

Chapter II

# FEDERAL REGULATIONS

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## REGULATORY BASIS

Except for minor involvement by several other Federal agencies, the safety, wholesomeness, and proper labeling of the food supply are the responsibility of the Food and Drug Administration (FDA) of the Department of Health, Education, and Welfare (HEW), and of the U.S. Department of Agriculture (USDA). USDA has concurrent jurisdiction with FDA over certain meat and poultry products through the Federal Meat Inspection Act<sup>1</sup> and the Poultry Products Inspection Act.<sup>2</sup> USDA is authorized to conduct its own inquiry into the safety of such products, but either through law or administrative deference, USDA's activities regarding safety involve enforcing decisions that have been made by FDA (USDA, 1978).

FDA's authority over substances added to animal feeds and over animal drugs comes primarily from two sections of the Federal Food, Drug, and Cosmetic Act (FFDCA):<sup>3</sup> (1) food additives, and (2) new animal drugs.

A substance is considered a food additive if:

... [Its] . . . intended use . . . results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food . . . if such substance is not generally recognized . . . to be safe under the conditions of intended use . . .<sup>4</sup>

To avoid regulation as a food additive, the petitioner must either provide evidence that the substance does not become a component or otherwise affect the characteristics of

food or, if it does, provide evidence that it is generally recognized as safe under the conditions of intended use.

The FFDCA expressly excludes "new animal drugs" from the definition of "food additive" and regulates them under a separate section of the law. New animal drugs are treated in the same way as new drugs for human use. An application must contain:

1. Full reports of investigations which have been made to show whether or not such drug is safe and effective for use;
2. A full list of the articles used as components of such drug;
3. A full statement of the composition of such drug;
4. A full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug;
5. Such samples of such drug and of the articles used as components thereof, of any animal feed for use in or on which such drug is intended, and of the *edible* portions or products (before or after slaughter) of animals to which such drug (directly or in or on animal feed) is intended *to be* administered, as the Secretary may require;
6. Specimens of the labeling proposed to be used for such drug, or in case such drug is intended for use in animal feed, proposed labeling appropriate for such use, and specimens of the labeling for the drug to be manufactured, packed, or distributed by the applicant;
7. A description of practicable methods for determining the quantity, if any, of such drug in or on food, and any substance formed in or on food, because of its use; and
8. The proposed tolerance or withdrawal period or other use restrictions for such drug if any tolerance or withdrawal period or other use restrictions are required in order to

<sup>1</sup>21 U.S.C. 601 et seq.

<sup>2</sup>21 U.S.C. 451 et seq.

<sup>3</sup>21 U.S.C. 301 et seq.

<sup>4</sup>21 U.S.C. 321(s).

assure that the proposed use of such drug *will be safe* (emphasis added),<sup>7</sup>

Some of the grounds for refusing the application include:

(A) [T]he investigations . . . do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof;

(B) [T]he results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; . . .

(D) [U]pon the basis of the information submitted . . . or upon the basis of any other information . . . with respect to such drug . . . there is insufficient information to determine whether such drug is safe for use under such conditions;

(E) [E]valuated on the basis of the information submitted . . . and any other information with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; . . .

(H) [S]uch drug induces cancer when ingested by man or animal or, after tests which are appropriate for the evaluation of the safety of such drug, induces cancer in man or animal, except that the foregoing provisions of this subparagraph shall not apply with respect to such drug if the Secretary finds that, under the conditions of use specified in proposed labeling and reasonably certain to be followed in practice (i) such drug will not adversely affect the animals for which it is intended, and (ii) no residue of such drug will be found (by methods of examination prescribed or approved by the Secretary by regulations . . .) in any edible portion of such animals after slaughter or in any food yielded by or derived from the living animals . . .<sup>8</sup>

The last reason for refusal enumerated above is one of the Delaney clauses in FFDCA that bans the use of carcinogenic substances that enter the food supply. The clause is similar to that applicable to food additives. In the latter, the exception to a total ban is for “the

use of a substance as an ingredient of feed for animals which are raised for food production.”

