2. A new § 989.210 is added, reading as follows:

§ 989.210 Handling of natural Thompson Seedless raisins acquired pursuant to a weight dockage system.

(a) *General.* Subject to prior agreement between handler and tenderer, a handler may acquire as standard raisins any lot of natural Thompson Seedless raisins containing more than 8 percent, by weight, of substandard raisins under a weight dockage system. The creditable weight of such lot acquired shall be that obtained by multiplying the net weight of the raisins in the lot by the applicable dockage factor from the dockage table prescribed in paragraph (g) of this section.

(b) *Free and reserve tonnage percentages.* Whenever free and reserve percentages are designated for natural Thompson Seedless raisins for a crop year, such percentages shall be applicable to the creditable weight of any lot of such raisins acquired by a handler pursuant to a weight dockage system.

(c) *Reserve tonnage.* A handler may hold as reserve tonnage raisins any lot, or portion thereof, of natural Thompson Seedless raisins acquired pursuant to a weight dockage system: *Provided,* That, only the creditable weight of such lot, or portion thereof, may be applied by the committee against the handler's reserve tonnage obligation.

(d) *Assessments.* Assessments on any lot of natural Thompson Seedless raisins acquired by a handler pursuant to a weight dockage system shall be applicable to the free tonnage portion of the creditable weight of such lot.

(e) *Payments for services on reserve tonnage.* Payment to a handler for services performed by him with respect to reserve tonnage natural Thompson Seedless raisins acquired pursuant to a weight dockage system shall be made on the basis of the creditable weight of such lot and at the applicable rate specified for such services in § 989.401 of Subpart—Schedule of Payments.

(f) *Identification.* Any lot of natural Thompson Seedless raisins acquired by a handler pursuant to a weight dockage system shall be so identified by the inspection service by affixing to one container on each pallet, or to each bin, in such lot, a prenumbered RAC control card (to be furnished by the Committee) which shall remain affixed to the container or bin until the raisins are processed or disposed of as natural condition raisins. The control card shall only be removed by, or under the supervision of, an inspector of the inspection service or authorized Committee personnel.

(g) ***Dockage table.***

% Substandard	Dockage Factor	% Substandard	Dockage Factor
8.0 or less	No dockage	15.1–15.5	.925
8.1–8.5	.995	15.6–16.0	.920
8.6–9.0	.990	16.1–16.5	.915
9.1–9.5	.985	16.6–17.0	.910
9.6–10.0	.980	17.1–17.5	.905
10.1–10.5	.975	17.6–18.0	.900
10.6–11.0	.970	18.1–18.5	.895
11.1–11.5	.965	18.6–19.0	.890
11.6–12.0	.960	19.1–19.5	.885
12.1–12.5	.955	19.6–20.0	.880
12.6–13.0	.950	20.1–20.5	.875
13.1–13.5	.945	20.6–21.0	.870
13.6–14.0	.940	21.1–21.5	.865
14.1–14.5	.935	21.6–22.0	.860
14.6–15.0	.930		

NOTE: Percentages in excess of 22 percent shall be expressed in the same increments as the foregoing, and the dockage factor for each such increment shall be .005 less than the dockage factor for the preceding increment.

Dated July 13, 1973.

CHARLES R. BRADER,
Acting Deputy Director,
Fruit and Vegetable Division.

[FR Doc.73-14701 Filed 7-18-73;8:45 am]

DEPARTMENT OF LABOR

Occupational Safety and Health Administration

[29 CFR Part 1910]

OCCUPATIONAL SAFETY AND HEALTH STANDARDS

Inspection Intervals for Fire Extinguishers with Aluminum Shells

Pursuant to section 6(b) of the Williams-Steiger Occupational Safety and Health Act of 1970 (84 Stat. 1593; 29 U.S.C. 655), Secretary of Labor's Order No. 12–71 (36 FR 8754) and 29 CFR Part 1911, it is hereby proposed to amend Table L–3 in 29 CFR 1910.157 d) (4) (iii) as set forth below.

Table L–3 in paragraph (d) (4) (iii) presently requires, among other things, that dry chemical extinguishers with aluminum shells, stainless steel shells or soldered-brass shells be hydrostatically tested at five year intervals. This table is derived from NFPA No. 10–1970, Standard for the Installation of Portable Fire Extinguishers. On May 18, 1973, the National Fire Protection Association revised its standard to place dry chemical fire extinguishers with aluminum shells in the same class with dry chemical extinguishers with brazed-brass shells and mild-steel shells, with the effect that the test interval for aluminum shells changes from five years to 12 years. (See 1973 NFPA Technical Committee Reports, Vol. B, P. 1273). In order to conform Table L–3 of § 1910.157(d) (4) (iii) to the revised NFPA Standard, it is proposed to revise Table L–3 so as to place dry chemical fire extinguishers with aluminum shells with fire extinguishers with brazed-brass shells and mild-steel shells and thus change the test interval for the former extinguishers from five years to 12 years.

