversight (i.e., from OTC to VFD marketing status) for many of these products. Therefore, the 3-year timeframe for voluntary phase-in noted above is intended to provide sufficient time for the necessary changes to the existing VFD requirements to be developed and implemented through notice and comment rulemaking. Although FDA is committed to completing this rulemaking process within the 3-year timeframe for implementing the changes discussed in this guidance, FDA is prepared to extend the timeframe, as necessary, to ensure that it coincides with the implementation of the revised VFD requirements.

The 3-year timeframe for voluntary phase-in is also intended to provide time for animal drug sponsors to make these changes in an efficient and practical manner, and for other stakeholders to prepare for the resulting changes in management/business practices. When several approved products are involved (e.g., combination drug approvals containing the same

active ingredients; same active ingredient in different dosage forms), sponsors are encouraged to coordinate implementation when practicable.

VI. Supplemental New Animal Drug Applications

A. Removing Production Uses/Changing Marketing Status

The procedures in this section (VI.A) apply to the situation where no new indications are being proposed. In the limited circumstances where a sponsor would be proposing that a new therapeutic indication be added, the procedures set forth at section VI.B below for submitting a supplemental application should be followed instead. As always, FDA encourages sponsors to consult with FDA prior to submitting supplemental applications to ensure that sponsors are targeting their submissions to answer questions that are relevant to the particular drug. The recommendations below, which, as guidance, establish no legally enforceable requirements, apply when sponsors who wish to voluntarily pursue judicious use changes are submitting supplemental new animal drug applications under 21 CFR 514.8.

1. Administrative Procedures

Sponsors who wish to voluntarily remove production use claims and change the marketing status for the remaining approved feed or water uses of affected products should indicate that their supplemental application is being submitted in accordance with GFI #213. Such supplemental applications do not need to include additional safety or effectiveness data. Sponsors of such applications would either (1) propose to change the marketing status to VFD or Rx and voluntarily withdraw the approval for all production uses or (2) for those applications without approved production uses, such sponsors would only propose a change in marketing status to VFD or Rx. No new indications would be proposed by the sponsors and in most cases the sponsors would only be required to submit revised labeling.

2. Applicable Supplemental New Animal Drug Application Technical Sections

Type A medicated articles and their associated medicated feeds should bear the VFD statement found in this Agency's regulations at 21 CFR 558.6(f) and medicated drinking water products (e.g., water soluble powders, concentrated solutions, etc.) should bear the Rx statement found in section 503(f)(4) of the FD&C Act (21 U.S.C. 353(f)(4)). The Type A medicated article and representative medicated feed labeling (Blue Bird) should be included in the supplemental application to verify: 1) the VFD statement found in this Agency's regulations at 21 CFR 558.6(f) has been appropriately added to all the labeling (Type A medicated article and Blue Bird feed labeling), and 2) the indications, mixing directions, feeding directions, etc., have been revised to reflect the voluntary withdrawal of the production use(s). Labeling for medicated drinking water products should be included in the supplemental application to verify: 1) the Rx statement found in section 503(f)(4) of the FD&C Act (21 U.S.C. 353(f)(4)) has been appropriately added to the labeling, and 2) the indications, directions for use, etc., have been revised to reflect the voluntary withdrawal of the production use(s).

B. Adding New Therapeutic Indications

In some cases, it has been suggested that there could be a therapeutic benefit associated with the production use of a drug. In situations where this could be the case, concerns have been raised that removing production uses from approved conditions of use will have negative animal health impacts. In those cases, where scientific evidence demonstrates a therapeutic benefit associated with the use of the drug for treating, controlling, or preventing a particular disease, sponsors could wish to seek new therapeutic indications to fill the therapeutic needs of animals.

FDA stresses that such new indications must be based on scientific evidence that such drug is safe and effective for the intended therapeutic use. Such new therapeutic indications should be directed at specifically identified diseases and should involve dosage regimens that provide the desired therapeutic effect while minimizing overall extent of use.

1. Administrative Procedures

Sponsors who wish to seek new therapeutic indications for use of affected products should indicate that their supplemental application is being submitted in accordance with GFI #213. Because new therapeutic indications are being proposed, these supplemental applications require the inclusion of additional safety and effectiveness data. These supplemental applications would need to include specific information as follows:

2. Applicable Supplemental New Animal Drug Application Technical Sections

a. Labeling

Type A medicated articles and their associated medicated feeds should bear the VFD statement found in this Agency's regulations at 21 CFR 558.6(f) and medicated drinking water products (e.g., water soluble powders, concentrated solutions, etc.) should bear the Rx statement found in section 503(f)(4) of the FD&C Act (21 U.S.C. 353(f)(4)). The Type A medicated article and representative medicated feed labeling (Blue Bird) should be included in the supplemental application to verify: 1) the VFD statement found in this Agency's regulations at 21 CFR 558.6(f) has been appropriately added to all the labeling (Type A medicated article and Blue Bird feed labeling), and 2) the indications, mixing directions, feeding directions, etc., have been revised to reflect the voluntary withdrawal of the production use(s). Labeling for medicated drinking water products should be included in the supplemental application to verify: 1) the Rx statement found in section 503(f)(4) of the FD&C Act (21 U.S.C. 353(f)(4)) has been appropriately added to the labeling, and 2) the indications, directions for use, etc., have been revised to reflect the voluntary withdrawal of the production use(s). In both cases, the labeling would need to reflect the new therapeutic indications for use.

b. Chemistry, Manufacturing, and Controls

The recommendations in this section assume there is no change in the chemistry, manufacturing and controls (CMC) information for the Type A medicated article or medicated drinking water products, including the product formulation, raw materials, manufacturing process, controls and packaging. If there are changes to the CMC information for the Type A

medicated article or medicated drinking water product associated with the new therapeutic indication, the sponsor should provide a description of such changes in the supplemental application, along with appropriate documentation and data to support the changes. See 21 CFR 514.8(b).

Medicated Drinking Water Product

If the new indication provides for use of the medicated drinking water product at the same concentration or concentration range as currently approved, no additional chemistry, manufacturing and controls (CMC) information is required. If the medicated drinking water product will be used to prepare medicated water at a different concentration than currently approved, the sponsor should address stability of the medicated drinking water at the new concentration (Ref. 1).

Type A Medicated Article

If the new indication is for a currently approved species and provides for a medicated feed inclusion rate currently approved for that species, no additional CMC information is required.

If the new indication is for a medicated feed inclusion rate outside of the currently approved inclusion rate or range (i.e., lower than the lowest currently approved inclusion rate or higher than the highest currently approved inclusion rate for that species), the sponsor should address homogeneity, non-segregation, and stability of the drug in representative medicated feeds at the higher/lower inclusion rate (Ref. 1). In addition, the sponsor should demonstrate that the approved medicated feed assay method is valid for assay of feeds manufactured at the higher/lower inclusion rate or provide a new method that is capable of assaying the feed (Refs. 2, 3, and 4).

If the new indication is for a species not currently approved, the sponsor should address homogeneity, non-segregation, stability, and medicated feed assay methodology in representative medicated feeds at the highest and lowest proposed medicated feed inclusion rates.

c. Human Food Safety

Toxicology/Residue Chemistry

Toxicology information associated with the original approval was considered for currently approved antimicrobial new animal drugs, and that information was the basis of the acceptable daily intake (ADI) that drove the residue chemistry conclusions (target tissue, tolerance, withdrawal times, etc.) for those approvals. The toxicological assessment is not expected to be reconsidered under proposed therapeutic indications with similar conditions of use to those corresponding to the production use (see Impact on Human Intestinal Flora below). If a new, proposed therapeutic indication has corresponding conditions of use (same species, with dose/duration/formulation/route of administration, etc.) that fit within existing residue chemistry parameters and are covered by previous residue chemistry evaluations, we do not anticipate that the sponsor will need to provide additional residue chemistry data or information. Sponsors are encouraged to contact CVM if they have any toxicological assessment questions.

Microbial Food Safety

Antimicrobial Resistance

It should be noted that, at the time of the original approval of older antimicrobial new animal drug applications, microbial food safety was most likely not considered in the same way or to the same extent as is currently the case. The Agency is concerned, consistent with the general elements of judicious use discussed in section II above and GFI#152, that giving antimicrobial drugs to food-producing animals at low levels for long periods of time and in large numbers of animals may contribute to antibiotic resistance. We expect any new indication(s) to (1) have an explicitly defined duration of dosing, (2) specify a therapeutic dose level, and (3) be available only to those animals that need the drug for the new indication, rather than the entire flock or herd when such use is not necessary.

Generally, these changes are expected to remove injudicious use indications, and to result only in the therapeutic use of medically important antimicrobial drugs in or on the feed or water of food-producing animals. In addition, such indications for use should include risk mitigation measures intended to reduce antimicrobial resistance when these drugs are used in or on the feed or water of food-producing animals.

To assure these goals have been met, the approval of any new indications for use would also necessitate that microbial food safety concerns be addressed consistent with the objectives of GFI #152. Prior to submission of an application, sponsors should discuss with CVM the type of information needed for this purpose. This information may include, but is not limited to:

(1) Basic information on the subject antimicrobial new animal drug, including information on mechanisms of action, spectrum of activity, resistance mechanisms, transfer of resistance, pharmacokinetics and/or pharmacodynamics if known, proposed conditions of use and how these could influence resistance development, and information on susceptibility among bacteria of human health concern;

(2) Information on the use of the subject antimicrobial new animal drug in or on the feed or water of food-producing animals, focusing on numbers of animals treated, class, consumption rates for food products from treated animals, and rates of contamination by bacteria of human health importance.

(3) Information on the use of the subject antimicrobial drug (or drugs similar to the subject drug) in human medicine. This information should address how loss of susceptibility of organisms of human health concern to the subject antimicrobial drug (or drugs similar to the subject drug) could impact human clinical medicine.

(4) Information detailing how FDA's general elements of judicious use discussed in section II have been addressed. Specifically, all approved indications should be for treatment, control and/or preventive use only, require veterinary oversight, and restrict use to an explicitly defined duration of dosing. FDA considers these measures to be significant risk mitigations consistent with the goals of GFI #152.

Upon review of this information, the Agency should be able to: 1) identify appropriate risk mitigations that would enable us to determine that the proposed use of the drug in food-producing animals is safe (i.e., a reasonable certainty of no harm to human health); and 2) advise on the types of additional information or data needed to address any existing data gaps associated with the new, proposed use of the subject antimicrobial new animal drug.

Impact of Antimicrobial Residues on Human Intestinal Flora

Based on the expected changes in use patterns for new indications described in the previous section, we do not anticipate that this issue will need to be addressed by sponsors. However, if changes in conditions of use (dose/duration/formulation/route of administration) are proposed that are expected to increase overall human exposure to residues of antimicrobial new animal drugs in animal-derived food products, then sponsors will be asked to address the safety of their proposed use with respect to impact of residues or metabolites of antimicrobial new animal drugs and compounds with antimicrobial activity on the intestinal flora of human consumers (Ref. 5).

d. Target Animal Safety

Regarding previously approved antimicrobial new animal drugs, target animal safety information associated with the original approval has already been considered. As long as any new, proposed therapeutic indication has conditions of use that are covered by previous target animal safety evaluations (same species, a dose within the approved dosage range, same or shorter duration, same route of administration, same formulation), we do not anticipate that the sponsor will need to provide additional data or information, unless the Agency becomes aware of human or animal health concerns that were not apparent at the time of the original target animal safety evaluation.

e. Evidence of Effectiveness

Sponsors seeking approval of a new therapeutic indication should provide substantial evidence in support of the effectiveness of the new animal drug for the proposed new therapeutic indication. As described in 21 CFR 514.4, the sponsor should provide information that will allow the Agency to determine that:

- parameters selected for measurement and the measured responses reliably reflect effectiveness;
- the results obtained are likely to be repeatable;
- valid inferences can be drawn from these sources to the use of the new animal drug in the target population; and
- the new animal drug is effective for the new therapeutic indication under the proposed conditions of use.

The type of information required to demonstrate effectiveness will need to be determined on a case-by-case basis and be consistent with substantial evidence as described in 21 CFR 514.4. The Center will consider data from a wide variety of sources including literature, data generated by food animal production facilities or universities, and other existing information for a substantial evidence package. Sponsors should not limit their consideration of potential useful

data to only data that is prospectively generated. Previously approved therapeutic indications that are very similar or "related" to the new therapeutic indication could also provide inferential value in support of the new indication (e.g., a new "control of bovine respiratory disease" indication added to an application that has a previously approved "treatment of bovine respiratory disease" indication with a similar dosage regimen).

Sponsors are encouraged to discuss approaches to satisfying the requirements of substantial evidence of effectiveness with CVM.

f. Environmental Impact

By regulation (see 21 CFR 514.1(b)(14)), the Environmental Impact section must include either an environmental assessment (EA) (see 21 CFR 25.40), or a claim for categorical exclusion (see 21 CFR 25.30, 25.33). Under 21 CFR 25.15(a), a claim of categorical exclusion must include a statement of compliance with the categorical exclusion criteria and must state that to the sponsor's knowledge, no extraordinary circumstances exist. "Environmental Impact Considerations" and directions for preparing an EA can be found in 21 CFR Part 25.

VII. Generic Drugs and Combinations

Revising the conditions of use in applications for a pioneer single ingredient new animal drug products may have an effect on abbreviated (generic) new animal drug applications and combination new animal drug applications that reference these single ingredient products. The effects that submission and approval of a supplement for the pioneer drug may have on these generic or combination drugs are discussed in this section. FDA intends to work expeditiously with the sponsors of affected generic and combination new animal drug applications to align their products with the revised conditions of use specified in the referenced (i.e., pioneer) applications for the single ingredient new animal drug products.

A. Generic Applications

If the approved conditions of use for a new animal drug application for a medically important antimicrobial new animal drug are revised under this guidance by voluntarily withdrawing a production use, the approved labeling for any currently approved generic application(s) that references the original new animal drug application must generally be revised in a similar fashion, as is now standard practice. FDA will contact affected generic drug sponsors when these revisions become necessary. Consistent with current practice, we expect that the generic sponsor will submit a supplemental application to come into compliance with the revised labeling of the reference listed new animal drug (RLNAD) within 60 days after FDA notifies the generic sponsor that the approved conditions of use for the RLNAD have been revised. In such cases, if the generic labeling is not revised accordingly, the generic application holder(s) faces the possibility of suspension of the generic application under section 512(c)(2)(G) of the FD&C Act (21 U.S.C. 360b(c)(2)(G)). With regard to suspension, FDA intends to follow the procedures outlined in its regulations at 21 CFR 314.153(b) relating to human generic drug

suspensions until generic new animal drug regulations implementing section 512(c)(2)(G) of the FD&C Act (21 U.S.C. 360b(c)(2)(G) are finalized.