For animal feed ingredients and animal drugs, the law directs the Secretary to promulgate regulations defining when “no residue” will be found, (It should be noted that for noncarcinogens, residues are allowed, subject to safety considerations [see numbers 5, 7, and 8, *supra*, on information to be contained in new animal drug applications]). For food additives generally, the definition itself includes the finding that the substance becomes or may reasonably be expected to become a component of food. Thus once a substance is legally labeled a food additive and is found to be a carcinogen, it is automatically banned because, by definition, it is present in the food.

Finally, some of the grounds for withdrawing approval for animal drugs include: (1) experience or scientific data showing that such drug is unsafe for use under the conditions of use on which the application was approved; (2) new evidence, evaluated together with the evidence available when the application was approved, showing that the drug is not shown to be safe under the approved conditions of use; and (3) new evidence, evaluated together with the evidence available when the application was approved, showing that there is a lack of substantial evidence that the drug will have the effect claimed under the conditions of use.<sup>9</sup>

In order to avoid food additive status, a substance must be “generally recognized as safe” (GRAS) “under the conditions of intended use” if it enters the food. But a food additive is unsafe and prohibited from use unless a regulation is issued “prescribing the conditions under which such additive may be safely used.” Although the language is nearly identical, the practical difference is that food additive status gives FDA authority to prescribe the actual conditions of use.

For drugs, FFDCA requires that the applicant provide adequate data on both the safety and effectiveness of the drug under the in-

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<sup>7</sup>21 U.S.C. 360(b).

<sup>8</sup>21 U.S.C. 360(b)(d)(1).

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<sup>9</sup>21 U.S.C. 360( b)(e)(1).

tended conditions of use, but FDA may deny or withdraw the approval on either safety or effectiveness grounds. For example, FDA may deny the use of a drug for some purposes and approve it for others, even if it is safe to be used under all of the petitioned conditions. Here, effectiveness would be the ultimate determinant of approval. Or, conversely, FDA may deny use of a drug for some purposes and approve it for others even if it were effective for all the petitioned conditions. Here safety would be the ultimate determinant of approval.

Some have criticized FDA for failing to consider socioeconomic benefits and costs in determinations allowing or disapproving the use of food additives and drugs. These critics claim that present law allows the consideration of such costs and benefits. Whether or not the law should include these considerations is a separate question. But FFDCA is quite conspicuous in its absence of language supporting such claims.

The law is clear that safety and effectiveness will be determined by scientific assessments:

In determining whether such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof, the Secretary shall consider,

among other relevant factors, (A) the probable consumption of such drug and of any substance formed in or on food because of the use of such drug, (B) the cumulative effect on man or animal of such drug, taking into account any chemically or pharmacologically related substance, (C) safety factors which in the opinion of experts, qualified by scientific training and experience to evaluate the safety of such drugs, are appropriate for the use.

... [The] term substantial evidence means evidence consisting of adequate and well-controlled investigations, including field investigation, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and reasonably be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

Although the statute presents these as independent assessments and does not provide any guide for FDA to decide when effectiveness outweighs safety and vice versa, these decisions are in reality risk-benefit assessments limited to scientific considerations.

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<sup>21</sup> U. S. C. 360(b)(2-3).

## CURRENT ACTIVITIES

Antibacterial used in human treatment are often used in animals, and limitations on use have been proposed for animal antibacterials, particularly for their subtherapeutic uses in animal feed. Over 40 percent of all the antibacterial produced in this country are used as feed additives or for other nonhuman purposes. Research on antibacterial-resistant bacteria has shown that, in some cases, genes for antibacterial resistance can be transferred between bacterial types and that humans and animals are interchangeable hosts for such bacteria.

Another major concern has been the possibility of more direct, adverse human health effects from eating meat, eggs, etc., contain-

ing residues of drugs. The health effect primarily at issue here is carcinogenesis. Federal law prohibits the use of carcinogenic food additives and also requires that food products from animals given carcinogenic substances for any purpose (e. g., therapeutic, growth promotant, etc. ) cannot contain any residue of such carcinogens. Among the animal drugs in use, furazolidone and DES are known carcinogens,

The antibacterial problem began to be addressed in the 1960's in the United States and other countries. One consequence was Great Britain's decision in 1971 to restrict the use of antibacterial for food animals and, in particular, their feed-additive uses.