All interested persons may submit written data, views and arguments concerning the proposal to the Office of Standards, Room 305, 400 First Street, NW., Washington, D.C. 20210 by August 18, 1973. The data, views, and arguments will be available for public inspection and copying at the Office of Standards located at the above address.

Pursuant to 29 CFR 1911.11 (b) and (c), interested persons may, in addition to filing written matter as provided above, file objections to the proposal, requesting an informal hearing with respect thereto, in accordance with the following conditions:

(1) The objections must include the name and address of the objector;

(2) The objections must be postmarked on or before August 18, 1973.

(3) The objections must specify with particularity the provision of the proposed rule to which objection is taken, and must state the grounds therefor;

(4) Each objection must be separately stated and numbered; and,

(5) The objections must be accompanied by a summary of the evidence proposed to be adduced at the requested hearing.

In § 1910.157(d) (4) (iii), Table L–3 is proposed to be revised to read as follows:

§ 1910.157 Portable fire extinguishers.

* * * * *

(d) *Inspection, maintenance, and hydrostatic tests* * * *

(4) *Hydrostatic tests.* * * *

(iii) At intervals not exceeding those specified in Table L–3 and subdivision (iv) of this subparagraph, extinguishers shall be hydrostatically tested. The first hydrostatic retest may be conducted between the fifth and sixth years for those with a designated test interval of 5 years.

TABLE L–3

HYDROSTATIC TEST INTERVAL FOR EXTINGUISHERS

Extinguisher type	*Test interval year*
Soda-acid	5
Cartridge-operated water and/or anti-freeze	5
Storage-pressure water and/or anti-freeze	5
Wetting agent	5
Foam	5
Loaded stream	5
Dry chemical extinguishers with stainless steel shells or soldered-brass shells	5
Carbon dioxide extinguishers	5
Dry chemical extinguishers with brazed-brass shells, mild-steel shells or aluminum shells	12
Bromotrifluoromethane	12
Dry powder extinguishers for metal fires	12

NOTE: Cylinders under jurisdiction of the U.S. Department of Transportation (formerly Interstate Commerce Commission) may require hydrostatic testing at more frequent periods.

* * * * *

(Sec. 6, Pub. L. 91–596, 84 Stat. 1593 (29 U.S.C. 655, Secretary of Labor's Order No. 12–71, 36 FR 8754)

Signed at Washington, D.C. this 12th day of July 1973.

JOHN STENDER,
Assistant Secretary of Labor.

[FR Doc.73-14823 Filed 7-18-73;8:45 am]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 27]

QUALITY STANDARD FOR CANNED CHERRIES

Proposed Revision of Blemish Limitation

Notice is given that a petition has been filed by the National Canners Association, 1133 20th St., NW., Washington, DC 20036, proposing that the standard of quality for canned cherries (21 CFR 27.31) be amended by:

(1) Changing the definition of a blemished cherry; and

(2) Increasing the aggregate area of the blemish from $\frac{3}{16}$ inch to $\frac{5}{32}$ inch in diameter.

Grounds set forth in the petition in support of the proposal are that: (1) The proposed change in the definition of a blemished unit would be consistent with objections received to an order, published in the FEDERAL REGISTER on February 23, 1971 (36 FR 3364), ruling on a proposed cherry pie standard of quality (21 CFR 28.2). These objections requested that the $\frac{3}{16}$ inch diameter limit for blemished units be changed to a $\frac{5}{32}$ inch diameter limit. The Commissioner of Food and Drugs granted this request in the FEDERAL REGISTER of June 13, 1973 (38 FR 15503).

(2) Mechanical harvesting and bulk handling in tanks of water have replaced the traditional hand picking and handling. As a result there has been a greatly increased problem with a mild form of discoloration known as "tank or water scald" which results in minor color variation but does not affect the tissues or eating quality or the cherries.

(3) Since the present standard was established 32 years ago, changes in cultural practices have resulted in the production of larger and softer cherries. Presently, there are as few as 100 to 110 cherries per pound as compared to 140 to 150 per pound when the standard was adopted. The larger, softer cherries have aggravated the blemish problem because they are more susceptible to blemishes and contain a greater surface area compared to the permitted area of skin discoloration.

(4) Increasing the area of the blemish to 9/32 inch would bring the quality standard for canned cherries (21 CFR 27.31) into agreement with the present voluntary U.S. Department of Agriculture standard for grades of frozen cherries.

(5) The proposed change will insure consumers a continued supply of canned cherries without significantly affecting the quality.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 401, 701, 52 Stat. 1046, 1055 as amended by 70 Stat. 919 and 72 Stat. 948; 21 U.S.C. 341, 371) and under authority delegated to the Commissioner of Food and Drugs, it is proposed that Part 27 be amended in § 27.31 by revising paragraph (a)(5) to read as follows:

§ 27.31 Canned cherries; quality; label statement of substandard quality.

