

SECTION 5. PLANNING THE 2000 FSIS IMPORT RESIDUE PLAN: VETERINARY DRUGS

PHASE I - GENERATING AND RANKING LIST OF CANDIDATE COMPOUNDS

LIST OF CANDIDATE COMPOUNDS

The candidate veterinary drugs of concern selected by members of the Surveillance Advisory Team (SAT) for the import residue plan are the same as those listed in Section 4.

RANKING OF CANDIDATE COMPOUNDS

Compound Scoring and Ranking

Using a simple 4-point scale (4 = high; 3 = moderate; 2 = low; 1 = none), the SAT scored each of the above veterinary drugs or drug classes in each of the following categories:

- Food Safety and Inspection Service (FSIS) Historical Testing Information on Violations
- Regulatory Concern
- Lack of FSIS Testing Information on Violations
- Withdrawal Time
- Impact on New and Existing Human Disease
- Acute or Chronic Toxicity Concerns

Categories used to score the veterinary drugs for the import residue plan parallel those for the domestic plan. However, two categories are different:

1. **FSIS Historical Testing Information on Violations:** The FSIS historical testing information for imported products is different from that for the domestic products.
2. **Relative Number of Animals Treated:** This category was not used in the design of the import residue plan because it is not possible to obtain detailed information on treatment practices in the animal populations of each country.

Definitions of each of these categories and the criteria used for scoring, appear at the end of this section, “*Scoring Key for Veterinary Drugs, 2000 Import Residue Plan.*”

The results of the scoring process are presented in Table 5.1, *Scoring Table for Veterinary Drugs.*

Background

As stated in Section 3, FSIS chose to employ techniques and principles from the field of risk assessment to obtain a ranking of the relative public health concern represented by each of the candidate compounds or compound classes.

The equation used to measure hazard is the same as that in the domestic plan:

$$\begin{aligned} \text{Risk} &= \text{Exposure} \times \text{Toxicity} \\ &= \text{Consumption} \times \text{Residue Levels} \times \text{Toxicity} \\ &= \text{Consumption} \times \text{"Risk Per Unit of Consumption"} \end{aligned} \quad (5.1)$$

As stated in Section 4, given the limited resources available for this priority-setting effort, FSIS did not attempt to associate different degrees of risk with different degrees of exceedance of the tolerance or action level. The FSIS instead determined that the best available method for the measurement of relative toxicity is associated with the tolerance or action level. *Specifically, the frequency of violation of the tolerance or action level was used as an indicator of the risk per unit of consumption of a product.*

The categories of "FSIS Historical Testing Information on Violations" represent the percent of tested product found to have residues in excess of the tolerance or action level. Therefore, based on this equation, it can be seen that the violation rate scores assigned in Table 5.1 represent a rough overall estimate of *relative* risk per unit consumption. However, since most of the candidate compounds or compound classes of concern are ones that have not yet been included in the FSIS National Residue program (NRP), data on violation rates is not available for them. Therefore, it was necessary to generate an estimate of the overall violation rate for each these untested compounds and compound classes.

Estimating the Violation Rate

In the domestic residue plan, based on those drugs for which "Historical Testing Information" was available, a regression equation was developed to predict violation history scores for those veterinary drugs that had not been tested. However, in the import residue plan the data from FSIS testing is not sufficient to independently develop a similar predictive formula. Since it would be expected that similar underlying data on usage should lead to similar violation rate in foreign countries, the SAT decided to predict the score for "FSIS Historical Testing Information on Violations" using the regression equation obtained from the domestic values. Therefore, for purpose of planning the import residue plan, it was assumed that the relationship among the categories of "Regulatory Concern," "Withdrawal Time," "Relative Number of Animals Treated" and "FSIS Historical Testing Information on Violations," in foreign countries is similar to that in the U.S. The "Regulatory Concern" scores used for each drug or drug class in the import plan were the same as those in the domestic plan, because the veterinary control practices in foreign countries were judged to be approximately similar to those in the U.S. However, if the veterinary control practices in foreign countries were known to be different from those in U.S., the "Regulatory Concern" scores for a drug or drug class in the import plan would reflect such differences. The "Withdrawal Time" is based upon the pharmacokinetic properties of the drug in the animal. Therefore, "Withdrawal Time" score for each drug in the import residue plan is the same as that used in the domestic residue plan.