Similar reviews were initiated in the United States by the FDA (FDA, 1966, 1972, 1977). The general thrust of these reports was similar to the report leading to Great Britain's curtailment of antibacterial for food animal uses, although they differed in the emphasis placed on specific antibacterial. There were also differences on specific conclusions and recommendations between the Subcommittee on Antibiotics in Animal Feeds, its parent National Advisory Food and Drug Committee to the FDA, and the FDA itself. (See USDA, 1978, for a chronicle of these events.)

As a consequence of these reviews, in 1973 FDA began a series of actions to update the effectiveness and safety data of approved animal antibacterial and to extend the criteria to new antibacterial.<sup>9</sup> These efforts subsequently were focused on the penicillins and tetracycline which, in the words of the FDA Commissioner, "were chosen as the initial subjects of regulation because of their importance in the treatment of human disease" (Kennedy, 1977).

In 1977, FDA proposed to withdraw approval of the use of penicillin and to restrict the use of tetracycline in feed premixes. The reasons for the proposed ban on the use of penicillin were that: (1) the new evidence on the hazards of bacterial resistance had shown that such use of penicillin was not safe, and (2) the applicants had failed to meet the record maintenance requirements of the law.<sup>10</sup> Similar reasons were given for the proposed restrictions on tetracycline, where they would be prohibited except where adequate substitutes for disease prevention were not available.<sup>11</sup>

As a corollary action, the FDA had proposed to limit the distribution of animal feed premixes containing penicillin and/or tetracycline to feed mills holding approved medicated feed applications for manufacturing these medicated feeds and to restrict further the distribution of those feeds to the order of a licensed veterinarian as part of the record maintenance requirements of the law.<sup>12</sup> Pub-

lic hearings on the proposal raised concerns over such matters as the inadequacy of the numbers, distribution, and kinds of veterinarians available to diagnose and write prescriptions under the proposed requirements; the economic disadvantage of the proposal to small producers; circumvention of the proposed restrictions, since soluble powder dosage forms would not be subject to the proposal; and allegations that it would interfere with the practice of veterinary medicine and State control over the feed industry. The FDA Commissioner therefore decided to delay a decision until such issues were resolved.<sup>13</sup>

Meanwhile, the U.S. Congress has taken several actions to delay the final outcome of these proposals. In May 1978 the House Appropriations Subcommittee on Agriculture and Related Agencies earmarked \$250,000 for fiscal year 1979 for a study on antibacterials used in animal feed, to be conducted by the National Academy of Sciences. In July 1978 the House Agriculture Committee approved a resolution to delay the proposed ban until new research studies could be completed and formal evidentiary hearings held. And in September 1978 House and Senate conferees agreed to require the FDA to hold up the proposals until such research and evidentiary hearings were completed.

The congressional actions have led the Director of the FDA's Bureau of Veterinary Medicine to conclude that the outcome of these proposals would not be reached before 1980 and that "(p)ublic and industry reaction to these proposals have made it abundantly clear that livestock producers are desirous of having penicillin, tetracycline, and similar antibiotics remain in animal feeds. Unless substitutions of antibiotics currently on the market are more readily accepted and unless viable alternatives to potentially restricted antibiotics can be developed, most likely the public outcry will continue regarding the proposed regulations. These are practicalities that are incident to the national acceptance of the proposed regulations" (Food Chemical News, Sept. 25, 1978).

Two other classes of antibacterial raise separate safety issues, in addition to the

<sup>9</sup>21 CFR 558.15

<sup>10</sup>42 F. R., 43772, Aug. 30, 1977.

<sup>11</sup>42 F.R. 56264, Oct. 21, 1977.

<sup>12</sup>43 F.R. 3032, Jan. 20, 1978.

<sup>13</sup>43 F.R. 35059, Aug. 8, 1978.

safety problems reflected in these proposals to restrict the use of penicillin and tetracycline. The sulfa drugs (i. e., sulfamethazine for swine feed and drinking water) have been found to have a high violation rate for residues in slaughtered hogs. And one of the nitrofurans, furazolidone, is carcinogenic in laboratory animals.