(a) * * *

(5) Not more than 15 percent by count of the cherries in the container are blemished with scab, hail injury, discoloration, scar tissue or other abnormality. A cherry showing skin discoloration (other than scald) having an aggregate area exceeding that of a circle 9/32 inch in diameter is considered to be blemished. A cherry showing discoloration of any area but extending into the fruit tissue is also considered to be blemished.

* * * * *

Interested persons may, on or before September 17, 1973 file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6-88, 5600 Fishers Lane, Rockville, MD 20852, written comments (preferably in quintuplicate) regarding this proposal. Comments may be accompanied by a memorandum or brief in support thereof. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: June 20, 1973.

VIRGIL O. WODICKA,
Director, Bureau of Foods.

[FR Doc.73-14749 Filed 7-18-73;8:45 am]

[21 CFR Part 135]

COMPOUNDS USED IN FOOD-PRODUCING ANIMALS

Procedures for Determining Acceptability of Assay Methods Used for Assuring the Absence of Residues in Edible Products of Such Animals

The Federal Food, Drug, and Cosmetic Act requires that compounds administered to animals as food additives, color additives, or animal drugs be shown to be safe for use. The term "safe" refers to the health of man or animal under section 201(u) of the act. In evaluating the safety of such compounds used in food-producing animals, consideration must be given to the safety of possible residues in the products of those animals which are a source of food for man. When there is insufficient evidence to establish that a finite or negligible residue of the compound is safe in human food, or when the anticancer clauses contained in sections 409(c)(3)(A), 512(d)(1)(H), and 706(b)(5)(B) of the act are applicable, a zero tolerance (no residue) must be required. (Under the provisions of the anticancer clauses no compound may be administered to animals which are raised for food production if such compound has been shown to induce cancer when ingested by man or animal, unless such compound will not adversely affect the animal and no residues, as determined by methods of analysis prescribed or approved by the Secretary, are found in the edible products of such animals under conditions of use specified in labeling and reasonably certain to be followed in practice. A decision is then required as to whether a practicable method exists to determine the absence of such residues in food, under sections 409(b)(2)(D), 512(b)(7), and 706(b)(5)(A)(iv) of the act.

The Commissioner of Food and Drugs has determined that it would be in the public interest to set forth the principles involved in application of these safety provisions of the law with respect to the adequacy of the sensitivity of the required regulatory assay method for monitoring compounds which may be administered to food-producing animals, but for which no residue is permitted in human food. Therefore, a new regulation is proposed to establish the minimum standards for determining the acceptability of assay methods used to assure the absence of residues in edible products of such animals. These proposed regulations do not apply to drugs for which a finite or negligible residue is established as safe for human food.

The proposed new regulation will apply to two classes of compounds administered to food-producing animals: (1) Exogenous compounds, defined as those compounds which are not produced by the normal animal and are not required for normal animal body function (e.g., diethylstilbestrol), and (2) Endogenous compounds, defined as those compounds which are present in and produced by the normal animal and are not required from an exogenous source (e.g., estradiol).

In evaluation of the safety of compounds of both classes the initial testing must involve detailed metabolism studies in the target species. Radiotracer studies are usually the method of choice. The purpose of these studies will be to identify the metabolites of the compound, both qualitatively and quantitatively, and the concentrations of the compound and its metabolites in specific tissues ("tissues" include milk and eggs, if applicable). Another aspect of these studies will be the determination of the effect of the administration of the compound on tissue levels of related endogenous compounds.

For acceptable studies, it is necessary to follow the degradation of the compound and/or its metabolites after slaughter and during the period that the edible tissue would normally be held under storage conditions as well as to determine the impact of cooking at appropriate temperatures on the compounds in question.

EXOGENOUS COMPOUNDS

Determination as to whether an exogenous compound and/or its metabolites will require carcinogenicity testing will be based on the results of the metabolism studies, standard toxicity testing, structural relationships of the compound and/or its metabolites to known carcinogens, modes of physiological actions and interactions, and the intended use pattern of the compound. Tests for carcinogenicity will be routinely required for any new compound for which a priori knowledge is incomplete and which is intended to be used for disease prophylaxis and/or production purposes (e.g., increased rate of weight gain, estrus synchronization, etc.).

If it is determined that tests for carcinogenicity are not required, or if the results of such tests are negative, consideration leading to approval will be based on standard toxicological procedures. These procedures will include, in addition to subacute studies in a minimum of two species, such studies as multi-generation reproduction studies, teratological and any other special studies which may be indicated from the nature of the biological action of the compound, including life-time studies. These studies will involve collecting data from appropriately designed dose-response experiments that demonstrate a maximum "no harmful effect level" as well as a minimum "harmful effect level" in appropriate animal species.

Where a residue is permitted as safe in human food (either as a finite tolerance level or as a negligible residue of less than a specified level), the sensitivity of the assay method will be required to meet the specified level, and the other provisions of this proposed new regulation relating to the required sensitivity of the method will be inapplicable. Where no residue (zero tolerance) is permitted, the provisions of this proposed new regulation are fully applicable.