As stated in section 4 the regression equation (Equation 4.2) used to predict the violation rate for the 2000 FSIS domestic plan used two variables "Regulatory Concern" and "Numbers of Animals Treated." The equation did not use the values of the "Withdrawal Time."

$$V_p = 0.20(R \cdot N) + 0.73 \quad (4.2)$$

where V_p = Predicted score for "FSIS Historical Testing Information on Violations"
 R = score for "Regulatory Concern"
 N = score for "Relative Number of Animals Treated"

In import residue plan, no data was available for the "Relative Number of Animals Treated." Therefore, to calculate the predicted violation rate for the import residue plan using equation 4.2 the "Regulatory

Concern" variable is multiplied and added to a constant. It was therefore decided to use the values of the regulatory concern as the predicted violation rate.

Thus, the equation used to predict the violation rate for the import residue plan is:

$$V_p = R \quad (5.2)$$

V_p = Predicted Violation Rate
 R = Regulatory Concern

Rating the Veterinary Drugs According to Relative Public Health Concern

As stated in Section 4, the scores for predicted violation rate combines information on residue levels and toxicity, and thus represents a rough overall estimate of the relative risk per unit of consumption for each drug or drug class. Although this score, once multiplied by relative consumption data for each production class, would conform most closely to a purely risk-based ranking, the RPC believes that additional attributes should also be considered in the ranking. Thus, the ranking according to relative public health concern incorporates, as modifiers, the remaining scoring categories presented in Table 5.3, *Drug Residues Rated with Various Weighting Formulas*. The equation used is similar to the equation in, Section 4.

$$\begin{aligned} \text{Relative Public Health Concern} &= \text{Predicted score for "FSIS Historical testing information on violations"} \\ & \text{(Estimate of Relative Hazard)} \\ & \times \text{modifier for "Acute or chronic toxicity concerns"} \\ & \times \text{modifier for "Impact on new and existing human disease"} \\ & \times \text{modifier for "Lack of FSIS testing information on violations"} \end{aligned} \quad (5.3)$$

The discussion on the use of modifiers is presented in Section 4 and following the same concept, the RPC decided to use the same weighting factors used in the domestic plan to calculate the relative public health concern for the import plan. In Table 5.2, *Drug Residues Rated with Various Weighting Formulas, 2000 Import Residue Plan*, the drugs are rated for relative public health concern by combining the scoring categories presented in Equation (3), above, using four different weighting formulas. As in the domestic plan, FSIS chose to use the second of these formulas (bolded and italicized in Table 5.2), based on a consensus about the relative importance of each modifier, and of how much each modifier should be allowed to alter the underlying risk-based score, " V_p ," in Equation (5.4), below. Equation (5.4) summarizes the way final adjustments were made.

Thus, a similar equation as in Section 4 was used to calculate the relative public health concern.

$$\text{Relative Public Health Concern, veterinary drugs} = V_p * ((D+3*T)/4) * \{1+[(L-1)*0.05]\} \quad (5.4)$$

Where:

- V_p = Predicted score for "FSIS Historical Information on Violations"
- D = score for "Impact on New and Existing Human Disease"
- T = score for "Acute or Chronic Toxicity Concerns"
- L = score for "Lack of FSIS Testing Information on Violations"

In Table 5.4, *Drug Residues Rated with Various Weighting Formulas, Sorted by Rating*, the drugs are ranked by their rating scores using the four different weighting formulas as discussed in Section 4. Results obtained with the selected formula are bolded. Inspection of this chart reveals the extent to which changes in the weighting formula result in changes in ranking. In this case, the results from all four formulas are relatively similar.

The rating scores and rankings presented in Table 5.4 enables FSIS to bring consistency, grounded in formal risk-based considerations, to its efforts to differentiate among a very diverse range of drugs and drug classes in a situation that is marked by minimal data on relative exposures.

PHASE II - SELECTING DRUGS FOR INCLUSION IN THE 2000 NRP

As stated in Section 4, after the completion of the ranking of the veterinary drugs, FSIS used these rankings to select those compounds and compound classes that should be included in the 2000 NRP, based purely on their relative public health concern. It also determined which of these compounds and compound classes actually could be included in the 2000 NRP, based on the availability of laboratory resources.

The consensus of FSIS and FDA was that those compounds and compound classes ranked 39th or higher represented a potential public health concern sufficient to justify their inclusion in the 2000. In addition, FDA expressed interest in having FSIS test for veterinary tranquilizers, a compound class that did not fall within this group of 39. Veterinary tranquilizers ranked 54.

Once the high-priority compounds and compound classes had been identified, it was necessary for FSIS to apply non-public health considerations to determine the compounds for which FSIS would actually sample. The principal consideration not related to public health was the availability of laboratory resources, especially the availability of appropriate analytical methods within the FSIS laboratories. When the laboratory resource was limited, FSIS decided that more resources be used to test for the domestic products since the import residue plan is the recheck of the product at the port of entry. Based on these considerations, the following compounds will be included in the 2000 FSIS Import Residue Plan.