Specific tolerances for residues of sulfa drugs in edible tissues of food-producing animals are set at 0 to 0.1 parts per million (ppm).<sup>14</sup> For sulfamethazine the tolerance level in swine is 0.1 ppm. These tolerances are accomplished by specified withdrawal time periods between last treatment and slaughter. For the last 6 months of 1977, USDA had found that the percentage of sampled hogs in violation of the 0.1-ppm residual tolerance averaged 13.1 percent. An FDA study concluded that 54 percent of the violations were probably caused by contamination of the withdrawal feed (which should not contain the drug) through insufficient cleanout of equipment, 26 percent were probably caused by failure to observe the withdrawal period, 12 percent were caused by feeding or feed-mixing errors, and 9 percent from other causes (FDA, 1979). New research data led FDA to change the preslaughter withdrawal time for sulfamethazine in swine feed and drinking water from 5, 7, or 10 days to 15 days.<sup>15</sup> FDA also expected to issue a proposal to establish action levels for cross-contamination carryover of animal drugs (including but not limited to sulfamethazine in swine feed) by the end of 1978 (*Food Chemical News*, Oct. 16, 1978).

Three nitrofurans were approved previously for feed premixes; furazolidone (the most widely used), nihydrazone, and nitrofurazone. Furaltadone, a nitrofuran, is used in injectable form to treat mastitis in lactating cows. Assay methods to meet the "no residue" requirement have not been approved for the nitrofurans. Furazolidone has produced cancer in laboratory animals. The other three compounds are suspected of being carcinogens but have not been adequately tested. All uses of nihydrazone were revoked because no

hearings were requested. Of the two sponsors of furaltadone, one approval was revoked because a hearing was also not requested.<sup>16</sup> Actions were pending against furazolidone and nitrofurazone as of January 1979.

The "no residue" exception to the ban on carcinogenic substances added to food is sometimes referred to as the "DES exception." DES has been known to be carcinogenic almost from the time it was first produced in 1938 (DES Task Force Report, 1978), its carcinogenic effect generally attributed to its estrogenic properties. The Food Additive Amendments of 1958<sup>17</sup> contained the first Delaney clause barring carcinogenic food additives. In order to allow the continued use of DES in food animals, a "no residue" exception was inserted in the Animal Drug Amendments of 1968.<sup>18</sup>

DES is added to feed or used in implants to fatten beef cattle. To a lesser extent, implants are used in lambs. Other drugs used to fatten cattle include: (1) melengesterol acetate (MGA) in feed for heifers, with the additional purpose of suppressing estrus; (2) monensin in feed, authorized only for increasing feed efficiency, although it also is authorized for disease prevention and growth promotion in poultry; (3) estradiol benzoate plus testosterone propionate for heifers by implants; (4) estradiol benzoate plus progesterone for steers by implants; and (5) zeranol implants for calves, cattle, and lambs. Estradiol monopalmitate injections are authorized for use in roasting chickens.<sup>19</sup> In addition to DES and the estradiols, zeranol has direct estrogenic activity, MGA (a synthetic progesterone) and progesterone result in increased estrogen production in treated heifers. Monensin is a compound produced by the bacterium *Streptomyces cinnamonensis* and is still used as an anticoccidial in poultry.

Starting in 1972, FDA first banned the use of DES in feeds and, later, in implants, on evidence of residues in beef livers detected

<sup>14</sup>21CFR 566.625-.700.

<sup>15</sup>43F.R. 19385, May 5, 1978.

<sup>16</sup>42 F.R. 17526, Apr. 1, 1977; 42 F.R. 18619, Apr. 8, 1977.

<sup>17</sup>Public Law 85-929.

<sup>18</sup>Public Law 90-399.

<sup>19</sup>21CFR 522, 21CFR 558.

by a new method. The withdrawal was vacated in 1974 by court order on the grounds that an insufficient notice of opportunity for hearing had been given to the affected parties because FDA had relied on a method of testing that it had not approved. Administrative hearings have been concluded and in September 1978 the administrative law judge recommended that DES be banned from feed and as an ear implant (*CNI Weekly Report*, Oct. 5, 1978). FDA's decision had not been made as of January 1979.