Under the proposed new regulation the dose-response slope estimated from the toxicological experiments will be used to extrapolate to the required level of sensitivity of the method using appropriate confidence interval techniques in accordance with the concepts underlying the Mantel-Bryan procedure discussed below. Where such extrapolation is not scientifically appropriate, e.g., if no dose-response slope can be estimated from the data, other conservative methods will be invoked to determine an appropriate safety margin based on a thorough evaluation of the quality of the experiments, their rigor as predictive tests and the nature and significance of the observed biological effects.

Where tests for carcinogenicity are required for a compound there are two basic objectives of the tests. The first is to determine whether or not the compound and/or its metabolites is a carcinogen. The second is to determine the relative potency of the compound and/or its metabolites with respect to both its carcinogenic and its noncarcinogenic but toxic effects, through appropriate oral dose-response experiments. Test systems will be selected which maximize sensitivity to detect a minimal dose which induces a carcinogenic effect. These systems will include a sufficiently stable control population to avoid false-positive indications of carcinogenesis.

There is a general lack of agreement within the scientific community regarding appropriate protocols for determining the dose-response relationship of carcinogenic compounds. Until they are revised, the guidelines for protocols set out by the Food and Drug Administration Advisory Committee on Protocols for Safety Evaluation: Panel on Carcinogenesis Report on Cancer Testing in the Safety Evaluation of Food Additives and Pesticides (Toxicology and Applied Pharmacology Vol. 20, pp 419–438, 1971) will be followed by the Food and Drug Administration.

If the results of the test for carcinogenicity establish that the compound or its metabolites will induce cancer in test animals, the required sensitivity of the regulatory assay method will be determined based on the Mantel-Bryan procedure described in the article entitled "Safety" Testing of Carcinogenic Agents (Journal of the National Cancer Institute, Vol. 27, pp 455–470, 1961). However, rather than assuming a dose-response relationship with a slope of one, as suggested in the reference, experimental data obtained from the carcinogenicity studies will be used to obtain a statistical estimate of the slope of the dose-response relationship. The lower 90 percent confidence limit of the estimated slope will be used for extrapolation to the required level of sensitivity of the regulatory assay method. If the data indicate that some linearizing transformation other than the probit-log transformation used in the modified Mantel-Bryan procedure better describes the observed response and has a biological rationale, then this other linearizing transformation may be used for such extrapolation. Examples of the application of this technique are given in the above reference.

Absolute safety can never be conclusively demonstrated experimentally. The level defined by the Mantel-Bryan procedure is an arbitrary but conservative level of maximum exposure resulting in a minimal probability of risk to an individual (e.g., 1/100,000,000), under those exposure conditions of the basic animal studies. Such test conditions generally involve continuous daily lifetime exposure to the compound in question. In contrast, many types of foods are consumed only intermittently, e.g., turkey or broiler kidneys, and therefore any drug residues contained in such foods will be consumed only intermittently. If the same procedure was used to determine the level of exposure for turkey kidneys as was used to determine the level of exposure for foods consumed more frequently, such as beef muscle, the population would not be equally protected in both situations. Consequently, it will be necessary to adjust the procedure for establishing the exposure level to account for usual as well as specific human consumption patterns. Any such adjustments initially will be made on a conservative basis. These adjustments will take into consideration the consumption expected by those who consume the greatest amounts of food, not the average consumption of the food. More definitive information is being complied on food consumption patterns by the Food and Drug Administration, and this information will be used to arrive at more refined adjustments as it becomes available.

It will also be necessary to modify the procedure for establishing the exposure level to account for drug usage, patterns, e.g., the administration of a drug in the treatment of diseased animals. As with consumption patterns, justified modifications will be made on a conservative basis. If a disease has a maximum incidence of 10 percent, then no more than 10 percent of the marketed animals would have been treated with the drug. Under these conditions, the probability of continuous daily exposure for an individual consumer could be very conservatively estimated as 0.10. In this situation, the true probability of risk for the individual consumer would then equal the probability of individual risk under conditions of continuous daily exposure to the drug multiplied by the probability of an individual actually experiencing continuous daily exposure to the drug. If a true exposure of 1/100,000,000 were deemed acceptable for an individual on the basis of risk-benefit considerations, this value could be held constant by assuming a continuous exposure risk of 1/10,000,000 (1/100,000,000=1/10,000,000 X 0.10) in the estimate of the Mantel-Bryan level. The true individual consumer risk would remain at 1/100,000,000 since the consumer is only intermittently exposed to residues of the compound in food.

The maximum level of exposure as estimated above, after standard adjustment for the differences between daily food intake per unit of body weight of the laboratory animal as compared with man, will be the required sensitivity of the assay method for a compound. In the event that both non-carcinogenic harmful effects and carcinogenic effects are observed during testing, the lowest level for the regulatory assay sensitivity as determined for the different effects will be adopted.