--Antibiotics:

- those antibiotics quantitated by the FSIS Bioassay and associated follow-up methodologies¹ [tetracycline, oxytetracycline, chlortetracycline, beta-lactams (penicillins and cephalosporins; not differentiated within this category), gentamicin, streptomycin/spectinomycin (not differentiated), erythromycin, tilmicosin, tylosin, neomycin, flavomycin, bacitracin, hygromycin, novobiocin, lincomycin*, pirlimycin*, clindamycin*, spiramycin*, oleandomycin*] *identification by mass spectrometry; not quantitated
- Choramphenicol
- Fluoroquinolones

--Other Veterinary Drugs:

- Arsenicals (detected as elemental arsenic)
- Avermectins in FSIS multi-residue method (doramectin and ivermectin)
- Carbadox
- Dexamethazone
- Flunixin
- Nitroimidazoles (ronidazole, dimetridazole and ipronidazole)

¹ FSIS quantitates most antibiotics using a 7-plate Bioassay that measures microbial inhibition. The pattern of inhibition (i.e., the combination of plates showing inhibition) is used to identify the antibiotic. However, there are some antibiotics that share the same pattern of inhibition. In these cases, it is necessary to undertake follow-up testing (HPLC or mass spectrometry) to identify the compound. The compounds that share patterns of inhibition, and which are thus individually identified through follow-up testing, are:
tetracycline/oxytetracycline/chlortetracycline - compounds individually identified by follow-up with HPLC method for tetracyclines
tilmicosin/tylosin - differentiated by mass spectrometry

- Phenylbutazone (detected in the CHC3 method)
- Ractopamine (beta agonist)
- Sulfonamides (sulfapyridine, sulfadiazine, sulfathiazole, sulfamerazine, sulfamethazine, sulfachloropyridazine, sulfadoxine, sulfamethoxypyridazine, sulfaquinoxaline, sulfadimethoxine, sulfisoxazole, sulfacetamide, sulfamethoxazole, sulfamethizole, sulfanilamide, sulfaguanidine, sulfabromomethazine, sulfasalazine, sulfaethoxypyridazine, sulfaphenazole, and sulfatroxazole)

In 2000, FSIS will employ 12 methodologies that analyze for over 50 veterinary drugs in the Import Residue Plan. Six of these are single-compound methodology, and six are multi-residue methods (phenylbutazone is detected by the FSIS multi-residue method for chlorinated hydrocarbon and chlorinated organophosphate compounds).

PHASE III - IDENTIFYING THE COMPOUND/PRODUCT CLASS PAIRS

FDA participants of SAT identified, for each of the drugs and drug classes to be included in the 2000 NRP, the product classes in which they might be of concern. The results are presented in Table 5.5, *Product Classes Considered for Each Drug/Drug Class*. Compound/product class pairs included in the 2000 NRP are designated by a "●." Those compound/product class pairs that are of potential public health concern, but that could not be included in the 2000 NRP because of laboratory resource constraints, are marked with a "○." Since all product classes will be sampled by the chlorinated hydrocarbon/chlorinated organophosphate (CHC/COP) method (see Section 7), and since this method also detects phenylbutazone, the latter, by default, will be sampled in all product classes. However, phenylbutazone is not of regulatory concern in all product classes. Those product classes in which phenylbutazone will be sampled, but where it is NOT of regulatory concern, are designated by a "◐ "

PHASE IV - ALLOCATION OF SAMPLING RESOURCES

ALLOCATION OF SAMPLING RESOURCES AMONG DIFFERENT PRODUCTION CLASSES

The samples for residue analysis for imported egg products are selected in a different manner than the other product classes

EGG PRODUCTS

As stated in Section 2, for egg products, the first ten shipments from individual foreign establishments are subjected to 100 % reinspection, to establish a history of compliance with the U.S. requirements for each egg product category. This rate is reduced to a random selection of one reinspection out of eight product lots from each foreign establishment, which will continue as long as the product is in compliance. During 2000, imported egg products will be tested for arsenic and sulfonamides. Egg whites are included in the random selection for testing arsenic and sulfonamides.