A closely related issue has been the method by which "no residue" would be determined. The increasing sensitivity of methods used to detect such residues has led FDA to seek methods "to keep the agency from always chasing zero in terms of an allowable tolerance of substances that will be administered to food-producing animals" (*Food Chemical News*, Oct. 16, 1978).

In early 1977, FDA issued new procedures and criteria for evaluating the assays for carcinogenic residues in edible products of animals.<sup>20</sup> Essentially, the intention of the new regulations was to cease trying to quantify the actual amount of carcinogenic residue because of the problem of chasing zero

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<sup>20</sup>42F.R. 10412, Feb. 11, 1977.

(newer methods were able to identify substances at less than one part per billion). Instead, the new regulations adopted a method whereby "no residue" would be defined through extrapolation from animal test data to man so that the lifetime risk to an individual would be less than 1 in 1 million ( $1/10^6$  or  $10^{-6}$ ). The published regulation stated that "such a risk level can properly be considered of insignificant public health concern." According to an FDA spokesman, the new method would "provide a mechanism whereby a reasonably safe level may be established and then, irrespective of further analytical developments, there will be that expectation that the originally set level will remain until toxicological evidence rather than analytical evidence demonstrates that to be an incorrect tolerance" (*Food Chemical News*, Oct. 16, 1978).

These regulations were revoked by FDA<sup>21</sup> after the U.S. District Court for the District of Columbia remanded the case to FDA "for further findings to rectify the omissions in the current record."<sup>22</sup> FDA expects to issue proposed new regulations in 1979.

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<sup>21</sup>43F.R. 22675, May 26, 1978,

<sup>22</sup>*Animal Health Institute v. Food and Drug Administration*, Civil No. 77-806, D. D. C., Feb. 8, 1978,

## APPROVED USES

Subtherapeutic uses of penicillin, tetracycline, sulfas, and nitrofurans vary according to the food animal. They may be used alone or in combination with each other or with other drugs. These other drugs may be antibacterial, anticoccidials, antihelminthics, or non-antibacterials, such as DES or other growth promotants. One drug may be approved for only some uses, but when combined with other drugs, the resulting feed mix may cover all uses.

**penicillin** is used extensively in poultry feeding programs and, to a lesser extent, in swine feeds, usually in combination with other drugs (sulfa, tetracycline, bacitracin, etc.). There are no approved uses for pen-

icillin in animal feed for cattle or sheep. Penicillin may be used alone for all possible indications—i.e., growth promotion, feed efficiency, disease prevention, and disease treatment. It also may be used in combination with other drugs.

Tables 1, 2, and 3 summarize the use of penicillin in animal feeds for chickens, turkeys, and swine. In chickens and turkeys, penicillin, when used alone, is approved for the separate uses of growth promotion, feed efficiency, disease prevention, or disease treatment. The amount of penicillin per ton of feed would vary for these uses. It may also be combined with other antibacterial so that the completed feed is approved for all uses,

Table 1. –Approved Uses for Penicillin in Chicken Feeds

<i>In combination with</i>	<i>Uses<sup>a b</sup></i>
	Growth promotion, feed efficiency
	Disease prevention
	Disease treatment
Streptomycin <sup>c</sup>	Growth promotion, feed efficiency
Streptomycin <sup>c</sup>	Maintain or Increase egg production
Streptomycin <sup>c</sup>	Disease prevention
Streptomycin <sup>c</sup>	Disease treatment
Amprolium <sup>d</sup>	Growth promotion, feed efficiency
Amprolium <sup>d</sup> and streptomycin <sup>c</sup>	Treatment of disease
Amprolium <sup>d</sup> and ethopabate <sup>e</sup>	Growth promotion, feed efficiency
Amprolium, d ethopabate, and streptomycin <sup>c</sup>	Treatment of disease.
Bacitracin methylene disalicylate <sup>c</sup>	Maintaining or Increasing hatchability of eggs
Bacitracin methylene disalicylate <sup>c</sup>	Treatment of disease
Bacitracin zinc <sup>c</sup>	Treatment of disease
Buquinolate <sup>e</sup>	Growth promotion, feed efficiency
Hygromycin B <sup>f</sup>	Treatment of disease
Hygromycin B <sup>f</sup> and streptomycin <sup>c</sup>	Treatment of disease
Hygromycin B <sup>f</sup> and bacitracin <sup>c</sup>	Treatment of disease