In addition, any future generic sponsor that wants to use such a drug as its referenced listed new animal drug cannot include the production use that was voluntarily withdrawn from the pioneer application in its generic application because under section 512(n)(1)(F) of the FD&C Act (21 U.S.C. 360b(n)(1)(F)) the generic sponsor must submit labeling that is the same as the labeling approved for the referenced listed new animal drug with a few exceptions not relevant here. Furthermore, under section 512(c)(2)(A)(vii) of the FD&C Act (21 U.S.C. 360(c)(2)(A)(vii)), the Agency cannot approve an abbreviated new animal drug application unless the labeling proposed for the generic product is the same as the labeling approved for the referenced listed new animal drug with a few exceptions not relevant for purposes of this draft guidance.

B. Combination New Animal Drugs

The term *Combination new animal drug* is defined in the substantial evidence provisions of 21 CFR Part 514 to mean a new animal drug that contains more than one active ingredient or an animal drug that is applied or administered simultaneously in a single dosage form or simultaneously in or on animal feed or drinking water (See 21 CFR 514.4(c)(1)(i)). Although the term combination new animal drug applies both to products intended for use in or on animal feed and products intended for use in the drinking water of animals, the majority of approved combination new animal drug products are feed use combination drug products.

Most feed use combination new animal drugs are combinations of individual Type A medicated articles that have previously been separately approved. So, for example, a 3-way feed use combination actually involves four approved new animal drug applications, one for the combination and one for each of the three individual Type A medicated articles. The holder of an approved feed use combination new animal drug application is typically also the holder of an approved application for at least one of the individual Type A medicated articles in the combination.

1. Production Uses.

As discussed above, FDA is requesting affected sponsors to voluntarily withdraw production uses of their medically important antimicrobial new animal drugs and combination new animal drug products. In those instances where an approved combination new animal drug product with a production claim includes a medically important antimicrobial new animal drug and the sponsor of the individually approved new animal drug application for a medically important antimicrobial new animal drug has voluntarily withdrawn the production use claims, FDA expects the sponsor of the affected combination new animal drug product will voluntarily follow suit and similarly withdraw the production use claim from the combination new animal drug application. If sponsors of these affected combination new animal drug products do not voluntarily withdraw the production use claim from the combination new animal drug application, FDA intends to consider further action as warranted in accordance with existing provisions of the FD&C Act for addressing matters related to the safety of approved combination new animal drugs.

2. Remaining Therapeutic Uses.

As discussed at section IV above, based on a number of factors FDA believes that the judicious use of medically important antimicrobial drugs intended for use in food-producing animals needs the scientific and clinical training of a licensed veterinarian. This belief applies not only to individual medically important antimicrobial new animal drugs but also to combination new animal drug products incorporating such drugs. However, as previously discussed, in recognition of the significant practical implications of revising the marketing status for these products, FDA has expressed its intent to pursue a strategy for voluntarily phasing in these changes over time in an effort to minimize the impacts and provide for an orderly transition. As explained more fully in section V, FDA is proposing clear timelines for sponsors of the affected products to make these changes in order to ensure effective progress under the cooperative framework outlined in this guidance.

However, once a sponsor of an individual Type A medicated article that is also part of a combination new animal drug submits a supplement to switch the marketing status of the individual product to VFD or Rx, FDA expects the sponsor of the affected combination new animal drug product to voluntarily follow suit. Indeed, for a combination new animal drug product containing individual Type A medicated articles intended for use in or on animal feed, this outcome is essentially compelled since a voluntary switch to VFD marketing status by one or more of the sponsors of the individual Type A medicated articles will automatically trigger the requirement for a VFD to be issued before the affected combination new animal drug product can be used in or on animal feed. This is the case because under section 504(a)(1) of the FD&C Act, "[a]ny animal feed bearing or containing a veterinary feed directive drug shall be fed to animals only by or upon a lawful veterinary feed directive issued by a licensed veterinarian in the course of the veterinarian's professional practice." (21 USC 354(a)(1)). Thus, the requirement for a VFD to be issued applies whenever a VFD drug will be used in feed, regardless of whether the VFD drug is being used by itself or in combination with other drugs. Because a voluntary switch to VFD marketing status by one or more of the Type A medicated articles contained in a combination new animal drug product results, by operation of law, in the requirement for a VFD to be issued before a feed containing the combination new animal drug product can be fed to animals, in effect, the combination new animal drug product takes on VFD status also.

Therefore, we believe that in such instances the combination new animal drug product sponsors should also submit their own supplements to formally change the marketing status of the affected combination new animal drug products to VFD in a timely manner.

This outcome is consistent with the Agency's policy, as expressed in the substantial evidence notice of proposed rulemaking (62 FR 59835; Nov. 5, 1997) which provides that a combination new animal drug should generally bear VFD or Rx marketing status if one or more of the new animal drugs that make up the combination product were individually approved with VFD or Rx marketing status for any of the intended uses or conditions of use that are also applicable to the combination product.

VIII. References

1. FDA 2008. Guidance for Industry 5: Drug Stability Guidelines
2. FDA 2005. Guidance for Industry 135: Validation of Analytical Procedures for Type C Medicated Feeds
3. FDA 2007. Guidance for Industry #136: Protocols for the Conduct of Method Transfer Studies for Type C Medicated Feed Assay Methods
4. FDA 2007. Guidance for Industry #137: Analytical Methods Description for Type C Medicated Feeds
5. FDA 2013. Guidance for Industry #159: Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish a Microbiological ADI VICH GL36(R)
6. FDA 2012. Guidance for Industry #209: The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals

#209

Guidance for Industry

The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals

Submit comments on this guidance at any time. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Submit electronic comments on the guidance at http://www.regulations.gov. All written comments should be identified with the Docket No. FDA-2010-D-0094.

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Additional copies of this 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 either http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm or http://www.regulations.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
April 13, 2012

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The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals

This guidance represents the Food and Drug Administration's (FDA) 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 the 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 number listed on the previous page of this guidance.

I. Executive Summary

Antimicrobial drugs have been widely used in human and veterinary medicine for more than 50 years, with tremendous benefits to both human and animal health. The development of resistance to this important class of drugs, and the resulting loss of their effectiveness as antimicrobial therapies, poses a serious public health threat. Misuse and overuse of antimicrobial drugs creates selective evolutionary pressure that enables antimicrobial resistant bacteria to increase in numbers more rapidly than antimicrobial susceptible bacteria and thus increases the opportunity for individuals to become infected by resistant bacteria. Because antimicrobial drug use contributes to the emergence of drug resistant organisms, these important drugs must be used judiciously in both animal and human medicine to slow the development of resistance. Efforts have been made to promote the judicious use of these drugs in humans (see http://www.cdc.gov/getsmart/index.html) as well as in animals (see http://www.avma.org/issues/default.asp). Using these drugs judiciously means that unnecessary or inappropriate use should be avoided. The focus of this document is on the use of medically important antimicrobial drugs[1] in food-producing animals. Based on a consideration of the available scientific information, FDA is providing a framework for the voluntary adoption of practices to ensure the appropriate or judicious use of medically important antimicrobial drugs in food-producing animals. This framework includes the principles of phasing in such measures as 1) limiting medically important antimicrobial drugs to uses in food-producing animals that are considered necessary for assuring animal health; and 2) limiting such drugs to uses in food-producing animals that include veterinary oversight or consultation. Developing strategies for reducing antimicrobial resistance is critically important for protecting both public and animal health. Collaboration involving the public, the public health, animal health, and animal agriculture communities on the development and implementation of such strategies is needed to assure that the public health is protected while also assuring that such strategies are feasible and that the health needs of animals are addressed.

[1] The term "medically important antimicrobial drugs" generally refers to antimicrobial drugs that are important for therapeutic use in humans.

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.

II. Introduction

Antimicrobial resistance[2], and the resulting failure of antimicrobial therapies in humans, is a mounting public health problem of global significance. This phenomenon is driven by many factors including the use of antimicrobial drugs in both humans and animals. In regard to animal use, this document addresses the use of medically important antimicrobial drugs in food-producing animals for production or growth-enhancing purposes. These uses, referred to as production[3] uses throughout this document, are typically administered through the feed or water on a herd- or flock-wide basis and are approved for such uses as increasing rate of weight gain or improving feed efficiency. Unlike other uses of these drugs in animals (e.g., for the treatment, control, and prevention of disease), these "production uses" are not intended to manage a specific disease that may be ongoing or at risk of occurring, but rather are expressly indicated and used for the purpose of enhancing the production of animal-derived products (e.g., increasing rate of weight gain or improving feed efficiency). This document summarizes some of the key reports and scientific literature related to the use of antimicrobial drugs in animal agriculture and outlines FDA's current thinking on strategies for assuring that medically important antimicrobial drugs are used judiciously in food-producing animals in order to help minimize antimicrobial resistance development. In finalizing this guidance, FDA has considered comments that were submitted to the docket, and other relevant information. If you have additional relevant information, please submit it to the docket at any time. We are particularly interested in any new information regarding the use of medically important antimicrobials in food-producing animals and its impact on the development of drug-resistant bacteria.

[2] The term "antimicrobial" refers broadly to drugs with activity against a variety of microorganisms including bacteria, viruses, fungi, and parasites. Antimicrobial drugs that have specific activity against bacteria are referred to as antibacterial or antibiotic drugs. However, the broader term "antimicrobial," commonly used in reference to drugs with activity against bacteria, is used in this document interchangeably with the terms antibacterial or antibiotic. Antimicrobial resistance is the ability of bacteria or other microbes to resist the effects of a drug. Antimicrobial resistance, as it relates to bacterial organisms, occurs when bacteria change in some way that reduces or eliminates the effectiveness of drugs, chemicals, or other agents designed to treat bacterial infections.

[3] Production uses are also referred to as "nontherapeutic" or "subtherapeutic" uses, terms that we believe lack sufficient clarity.

III. Key Reports and Peer-Reviewed Scientific Literature on the Issue

Questions regarding the use of antimicrobial drugs in food-producing animals have been raised and debated for many years. A variety of recognized international, governmental, and professional organizations have studied the issue. We have briefly summarized below the findings and recommendations from some of the notable reports that have addressed this issue over the past 40 years. These reports provide context to FDA's current thinking on this issue, and highlight the longstanding concerns that have been the subject of discussion in the scientific community as a whole.

We have also provided a list below of some of the more recent primary scientific literature that FDA has considered. This is not intended to represent an exhaustive summary of the scientific literature, but rather to highlight some of the more recent scientific research related to the use of antimicrobial drugs in animal agriculture and the impact of such use on antimicrobial resistance. We acknowledge that a significant body of scientific information exists, including some information that may present equivocal findings or contrary views.

Unless otherwise indicated, the page numbers cited in this section refer to the relevant page numbers in the referenced report. A complete list of the reports summarized in this section is provided at Section IX of this document.

Reports Prepared by Various International, Governmental, and Professional Organizations

1969 Report of the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine

In July 1968, a Joint Committee was established in the United Kingdom to obtain information regarding the use of antibiotics in animal husbandry and veterinary medicine, particularly with respect to antibiotic resistance. This report, often referred to as the "Swann Report," was presented to Parliament in November 1969 by the Secretary of State for Social Services, the Secretary of State for Scotland, the Minister of Agriculture, Fisheries and Food, and the Secretary of State for Wales. The report concluded that the administration of antimicrobials to food-producing animals, particularly at subtherapeutic levels, poses a hazard to human and animal health.

The report stated, "It is clear that there has been a dramatic increase over the years in the numbers of strains of enteric bacteria of animal origin which show resistance to one or more antibiotics. Further, these resistant strains are able to transmit this resistance to other bacteria. This resistance has resulted from the use of antibiotics for growth promotion and other purposes in farm livestock" (*Ref. 1*, p. 60). The report also noted, "There is ample and incontrovertible evidence to show that man may commonly ingest enteric bacteria of animal origin" (*Ref. 1,* p. 60).

The report provided a number of recommendations including that only antimicrobials which "have little or no application as therapeutic agents in man or animals and will not impair the efficacy of a prescribed therapeutic drug or drugs through the development of resistant strains of organisms" should be used without prescription in animal feed (*Ref. 1*, p. 61). Furthermore, the report concluded that antimicrobials used for therapeutic purposes in food-producing animals should remain available but only under veterinary supervision.

1970 FDA Task Force Report, "The Use of Antibiotics in Animal Feed"

In April 1970, FDA established a task force of scientists to undertake a comprehensive review of the use of antibiotics in animal feed *(Ref. 2)*. The task force included ten specialists on infectious diseases and animal science from FDA, the National Institutes of Health, the U.S. Department of Agriculture, and the Centers for Disease Control and Prevention, as well as five consultants from universities and industry.

This task force acknowledged that the understanding at the time it conducted its study was that the use of antimicrobials in food-producing animals, especially in subtherapeutic amounts, was associated with the development of resistant bacteria, and that treated animals might serve as a reservoir of antimicrobial-resistant pathogens that could produce human disease.

The recommendations of the Task Force included that antimicrobial drugs used in human clinical medicine that failed to meet certain guidelines established by the Task Force should be prohibited from growth promotion and any subtherapeutic use in food-producing animals by certain dates. Furthermore, those antimicrobials that failed to meet the guidelines should be limited to short-term therapeutic use and use only by a veterinarian or on a veterinarian's prescription.

As a consequence of the 1970 Task Force report, requirements for data to address microbiological safety concerns for subtherapeutic uses of antimicrobials in food-producing animals were outlined in the Code of Federal Regulations (21 CFR 558.15). Sponsors of antibiotic products administered in animal feed for subtherapeutic purposes were required to submit study results demonstrating that their product did not promote bacterial drug resistance. Depending on the class of drug, sponsors were required to submit all information to the agency on the impact of their drug on enteric salmonella in treated animals by specific dates.

1980 National Academy of Sciences Report, "The Effects on Human Health of Subtherapeutic Use of Antimicrobial Drugs in Animal Feeds"

In 1977, FDA proposed to withdraw the new animal drug approvals for subtherapeutic uses of penicillin and tetracyclines in animal feed on the ground that evidence showed that these drugs, when used for such purposes in animal feed, had not been shown to be safe. These two drugs were chosen because of their importance in human medicine. The proposal was criticized because, at that time, there was not adequate epidemiological evidence (or only just-emerging evidence) to show that drug-resistant

bacteria of animal origin were commonly transmitted to humans and caused serious illness. Subsequently, Congress directed FDA to conduct further studies related to the use of antimicrobials in animal feed and to hold in abeyance the implementation of the proposed antimicrobial withdrawal actions pending the outcome of these studies.

In accordance with Congress' directive to conduct further studies, FDA contracted with the National Academy of Science to conduct a study of the safety issues related to the use of antimicrobials in animal feed. In particular, FDA asked the National Academy of Science to: 1) study the human health effects of the subtherapeutic use of penicillin and tetracycline in animal feed; 2) review and analyze published and unpublished data relevant to assessing human health consequences of such use; 3) assess the scientific feasibility of additional epidemiological studies; and (4) make recommendations about additional research needed.