Withdrawal or post-medication periods for exogenous compounds shall be based on data obtained from tissue depletion studies. The compound must be administered to test animals for a sufficient time for concentration equilibrium to be achieved. On the basis of the developed assay and/or other suitable methods, a determination must be made as to the time when tissue levels of the parent compound and/or its metabolites and/or any affected endogenous compounds are below the required level of sensitivity for the regulatory assay method.

The withdrawal period shall be the longer of: (1) The number of days for tissue levels to be depleted to less than the maximum level of exposure extrapolated by the modified Mantel-Bryan procedure plus a safety factor to account for animal to animal variation (as determined by appropriate confidence interval techniques) or (2) the number of days for any affected endogenous compound to return to normal levels plus a safety factor to account for animal to animal variation. (The normal level of the affected endogenous compound will be established as described below for endogenous compounds.) For example, if excretion data indicate that the average depletion time for an exogenous compound is 72 hours with a safety factor of 27 hours, the withdrawal period becomes (72 hours+27 hours)÷24 hours or, after

rounding upward, 5 days. Current livestock management techniques must be considered in establishing the withdrawal period and may necessitate the lengthening of this period.

The provisions of the proposed new regulation govern the required level of sensitivity of the regulatory assay method for those compounds for which a zero tolerance (no residue) is established. If a regulatory assay method of lower sensitivity is later developed and validated, however, the Commissioner will adopt that more sensitive method and publish it in the FEDERAL REGISTER, even though its development was not required under the law.

ENDOGENOUS COMPOUNDS

It is proposed that animals shown to contain tissue levels of endogenous compounds above the normal due to the administration of such compounds will not be permitted to be marketed for human consumption. Thus, neither tests for carcinogenicity nor standard toxicity testing will be required for endogenous compounds.

Naturally occurring (background) tissue levels of endogenous compounds and/or their metabolites and/or other related endogenous compounds in the target species must be determined in studies designed to show the effect of geographical location, stage of estrus, age, etc., on normal animals receiving no external source of the endogenous compound. The tissue distribution of the levels of the compound and/or its metabolites and/or other related endogenous compounds will be estimated from these studies. This distribution will be used to establish the required sensitivity of the regulatory assay method. The required sensitivity will be that level of the tissue distribution which is exceeded by only one percent of the normal animals. Tissue samples from animals at slaughter will be considered suspect if a level is found above normal background. For example, if 99.0 percent of background tissue levels for a parent endogenous compound and/or its metabolites and/or other related endogenous compounds are below 16 ppt., then a tissue level greater than 16 ppt shall be considered suspect. The final determination with respect to regulatory action will be based on a field investigation to determine if the observed value was due to a misuse of the compound or if it was due to normal biological variability.

Withdrawal periods following the last dosage for endogenous compounds shall be established based on the time required for the level of the parent compound and/or its metabolites and/or other related endogenous compounds in the tissue to return to the median background level of contemporary controls. The maximum approvable level of the compound shall be administered to target animals for a period of time sufficient to establish equilibrium in tissues. The number of days required for tissue levels of any affected endogenous compounds to return to the median background level plus a safety factor to account for animal to animal variation (as determined by appropriate confidence interval techniques) shall be used to establish the required withdrawal period. Current livestock management techniques must be considered in establishing the withdrawal period and may necessitate the lengthening of this period.

ASSAY EVALUATION CRITERIA

Prior to approval, the accuracy and reliability of the regulatory assay must be determined by validation of the method in appropriate Food and Drug Administration laboratories and other laboratories. The objectives of the validation will be to determine the feasibility, specificity, accuracy, and precision of the method (including a determination of the amounts recovered as well as an estimation of the variation associated with the recovered amounts).

Prior to submission of a method for evaluation and subsequent validation, it is recommended that the method be reviewed and tested, both qualitatively and quantitatively, by independent laboratories. This evaluation should fulfill the objectives of the validation as listed above.

The required sensitivity of the regulatory assay method as previously defined will be the regulatory action level and will be published in the FEDERAL REGISTER. Since any "positive" finding reported at a level lower than the published level of sensitivity may actually be a false positive, regulatory action will be taken only at or above the published level. This is necessary in order to assure that a residue is in fact a true positive. In the past the lack of such a procedure has led to finding violative samples in one laboratory which could not be confirmed in a second laboratory.

The assay method will be published or referenced in the FEDERAL REGISTER and will include a definition of the response criteria unique for each method which represents a reliable positive finding based on the validation studies. The criteria will take into account adjustments based on the accuracy and precision of the method. If the method is not specific for the identification of the compound or there are reasons to suspect the occurrence of false positives due to interference, a practical confirmatory test must be provided which will identify the residue at the level of sensitivity required.

In summary, the development and validation of a regulatory assay method for monitoring purposes must consider the following criteria:

1. The method must be capable of reproducibly extracting, at the required level of sensitivity, the significant compounds from target tissues obtained from treated animals as well as from tissues containing known added amounts of the compounds.