<sup>a</sup>For a specific food animal different concentrations of same drug may be approved for different purposes –e.g. for chickens one concentration is approved for growth promotion and feed efficiency another concentration for prevention of disease

<sup>b</sup>Specific diseases omitted

<sup>c</sup>Same indications for use as penicillin

<sup>d</sup>For development of active immunity to or prevention of coccidiosis

<sup>e</sup>For prevention of coccidiosis

<sup>f</sup>For control of worms

SOURCE: 21 CFR 558 and related sections

even though the separate antibacterial are not. In swine, when penicillin is combined with tetracycline and sulfa, the completed feed is approved for all uses.

Tetracycline, as oxytetracycline or chlor-tetracycline, is used in all food animals. Like penicillin, it maybe used alone or in combination with other drugs, and for all or only some of the approved uses. Tables 4, 5, 6, and 7 summarize the use of tetracycline in animal feed for chickens, turkeys, swine, cattle, and sheep. Tetracycline is the most widely used antibacterial in feed.

Sulfa drugs are used primarily in swine in combination with penicillin and tetracycline (tables 3 and 6) for disease treatment, disease prevention, growth promotion, and feed efficiency, or with tylosin for disease prevention. They also are used in combination with tetracycline for disease prevention in cattle (table 7). Sulfaethoxypyridazine premixes are used for disease treatment in swine and cattle for use by or on the order of a licensed veterinarian.<sup>23</sup> Sulfadimethoxine is used in chicken and

<sup>23</sup>21CFR 558.579.

Table 2.–Approved Uses for Penicillin in Turkey Feeds

<i>In combination with</i>	<i>Uses<sup>a b</sup></i>
	Growth promotion, feed efficiency
	Disease prevention,
	Disease treatment
Streptomycin	Growth promotion, feed efficiency
Amprolium <sup>d</sup>	Growth promotion, feed efficiency.
Amprolium <sup>d</sup> and streptomycin <sup>c</sup>	Disease treatment
Amprolium <sup>d</sup> and bacitracin <sup>c</sup>	Disease treatment
Bacitracin methylene disalicylate <sup>c</sup>	Disease treatment
Bacitracin zinc <sup>c</sup>	Disease treatment

<sup>a</sup>For a specific food animal different concentrations of the same drug may be approved for different purposes

<sup>b</sup>Specific diseases omitted

<sup>c</sup>Same indications for use as penicillin

<sup>d</sup>For development of active immunity to or prevention Of coccidiosis

SOURCE: 21 CFR 558 and related sections

Table 3.–Approved Uses for Penicillin in Swine Feeds

<i>In combination with</i>	<i>Uses<sup>a b</sup></i>
	Growth promotion, feed efficiency
	Growth promotion feed efficiency
	Disease prevention
	Disease treatment
Streptomycin <sup>c</sup>	
Streptomycin <sup>c</sup>	
Streptomycin <sup>c</sup>	
Chlortetracycline <sup>c</sup> and sulfamethazine <sup>c</sup>	Growth promotion, feed efficiency, disease prevention, disease treatment
Chlortetracycline <sup>c</sup> and sulfathiazole <sup>c</sup>	Growth promotion, feed efficiency, disease prevention, disease treatment.
Bacitracin methylene disalicylate <sup>c</sup>	Disease treatment
Bacitracin zinc <sup>c</sup>	Disease treatment

<sup>a</sup>For a specific food animal different concentrations of the same drug may be approved for different purposes

<sup>b</sup>Specific diseases omitted

<sup>c</sup>Same indications for use as penicillin

SOURCE: 21 CFR 558 and related sections

turkey feeds for disease prevention. In chicken feed, it may be combined with a growth promotion and feed efficiency drug.<sup>24</sup> There are no approved uses for sheep feed. These uses of sulfa are summarized in table 8.