The National Academy of Sciences issued a study report in 1980. The study report concluded that a very limited amount of epidemiological research had been completed on either the subtherapeutic or therapeutic use of antimicrobials in animal feed. According to the study report, much of the information available on the subject involved "poorly controlled studies of small numbers of subjects for brief periods" (*Ref. 3*, p. 52). Based on a consideration of available evidence, the report concluded that existing data could neither prove nor disprove the postulated hazards to human health from subtherapeutic antimicrobial use in animal feed. However, the report cautioned that "The lack of data linking human illness with subtherapeutic levels of antimicrobials must not be equated with proof that the proposed hazards do not exist. The research necessary to establish and measure a definitive risk has not been conducted and, indeed, may not be possible" (*Ref. 3*, p. 53).

1984 Seattle-King County Study: "Surveillance of the Flow of Salmonella and Campylobacter in a Community"

As noted above, Congress directed FDA to hold in abeyance any implementation of the proposed withdrawal of new animal drug approvals for the subtherapeutic uses of penicillin and tetracyclines in animal feed, pending completion of additional studies related to the use of antimicrobials in animal feed. Therefore, in addition to the National Academy of Sciences study described above, the FDA also contracted with the Seattle-King County Health Department to complete a study intended to provide additional information regarding potential public health concerns regarding the use of antimicrobial drugs in animal feed. Under the contract, the Communicable Disease Control Section of the Seattle-King County Health Department was tasked with studying the relationship between the occurrence of Salmonella spp. (*Salmonella*) and Campylobacter jejuni (*C. jejuni*) in foods of animal origin and the occurrence of human illness caused by those two organisms. These two organisms, *Salmonella* and *C. jejuni*, were chosen to serve as models to estimate the flow of potentially pathogenic bacteria from animals to man through the food chain. The study involved a two-pronged surveillance system that included sampling of retail meats over a 20 month period and simultaneous investigation of *Salmonella* and *C. jejuni* enteritis cases in humans. Bacterial isolates from food and human cases were subjected to

antibiotic susceptibility testing, plasmid analysis, and serotyping. In 1984, the Seattle-King County Health Department prepared a report summarizing the results of the study. The 1984 study report found that *C. jejuni* was a more common cause of enteritis than *Salmonella*. Also, it concluded that *C. jejuni* "does appear to flow from chickens to man via consumption of poultry products" (*Ref. 4*, p. 3). The report stated, "isolates from human cases and those from retail poultry had similar antibiotic susceptibility patterns, including prevalence of 29.7% and 32.8%, respectively, for tetracycline resistance, which was found to be plasmid-mediated" (*Ref. 4*, p. 3).

1988 Institute of Medicine (IOM) Report: "Human Health Risks with the Subtherapeutic Use of Penicillin or Tetracyclines in Animal Feed"

In 1987, FDA asked the IOM to conduct an independent review of the human health risks associated with the subtherapeutic use of penicillin and tetracycline in animal feed. IOM established a committee and directed it to perform "a quantitative risk assessment" of these human health consequences and to "assess the adequacy of the existing human health data and use such data to arrive at an estimate of risk" (*Ref. 5*, p. iii). If quantification of human health risks was not possible due to inadequate data, the Committee was to evaluate the scientific information that had become available since the 1980 National Academy of Science report cited above.

The Committee developed a risk-analysis model, using data only on *Salmonella* infections that resulted in human death. However, the Committee was unable to find a substantial body of direct evidence demonstrating that the subtherapeutic use of penicillin or tetracycline in animal feed posed a human health hazard. Nonetheless, the Committee's 1988 report found a considerable body of indirect evidence implicating both subtherapeutic and therapeutic use of antimicrobials as a potential human health hazard. The Committee also strongly recommended further study of the issue.

1997 World Health Organization (WHO) Report, "The Medical Impact of Antimicrobial Use in Food Animals"

In October 1997, the WHO convened a meeting of experts to examine the question of whether the use of antimicrobials in livestock production, including through use in animal feed, contributes to the escalation of antimicrobial resistance in humans. The findings of the meeting, which were summarized in a report, included the conclusion that all uses of antimicrobials lead to the selection of resistant forms of bacteria. Furthermore, the report stated that "low-level, long-term exposure to antimicrobials may have greater selective potential than short-term, full-dose therapeutic use" (*Ref. 6*, p. 5). The report found that the selection of resistant bacteria has adverse consequences for preventing and treating disease in humans, animals, and plants.

The WHO expert committee recommended that the use of antimicrobial drugs for growth promotion in animals be terminated if these drugs are also prescribed for use as anti-infective agents in human medicine or if they are known to induce cross-resistance to antimicrobials used for human medical therapy. The Committee also recommended the

development of a systematic approach towards replacing growth-promoting antimicrobials with safer non-antimicrobial alternatives. The expert committee called for enhanced monitoring of resistance among isolates of enteric bacteria from food animals and food of animal origin. In addition, the Committee recommended managing risk at the primary production level through measures that promote the prudent use of antimicrobials, including enforcement of relevant laws pertaining to antimicrobial use, education for prescribers and producers, and requiring that use of antimicrobials for treatment of infections in animals be prescribed by veterinarians.

1999 National Research Council (NRC) Report: "The Use of Drugs in Food Animals – Benefits and Risks"

The Panel on Animal Health, Food Safety, and Public Health, jointly sponsored by the NRC's Board on Agriculture and IOM's Food and Nutrition Board, initiated a project to review the issues and relevant information regarding the use of drugs in food-producing animals and to make recommendations about such use. The panel convened the Committee on Drug Use in Food Animals to examine the benefits and risks associated with drug use in food-producing animals and to prepare a report and make recommendations.

The Committee's 1999 report included a review of the issues related to antibiotic use in food-producing animals and provided a number of recommendations. The report recommended establishing national databases to support scientific process and policy development for the approval and use of antibiotics in food-producing animals. The report also recommended that FDA use interdisciplinary panels of experts so that "further development and use of antibiotics in both human and animal medicine have oversight by an interdisciplinary panel of experts composed of representatives of the veterinary and animal health industry, the human medicine community, consumer advocacy groups, the animal production industry, and the regulatory agencies" (*Ref. 7*, p. 11).

1999 United States Government Accountability Office (GAO) Report – "Food Safety: The Agricultural Use of Antibiotics and Its Implications for Human Health"

In response to a request from Congress, the GAO initiated a study in May 1998 to examine: "1) how antibiotics are used in agriculture and the implications of that use for human health; 2) federal roles and responsibilities for overseeing the use of antibiotics in agriculture; and 3) issues surrounding the debate over whether to further regulate or restrict the use of antibiotics in agriculture" (*Ref. 8*, p. 1).

In its study report, dated April 1999, GAO concluded that although research has linked the use of antibiotics in agriculture to the emergence of resistant foodborne pathogens, "there are no current comprehensive estimates of the extent to which antibiotic-resistance strains have resulted in illness and deaths" (*Ref. 8*, p. 1). GAO concluded that the debate over whether antibiotic use should be restricted in agriculture centers on the risk antibiotics pose to human health relative to their benefits to agriculture. The GAO report recommended that "the departments of Agriculture and Health and Human Services work

together to develop and implement a plan with specific goals, time frames and resources needed for determining the safe use of antibiotics in agriculture."

1999 European Commission Report, "Opinion of the Scientific Steering Committee on Antimicrobial Resistance"

Due to the public and animal health concerns associated with the increasing rate of antimicrobial resistance development, the European Commission, Directorate-General XXIV, asked that organization's Scientific Steering Committee to "scientifically evaluate the current position regarding the prevalence and development of antimicrobial resistance, examine its implications for human and animal health, particularly with regard to the development and management of infections" (*Ref. 9*, p. 7).

The Committee's report concluded that actions should be taken promptly to reduce the overall use of antimicrobials. Four primary recommendations were forwarded: (1) antimicrobial drugs should be used prudently; (2) infections should be prevented and resistant organisms contained; (3) research for new modalities of prevention and treatment of infections should be undertaken; and (4) the effects of such interventions should be monitored and evaluated.

2000 World Health Organization (WHO) Expert Consultation: "WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food"

The Food and Agriculture Organization of the United Nations (FAO) and the World Organization for Animal Health (OIE) participated in the June 2000 WHO expert consultation, the purpose of which was to develop global principles for minimizing the negative public health impact associated with the use of antimicrobial agents in food-producing animals while providing for their safe and effective use in veterinary medicine *(Ref. 10).*

The principles were part of a comprehensive WHO global strategy for the containment of antimicrobial resistance and provided a framework of recommendations to reduce the overuse and misuse of antimicrobials in food-producing animals for the protection of human health. The principles strengthened and endorsed earlier WHO recommendations such as the need to terminate the use of antimicrobial growth promoters pending comprehensive human health safety evaluations, the need to ensure that all antimicrobials for animal use are only supplied through authorized outlets (e.g., by veterinary prescription), and the need to establish surveillance systems on antimicrobial drug consumption.

2003 Report, "Joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Scientific assessment"

In December 2003, the Food and Agriculture Organization of the United Nations (FAO), the World Organization for Animal Health (OIE), and the World Health Organization (WHO) convened a workshop to "perform a scientific assessment of the antimicrobial resistance risks arising from non-human usage of antimicrobials and to

formulate recommendations and options for future risk management actions to be considered by the Codex Alimentarius Commission (Codex) and OIE" (*Ref. 11*, p. 1).

The expert panel's findings from the workshop were documented in a report which contained a number of conclusions, including: 1) "there is clear evidence of adverse human health consequences due to resistant organisms resulting from non-human usage of antimicrobials;" 2) "the amount and pattern of non-human usage of antimicrobials impact the occurrence of resistant bacteria in animals and on food commodities and thereby human exposure to these resistant bacteria;" 3) "the foodborne route is the major transmission pathway for resistant bacteria and resistance genes from food animals to humans, but other routes of transmission exist;" and 4) the "consequences of antimicrobial resistance are particularly severe when pathogens are resistant to antimicrobials critically important in humans" (*Ref. 11*, p. 1).

The expert panel recommended that WHO appoint a group of experts to define which antimicrobials are considered critically important in humans. In addition, the panel commented on the need to further develop risk assessment approaches that adequately address the broad range of potential human health impacts and encouraged OIE to continue its work on risk analysis in coordination with FAO and WHO. Finally, the panel recommended that Codex collaborate with OIE to define a more efficient risk management system for addressing the risks.

<u>2003 Institute of Medicine (IOM) Report, "Microbial Threats to Health: Emergence, Detection and Response"</u>

The Committee on Emerging Microbial Threats to Health in the 21st Century was charged by the IOM to "review the current state of knowledge on the emergence of infectious diseases; assess the capacity of the United States to detect and respond to microbial threats to public health; and identify potential challenges and opportunities for public health actions, both global and domestic, to strengthen capabilities in prevention, detection, and response" (*Ref. 12*, p. 3).

The Committee's report discussed thirteen factors[4] that account for the emergence of new or enhanced microbial threats. The report noted "the convergence of any number of factors can create an environment where infectious diseases can emerge…" (*Ref. 12*, p. 4). In addition, the Committee provided a number of recommended actions for responding to the increasing infectious disease rates prompted by these emergence factors. One of the recommendations was to "more finely target the use of antimicrobials" including expanding efforts to decrease the inappropriate use of antimicrobials in human medicine (*Ref. 12*, p. 6). In addition, the committee recommended that "FDA ban the use of

[4] The thirteen factors included 1) microbial adaptation and change, 2) human vulnerability, 3) climate and weather, 4) changing ecosystems, 5) economic development and land use, 6) human demographics and behavior, 7) technology and industry, 8) international travel and commerce, 9) breakdown of public health measures, 10) poverty and social inequality, 11) war and famine, 12) lack of political will, and 13) intent to harm.

antimicrobials for growth promotion in animals if those classes of antimicrobials are also used in humans" (*Ref. 12*, p. 15).

2004 Report, "Second Joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Management Options"

As summarized above, a preliminary scientific assessment of the antimicrobial resistance risks arising from non-human usage of antimicrobials was conducted by the first Joint Expert Workshop on Non-Human Antimicrobial Usage in December 2003 in Geneva *(Ref. 13)*. The outcome of the first workshop, plus other relevant information, formed the basis for consideration by this second workshop. The report of this second workshop included suggestions to Codex, FAO, WHO, and OIE for moving forward on the issue.

Some of the key conclusions and recommendations in the report included: 1) the risks associated with non-human antimicrobial use and antimicrobial resistance should be part of human safety assessments for regulatory decisions relating to veterinary antimicrobials, 2) the concept of "critically-important" classes of antimicrobials for humans should be developed by WHO, 3) good agricultural practices can reduce the necessity for antimicrobials, 4) there is a need for capacity building and networking to help implement antimicrobial resistance surveillance systems in various countries, and 5) a Codex/OIE Task Force should be established to develop risk management options for antimicrobial resistance related to non-human use of antimicrobials.

2004 United States Government Accountability Office (GAO) Report – "Antibiotic Resistance: Federal Agencies Need to Better Focus Efforts to Address Risks to Humans from Antibiotic Use in Animals"

In response to a request from Congress, GAO initiated a study in May 2003 to "examine 1) scientific evidence on the transference of antibiotic resistance from animals to humans and extent of potential harm to human health, 2) agencies' efforts to assess and address these risks, 3) the types of data needed to support research on these risks and extent to which the agencies collect these data, 4) use of antibiotics in animals in the United States compared with its key agricultural trading partners and competitors, and 5) information on how use has affected trade" (*Ref. 14*, p. 3).

In its study report, dated April 2004, GAO concluded that antibiotic-resistant bacteria have been transferred from animals to humans. GAO also stated that many of the studies reviewed as part of GAO's research found that this transference from animals to humans poses significant risks for human health. According to GAO's findings, studies have shown two types of evidence related to the transfer of antibiotic-resistant bacteria from animals to humans. First, some studies have provided evidence of associations between changes in antibiotic use in animals and resistance to antibiotics in human bacteria. For example, researchers have found that antibiotic-resistant *Escherichia coli* (*E. coli*) and *Campylobacter* increased in humans as use of the antibiotics increased in animals.

Second, GAO concluded that studies that have examined the genetic makeup of the bacteria have provided stronger scientific evidence that antibiotic-resistant *Campylobacter*

and *Salmonella* bacteria are transferred from animals to humans. In those studies, strains of antibiotic-resistant bacteria infecting humans were indistinguishable from those found in animals, leading researchers to conclude that the animals were the source of human infection.

The GAO report noted that researchers disagree about the extent of the human health risk caused by this transference. According to the report, "many researchers contend that antibiotic use in animals poses significant risk for human health." The GAO report also noted that "a small number of studies contend that the health risks of the transference are minimal" (*Ref. 14*, p. 23).