ANIMAL PRODUCT CLASSES

Table-5.6, *Estimated Annual Amount of Product Imported*, lists the estimated amount of all the product classes imported into US and the percentage of each of the product classes. The percent of each product class imported annually is calculated using the following formula:

$$\% \text{ Product Class Imported } (P_C) = \frac{\text{Amount Product Class Imported}}{\text{Total Product Imported}} \times 100 \quad (5.5)$$

The relative sampling priority is obtained by multiplying the percent product class (P_C) by the drug scores obtained in Phase I, using the following equation

$$\text{Relative Sampling Priority} = (P_C) \times \text{Drug Score} \quad (5.6)$$

Based on the scores, four different sampling options were chosen; very high regulatory concern (460 analyses/year); high regulatory concern (300 analyses/year); moderate regulatory concern (230 samples/year); low regulatory concern (90 samples/year). This is indicated in Table 5.9, *Number of Drug Samples/Product Class*, in the column labeled “Number of Samples.”

If a product class represents less than one percent (by weight) of total combined U.S. imports of meat, poultry and egg products, then the total number of samples analyzed for any compound or compound class is eight times the number of countries from which that product is imported. For example, fresh goat is imported from only three countries. The amount imported is 0.27 % relative to the total U.S. import. Therefore, twenty four samples of fresh goat would be taken for each analysis, eight from each country.

In case of carbadox, chloramphenicol, dexamethazone, flunixin, nitroimidazoles, and ractopamine based on the laboratory capacity, the number of samples was adjusted downwards.

The adjusted numbers of samples is listed in Table 5.9, *Number of Drug Samples/Product Class*, in the column labeled “Adjusted Number of Samples.” The final number of samples for a compound/product class is obtained after the allocation of samples among different countries is completed. The final number of samples is listed in Table 5.9 in the column labeled “Final Number of Samples.” The numbers in the column labeled “Adjusted Number of Samples” and “Final Number of Samples” may vary slightly because of the rounding upwards or downwards of the samples.

ALLOCATION OF SAMPLES AMONG DIFFERENT COUNTRIES

The total number of samples chosen for each compound/product class pair was subdivided among the different countries. The number of samples for each country was based on the relative amount of total product class imported: less than one percent and greater than one percent.

Allocation of Samples in Product Classes Whose Total Volume Imported is less than 1%

As stated above, if the amount of an import product class was less than 1%, eight samples per compound/compound class were taken from each country. The relative amounts of fresh goat, fresh chicken, beef/pork processed, turkey fresh and processed, other fowl fresh and processed, lamb/mutton processed, and veal processed were less than 1%. The numbers of samples per country per product class for each compound/compound class are listed in Tables 5.10-5.19.

Allocation of Samples in Product Classes Whose Total Volume Imported is Greater Than 1%

For major product classes, the number of samples was allocated to each country depending upon the relative amount of product imported from that country. Table 5.8, *Estimated Annual Volume of Import Product/Country*, lists the amount of product imported from each country. The percent of a product class imported from a country was calculated as follows and is in Table 5.9, *Relative Annual Amount of Import Product /Country*.

$$\text{Percent Product Class Imported per Country } (P_{CC}) = \frac{\text{Amount of Product Class from Country}}{\text{Total Amount of Product Class}} \times 100 \quad (5.7)$$

Based upon the relative amount of product class imported per country, the number of samples that should be taken at the port of entry was calculated using the following formula:

$$\text{Unadjusted Number of Samples per Country (U}_{C/S}) = \text{Total Number of Samples} \times \frac{(P_{C/C})}{100} \quad (5.8)$$

This is indicated in the column labeled “Unadjusted Number of Samples (U_{C/S}),” in Tables 5.20 to 5.26 (except 2.22b and 5.24b).

After the determination of the number of samples from each country, each country with less than eight samples was assigned a minimum of eight samples. This is indicated in the column labeled “Adjustment #1” in Tables 5.20 to 5.26(except 2.22b and 5.24b). The results of this adjustment are in the column labeled “Initial Adj #.” After this adjustment, the total number of samples for a compound/product class resulted in more than the total number of samples allocated to that compound/product class pair. A second adjustment then had to be made, so that the total number of samples would be within an allocated number. This adjustment was made only to those countries from which greater than eight samples were to be taken. This was accomplished using the following equations:

$$\text{Number of Samples after Adjustment \#2} = (U_{C/S}) - \frac{(N \times P_{C/C})}{(P_{T/C})} \quad (5.9)$$

where ,

$$N = (N_I) - (N_T)$$

N_I = Total Number of Samples after Adjustment #1

N_T = Total Number of Samples Allocated

P_{T/C} = Total Percent of Product Class from the Countries That Had Greater Than Eight Samples

P_{C/C} = Percent Product Class Imported Per Country

U_{C/S} = Unadjusted Number of Samples

The final numbers of product sampled are indicated in Tables 5.20 to 5.26 (except 5.22b and 5.24b)in the column labeled “Final Adj.#.”