2. The method must be capable of measuring residues with a sufficient degree of specificity, precision, and accuracy to preclude the occurrence of false negatives or false positives.

3. The equipment, reagents and compounds used in the assay must be commercially available. Any required specialization in terms of equipment or personnel must be consistent with that normally available in a modern well-equipped analytical control laboratory.

4. The time required for completion of the assay must not be so excessive as to delay regulatory action, when necessary.

5. The assay must offer minimal hazard in the laboratory.

It is proposed that the requirements contained in this regulation will be applicable to all NADA's and supplemental NADA's approved by the Food and Drug Administration after the effective date of the new regulation. In determining the applicability of the provisions of the regulation to already-existing new animal drug approvals, the Commissioner will first determine those drugs for which a zero residue requirement now exists but for which a finite or negligible residue should instead be permitted. The Commissioner recognizes that many of these zero tolerances were established several years ago, at a time when detection methodology was substantially less sensitive and the available toxicology information was not as extensive. For some of these zero tolerances, it may now be possible and consistent with protection of the public health, to establish a finite or negligible residue. Where a finite or negligible residue is established on the basis of adequate safety data, the provisions of the new regulation will not be applicable.

Where a zero tolerance is deemed necessary, either because of a determination of carcinogenicity or because the compound is a suspect carcinogen or is otherwise sufficiently toxic that a determination of a safe level of residue in human food cannot be made at this time, the provisions of the new regulation will be applicable. The Commissioner recognizes that these new requirements cannot be imposed immediately. Accordingly, a determination will be made with respect to each drug as to a reasonable amount of time within which compliance will be permitted. In those instances in which the Commissioner concludes that a health hazard may exist, or where there is a failure to undertake the requisitie studies, the Commissioner will proceed immediately to withdraw approval of the drug. Hence, the above approach will permit a reasonable transition to the new requirements without compromising the public health or disrupting the use of drugs for which there is no known health hazard.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 402, 403, 409, 512, 701(a), 706, 52 Stat. 1046–1048, 1055, 72 Stat. 1785–1788 as amended, 74 Stat. 399–404, 82 Stat. 343–351; U.S.C. 342, 343, 348, 706, 360b, 371(a), 376), and under authority delegated to the Commissioner (21 CFR

2.120), it is proposed that Part 135 be amended by adding the following new section:

§ 135.38 Compounds used in food-producing animals; procedures for determining the acceptability of assay methods used for assuring the absence of residues in edible products of such animals.

(a) The act provides that feed and drugs intended for animals shall be safe, that food produced from animals shall be safe, and that any compound administered to a food-producing animal which is found to induce cancer when ingested by man or animal is prohibited from the food supply, unless it can be determined by methods of examination prescribed or approved by the Secretary by regulation, that no residues of any such compound are found in the food produced from such animals under conditions of use reasonably certain to be followed in practice. Petitions for use of a compound in food-producing animals shall include data for determining the absence of residues of any unsafe compounds in the food produced from such animals. The provisions of this section shall determine the required level of sensitivity of the regulatory assay method for any compound for which the Commissioner of Food and Drugs has established a zero tolerance (no residue) in food.

(b) Exogenous compounds, defined as those compounds which are not produced by the normal animal and are not required for normal animal body function, are subject to the following requirements:

(1) Metabolism studies shall be conducted in the target species to identify and quantify metabolites of the parent compound and the concentrations of the compound and its metabolites in specific tissues ("tissues" to include milk and eggs, if applicable). The effect of the exogenous compound on tissue levels of related endogenous compounds also shall be determined.

(2) Degradation of the compound and/or its metabolites during the period of time after slaughter that edible tissue would normally be held under storage conditions and the impact of cooking on the compound and/or its metabolites in question shall be determined.

(3) Determination of whether an exogenous compound and/or its metabolites shall be subjected to appropriate testing for carcinogenicity will be based on the results of the metabolism studies, standard toxicity testing, structural relationships of the compound and/or its metabolites to known carcinogens, modes of physiological actions and interactions, and the intended use patterns of the compounds.

(4) If it is determined that carcinogenicity tests are not required or if the results of carcinogenic testing are negative, consideration for approval shall be based on standard toxicological procedures. These procedures shall include in addition to subacute studies in a minimum of two species, such studies as a multi-generation reproduction studies, teratology and any other special studies which may be indicated from the nature of the biological action of the compound, including lifetime studies. These studies shall involve collection of data from appropriately designed dose-response experiments that demonstrate a "maximum no harmful effect level" as well as a "minimum harmful effect level" in appropriate animal species.

(i) Where a finite or negligible residue of the parent compound and/or its metabolites is determined to be safe in food, the required level of sensitivity of the regulatory assay method will be the level of the tolerance published in the FEDERAL REGISTER and the remaining provisions of this paragraph shall be inapplicable.