GAO recommended that "the Commissioner of FDA expedite FDA's risk assessments of the antibiotics used in animals that the agency has identified as critically important to human health to determine if action is necessary to restrict or prohibit animal uses in order to safeguard human health" (*Ref. 14*, p. 48). GAO also recommended that the Secretaries of Agriculture and of Health and Human Services "jointly develop and implement a plan for collecting data on antibiotic use in animals..." (*Ref. 14*, p. 48).

The Department of Health and Human Services (HHS) reviewed and subsequently responded to the 2004 GAO Report on Antibiotic Resistance. In its response, HHS cited 11 additional supporting studies not included in the GAO report (See End Note)[i], and provided the following comments:

"The draft report presents or refers to significant and growing evidence demonstrating the human health consequences of drug resistant infections related to antibiotic use in agriculture." "These [11 additional] studies, along with those cited in the GAO report, all demonstrate a relationship between the use of antimicrobials in food-producing animals, antibiotic resistance in humans, and adverse human health consequences as a result. We believe that there is a preponderance of evidence that the use of antimicrobials in food-producing animals has adverse human consequences." "There is little evidence to the contrary."

2005 Codex Alimentarius Commission (Codex), "Code of Practice to Minimize and Contain Antimicrobial Resistance" (Code of Practice)

The Code of Practice provides guidance for the responsible and prudent use of antimicrobials in food-producing animals *(Ref. 15)*. Its objectives are to minimize adverse impacts on public health associated with the use of antimicrobial drugs in food-producing animals.

The Code of Practice makes a number of recommendations regarding the responsible use of antimicrobials in food-producing animals. For example, the document recommends that responsible use 1) should be controlled by the veterinary profession or other parties with the requisite expertise, and 2) does not include the use for growth promotion of veterinary antimicrobial drugs that belong to or are able to cause cross-resistance to classes

of antimicrobial agents used in humans (or submitted for approval for use in humans) in the absence of an appropriate risk analysis.

2006 Antimicrobial Resistance: Implications for the Food System, Comprehensive Reviews in Food Science and Food Safety

This report was conducted under the auspices of the Institute of Food Technologists and the IFT foundation *(Ref. 16)*. The panelists found the extent to which antibiotic use in food animals produces clinically important antibiotic resistant infections in humans is unknown. However, they do state in their recommendations that "In veterinary medicine and production agriculture implementation of various management strategies (such as responsible use guidelines, quality assurance programs, and antibiotic alternatives), coupled with government regulations, should decrease opportunities for the selection of antibiotic resistant microorganisms." Specifically, they stated "Always practice prudent use of antimicrobials to limit resistance selection and to maintain maximal benefit of antimicrobials in the future."

2009 American Academy of Microbiology. Antibiotic Resistance: An Ecological Perspective on an Old Problem

This report emphasizes the ecological fact that antibiotic resistance is a natural phenomenon that cannot be eliminated *(Ref. 17)*. The practical approach is to find effective ways to cope with antibiotic resistant bacteria harmful to humans and animals and to control the development of new types of resistance. Controlling antibiotic-resistant bacteria and subsequent infections requires vigilance on many fronts. The prudent and responsible use of antibiotics and the elimination of unnecessary use (e.g., viral infections; unnecessary, prolonged treatment) are noted as mandatory steps to an appropriate public health strategy to limit infections by resistant organisms.

2011 WHO Report: Tackling antibiotic resistance from a food safety perspective in Europe

This report follows a long series of WHO reports addressing antibiotic resistance in the food chain *(Ref. 18)*. The WHO continues to highlight the urgent need for action in remediating antibiotic resistance through a holistic, intersectoral, and multifaceted approach that includes all efforts to reduce unnecessary use of antibiotics, including those uses in food production. Specific regulatory strategies include: 1) eliminating the use of antibiotics as growth promoters in food animals; 2) requiring that antibiotics be administered to animals only when prescribed by a veterinarian; and 3) requiring the antibiotics identified as critically important in human medicine - especially fluoroquinolones and third- and fourth-generation cephalosporins - only be used in food animals when their use is justified.

Brief Summary of Recent Peer-Reviewed Scientific Literature

2008. Applied and Environmental Microbiology. Longitudinal study of antimicrobial resistance among *Escherichia coli* isolates from integrated multisite cohorts of humans and swine. Alali et al.

This study longitudinally examined the relationship between antimicrobial resistant *E. coli* from human wastewater and swine fecal samples and several risk factors including host species, production type, vocation (e.g., slaughter plant workers), and season. Authors reported that the higher levels of *E. coli* resistance in swine isolates as compared with human isolates was likely associated with either the past or current use of injectable antimicrobial agents (e.g., ceftiofur sodium) or the use of antimicrobial agents in feed (e.g., chlortetracycline) or water. Furthermore, slaughter plant workers were shown to be at higher risk of carrying multidrug-resistant *E. coli* than non-swine workers.

2008. Applied and Environmental Microbiology. Diversity and distribution of commensal fecal *Escherichia coli* bacteria in beef cattle administered selected subtherapeutic antimicrobials in a feedlot setting. Sharma et al.

This study investigated the influence of administration of chlortetracycline alone or in combination with sulfamethazine on the development of resistance, dissemination of defined strain types, and prevalence of resistance determinants in feedlot cattle *(Ref. 20)*. Shedding of tetracycline-resistant *E. coli* was higher in animals receiving both treatments. While tetracycline resistance was detected in cattle with no prior antimicrobial exposure, shedding of tetracycline-resistant *E. coli* was higher in animals subjected to either of the two treatments.

2008. Applied and Environmental Microbiology. Effect of subtherapeutic administration of antibiotics on the prevalence of antibiotic-resistant *Escherichia coli* bacteria in feedlot cattle. Alexander et al.

This study involved the collection of 3,300 fecal samples over a 314-day period from 300 feedlot steers receiving subtherapeutic levels of antibiotics *(Ref. 21)*. Study findings indicated that administration of tetracycline in combination with sulfamethazine clearly increased the prevalence of tetracycline- and ampicillin-resistant *E. coli* in cattle and the numbers of resistant *E. coli* organisms shed.

2009. American Journal of Veterinary Research. A metagenomic approach for determining prevalence of tetracycline resistance genes in the fecal flora of conventionally raised feedlot steers and feedlot steers raised without antimicrobials. Harvey et al.

This study compared the prevalence of tetracycline-resistance genes in the fecal flora of conventionally raised feedlot steers and feedlot steers raised without antimicrobials *(Ref. 22)*. Authors observed that the percentage of fecal samples with 11 tetracycline resistance genes was significantly higher for fecal samples from conventionally raised cattle (35/61 [57%]) than for fecal samples from antimicrobial-free cattle (16/61 [26%]).

2009. Foodborne Pathogens and Disease. Association between tetracycline consumption and tetracycline resistance in *Escherichia coli* from healthy Danish slaughter pigs. Vieira et al.

The objective of this Danish study was to investigate the association between tetracycline-resistant *Escherichia coli* isolates from the intestinal tract of healthy pigs and patterns of tetracycline consumption in the herds of origin, together with other risk factors *(Ref. 23)*. The study showed that the larger the time since the last administration of tetracycline, the lower the likelihood of isolating a resistant *E. coli* .

2009. Preventive Veterinary Medicine. Associations between reported on-farm antimicrobial use practices and observed antimicrobial resistance in generic fecal *Escherichia coli* isolated from Alberta finishing swine farms. Varga et al.

This study used statistical models to evaluate the associations between various antimicrobial use practices and resistance to antimicrobials among generic fecal Escherichia coli isolated from Alberta finishing swine *(Ref. 24)*. In-feed antimicrobial use was significantly associated with an increased risk of resistance to ampicillin, chloramphenicol, streptomycin, and sulfisoxazole in *E. coli* isolates. Chlortetracycline use in grower rations was associated with ampicillin and tetracycline resistance.

2010. International Journal of Food Microbiology. Farm-to-fork characterization of *Escherichia coli* associated with feedlot cattle with a known history of antimicrobial use. Alexander et al.

This study investigated antimicrobial-resistant *Escherichia coli* isolated from cattle fed diets containing chlortetracycline plus sulfamethazine (AS700) *(Ref. 25)*. Compared to the control, in which no feed antibiotics were administered, the prevalence of ampicillin-resistant and tetracycline-resistant *E. coli* was three- and four-fold greater in feces from treated animals respectively, but was similar between treatments for animal hide samples.

2011. Environmental Health Perspectives. Lower prevalence of antibiotic-resistant Enterococci on U.S. conventional poultry farms that transitioned to organic practices. Sapkota et al.

This study compared antimicrobial resistance in enterococci recovered from conventional poultry farms using antibiotics with farms that transitioned to antibiotic-free production practices and had just received organic certification *(Ref. 26)*. Over 40% of *Enterococcus faecalis* isolates from conventional poultry houses were multidrug resistant, compared with 10% of isolates from newly organic poultry houses. In addition, 84% of *Enterococcus faecium* isolates from conventional poultry houses were multidrug resistant, compared with 17% of isolates from newly organic poultry houses.

2011. Foodborne Pathogens and Disease. Association between antimicrobial resistance in *Escherichia coli* isolates from food animals and blood stream isolates from humans in Europe: an ecological study. Vieira et al.

The authors analyzed the correlation between the prevalence of antimicrobial resistance in *E. coli* isolates from blood stream infections in humans and in *E. coli* isolates from poultry, pigs, and cattle in 11 countries between 2005 and 2008 *(Ref. 27)*. Resistance against multiple drugs in *E. coli* isolates from food animals (especially poultry and pigs) was highly correlated with resistance in isolates from humans.

2011. BMC Microbiology. Distribution and characterization of ampicillin- and tetracycline-resistant *Escherichia coli* from feedlot cattle fed subtherapeutic antimicrobials. Mirzaagha et al.

Authors characterized *E. coli* isolates recovered from cattle that either received no dietary antimicrobials or were intermittently administered subtherapeutic levels of chlortetracycline, chlortetracycline and sulfamethazine (SMX), or virginiamycin over a 9-month feeding period *(Ref. 28)*. This study showed that strains exhibited multidrug resistance to SMX and chloramphenicol (a drug not in the antibiotic regimen) more frequently when obtained from steers fed chlortetracycline plus sulfamethazine than from cattle treated with either chlortetracycline alone or with virginiamycin. Results further suggested that the administration of chlortetracycline, even in the absence of SMX, can lead to the emergence of resistance to SMX, as well as other antibiotics, including ampicillin and chloramphenicol.

2012. Proceedings of the National Academy of Sciences. In-feed antibiotic effects on the swine intestinal microbiome. Looft et al.

This study involved pigs raised in a highly controlled environment, with one group of littermates receiving a diet containing a growth-enhancing antibiotic combination product [chlortetracycline, sulfamethazine, and penicillin (known as ASP250)] and the other receiving the same diet without the antibiotics *(Ref. 29)*. Even a low, short-term (14-day) dose of in-feed antibiotics increased the prevalence and diversity of antibiotic resistance genes, including resistance to antibiotics not administered in the study, and increased the prevalence of *E. coli*.

IV. Strategies for Controlling Antimicrobial Resistance Are Needed

As summarized above in Section III, the public health concerns associated with the use of medically important antimicrobial drugs in food-producing animals have been the subject of scientific interest for the past 40 years. FDA has considered all available information and believes that the weight of scientific evidence supports the recommendations outlined in this guidance document.

To effectively respond to the public health concerns associated with antimicrobial resistance, FDA believes it is important to broadly consider how antimicrobial drugs are being used. The scientific community generally agrees that antimicrobial drug use is a key driver for the emergence of antimicrobial-resistant bacteria. It is imperative that strategies

for controlling antimicrobial resistance include a consideration of how antimicrobial drugs are being used and measures to address those uses that are injudicious in nature.

V. Current Regulatory Framework

FDA considers the issue of antimicrobial resistance as part of its human food safety review related to new animal drugs used in food-producing animals. FDA considers an antimicrobial new animal drug to be "safe" if the agency concludes that there is "reasonable certainty of no harm to human health" from the proposed use of the drug in food-producing animals. This standard applies to safety evaluations completed prior to new animal drug approvals, as well as to those completed for drugs after approval. If this safety standard is not met before approval, the drug cannot be approved. If safety issues arise after approval, the Federal Food, Drug, and Cosmetic Act (the Act) provides grounds for withdrawal of approval of new animal drug applications for safety reasons. For example, section 512(e)(1)(B) of the Act provides for withdrawal of new animal drug application approvals when new evidence, along with evidence contained in the application, shows that the drug is not shown to be safe under the approved conditions of use. Under this provision, if FDA initiates a withdrawal action, it must produce evidence to show that there is a reasonable basis from which serious questions may be inferred about the ultimate safety of the drug and any substance that may be formed in or on food as a result of use of such drug under approved conditions. Once the agency meets this initial burden, the burden then shifts to the sponsor to demonstrate the safety of the drug (Docket no. 00N-1571, at p. 5, Mar. 16, 2004).

In 2003, FDA implemented new policies for evaluating antimicrobial resistance associated with use of antimicrobial new animal drugs in food-producing animals through the issuance of Guidance for Industry (GFI) #152, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern" (http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052519.pdf). This guidance document describes a risk-based assessment process for evaluating antimicrobial resistance associated with the use of antimicrobial new animal drugs in food-producing animals. The guidance also recommends measures for mitigating such risk.

In general, FDA's GFI #152 is premised on the concept that increasing the exposure of bacterial populations to antimicrobial drugs increases the risk of generating resistance to those antimicrobial drugs. Pursuant to this principle, the administration of medically important antimicrobial drugs to entire herds or flocks of food-producing animals (e.g., for production purposes) would represent a use that poses a qualitatively higher risk to public health than the administration of such drugs to individual animals or targeted groups of animals (e.g., to prevent, control, or treat specific diseases). In addition to factors that impact the potential extent of use of the drug, the guidance also considers such factors as the properties of the drug in question including mechanism of action and mechanism of resistance, the prevalence of zoonotic foodborne bacteria in the food-producing animal species for which the drug is intended, and the importance of the drug in question as a therapy in humans. Risk mitigating

factors that are considered include such limitations as restricting use of the drug to use by or on the order of a veterinarian.

Although FDA developed GFI #152 primarily to assess antimicrobial resistance risks as part of the new animal drug approval process, the underlying concept described above is also applicable to safety evaluations conducted for previously-approved antimicrobial new animal drugs. Therefore, FDA considers this same concept when it conducts safety evaluations for currently approved antimicrobial drugs, including those approved for use in animal feed.