**Nitrofurans** are used extensively in chickens and turkeys and to a lesser extent in swine. Of the two nitrofurans still approved for use in feeds, furazolidone is the most widely used. It and, to a lesser extent, nitrofurazone are used in poultry for all four purposes—i.e., growth promotion, feed efficiency, disease prevention, and disease treatment. Furazolidone is used in sows for prevention of bacterial scours in baby pigs and is added to feed 1 week before farrowing and 2

<sup>24</sup>21CFR 558.575.



weeks after farrowing. It is also used for disease-prevention and treatment purposes. It is concurrently approved for growth promotion when the swine are on the medication for the purposes outlined. These uses are summarized in table 9.

**DES** is used to promote growth and increase feed efficiency in cattle and, to a lesser extent, in sheep. In feeds, it is given alone or in combination with antibiotics. It is administered separately by ear implantation. These uses are summarized in table 10.

**Table 4.—Approved Uses for Tetracycline in Chicken Feeds**

<i>In combination with</i>	<i>Uses<sup>b c</sup></i>
----	Growth promotion, feed efficiency.
----	Disease prevention.
----	Disease treatment.
Monensin <sup>d</sup> (as coccidiostat).	Disease prevention, disease treatment.
Nequinolate <sup>d</sup> . . . . .	Disease prevention, disease treatment.
Robenidine hydrochloride . . . . .	Disease prevention,
Amprolium <sup>e</sup> . . . . .	Disease treatment.
Amprolium and ethopabate <sup>f</sup> . . . . .	Disease prevention, disease treatment,
Buquinolate <sup>g</sup> . . . . .	Disease prevention, disease treatment,
Clopidol <sup>h</sup> . . . . .	Disease prevention.
Decoquinolate <sup>h</sup> . . . . .	Disease prevention, disease treatment.
Hygromycin B <sup>i</sup> . . . . .	Disease treatment.
Roxarsone <sup>j</sup> . . . . .	Growth promotion, feed efficiency.
Zoalene <sup>k</sup> . . . . .	Disease prevention, disease treatment.

<sup>a</sup>Chlortetracycline or oxytetracycline  
<sup>b</sup>For a specific food animal, different concentrations of the same drug may be approved for different purposes  
<sup>c</sup>Specific diseases omitted  
<sup>d</sup>Same indications for use as penicillin  
<sup>e</sup>For development of active immunity to or prevention of coccidiosis  
<sup>f</sup>For prevention of coccidiosis  
<sup>g</sup>For prevention of coccidiosis, growth promotion, and feed efficiency  
<sup>h</sup>For prevention and treatment of disease  
<sup>i</sup>For control of worms  
<sup>j</sup>For growth promotion, feed efficiency  
<sup>k</sup>For development of active immunity to coccidiosis  
SOURCE 21 CFR 558 and related sections

**Table 5.—Approved Uses for Tetracycline in Turkey Feeds**

<i>In combination with</i>	<i>Uses<sup>b c</sup></i>
----	Growth promotion, feed efficiency.
----	Disease prevention,
----	Disease treatment.
Roxarsone <sup>d</sup> . . . . .	Growth promotion, feed efficiency, disease prevention,

<sup>a</sup>Chlortetracycline or oxytetracycline  
<sup>b</sup>Different concentrations of the same drug may be approved for different purposes  
<sup>c</sup>Specific diseases omitted  
<sup>d</sup>For growth promotion, feed efficiency  
SOURCE 21 CFR 558 and related sections

**Table 6.—Approved Uses for Tetracycline in Swine Feeds**

<i>in combination with</i>	<i>Uses<sup>b c</sup></i>
--	Growth promotion, feed efficiency,
----	Disease prevention.
----	Disease treatment.
Penicillin and sulfamethazine <sup>d</sup> . . . . .	Growth promotion, feed efficiency, disease prevention, disease treatment.
Penicillin and sulfathiazole <sup>d</sup> . . . . .	Growth promotion, feed efficiency, disease prevention, disease treatment.
Hygromycin B <sup>e</sup> . . . . .	Disease treatment.