(ii) Where no residue of the compound and/or its metabolites is determined to be safe in food, the dose-response slope estimated from the toxicological experiments will be used to extrapolate to the required level of sensitivity of the method using appropriate confidence interval techniques in accordance with the concepts underlying the Mantel-Bryan procedure described in paragraph (b)(6) of this section. Where such extrapolation is not scientifically appropriate, e.g., if no dose-response slope can be estimated from the data, other conservative methods shall be invoked to determine an appropriate safety margin based on a thorough evaluation of the quality of the experiments, their rigor as predictive tests and the nature and significance of the observed biological effects.

(5) If it is determined that testing for carcinogenicity is required, test procedures shall be used which maximize sensitivity to detect a minimal dose which induces a carcinogenic effect and with a sufficiently stable control population to avoid false positive indications of carcinogenesis. Appropriate dose-response experiments shall be conducted to (i) clearly establish whether or not the compound and/or its metabolites are carcinogens, and (ii) determine the relative potency of the compound and/or its metabolites with respect to both its carcinogenic and its other toxic effects.

(6) If it is determined that the compound is carcinogenic, the required sensitivity of the regulatory assay method shall be established according to a modification of the Mantel-Bryan procedure. (Mantel, N. and W. R. Bryan, "Safety" Testing of Carcinogenic Agents, Journal of the National Cancer Institute, Vol. 27, pp. 455–470, 1961).[1] This modification shall consist of using the lower 90 percent confidence limit of the experimentally determined dose-response slope from the carcinogenicity studies for extrapolation to a maximum exposure level with appropriate adjustments to account for drug usage and human consumption patterns and for the differences between daily food intake per unit of body weight of the laboratory animal and of man. (i) If the data indicate that some linearizing transformation other than the probit-log transformation used in the modified Mantel-Bryan procedure better describes the observed response and has a biological rationale, then this other linearizing transformation will be used for the extrapolation. (ii) In the event that both significant noncarcinogenic harmful effects and carcinogenic effects are observed during testing, the lowest level for the regulatory assay sensitivity as determined for the different effects shall be adopted.

(7) The sensitivity of the regulatory assay method as defined above, the method, and a definition of the criteria used to establish a reliable positive finding shall be published in the FEDERAL REGISTER.

(8) The withdrawal period for the compound shall be based, using the regulatory assay method and/or other suitable methods, on the time required after the last dosage for tissue levels of the parent compound and/or its metabolites and/or any affected endogenous compounds to fall below the required regulatory assay sensitivity.

(9) The withdrawal period shall be the longer of either (i) the number of days required for tissue levels to be depleted to less than the maximum exposure level plus a safety factor to account for animal to animal variation as determined by appropriate confidence interval techniques or (ii) the number of days required for any affected endogenous compound to return to a normal level plus a safety factor to account for animal to animal variation. Current livestock management techniques may justify a longer withdrawal period. The normal level of any affected endogenous compound shall be established as described in paragraph (c) of this section.

(10) Based on tissue depletion studies and animal management practices, conditions of use that are reasonably certain to be followed in practice shall be specified for the compounds so that, if followed, they assure that no residue shall occur in food produced from treated animals.

(11) Notwithstanding a determination pursuant to this paragraph of the required level of sensitivity of the regulatory assay method, if a regulatory assay method of lower sensitivity is later developed and validated the Commissioner will adopt that more sensitive method and publish it in the FEDERAL REGISTER even though its development was not required.

(c) Endogenous compounds, defined as those compounds which are present in and are produced by the normal animal and are not required from an external source, are subject to the following requirements:

[1] Copies may be obtained from: Director, Division of Nutritional Sciences (VM-100), Bureau of Veterinary Medicine, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852.

(1) Metabolism studies shall be conducted in the target species to identify and quantify the metabolites of the parent compound and the concentrations of the compound and its metabolites in specific tissues ("tissues" include milk and eggs, if applicable). The effect of the endogenous compound on tissue levels of related endogenous compounds also shall be determined.

(2) Degradation of the compound and/or its metabolites during the period of time after slaughter that the edible tissue would normally be held under storage conditions and the impact of cooking on the compounds and/or its metabolites in question shall be determined.

(3) Animals containing tissue levels of endogenous compounds above the normal due to the administration of endogenous compounds may not be marketed for human consumption. Thus, neither tests for carcinogenicity nor standard toxicity testing shall be required for endogenous compounds.

(4) The naturally occurring or background tissue levels of endogenous compounds and/or their metabolites and/or other related endogenous compounds in the target species shall be determined in studies designed to show the effect of geographical location, stage of estrus, age, etc., on normal animals receiving no external source of the endogenous compound. The tissue distribution will be used to establish the required sensitivity of the regulatory assay method. The required sensitivity of the regulatory assay method will be that value of the distribution which is exceeded by only one percent of the normal animals.

(5) The sensitivity of the regulatory assay method as defined above, the method, and a definition of the criteria used to establish a reliable positive finding shall be published in the FEDERAL REGISTER.