From a practical standpoint, however, some significant differences exist between applying the GFI #152 risk assessment approach to the pre-approval process and applying it to safety reviews of currently-approved products. On the pre-approval side, the GFI #152 assessment process, including the various risk mitigation measures described, is taken into consideration by drug sponsors upstream in the drug development process and, in effect, steers product development in a direction that is most consistent with the guidance. On the post-approval side, FDA may examine certain currently-approved products to determine whether such products appear consistent with GFI #152. However, initiating action to withdraw an approved new animal drug application (NADA), in whole or in part, based on the results of a post-approval safety review would require the agency to make the showing required under section 512(e)(1) of the Act.

Alternatively, concerns associated with approved NADAs can sometimes be addressed through more informal processes. For example, in certain cases FDA has worked collaboratively with the sponsor of an NADA to address concerns raised regarding their product and has initiated steps to permit the sponsor to voluntarily withdraw part or all of the NADA or to revise the product labeling to address the concern. This alternative pathway can in some cases be an effective and expedient mechanism for resolving issues associated with an NADA.

VI. Status of FDA's Current Activities

In general, the antimicrobial new animal drug applications that FDA is addressing as part of its efforts to evaluate the public health concerns associated with the use of medically important antimicrobial drugs in food-producing animals can be divided into two broad categories: 1) those NADAs submitted after the issuance of GFI #152 in 2003 and for which FDA is assessing the microbiological safety of the new animal drug on a pre-approval basis using the principles outlined in GFI #152; and 2) those NADAs approved before the final version of GFI#152 was issued in 2003. In regard to the first category, FDA believes the approach outlined in GFI #152 for evaluating microbiological safety as part of the drug approval process has been very effective. As noted above, that assessment process and the associated risk mitigation measures are usually taken into consideration by industry during the drug development process. Thus, products that ultimately move forward toward approval are those products that include use conditions that are consistent with the guidance and are intended to minimize the extent to which product use would contribute to resistance development.

FDA believes the approach outlined in GFI #152 is scientifically sound and is protective of the public health. FDA recognizes that the list of drugs in Appendix A is not static and should be periodically reassessed and updated as necessary. Such reassessment is necessary to take into consideration such factors as the development of new antimicrobials for human therapy, the emergence of diseases in humans, or changes in prescribing practices in the United States. FDA will update Appendix A, as necessary, through a separate process that will also be subject to public comment.

The second category of products are those antimicrobial NADAs that were approved prior to the implementation of GFI #152. Some of the products in this category include products that were approved for use in food-producing animals more than 30 years ago. Of particular concern, as discussed in section IV, are those products that are approved for use in animal feed for production or growth-enhancing purposes. Although these products are FDA-approved, their approval occurred prior to implementation of current processes for assessing safety with respect to antimicrobial resistance. Furthermore, the scientific understanding regarding antimicrobial resistance has advanced significantly over this time frame and, as discussed earlier in this document, a number of scientific reports have raised public health concerns regarding the use of medically important antimicrobials in food-producing animals.

As a result, FDA is examining available information regarding medically important antimicrobial drugs currently approved for use in food-producing animals and considering potential steps for agency action.

VII. Recommended Principles Regarding Judicious Use in Animals

The continued availability of effective antimicrobial drugs is critically important for combating infectious disease in both humans and animals. This includes the continued availability of feed and water uses of such drugs for managing disease in animal agriculture. Therefore, it is in the interest of both human and animal health that we take a more proactive approach to considering how antimicrobial drugs are being used, and take steps to assure that such uses are appropriate and necessary for maintaining the health of humans and animals. Using medically important antimicrobial drugs as judiciously as possible is key to minimizing resistance development and preserving the effectiveness of these drugs as therapies for humans and animals. Although FDA applauds the efforts to date by various veterinary and animal producer organizations to institute guidelines for the judicious use of antimicrobial drugs, the agency believes additional, voluntary steps are needed.

To further address this public and animal health concern, FDA is recommending two additional principles about the appropriate or judicious use of medically important antimicrobial drugs in food-producing animals. These principles are consistent with the recommendations of a number of recent scientific panels or committees referenced earlier in this document including the 1997, 2000, and 2011 reports of the WHO, the 2003 IOM Report, and the 2005 Codex Code of Practice.

FDA recognizes the need to collaborate with the animal health and animal producer communities on strategies for minimizing animal health impacts or industry disruption that may be associated with the implementation of changes by animal drug sponsors to voluntarily align the use conditions of affected drug products with the principles outlined below. Furthermore, FDA intends to consult with the United States Department of Agriculture (USDA) on implementation strategies, including the development of a framework for veterinary oversight and consultation requirements. FDA is committed to assuring that the public health is protected while also assuring that the health needs of animals are addressed.

Principle 1: *The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that are considered necessary for assuring animal health.*

In light of the risk that antimicrobial resistance poses to public health, FDA believes the use of medically important antimicrobial drugs in food-producing animals for production purposes (e.g., to promote growth or improve feed efficiency) represents an injudicious use of these important drugs. Production uses are not directed at any specifically identified disease, but rather are expressly indicated and used for the purpose of enhancing the production of animal-derived products. In contrast, FDA considers uses that are associated with the treatment, control, or prevention[5] of specific diseases, including administration through feed or water, to be uses that are necessary for assuring the health of food-producing animals.

Some may have concerns that the use of medically important antimicrobial drugs in food-producing animals for disease prevention purposes is not an appropriate or judicious use. However, FDA believes that some indications for prevention use are necessary and judicious as long as such use includes professional veterinary involvement. Veterinary involvement in the decision-making process associated with the use of medically important antimicrobial drugs is an important aspect of assuring appropriate use, including judicious prevention use. When determining the appropriateness of a prevention use, veterinarians consider several important factors such as determining the medical rationale for such use, and that such use is appropriately targeted at a specific etiologic agent and appropriately timed relative to the disease. For example, if a veterinarian determines, based on the client's production practices and herd health history, that cattle being transported or otherwise stressed are more likely to develop a certain bacterial infection, preventively treating these cattle with an antimicrobial approved for prevention of that bacterial infection would be considered a judicious use. Another example would be the prevention of necrotic enteritis in broiler chickens. In this case, the prevention use of an antimicrobial is important to manage this disease in certain flocks in the face of concurrent coccidiosis, a significant parasitic disease in chickens. On the other hand, FDA would not consider the administration of a drug to apparently healthy animals in the absence of any information

[5] Disease prevention involves the administration of an antimicrobial drug to animals, none of which are exhibiting clinical signs of disease, in a situation where disease is likely to occur if the drug is not administered.

that such animals were at risk of a specific disease to be a judicious use. The decision to use a specific drug or combination drug is generally based on factors that veterinarians are uniquely qualified to consider, including the mode of antibacterial action, drug distribution in specific tissues, and the duration of effective drug levels at the site of infection.

Principle 2: *The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that include veterinary oversight or consultation.*

Most of the feed-use antimicrobial drugs are currently approved for over-the-counter use in food-producing animals for purposes that include the treatment, control, and prevention of disease as well as for production purposes (i.e., for growth promotion uses such as increased rate of weight gain). In addition to instituting voluntary measures that would limit use of medically important antimicrobial drugs in food-producing animals to uses that are considered necessary to assure the animals' health, FDA also believes it is important to phase-in the voluntary practice of including veterinary oversight or consultation in the use of these drugs. As noted above, FDA believes that this practice is an important mechanism for helping to assure appropriate use. Veterinarians can play a critical role in the diagnosis of disease and in the decision-making process related to instituting measures to treat, control, or prevent disease. FDA recognizes that the nature of veterinary involvement can vary due to numerous factors such as geographic location and animal production setting. In fact, there are limited numbers of large animal veterinarians, which can make consultation or oversight challenging in certain situations. For example, some animal disease events require immediate attention. In some cases, veterinarians may be directly diagnosing and administering therapies, while in other cases they are visiting and consulting with producers periodically to establish customized disease management protocols for that producer's herd or flock. Of key importance to FDA is the fact that, in both of these cases, the veterinarian is involved in the decision-making process regarding antimicrobial drug use. FDA recognizes that increasing veterinary involvement in the use of antimicrobial drugs has significant practical implications for animal producers, veterinary practitioners, and the veterinary profession as whole. Therefore, FDA is particularly interested in receiving comments on strategies for effectively promoting the voluntary adoption of such a change.

VIII. Conclusion

In order to minimize the development of antimicrobial resistance, FDA believes that it is important to ensure the judicious use of medically important antimicrobial drugs in animal agriculture. We recommend several steps to accomplish this including voluntary measures that would limit medically important antimicrobial drugs to uses in food-producing animals that are considered necessary for assuring animal health and that include veterinary oversight or consultation. Such limitations would reduce overall medically important antimicrobial drug use levels, thereby reducing antimicrobial resistance selection pressure, while still maintaining the availability of these drugs for appropriate use.

IX. References

1. 1969 Report of the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine.

2. 1970 FDA Task Force Report, "The Use of Antibiotics in Animal Feed."

3. 1980 National Academy of Sciences Report, "The Effects on Human Health of Subtherapeutic Use of Antimicrobial Drugs in Animal Feeds."

4. 1984 Seattle-King County Study: "Surveillance of the Flow of *Salmonella* and *Campylobacter* in a Community."

5. 1988 Institute of Medicine (IOM) Report: "Human Health Risks with the Subtherapeutic Use of Penicillin or Tetracyclines in Animal Feed."

6. 1997 World Health Organization (WHO) Report, "The Medical Impact of Antimicrobial Use in Food Animals." http://whqlibdoc.who.int/hq/1997/WHO_EMC_ZOO_97.4.pdf

7. 1999 National Research Council (NRC) Report: "The Use of Drugs in Food Animals – Benefits and Risks."

8. 1999 United States Government Accountability Office (GAO) Report – "Food Safety: The Agricultural Use of Antibiotics and Its Implications for Human Health." http://www.gao.gov/archive/1999/rc99074.pdf

9. 1999 European Commission Report, "Opinion of the Scientific Steering Committee on Antimicrobial Resistance." http://ec.europa.eu/food/fs/sc/ssc/out50_en.pdf

10. 2000 World Health Organization (WHO) Expert Consultation: "WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food." http://whqlibdoc.who.int/hq/2000/WHO_CDS_CSR_APH_2000.4.pdf

11. 2003 Report, "Joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Scientific assessment." http://www.who.int/foodsafety/publications/micro/en/amr.pdf

12. 2003 Institute of Medicine (IOM) Report, "Microbial Threats to Health: Emergence, Detection and Response."

13. 2004 Report, "Second Joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Management options." http://www.oie.int/fileadmin/Home/eng/Conferences_Events/docs/pdf/WHO-CDS-CPE-ZFK-2004.8.pdf

14. 2004 United States Government Accountability Office (GAO) Report – "Antibiotic Resistance: Federal Agencies Need to Better Focus Efforts to Address Risks to Humans from Antibiotic Use in Animals." http://www.gao.gov/new.items/d04490.pdf

15. 2005 Codex Alimentarius Commission (Codex), "Code of Practice to Minimize and Contain Antimicrobial Resistance." http://www.codexalimentarius.net/download/standards/10213/CXP_061e.pdf

16. 2006 Antimicrobial Resistance: Implications for the Food System, Comprehensive Reviews in Food Science and Food Safety, Vol. 5, 2006.

17. 2009. American Academy of Microbiology. Antibiotic Resistance: An Ecological Perspective on an Old Problem. 1752 N Street, NW Washington, DC 20036 http://www.asm.org

18. 2011. Tackling antibiotic resistance from a food safety perspective in Europe. World Health Organization (WHO), Regional Office for Europe Scherfigsvej 8, DK-2100 Copenhagen Ø, Denmark. http://www.euro.who.int/__data/assets/pdf_file/0005/136454/e94889.pdf

19. 2008. Longitudinal study of antimicrobial resistance among *Escherichia coli* isolates from integrated multisite cohorts of humans and swine. Alali WQ, Scott HM, Harvey RB, Norby B, Lawhorn DB, Pillai SD. Appl Environ Microbiol. 74(12):3672-81.

20. 2008. Diversity and distribution of commensal fecal *Escherichia coli* bacteria in beef cattle administered selected subtherapeutic antimicrobials in a feedlot setting. Sharma R, Munns K, Alexander T, Entz T, Mirzaagha P, Yanke LJ, Mulvey M, Topp E, McAllister T. Appl Environ Microbiol.;74(20):6178-86.

21. 2008. Effect of subtherapeutic administration of antibiotics on the prevalence of antibiotic-resistant *Escherichia coli* bacteria in feedlot cattle. Alexander, T.W., L.J. Yanke, E. Topp, M.E. Olson, R.R. Read, D.W. Morck, and T.A. McAllister. Applied and Environmental Microbiology. 74:4405-4416.

22. 2009. A metagenomic approach for determining prevalence of tetracycline resistance genes in the fecal flora of conventionally raised feedlot steers and feedlot steers raised without antimicrobials. Harvey, R., J. Funk, T.E. Wittum, and A.E. Hoet. American Journal of Veterinary Research. 70:198-202.

23. 2009. Association between tetracycline consumption and tetracycline resistance in *Escherichia coli* from healthy Danish slaughter pigs. Vieira, A.R., H. Houe, H.C. Wegener, D.M. Lo Fo Wong, and H.D. Emborg. Foodborne Pathogens and Disease. 6:99-109.

24. 2009. Associations between reported on-farm antimicrobial use practices and observed antimicrobial resistance in generic fecal *Escherichia coli* isolated from Alberta

finishing swine farms. Varga C., A. Rajic, M.E. McFall, R.J. Reid-Smith, A.E. Deckert, S.L. Checkley, and S.A. McEwen. Preventive Veterinary Medicine. 88:185-192.

25. 2010. Farm-to-fork characterization of *Escherichia coli* associated with feedlot cattle with a known history of antimicrobial use. Alexander, T.W., G.D. Inglis, L.J. Yanke, E. Topp, R.R. Read, T. Reuter, and T.A. McAllister. International Journal of Food Microbiology. 137:40-48.

26. 2011. Lower prevalence of antibiotic-resistant Enterococci on U.S. conventional poultry farms that transitioned to organic practices. Sapkota AR, Hulet RM, Zhang G, McDermott P, Kinney EL, Schwab KJ, Joseph SW. Environ Health Perspect. 119(11):1622-8.

27. 2011. Association between antimicrobial resistance in *Escherichia coli* isolates from food animals and blood stream isolates from humans in Europe: an ecological study. Foodborne Pathogens and Disease. Vieira, A.R., P. Collignon, F.M. Aarestrup, S.A. McEwen, R.S. Hendriksen, T. Hald, and H.C. Wegener. 8:1295-1301.

28. 2011. Distribution and characterization of ampicillin- and tetracycline-resistant *Escherichia coli* from feedlot cattle fed subtherapeutic antimicrobials. Mirzaagha P, Louie M, Sharma R, Yanke LJ, Topp E, McAllister TA. BMC Microbiol. 19;11:78.