<sup>a</sup>Chlortetracycline or oxytetracycline  
<sup>b</sup>Different concentrations of the same drug may be approved for different purposes  
<sup>c</sup>Specific diseases omitted  
<sup>d</sup>Same uses as for tetracycline  
<sup>e</sup>For control of worms  
SOURCE 21 CFR 558 and related sections

**Table 7.—Approved Uses for Tetracycline in Cattle and Sheep Feeds**

<i>Animal</i>	<i>In combination with</i>	<i>Uses<sup>b c</sup></i>
Cattle . . . . .	----	Growth promotion, feed efficiency, disease prevention.
	Sulfamethazine <sup>d</sup> . . . . .	Disease prevention.
	Diethylstilbestrol <sup>e</sup> . . . . .	Disease prevention.
Sheep . . . . .	----	Disease prevention, feed efficiency.

<sup>a</sup>Chlortetracycline or oxytetracycline  
<sup>b</sup>Different concentrations of the same drug may be approved for different purposes  
<sup>c</sup>Specific diseases omitted  
<sup>d</sup>Same uses as for tetracycline  
<sup>e</sup>For growth promotion, feed efficiency  
SOURCE 21 CFR 558 and related sections

**Table 8.—Approved Uses for Sulfas<sup>a</sup> in Animal Feeds**

<i>An/ma/</i>	<i>In combination with</i>	<i>Uses<sup>b c</sup></i>
Chickens	Ormetoprim <sup>d</sup>	Disease prevention
	Ormetoprim <sup>d</sup> and 3-nitro-4-hydroxy-phenylarsonic acid <sup>e</sup>	Disease prevention
Turkeys	Ormetoprim <sup>d</sup>	Disease prevention
	Ormetoprim <sup>d</sup> and ipronidazole <sup>f</sup>	Disease prevention
Swine		Disease prevention
		Disease treatment (only for use by or on order of a licensed veterinarian)
	Penicillin <sup>d</sup> and tetracycline	Growth promotion, feed efficiency, disease prevention, disease treatment
	Tylosin <sup>d</sup>	Disease prevention
		Disease treatment (only for use by or on order of a licensed veterinarian)
	Tetracycline <sup>d</sup>	Disease prevention

<sup>a</sup>Identity of specific sulfonamide derivatives omitted

<sup>b</sup>Different concentrations of the same drug may be approved for different purposes

<sup>c</sup>Specific diseases omitted

<sup>d</sup>Same uses as for sulfa

<sup>e</sup>For growth promotion feed efficiency

<sup>f</sup>Prevention of blackhead (histomoniasis)

SOURCE 21CFR 558 and related sections

**Table 9.—Approved Uses for Nitrofurans<sup>a</sup> in Animal Feeds**

<i>Animal</i>	<i>In combination with</i>	<i>Uses<sup>b c</sup></i>
Chickens and turkeys	----	Growth promotion, feed efficiency Disease prevention Growth promotion, feed efficiency, disease prevention Disease prevention, disease treatment
Swine	----	Disease prevention, growth promotion Disease treatment, growth promotion.

<sup>a</sup>Furazolidone or nitrofurazone

<sup>b</sup>Different concentrations of the same drug may be approved for different purposes

<sup>c</sup>Specific diseases omitted

SOURCE 21CFR 55815 and 558262

**Table 10.—Approved Uses for Diethylstilbestrol in Food Animals**

<i>An/real</i>	<i>Route of administration</i>	<i>In combination with</i>	<i>Uses</i>
Cattle.	Feed	----	Growth promotion, feed efficiency.
	F e e d	Bacitracin methylene disalicylate <sup>a</sup>	Growth promotion, feed efficiency
	F e e d	Bacitracin zinc <sup>b</sup>	Growth promotion, feed efficiency
	F e e d	Tetracycline <sup>c</sup>	Growth promotion, feed efficiency
	Ear Implant.	----	Growth promotion, feed efficiency
Sheep	Feed	----	Growth promotion, feed efficiency
	Ear implant (lambs)	----	Growth promotion, feed efficiency.

<sup>a</sup>For disease prevention

<sup>b</sup>For growth promotion feed efficiency

<sup>c</sup>As chlortetracycline or oxytetracycline for disease prevention

SOURCE 21 CFR 522640 and 558225