Notes:

Because of limited laboratory resources twenty-four samples were allocated for chloramphenicol in fresh veal.

Since US imports processed pork from sixteen countries, the total number of samples were adjusted from 90 to 128, i.e. 8 samples/country.

Phenylbutazone is detected by the FSIS CHC/COP method. Therefore, all product classes that are sampled for CHC/COP are sampled for phenylbutazone. The number of samples/product class/country is discussed in Section 7.

SCORING KEY FOR VETERINARY DRUGS 2000 FSIS IMPORT RESIDUE PLAN

FSIS Historical Testing Information on Violations

Information based on the testing performed by FSIS on the imported product collected at port of entry from 1989 to 1998

- 4 = More than 5 violations detected over all years of sampling.
- 3 = Total of three to five violations detected over all years of sampling
- 2 = Total of one or two violations detected over all years of sampling
- 1 = No violations detected over all years of sampling
- NT = Not tested by FSIS
- NA = Tested by FSIS but the violation information does not apply because of change in withdrawal time, or new information

Regulatory Concern

This consists of professional judgments made about the likelihood of occurrence of violations, based on regulatory intelligence information about possible misuse. Due to the public health significance of drug residue violations, surveillance data pertaining to a compound must meet only one of the requirements listed under each number below to receive that numerical ranking.

- 4 = Well-documented intelligence information gathered from a variety of reliable sources indicates possible widespread misuse of the compound, and/or this compound is banned, or is on the list of compounds prohibited from use in food animals under AMDUCA, or is not approved for use in the U.S.
- 3 = Intelligence information gathered through a variety of sources indicates only occasional misuse of this compound. The dosage form/package of this compound has potential for misuse.
- 2 = Intelligence information rarely indicates misuse of this compound.
- 1 = Intelligence information has never indicated misuse of this compound.

Lack of FSIS Testing Information on Violations

Represents the extent to which FSIS analytical testing information (1989 to 1998) on a residue is lacking.

- 1 = FSIS has included this compound in its sampling program within the past 5 years
- 2 = FSIS has included this compound in its sampling program within the past 8 years
- 3 = FSIS has included this compound in its sampling program within the past 10 years
- 4 = FSIS has never included this compound in its sampling program or has included it in its sampling program but the data is not relevant because of change in method, tolerance, etc.

Withdrawal Time

Producers using approved animal drugs are required to follow approved "conditions of use." For each drug, in each production class in which it is approved, the conditions of use specify the dosing regimen and the withdrawal time. The withdrawal time is the number of days that must pass between completion of the dosing regimen and the time of slaughter. This allows sufficient time for the concentration of drug in the animal to decrease below the tolerance. For approved drugs, the following scores were used. For unapproved drugs, scores in this category were assigned based on estimates of their half-lives.

- 4 = Withdrawal time greater than 14 days
- 3 = Withdrawal time between 8 and 14 days
- 2 = Withdrawal time between 1 and 7 days
- 1 = Zero-day withdrawal time

Impact on New and Existing Human Disease

This represents the extent to which the use or misuse of this compound may contribute to new and existing human disease. Examples could include the possible creation of antibiotic-resistant human pathogens from the use of antibiotics in animals, or the potentiation of new zoonotic diseases (which might subsequently be altered and transferred to humans) following pesticide-induced immunosuppression.

- 4 = Scientific information gathered from a variety of reliable sources indicate that possible widespread use of this compound might significantly modify drug resistance patterns of human pathogenic organisms.
- 3 = Limited scientific information is available to suggest or document public health risk but compound has the potential to affect microflora.
- 2 = No scientific information available to suggest or document public health risk.
- 1 = Current scientific information available suggests no public health risk.

Acute or Chronic Toxicity Concerns

This represents a combination of the toxicity of the compound and the severity associated with the compound's toxic endpoint

- 4 = Compound is a carcinogen, or potentially life threatening, or has significant acute effects including the anaphylactic response to an allergen.
- 3 = Systemic no observed effect levels (NOEL's) seen at intermediate to low doses in laboratory test animals. Antimicrobial effects with a high potential to alter intestinal microflora.
- 2 = Systemic NOEL's seen at high oral doses in laboratory test animals. Antimicrobial effects with a moderate potential to alter intestinal microflora.
- 1 = Compound generally shows no toxicity in laboratory test animals even at doses much higher than present in edible tissues at zero-day withdrawal.