29. 2012. In-feed antibiotic effects on the swine intestinal microbiome. Looft, T., T.A. Johnson, H.K. Allen, D.O. Bayles, D.P. Alt, R.D. Stedtfeld, W.J. Sul, T.M. Stedtfeld, B. Chai, J.R. Cole, S.A. Hashsham, J.M. Tiedje, and T.B. Stanton. Proceedings of the National Academy of Sciences USA. 109:1691-1696.

End Note

Other studies referenced by the Department of Health and Human Services in response to 2004 United States Government Accountability Office (GAO) Report – "Antibiotic Resistance: Federal Agencies Need to Better Focus Efforts to Address Risks to Humans from Antibiotic Use in Animals":

1. Phillips I, Casewell M, Cox T, *et al. Does the use of antibiotics in food animals pose a risk to human health?* A critical review of published data. J Antimicrob Chemother 2004;53:28-52.

2. Holmberg SD, Wells JG, Cohen ML. *Animal-to-man transmission of antimicrobial-resistant Salmonella: investigations of U.S. outbreaks*, 1971-1983. Science 1984;225:833-5.

3. Holmberg SD, Solomon SL, Blake PA. *Health and economic impacts of antimicrobial resistance.* Rev Infect Dis 1987; 9:1065-78.

4. Lee LA, Puhr ND, Maloney K, et al. *Increase in antimicrobial-resistant Salmonella infections in the United States, 1989-1990.* J Infect Dis 1994;170:128-34.

5. Varma J, Mølbak K, Rossiter S, et al. *Antimicrobial resistance in Salmonella is associated with increased hospitalization; NARMS 1996-2000.* International Conference on Emerging Infectious Diseases. March 2002. Atlanta, GA.

6. Varma J, Mølbak K, Rossiter S, et al. *Antimicrobial resistance in non-typhoidal Salmonella is associated with increased hospitalization and bloodstream infection--United States, 1996-2000. 51st Annual EIS Conference.* April 22-26, 2002. Atlanta, GA.

7. Helms M, Vastrup P, Gerner-Smidt P, Mølbak K. *Excess mortality associated with antimicrobial drug-resistant Salmonella Typhimurium.* Emerg Infect Dis 2002;8:490-5.

8. Martin L, Fyfe M, Doré K, et al. *Increased burden of illness associated with antimicrobial-resistant Salmonella enterica serotype Typhimurium infections.* J Infect Dis 2004;189:377-84.

9 Smith KE, Besser JM, Hedberg CW, et al. *Quinolone-resistant Campylobacter jejuni infections in Minnesota, 1992-1998.* N Engl J Med 1999;340:1525-32.

10. Neimann J, Mølbak K, Engberg J, et al. *Longer duration of illness among Campylobacter patients treated with fluoroquinolones. 11th International Workshop on Campylobacter, Helicobacter, and Related Organisms, 1-5 September, 2001.* Freiburg, Germany.

11. Nelson JM, Smith KE, Vugia DJ, et al. *Prolonged diarrhea due to ciprofloxacin-resistant Campylobacter infections.* J Infect Dis 2004; 190:1150-7.

VFD and VCPR, Client

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What VCPR standard applies?

FDA provides a **list** of states whose VCPR includes the key elements of the federally-defined VCPR and requires a VCPR for the issuance of a VFD. If your state appears on this list you must follow your state VCPR, if your state does not you must follow the federal VCPR as defined in 21 CFR 530.3(i).

Who is the "client" on the VFD?

"Client" is typically the client in the VCPR; the person responsible for the care and feeding of the animals receiving the VFD feed.

What is an "extralabel use" of a VFD drug and is it allowed?

"Extralabel use" is defined in FDA's regulations as actual or intended use of a drug in an animal in a manner that is not in accordance with the approved labeling. For example, feeding the animals a VFD for a duration of time that is different from the duration specified on the label, feeding a VFD formulated with a drug level that is different from what is specified on the label, or feeding a VFD to an animal species different than what is specified on the label would all be considered extralabel uses. Extralabel use of medicated feed, including medicated feed containing a VFD drug or a combination VFD drug, is not permitted.

Reorders (refills)

When can I authorize a reorder (refill)?

If the drug approval, conditional approval, or index listing expressly allows a reorder (refill) you can authorize up to the permitted number of reorders. If a drug is silent on reorders (refills), then you may not authorize a reorder (refill).

Use of medicated feed is authorized by a VFD not Rx

A lawful VFD has to be complete

What do I have to include in a VFD?

This information is required on a lawful VFD:

- veterinarian's name, address, and telephone number;
- client's name, business or home address, and telephone number;
- premises at which the animals specified in the VFD are located;
- date of VFD issuance;
- expiration date of the VFD;
- name of the VFD drug(s);
- species and production class of animals to be fed the VFD feed;
- approximate number of animals to be fed the VFD feed by the expiration date of the VFD;
- indication for which the VFD is issued;
- level of VFD drug in the feed and duration of use;
- withdrawal time, special instructions, and cautionary statements necessary for use of the drug in conformance with the approval;
- number of reorders (refills) authorized, if permitted by the drug approval, conditional approval, or index listing;
- statement: "Use of feed containing this veterinary feed directive (VFD) drug in a manner other than as directed on the labeling (extralabel use), is not permitted";
- an affirmation of intent for combination VFD drugs as described in 21 CFR 558.6(b)(6); and
- veterinarian's electronic or written signature.

You may also include the following optional information on the VFD:

- a more specific description of the location of the animals (for example, by site, pen, barn, stall, tank, or other descriptor the veterinarian deems appropriate);
- the approximate age range of the animals;
- the approximate weight range of the animals; and
- any other information the veterinarian deems appropriate to identify the animals at issue.

The veterinarian must keep the original VFD for two years

FDA

Center for Veterinary Medicine

Protecting Human and Animal Health

Veterinary Feed Directive (VFD)

Requirements for Veterinarians 2015

For more information:

AskCVM@fda.hhs.gov

Guidance for Industry #120

21 CFR 558.6 (VFD)

Website: http://www.fda.gov/safefeed

VFD Statement

What is a VFD?

A VFD is a written (nonverbal) statement issued by a licensed veterinarian in the course of the veterinarian's professional practice that authorize the use of a VFD drug or combination VFD drug in or on an animal feed. This written statement authorizes the client (the owner of the animal or animals or other caretaker) to obtain and use animal feed bearing or containing a VFD drug or combination VFD drug to treat the client's animals only in accordance with the conditions for use approved, conditionally approved, or indexed by the FDA. A VFD is also referred to as a VFD order.

VFD drug and combination VFD drug

What is a "VFD drug"?

A"VFD drug" is a drug intended for use in or on animal feed, which is limited to use under the professional supervision of a licensed veterinarian.

What is a "combination VFD drug"?

A "combination VFD drug" is an approved combination of new animal drugs intended for use in or on animal feed under the professional supervision of a licensed veterinarian, and at least one of the new animal drugs in the combination is a VFD drug.

VFD Drugs and Prescription Drugs

What is the difference between a VFD drug and a prescription (Rx) drug?

FDA approves drugs in these two separate regulatory categories for drugs that require veterinary supervision and oversight for their use. When the drug being approved is for use in or on animal feed (a medicated feed), FDA approves these drugs as a VFD drug. When the drug being approved is not for use in or on animal feed, the drug is approved as a prescription drug.

Why VFD instead of prescription?

When the VFD drug category was created, the Act made it clear that VFD drugs are not prescription drugs. This category was created to provide veterinary supervision without invoking state pharmacy laws for prescription drugs that were unworkable for the distribution of medicated feed.

Veterinarians' Responsibilities

- must be licensed to practice veterinary medicine;
- must be operating in the course of the veterinarian's professional practice and in compliance with all applicable veterinary licensing and practice requirements;
- must write VFD orders in the context of a valid client-patient relationship (VCPR);
- must issue a VFD that is in compliance with the conditions for use approved, conditionally approved, or indexed for the VFD drug or combination VFD drug;
- must prepare and sign a written VFD providing all required information;
- may enter additional discretionary information to more specifically identify the animals to be treated/fed the VFD feed;
- must include required information when a VFD drug is authorized for use in a drug combination that includes more than one VFD drug;
- must restrict or allow the use of the VFD drug in combination with one or more OTC drug(s);
- must provide the feed distributor with a copy of the VFD;
- must provide the client with a copy of the VFD order;
- must retain the original VFD for 2 years, and
- must provide VFD orders for inspection and copying by FDA upon request.

Major and Minor Animal Species

What are "major and minor animal species"?

FDA regulations define cattle, horses, swine, chickens, turkeys, dogs, and cats, as major species. All animal species, other than humans, that are not major species are minor species.

When is a VFD needed for a minor species?

The VFD requirements apply to all VFD drugs for use in major or minor species. One VFD drug is already approved for use in minor species (e.g., florfenicol in aquaculture). Other medicated feed drugs for minor species are expected to convert from their present over-the-counter (OTC) status to VFD (e.g., oxytetracycline in honey bees) and at that time a VFD will be required for their use.

ELU of VFD feed is not permitted

VFD transmitting and other topics

How do I send a VFD to the feed distributor?

You must send a copy of the VFD to the distributor via hardcopy, facsimile (fax), or other electronic means. If in hardcopy, you are required to send the copy of the VFD to the distributor either directly or through the client.

Who gets the original or a copy?

You, the veterinarian, must retain the original VFD in its original form (electronic or hardcopy) and must send a copy to the distributor and client.

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VFD drug sponsors may make the VFD order for their drugs available, or, as a veterinarian you may create your own VFD for a VFD drug.

How do I issue a VFD for a combination VFD drug?

You may expand or limit the use of a VFD drug along with OTC animal drug(s) in an approved combination(s), as appropriate, by stating the affirmation of intent on the VFD order.

What is an "expiration date" on the VFD?

The expiration date on the VFD specifies the last day the VFD feed can be fed.

What is the difference between an "expiration date" on the VFD and duration of use?

While the VFD expiration date defines the period of time for which the authorization to feed an animal feed containing a VFD drug is lawful, the duration of use determines the length of time, established as part of the approval, conditional approval, or index listing process, that the animal feed containing the VFD drug is allowed to be fed to the animals.

How do I allow pioneer/generic drug substitution on the VFD?

By default, the VFD feed manufacturer may use an approved substitute (e.g., one brand of Type A medicated article instead of another). If you do not want a substitution, you may specify on the VFD that a substitution is not allowed.

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U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Veterinary Feed Directive Requirements for Veterinarians

Printer-friendly Brochure (/downloads/AnimalVeterinary/DevelopmentApprovalProcess/UCM455480.pdf) - For best results, print on legal paper (8 1/2" x 14").

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For More Information

AskCVM@fda.hhs.gov (mailto:AskCVM@fda.hhs.gov)
Guidance for Industry #120 (/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052660.pdf)
21 CFR 558.6 (VFD)
Website: **http://www.fda.gov/safefeed (http://www.fda.gov/safefeed)**

More in Development & Approval Process (/AnimalVeterinary/DevelopmentApprovalProcess/default.htm)

Food Additive Petitions for Animal Food (/AnimalVeterinary/DevelopmentApprovalProcess/ucm056809.htm)

Public Master Files (PMFs) Supporting Applications for Major Use and Major Species Drugs (/AnimalVeterinary/DevelopmentApprovalProcess/ucm416607.htm)

Veterinary Feed Directive (VFD) (/AnimalVeterinary/DevelopmentApprovalProcess/ucm071807.htm)

Veterinary Master Files (/AnimalVeterinary/DevelopmentApprovalProcess/ucm071808.htm)

User Fees (/AnimalVeterinary/DevelopmentApprovalProcess/UserFees/default.htm)

Electronic Submissions

(/AnimalVeterinary/DevelopmentApprovalProcess/ElectronicSubmissions/default.htm)

Minor Use/Minor Species (/AnimalVeterinary/DevelopmentApprovalProcess/MinorUseMinorSpecies/default.htm)	⌄
Environmental Impact Considerations (/AnimalVeterinary/DevelopmentApprovalProcess/EnvironmentalAssessments/default.htm)	⌄
Genetic Engineering (/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/default.htm)	⌄
New Animal Drug Applications (/AnimalVeterinary/DevelopmentApprovalProcess/NewAnimalDrugApplications/default.htm)	⌄
Aquaculture (/AnimalVeterinary/DevelopmentApprovalProcess/Aquaculture/default.htm)	⌄

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- species and production class of animals to be fed the VFD feed;
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- indication for which the VFD is issued;
- level of VFD drug in the feed and duration of use;
- withdrawal time, special instructions, and cautionary statements necessary for use of the drug in conformance with the approval;
- number of reorders (refills) authorized, if permitted by the drug approval, conditional approval, or index listing;
- statement: "Use of feed containing this veterinary feed directive (VFD) drug in a manner other than as directed on the labeling (extralabel use), is not permitted";
- an affirmation of intent for combination VFD drugs as described in 21 CFR 558.6(b)(6); and
- veterinarian's electronic or written signature.

You may also include the following optional information on the VFD:

- a more specific description of the location of the animals (for example, by site, pen, barn, stall, tank, or other descriptor the veterinarian deems appropriate);
- the approximate age range of the animals;
- the approximate weight range of the animals; and
- any other information the veterinarian deems appropriate to identify the animals at issue.

The veterinarian must keep the original VFD for two years

FDA

Center for Veterinary Medicine

Protecting Human and Animal Health

Veterinary Feed Directive (VFD)

Requirements for Veterinarians 2015

For more information:

AskCVM@fda.hhs.gov

Guidance for Industry #120

21 CFR 558.6 (VFD)

Website: http://www.fda.gov/safefeed

For Veterinary Students

VFD drug and combination VFD drug

What is a "VFD drug"?
A"VFD drug" is a drug intended for use in or on animal feed, which is limited to use under the professional supervision of a licensed veterinarian.

What is a "combination VFD drug"?
A "combination VFD drug" is an approved combination of new animal drugs intended for use in or on animal feed under the professional supervision of a licensed veterinarian, and at least one of the new animal drugs in the combination is a VFD drug.

What is a VFD?
A VFD is a written (nonverbal) statement issued by a licensed veterinarian in the course of the veterinarian's professional practice that authorize the use of a VFD drug or combination VFD drug in or on an animal feed. This written statement authorizes the client (the owner of the animal or animals or other caretaker) to obtain and use animal feed bearing or containing a VFD drug or combination VFD drug to treat the client's animals only in accordance with the conditions for use approved, conditionally approved, or indexed by the FDA. A VFD is also referred to as a VFD order.

VFD Statement

VFD Drugs and Prescription Drugs

What is the difference between a VFD drug and a prescription (Rx) drug?
FDA approves drugs in these two separate regulatory categories for drugs that require veterinary supervision and oversight for their use. When the drug being approved is for use in or on animal feed (a medicated feed), FDA approves these drugs as a VFD drug. When the drug being approved is not for use in or on animal feed, the drug is approved as a prescription drug.