(6) The withdrawal period for the compound shall be based, using the regulatory assay method and/or other suitable methods, on the time required after the last dosage for the tissue levels of the parent compound and/or its metabolites and/or any affected other related endogenous compounds to return to the median background level of contemporary controls. The withdrawal period shall be the number of days required for tissue levels of any affected endogenous compounds to return to the median background level plus a safety factor to account for animal to animal variation as determined by appropriate confidence interval techniques. Current livestock management techniques may justify a longer withdrawal period.

(7) The characteristics of the distribution of tissue levels of the compound normally found in animals not exposed to external sources of the compound and the specified conditions of use shall be published in the FEDERAL REGISTER as part of the approval of any endogenous drug compound.

(8) Based on tissue depletion studies and animal management practices, a withdrawal period and conditions of use that are reasonably certain to be followed in practice shall be specified for the compound so that, if followed, they assure that no residue shall occur in excess of the established normal level in food from untreated animals.

(d) Prior to approval, the adequacy of the regulatory assay method shall be determined by validation of the method in appropriate Food and Drug Administration laboratories and other laboratories. The validation shall determine the feasibility, specificity, accuracy, and precision of the method. This validation of an assay method used for regulatory purposes shall be based on the following criteria:

(1) The method shall be capable of reproducibly extracting, at the required level of sensitivity, the significant compounds from target tissues obtained from treated animals, as well as from tissues containing known added amounts of the compounds.

(2) The method shall be capable of measuring residues with a sufficient degree of specificity, precision, and accuracy to preclude the occurrence of false negatives or false positives.

(3) The equipment, reagents and compounds used in the assay shall be commercially available. Any required specialization in terms of equipment or personnel shall be consistent with that normally available in a modern well-equipped analytical control laboratory.

(4) The time required for completion of the assay shall not be so excessive as to delay regulatory action.

(5) The assay shall offer minimal hazard in the laboratory.

(e) After publication in the FEDERAL REGISTER of an assay method in accordance with paragraphs (b) through (d) of this section, compliance shall be determined as follows:

(1) Samples of the food produced from appropriate animals will be routinely collected and evaluated using the regulatory assay method(s).

(2) Any sample subject to paragraph (b) of this section yielding a residue of the compound at or above the published level of sensitivity of the method will be liable to regulatory action.

(3) Any sample subject to paragraph (c) of this section yielding a residue of the compound at or above the published level of sensitivity of the method will be subject to investigation. Any such residue which is determined to be the result of improper use of the compound will be liable to regulatory action.

(4) No regulatory action may be based on the measurement of a value which is below the established level of sensitivity of the approved regulatory assay method(s) as published in the FEDERAL REGISTER.

(f) The provisions of this section shall be applicable to all new animal drug applications, including supplements, approved by the Food and Drug Administration subsequent to the effective date of the final regulation, except that supplemental applications meeting the requirements of § 135.13a(d) or that in the opinion of the Commissioner otherwise protect the public health will be permitted to be put into effect in accordance with § 135.13a(e) through (k).

(g) The provisions of this section shall be applicable to existing approvals of new animal drugs in accordance with the following priorities:

(1) The Commissioner will review existing zero tolerances (no residues) to determine whether the drugs involved should be the subject of finite or negligible residues. Those drugs for which finite or negligible residues are established are not subject to the provisions of paragraphs (b) or (c) of this section.

(2) Those drugs for which the Commissioner has determined the appropriateness of a zero tolerance (no residue) will be the subject of a notice published in the FEDERAL REGISTER or a letter to every holder of a new animal drug application establishing a time within which the provisions of this section shall be satisfied. Notices already published in the FEDERAL REGISTER and letters already sent by the Food and Drug Administration requiring additional studies and/or a more sensitive regulatory assay method for a drug subject to a zero tolerance shall remain in effect, and the provisions of this section shall be used in determining compliance with the requirements of the act pursuant to those notices and letters. The Commissioner will immediately proceed to withdraw approval of any drug on the basis of data or information indicating a health hazard or a failure to undertake studies necessary to comply with the provisions of this section.

Interested persons may, on or before September 17, 1973, file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6-88, 5600 Fishers Lane, Rockville, MD 20852, written comments (preferably in quintuplicate) regarding this proposal. Comments may be accompanied by a memorandum or brief in support thereof. Received comments may be viewed in the above office during working hours, Monday through Friday.

Dated: July 13, 1973.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

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Social Security Administration

[20 CFR Part 405]

[Reg. No. 5]

FEDERAL HEALTH INSURANCE FOR THE AGED AND DISABLED

Payment for Services of Physicians in Teaching Hospitals, for Physician Costs to Hospitals and Medical Schools, and for Volunteer Services

Notice is hereby given, pursuant to the Administrative Procedure Act (5 U.S.C. 552 et seq.) that the amended regulations set forth in tentative form below are proposed by the Acting Commissioner of Social Security, with the approval of