Why VFD instead of prescription?
When the VFD drug category was created, the Federal Food, Drug and Cosmetic Act (the Act) made it clear that VFD drugs are not prescription drugs. This category was created to provide veterinary supervision without invoking state pharmacy laws for prescription drugs that were unworkable for the distribution of medicated feed.

FDA approves a drug for feed use as Over-the-Counter (OTC) or as VFD

Veterinary Students and VFD

I don't plan to practice food animal medicine, why should I learn about VFD?
The law allows any licensed veterinarian to issue a VFD in the course of his or her practice and you may find yourself in a situation that requires one. For example, your pet owner client could ask you to issue a VFD for the flock of his/her backyard chickens.

Veterinary students and medicated feed

What is really important for me to know about medicated feeds in addition to VFD?

- FDA regulates medicated feeds;
- Every use of a drug in feed has to be approved;
- There are three types of products in relation to medicated feed use:
  - Type A medicated article,
  - Type B medicated feed, and
  - Type C medicated feed;

- Type A medicated article and Type B medicated feed can be used only for further manufacture of other products. Only Type C medicated feed can be fed to animals;

- Medicated feeds are approved only as over-the-counter or VFD; they cannot be used under prescription;
- All drugs approved for use in feed are placed in two drug categories on the basis of their potential to create unsafe drug residues. Category I drugs have lower potential for unsafe drug residues than Category II drugs; and
- Finally, extra-label use of medicated feeds is prohibited by law.

How are VFD (blank) orders obtained?
VFD drug sponsors may make the VFD order for their drugs available, or, as a veterinarian, you will be able to create your own VFD.

How do I send a VFD to the feed distributor?
You must send a copy of the VFD to the distributor via hard-copy, facsimile (fax), or other electronic means. If in hard-copy, you are required to send the copy of the VFD to the distributor either directly or through the client. You must keep the original VFD in its original form (electronic or hard copy) and must send a copy to the distributor and client.

ELU of VFD feed is not permitted

Veterinarians' responsibilities

- must be licensed to practice veterinary medicine;
- must be operating in the course of the veterinarian's professional practice and in compliance with all applicable veterinary licensing and practice requirements;
- must write VFD orders in the context of a valid client-patient relationship (VCPR);
- must issue a VFD that is in compliance with the conditions for use approved, conditionally approved, or indexed for the VFD drug or combination VFD drug;
- must prepare and sign a written VFD providing all required information;
- may enter additional discretionary information to more specifically identify the animals to be treated/fed the VFD feed;
- must include required information when a VFD drug is authorized for use in a drug combination that includes more than one VFD drug;
- must restrict or allow the use of the VFD drug in combination with one or more OTC drug(s);
- must provide the feed distributor with a copy of the VFD;
- must provide the client with a copy of the VFD order;
- must retain the original VFD for 2 years, and
- must provide VFD orders for inspection and copying by FDA upon request.

Major and Minor Animal Species

What are "major and minor animal species"?
FDA regulations define cattle, horses, swine, chickens, turkeys, dogs, and cats, as major species. All animal species, other than humans, that are not major species are minor species.

When is a VFD needed for a minor species?
The VFD requirements apply to all VFD drugs for use in major or minor species. One VFD drug is already approved for use in minor species (e.g., florfenicol in aquaculture). Other medicated feed drugs for minor species are expected to convert from their present over-the-counter (OTC) status to VFD (e.g., oxytetracycline in honey bees) and at that time a VFD will be required for their use.

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Veterinary Feed Directive Requirements for Veterinarians - For Veterinary Students

Printer-friendly Brochure (/downloads/AnimalVeterinary/DevelopmentApprovalProcess/UCM455481.pdf) - For best results, print on legal paper (8 1/2" x 14").

VFD Drug and Combination VFD Drug

What is a "VFD drug"?

A "VFD drug" is a drug intended for use in or on animal feed, which is limited to use under the professional supervision of a licensed veterinarian.

What is a "combination VFD drug"?

A "combination VFD drug" is an approved combination of new animal drugs intended for use in or on animal feed under the professional supervision of a licensed veterinarian, and at least one of the new animal drugs in the combination is a VFD drug.

What is a VFD?

A VFD is a written (nonverbal) statement issued by a licensed veterinarian in the course of the veterinarian's professional practice that authorizes the use of a VFD drug or combination VFD drug in or on an animal feed. This written statement authorizes the client (the owner of the animal or animals or other caretaker) to obtain and use animal feed bearing or containing a VFD drug or combination VFD drug to treat the client's animals only in accordance with the conditions for use approved, conditionally approved, or indexed by the FDA. A VFD is also referred to as a VFD order.

VFD Statement

VFD Drugs and Prescription Drugs

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FDA approves drugs in these two separate regulatory categories for drugs that require veterinary supervision and oversight for their use. When the drug being approved is for use in or on animal feed (a medicated feed), FDA approves these drugs as a VFD drug. When the drug being approved is not for use in or on animal feed, the drug is approved as a prescription drug.

Why VFD instead of prescription?

When the VFD drug category was created, the Federal Food, Drug and Cosmetic Act (the Act) made it clear that VFD drugs are not prescription drugs. This category was created to provide veterinary supervision without invoking state pharmacy laws for prescription drugs that were unworkable for the distribution of medicated feed.

FDA approves a drug for feed use as Over-the-Counter (OTC) or as VFD.

Veterinary Students and VFD

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The law allows any licensed veterinarian to issue a VFD in the course of his or her practice and you may find yourself in a situation that requires one. For example, your pet owner client could ask you to issue a VFD for the flock of his/her backyard chickens.

Veterinary Students and Medicated Feed

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  - Type A medicated article,
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- Type A medicated article and Type B medicated feed can be used only for further manufacture of other products. Only Type C medicated feed can be fed to animals;
- Medicated feeds are approved only as over-the-counter or VFD; they cannot be used under prescription;
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- Finally, extra-label use of medicated feeds is prohibited by law.

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VFD drug sponsors may make the VFD order for their drugs available, or, as a veterinarian, you will be able to create your own VFD.

How do I send a VFD to the feed distributor?

You must send a copy of the VFD to the distributor via hardcopy, facsimile (fax), or other electronic means. If in hardcopy, you are required to send the copy of the VFD to the distributor either directly or through the client. You must keep the original VFD in its original form (electronic or hard copy) and must send a copy to the

distributor and client.

ELU of VFD feed is not permitted.

Veterinarians' Responsibilities

- must be licensed to practice veterinary medicine;
- must be operating in the course of the veterinarian's professional practice and in compliance with all applicable veterinary licensing and practice requirements;
- must write VFD orders in the context of a valid client-patient relationship (VCPR);
- must issue a VFD that is in compliance with the conditions for use approved, conditionally approved, or indexed for the VFD drug or combination VFD drug;
- must prepare and sign a written VFD providing all required information;
- may enter additional discretionary information to more specifically identify the animals to be treated/fed the VFD feed;
- must include required information when a VFD drug is authorized for use in a drug combination that includes more than one VFD drug;
- must restrict or allow the use of the VFD drug in combination with one or more OTC drug(s);
- must provide the feed distributor with a copy of the VFD;
- must provide the client with a copy of the VFD order;
- must retain the original VFD for 2 years, and
- must provide VFD orders for inspection and copying by FDA upon request.

Major and Minor Animal Species

What are "major and minor animal species"?

FDA regulations define cattle, horses, swine, chickens, turkeys, dogs, and cats, as major species. All animal species, other than humans, that are not major species are minor species.

When is a VFD needed for a minor species?

The VFD requirements apply to all VFD drugs for use in major or minor species. One VFD drug is already approved for use in minor species (e.g., florfenicol in aquaculture). Other medicated feed drugs for minor species are expected to convert from their present over-the-counter (OTC) status to VFD (e.g., oxytetracycline in honey bees) and at that time a VFD will be required for their use.

VFD and VCPR, Client

What is required for veterinarian supervision?

The veterinarian-client-patient relationship (VCPR) is the basis of professional supervision. A VFD must be issued by a licensed veterinarian operating in the course of his/her professional practice and in compliance with all applicable veterinary licensing and practice requirements, including issuing the VFD in the context of a

veterinarian-client-patient relationship (VCPR).

What VCPR standard applies?

FDA provides a list of states whose VCPR includes the key elements of the federally-defined VCPR and requires a VCPR for the issuance of a VFD. If your state appears on this list you must follow your state VCPR, if your state does not you must follow the federal VCPR as defined in 21 CFR 530.3(i).

Who is the "client" on the VFD?

"Client" is typically the client in the VCPR; the person responsible for the care and feeding of the animals receiving the VFD feed.

What is an "extralabel use" of a VFD drug and is it allowed?

"Extralabel use" (ELU) is defined in FDA's regulations as actual or intended use of a drug in an animal in a manner that is not in accordance with the approved labeling. For example, feeding the animals a VFD for a duration of time that is different from the duration specified on the label, feeding a VFD formulated with a drug level that is different from what is specified on the label, or feeding a VFD to an animal species different than what is specified on the label would all be considered extralabel uses. Extralabel use of medicated feed, including medicated feed containing a VFD drug or a combination VFD drug, is not permitted.

Reorders (Refills)

When can I authorize a reorder (refill)?

If the drug approval, conditional approval, or index listing expressly allows a reorder (refill) you can authorize up to the permitted number of reorders. If a drug is silent on reorders (refills), then you may not authorize a reorder (refill).

Use of medicated feed is authorized by a VFD not Rx.

A Lawful VFD Has to Be Complete

What do I have to include in a VFD?

You must include the following information on the VFD for it to be lawful:

- veterinarian's name, address, and telephone number;
- client's name, business or home address, and telephone number;
- premises at which the animals specified in the VFD are located;
- date of VFD issuance;
- expiration date of the VFD;
- name of the VFD drug(s);
- species and production class of animals to be fed the VFD feed;
- approximate number of animals to be fed the VFD feed by the expiration date of the VFD;

- indication for which the VFD is issued;
- level of VFD drug in the feed and duration of use;
- withdrawal time, special instructions, and cautionary statements necessary for use of the drug in conformance with the approval;
- number of reorders (refills) authorized, if permitted by the drug approval, conditional approval, or index listing;
- statement: “Use of feed containing this veterinary feed directive (VFD) drug in a manner other than as directed on the labeling (extralabel use), is not permitted”;
- an affirmation of intent for combination VFD drugs as described in 21 CFR 558.6(b)(6); and
- veterinarian’s electronic or written signature.

You may also include the following optional information on the VFD:

- a more specific description of the location of the animals (for example, by site, pen, barn, stall, tank, or other descriptor the veterinarian deems appropriate);
- the approximate age range of the animals;
- the approximate weight range of the animals; and
- any other information the veterinarian deems appropriate to identify the animals at issue.

The veterinarian must keep the original VFD for two years.

For More Information

AskCVM@fda.hhs.gov (mailto:AskCVM@fda.hhs.gov)
Guidance for Industry #120 (/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052660.pdf)
21 CFR 558.6 (VFD)
Website: **http://www.fda.gov/safefeed (http://www.fda.gov/safefeed)**

More in Development & Approval Process (/AnimalVeterinary/DevelopmentApprovalProcess/default.htm)

Food Additive Petitions for Animal Food (/AnimalVeterinary/DevelopmentApprovalProcess/ucm056809.htm)

Public Master Files (PMFs) Supporting Applications for Major Use and Major Species Drugs (/AnimalVeterinary/DevelopmentApprovalProcess/ucm416607.htm)

Veterinary Feed Directive (VFD) (/AnimalVeterinary/DevelopmentApprovalProcess/ucm071807.htm)

Veterinary Master Files (/AnimalVeterinary/DevelopmentApprovalProcess/ucm071808.htm)

User Fees (/AnimalVeterinary/DevelopmentApprovalProcess/UserFees/default.htm)

Electronic Submissions (/AnimalVeterinary/DevelopmentApprovalProcess/ElectronicSubmissions/default.htm)
Minor Use/Minor Species (/AnimalVeterinary/DevelopmentApprovalProcess/MinorUseMinorSpecies/default.htm)
Environmental Impact Considerations (/AnimalVeterinary/DevelopmentApprovalProcess/EnvironmentalAssessments/default.htm)
Genetic Engineering (/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/default.htm)
New Animal Drug Applications (/AnimalVeterinary/DevelopmentApprovalProcess/NewAnimalDrugApplications/default.htm)
Aquaculture (/AnimalVeterinary/DevelopmentApprovalProcess/Aquaculture/default.htm)

Use of a VFD feed

How do I use a VFD feed?
The VFD feed must be used according to the information specified in the labeling and on the VFD. This means for example that the feed can only be used for the indications and duration of use specified on the label and VFD, and in the animals at premises specified in the VFD. Furthermore, if the VFD authorizes use of a VFD drug in an approved combination, that combination also must be used according to the labeling and VFD.

What is the difference between an "expiration date" on the VFD and duration of use?
While the VFD expiration date defines the period of time for which the authorization to feed an animal feed containing a VFD drug is lawful, the duration of use determines the length of time, established as part of the approval, conditional approval, or index listing process, that the animal feed containing the VFD drug is allowed to be fed to the animals. For example, in swine the currently approved VFD drug tilmicosin has a duration of use of 21 days and an expiration date of 90 days, which means the client has 90 days to obtain the VFD feed and complete the 21 day course of therapy.

As a client can I feed a VFD feed past the VFD expiration date?
No. A VFD feed or combination VFD feed must not be fed to animals after the expiration date on the VFD.

My VFD order is set to expire before I can complete the duration of use on the order, what should I do?
A VFD feed or combination VFD feed must not be fed to animals after the expiration date on the VFD. You should contact your veterinarian to request a new VFD order.

Extralabel use

What is an "extralabel use" of a VFD drug and is it allowed?
"Extralabel use" is defined in FDA's regulations as actual or intended use of a drug in an animal in a manner that is not in accordance with the approved labeling. For example, feeding the animals VFD feed for a duration of time that is different from the duration specified on the label, feeding VFD feed formulated with a drug level that is different from what is specified on the label, or feeding VFD feed to an animal species different than what is specified on the label would all be considered extralabel uses. Extralabel use of medicated feed, including medicated feed containing a VFD drug or a combination VFD drug, is not permitted.

Extra-label use of VFD feed (or any other medicated feed) is not permitted

Client's responsibilities

What are my responsibilities as the "client"?
As the client, a producer must:

- only feed animal feed bearing or containing a VFD drug or a combination VFD drug (a VFD feed or combination VFD feed) to animals based on a VFD issued by a licensed veterinarian;
- not feed a VFD feed or combination VFD feed to animals after the expiration date on the VFD;
- provide a copy of the VFD order to the feed distributor if the issuing veterinarian sends the distributor's copy of the VFD through you, the client;
- maintain a copy of the VFD order for a minimum of 2 years; and
- provide VFD orders for inspection and copying by FDA upon request.

VFD has to be kept for 2 years

Veterinary Feed Directive (VFD)

Producer Requirements
January 1, 2017

For more information:
AskCVM@fda.hhs.gov
Guidance for Industry #120
21 CFR 558.6 (VFD)

http://www.fda.gov/safefeed

A VFD feed can only be used under the professional supervision of a licensed veterinarian

VFD drug and combination VFD drug

What is a "VFD drug"?
A"VFD drug" is a drug intended for use in or on animal feed that is limited to use under the professional supervision of a licensed veterinarian

What is a "combination VFD drug"?
A "combination VFD drug" is an approved combination of new animal drugs intended for use in or on animal feed under the professional supervision of a licensed veterinarian, and at least one of the new animal drugs in the combination is a VFD drug.

How do I know if a drug is a VFD drug, rather than an OTC drug?
Read the label. All labeling and advertising for VFD drugs, combination VFD drugs, and feeds containing VFD drugs or combination VFD drugs must prominently and conspicuously display the following cautionary statement: "Caution: Federal law restricts medicated feed containing this veterinary feed directive (VFD) drug to use by or on the order of a licensed veterinarian." Over-the-counter (OTC) drugs do not have this statement.

VFD statement

What is a VFD?
A VFD is a written (nonverbal) statement issued by a licensed veterinarian in the course of the veterinarian's professional practice that authorizes the use of a VFD drug or combination VFD drug in or on an animal feed. This written statement authorizes the client (the owner of the animal or animals or other caretaker) to obtain and use animal feed bearing or containing a VFD drug or combination VFD drug to treat the client's animals only in accordance with the conditions for use approved, conditionally approved, or indexed by the FDA. A VFD is also referred to as a VFD order.

What is an "expiration date" on the VFD?
The expiration date on the VFD specifies the last day the VFD feed can be fed.

VFD drug labeling and advertising must prominently and conspicuously display the VFD caution statement

Obtaining a VFD feed

How does a producer obtain a VFD feed?
Use of a VFD feed requires the professional supervision of a licensed veterinarian. Producers must obtain a VFD order from their veterinarian, then send, or take, the VFD order to a feed manufacturer or supplier to get the VFD feed. Producers who manufacture their own feed must have a VFD in order to get the medicated VFD feed to manufacture from. Producers who also manufacture feed for others should be aware that they are acting as a distributor and additional requirements apply. More information on manufacturing and distributing VFD feeds is available at: www.fda.gov/safefeed

"Caution: Federal law restricts medicated feed containing this veterinary feed directive (VFD) drug to use by or on the order of a licensed veterinarian."

What does professional supervision mean?
The veterinarian-client-patient relationship (VCPR) is the basis of professional supervision. Veterinarians who issue a VFD order must practice veterinary medicine in compliance with all applicable veterinary licensing and practice requirements, including issuing the VFD in the context of a VCPR as defined by the state. If applicable VCPR requirements as defined by such state do not include the key elements of a valid VCPR as defined by Federal law, the veterinarian must issue the VFD in the context of a valid VCPR as defined by the Federal law.

What should be on a VFD order?

This information is required on a lawful VFD order:

- veterinarian's name, address, and telephone number;
- client's name, business or home address, and telephone number;
- premises at which the animals specified in the VFD are located;
- date of VFD issuance;
- expiration date of the VFD;
- name of the VFD drug(s);
- species and production class of animals to be fed the VFD feed;
- approximate number of animals to be fed the VFD feed by the expiration date of the VFD;
- indication for which the VFD is issued;
- level of VFD drug in the feed and duration of use;
- withdrawal time, special instructions, and cautionary statements necessary for use of the drug in conformance with the approval;
- number of reorders (refills) authorized, if permitted by the drug approval, conditional approval, or index listing;
- statement: "Use of feed containing this veterinary feed directive (VFD) drug in a manner other than as directed on the labeling (extralabel use), is not permitted";
- an affirmation of intent for combination VFD drugs as described in 21 CFR 558.6(b)(6); and
- veterinarian's electronic or written signature.

You may also see the following optional information on the VFD:

- a more specific description of the location of the animals (for example, by site, pen, barn, stall, tank, or other descriptor the veterinarian deems appropriate);
- the approximate age range of the animals;
- the approximate weight range of the animals; and
- any other information the veterinarian deems appropriate to identify the animals at issue.

A lawful VFD has to be complete

U.S. Food and Drug Administration
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Veterinary Feed Directive Producer Requirements

Printer-friendly Brochure (/downloads/AnimalVeterinary/DevelopmentApprovalProcess/UCM455419.pdf)

A VFD feed can only be used under the professional supervision of a licensed veterinarian.

VFD Drug and Combination VFD Drug

What is a "VFD drug"?

A "VFD drug" is a drug intended for use in or on animal feed that is limited to use under the professional supervision of a licensed veterinarian.

What is a "combination VFD drug"?

A "combination VFD drug" is an approved combination of new animal drugs intended for use in or on animal feed under the professional supervision of a licensed veterinarian, and at least one of the new animal drugs in the combination is a VFD drug.

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A VFD is a written (nonverbal) statement issued by a licensed veterinarian in the course of the veterinarian's professional practice that authorizes the use of a VFD drug or combination VFD drug in or on an animal feed. This written statement authorizes the client (the owner of the animal or animals or other caretaker) to obtain and use animal feed bearing or containing a VFD drug or combination VFD drug to treat the client's animals only in accordance with the conditions for use approved, conditionally approved, or indexed by the FDA. A VFD is also referred to as a VFD order.

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VFD Drug Labeling and Advertising Must Prominently and Conspicuously Display the VFD Caution Statement.

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- premises at which the animals specified in the VFD are located;
- date of VFD issuance;
- expiration date of the VFD;
- name of the VFD drug(s);
- species and production class of animals to be fed the VFD feed;
- approximate number of animals to be fed the VFD feed by the expiration date of the VFD;
- indication for which the VFD is issued;
- level of VFD drug in the feed and duration of use;
- withdrawal time, special instructions, and cautionary statements necessary for use of the drug in conformance with the approval;
- number of reorders (refills) authorized, if permitted by the drug approval, conditional approval, or index listing;

- statement: “Use of feed containing this veterinary feed directive (VFD) drug in a manner other than as directed on the labeling (extralabel use), is not permitted”;
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- the approximate weight range of the animals; and any other information the veterinarian deems appropriate to identify the animals at issue.

A lawful VFD has to be complete.

Use of a VFD Feed

How do I use a VFD feed?

The VFD feed must be used according to the information specified in the labeling and on the VFD. This means for example that the feed can only be used for the indications and duration of use specified on the label and VFD, and in the animals at premises specified in the VFD. Furthermore, if the VFD authorizes use of a VFD drug in an approved combination, that combination also must be used according to the labeling and VFD.

What is the difference between an “expiration date” on the VFD and duration of use?

While the VFD expiration date defines the period of time for which the authorization to feed an animal feed containing a VFD drug is lawful, the duration of use determines the length of time, established as part of the approval, conditional approval, or index listing process, that the animal feed containing the VFD drug is allowed to be fed to the animals. For example, in swine the currently approved VFD drug tilmicosin has a duration of use of 21 days and an expiration date of 90 days, which means the client has 90 days to obtain the VFD feed and complete the 21 day course of therapy.

As a client can I feed a VFD feed past the VFD expiration date?

No. A VFD feed or combination VFD feed must not be fed to animals after the expiration date on the VFD.

My VFD order is set to expire before I can complete the duration of use on the order, what should I do?

A VFD feed or combination VFD feed must not be fed to animals after the expiration date on the VFD. You should contact your veterinarian to request a new VFD order.

Extralabel Use

What is an “extralabel use” of a VFD drug and is it allowed?

"Extralabel use" is defined in FDA's regulations as actual or intended use of a drug in an animal in a manner that is not in accordance with the approved labeling. For example, feeding the animals VFD feed for a duration of time that is different from the duration specified on the label, feeding VFD feed formulated with a drug level that is different from what is specified on the label, or feeding VFD feed to an animal species different than what is specified on the label would all be considered extralabel uses. Extralabel use of medicated feed, including medicated feed containing a VFD drug or a combination VFD drug, is not permitted.

Extra-label use of VFD feed (or any other medicated feed) is not permitted.

Client's Responsibilities

What are my responsibilities as the "client"?

As the client, a producer must:

- only feed animal feed bearing or containing a VFD drug or a combination VFD drug (a VFD feed or combination VFD feed) to animals based on a VFD issued by a licensed veterinarian;
- not feed a VFD feed or combination VFD feed to animals after the expiration date on the VFD;
- provide a copy of the VFD order to the feed distributor if the issuing veterinarian sends the distributor's copy of the VFD through you, the client;
- maintain a copy of the VFD order for a minimum of 2 years; and provide VFD orders for inspection and copying by FDA upon request.

For More Information

AskCVM@fda.hhs.gov (mailto:AskCVM@fda.hhs.gov)
Guidance for Industry #120 (/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052660.pdf)
21 CFR 558.6 (VFD)
http://www.fda.gov/safefeed (http://www.fda.gov/safefeed)

More in Development & Approval Process (/AnimalVeterinary/DevelopmentApprovalProcess/default.htm)

Food Additive Petitions for Animal Food (/AnimalVeterinary/DevelopmentApprovalProcess/ucm056809.htm)

Public Master Files (PMFs) Supporting Applications for Major Use and Major Species Drugs (/AnimalVeterinary/DevelopmentApprovalProcess/ucm416607.htm)

Veterinary Feed Directive (VFD) (/AnimalVeterinary/DevelopmentApprovalProcess/ucm071807.htm)

Veterinary Master Files (/AnimalVeterinary/DevelopmentApprovalProcess/ucm071808.htm)

User Fees (/AnimalVeterinary/DevelopmentApprovalProcess/UserFees/default.htm)

Electronic Submissions (/AnimalVeterinary/DevelopmentApprovalProcess/ElectronicSubmissions/default.htm)
Minor Use/Minor Species (/AnimalVeterinary/DevelopmentApprovalProcess/MinorUseMinorSpecies/default.htm)
Environmental Impact Considerations (/AnimalVeterinary/DevelopmentApprovalProcess/EnvironmentalAssessments/default.htm)
Genetic Engineering (/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/default.htm)
New Animal Drug Applications (/AnimalVeterinary/DevelopmentApprovalProcess/NewAnimalDrugApplications/default.htm)
Aquaculture (/AnimalVeterinary/DevelopmentApprovalProcess/Aquaculture/default.htm)

§ 90-181. Definitions.

When used in this Article these words and phrases shall be defined as follows:

(1) "Accredited school of veterinary medicine" means any veterinary college or division of a university or college that offers the degree of doctor of veterinary medicine or its equivalent and that conforms to the standards required for accreditation by the American Veterinary Medical Association.

(2) "Animal" means any animal, mammal other than man and includes birds, fish, and reptiles, wild or domestic, living or dead.

(2a) "Animal dentistry" means the treatment, extraction, cleaning, adjustment, or "floating" (filing or smoothing) of an animal's teeth, and treatment of an animal's gums.

(3) "Board" means the North Carolina Veterinary Medical Board.

(3a) "Cruelty to animals" means to willfully overdrive, overload, wound, injure, torture, torment, deprive of necessary sustenance, cruelly beat, needlessly mutilate or kill any animal, or cause or procure any of these acts to be done to an animal; provided, that the words "torture," "torment," or "cruelty" include every act, omission, or neglect causing or permitting unjustifiable physical pain, suffering, or death.

(4) "Limited veterinary license" or "limited license" means a license issued by the Board under authority of this Article that specifically, by its terms, restricts the scope or areas of practice of veterinary medicine by the holder of the limited license; provided, that no limited license shall confer or denote an area of specialty of the holder of this limited veterinary license; and provided further, that unless otherwise provided by Board rule, the licensing requirements shall be identical to those specified for a veterinary license.

(5) "Person" means any individual, firm, partnership, association, joint venture, cooperative or corporation, or any other group or combination acting in concert; and whether or not acting as a principal, trustee, fiduciary, receiver, or as any kind of legal or personal representative, or as the successor in interest, assignee, agent, factor, servant, employee, director, officer, or any other representative of such person.

(6) "Practice of veterinary medicine" means:

a. To diagnose, treat, correct, change, relieve, or prevent animal disease, deformity, defect, injury, or other physical or mental conditions; including the prescription or administration of any drug, medicine, biologic, apparatus, application, anesthetic, or other therapeutic or diagnostic substance or technique on any animal.

b. To represent, directly or indirectly, publicly or privately, an ability and willingness to do any act described in sub-subdivision a. of this subdivision.

c. To use any title, words, abbreviation, or letters in a manner or under circumstances which induce the belief that the person using them is qualified to do any act described in sub-subdivision a. of this subdivision.

(7) "Veterinarian" shall mean a person who has received a doctor's degree in veterinary medicine from an accredited school of veterinary medicine and who is licensed by the Board to practice veterinary medicine.

(7a) "Veterinarian-client-patient relationship" means that:

a. The veterinarian has assumed the responsibility for making medical judgments regarding the health of the animal and the need for medical treatment, and the client (owner or other caretaker) has agreed to follow the instruction of the veterinarian.

b. There is sufficient knowledge of the animal by the veterinarian to initiate at least a general or preliminary diagnosis of the medical condition of the animal. This means that the veterinarian has recently seen and is personally acquainted with the keeping and care of the animal by virtue of an examination of the animal, or by medically appropriate and timely visits to the premises where the animal is kept.

c. The practicing veterinarian is readily available or provides for follow-up in case of adverse reactions or failure of the regimen of therapy.

(7b) "Veterinary license" or "license" means a license to practice veterinary medicine issued by the Board.

(8) "Veterinary medicine" includes veterinary surgery, obstetrics, dentistry, and all other branches or specialties of veterinary medicine.

(9) "Veterinary student intern" means a person who is enrolled in an accredited veterinary college, has satisfactorily completed the third year of veterinary college education, and is registered with the Board as a veterinary student intern.

(10) "Veterinary student preceptee" means a person who is pursuing a doctorate degree in an accredited school of veterinary medicine that has a preceptor or extern program, has completed the academic requirements of that program, and is registered with the Board as a veterinary student preceptee.

(11) "Veterinary technician" means either of the following persons:

a. A person who has successfully completed a post-high school course in the care and treatment of animals that conforms to the standards required for accreditation by the American Veterinary Medical Association and who is registered with the Board as a veterinary technician.

b. A person who holds a degree in veterinary medicine from a college of veterinary medicine recognized by the Board for licensure of veterinarians and who is registered with the Board as a veterinary technician. (1961, c. 353, s. 2; 1973, c. 1106, s. 1; 1993, c. 500 s. 1.)