DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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Dear Dr. Carnevale:

This letter is in reference to your January 4, 2001, request on behalf of the Animal Health Institute for clarification regarding concepts included in the CVM discussion document entitled, *An Approach for Establishing Thresholds in Association with the Use of Antimicrobial Drugs in Food-producing Animals*. You provided a number of questions for our consideration.

We have considered your questions and have the following comments.

1. *How would the (k-res) proportionality factor be developed? Would it be an analysis of historical data? Would a different (k-res) be developed for each drug and each labeled use? Would currently approved compounds for which concerns exist have a (k-res) developed or only new animal drugs pending approval?*

   As described in the threshold document, the factor, k-res, is a key component of the approach outlined for deriving resistance thresholds. It is intended to approximate the relationship between exposure to resistant bacteria (i.e., represented by some quantity, Q, of food containing resistant bacteria) and some effect on human health (i.e., H). The ability to calculate k-res is dependent on the availability of data to derive values for the parameters H and Q. The most directly applicable data would be data on the specific drug/bacteria/use of interest. However, depending on data availability, CVM believes there may be several alternative approaches for developing k-res. These may include:

   - Calculate k-res using information on exposure (Q) and human health impact (H) that is attributable to the drug of interest. This would require that information be available on the quantity of the relevant food commodity that contains bacteria resistant to the drug of interest. In addition, information would be required on human health effects attributed to resistance and associated with the specific drug/bacteria/food commodity of concern. Therefore,

     $$\text{k-res} = \frac{\text{mean number of } \textit{resistant} \text{ disease cases attributable to the food commodity}}{\text{prevalence of contamination by } \textit{resistant} \text{ bacteria in the food commodity}}$$

   - Calculate k-res using information on exposure (Q) and human health impact (H) that is attributable to the bacterial disease of interest, but *not* to the drug of interest. With this approach, it is assumed that the rate constant (k) which relates the amount of bacterial

contamination in the food commodity to the number of cases of human illness attributable to the commodity, is the same for resistant and susceptible bacteria.

This assumption should be valid if the distributions of the total number of bacteria that contaminate carcasses are the same for resistant and susceptible bacterial populations, and if resistant and susceptible bacteria have similar survivability and virulence characteristics. With this approach, k-res is calculated as follows:

$$\text{k-res} = \frac{\text{mean number of disease cases attributable to the food commodity}}{\text{prevalence of contamination in the food commodity}}$$

This approach relies on knowledge of the dynamics of the disease itself irrespective of resistance. In particular, it requires knowledge of the extent to which bacteria on a given food commodity are transferred to humans and cause disease.

- Alternatively, k-res could be derived using historical information on related drug/bacteria/use scenarios. This approach would require justification that the historical data and the resulting k-res was applicable to the drug use under consideration.

If an approach for establishing thresholds, such as that outlined in the CVM threshold document, is implemented, a k-res factor would need to be derived for all antimicrobial uses for which establishment of a threshold is determined to be necessary. This includes currently approved products as well as new animal drugs pending approval. As noted above, how the k-res is derived would be dependent on what information is available that is relevant to the drug use under consideration.

2. *In developing H(x) from what time period are the factors that determine the value of Q obtained. Would the Q value be essentially what is calculated in Section 4 of the Vose risk assessment model? Is H(x) expressed in terms in the same manner as in the risk assessment ie: "persons who would have resistant Campy resulting from the consumption of poultry who received Fluoroquinolones." Is H(x) designed to be some sort of baseline level of human health impact? Would H(x) be determined or calculated generally prior to the approval of a drug product? Would H(x) be calculated for products which were already approved? Is the value 11,000 +or- or 5000 +or- for human health impact as determined by the Vose risk assessment equivalent to H(x)?*

Comments regarding (Q): The threshold document defines Q as the quantity of product (i.e., food commodity) that contains bacteria resistant to the antimicrobial drug of interest. This quantity is similar to what is described in Section 4 of the CVM risk assessment, *Human Health Impact of Fluoroquinolone Resistant Campylobacter Attributed to the Consumption of Chicken.* The threshold document notes that the quantity, Q, is not measured directly, but can be derived as a product of several independently measured parameters. The document notes that Q could be estimated as follows:

$$Q = \text{total pounds of product consumed} \times \text{proportion of sampled pounds containing bacteria} \times \text{proportion of samples from which resistant bacteria are isolated}$$

The data on total commodity consumed can be obtained from USDA records and is reported on a yearly basis. For the purposes of calculating Q, it would be appropriate to use the most recent consumption data. The other parameters used to calculate Q would be estimated or measured for that same time period.

Comments Regarding (H(x)): The threshold document defines H(x) as the current measured prevalence of infections in humans that are treated with the antimicrobial drug of concern, are associated with bacteria resistant to the drug of concern, and for which the resistance is attributable to the use of an antimicrobial drug in animals. H(x) is similar to what is described and quantified in Section 3 of the CVM risk assessment, *Human Health Impact of Fluoroquinolone Resistant Campylobacter Attributed to the Consumption of Chicken.* As you noted, it is a measure of human disease cases associated with resistant bacteria resulting from the consumption of food derived from an animal that received the drug of interest. In terms of units of measure, the threshold document refers to H(x) as a prevalence of cases.

H(x) is the current measured human health impact attributable to the use of the drug in animals. In the model, H(x) is primarily needed (along with Q) to derive k-res. However, H(x) may serve as a type of baseline for human health impacts that may already be measurable. According to this approach, a drug could not be considered safe if H(x) exceeds T(x). As is noted in the threshold document, "when considering data to derive the factor, k-res, it should be noted that, based on current safety standards, existing information relevant to drug-related human health effects must not preclude a determination of reasonable certainty of no harm."

3. *T(x) is the unacceptable level of infections in humans ... Is T(x) expressed in terms of persons with illness or in some other form like a percentage of resistance. If hypothetically Q=Qt(x) then it appears that T(x) would equal H(x) -- would that then mean that the current level on human health impact was unacceptable? What if T(x) is less than H(x). How could T(x) be unacceptable? Is there some policy determination necessary to determine the exact level of T(x) that is unacceptable or is it determined purely as a result of Equation 2 (T(x)=(k-res)*Qt(x)?*

The human health threshold (T(x)) is the unacceptable prevalence of infections in humans that are treated with the antimicrobial drug of concern, are associated with bacteria resistant to the drug of concern, and for which the resistance is attributable to the use of an antimicrobial drug in animals. Therefore, in terms of units of measure, T(x) is expressed as a prevalence of cases of human illness.

Human health thresholds specifically focus on the incremental effects on enteric illness or systemic illness in humans as a consequence of the causative bacteria being resistant to the antimicrobial drug the affected persons are expected to receive. Based on current safety standards, the "unacceptable prevalence" is considered that level at which there is no longer reasonable certainty that there is no harm to human health.

As you noted, if the current measured quantity of food commodity (Q) that contains drug-resistant bacteria is equal to the exposure level (i.e, quantity of food commodity that contains drug-resistant bacteria) associated with the human health threshold ($Q_t(x)$), then

it would follow that the human health threshold (T(x)) would equal the current measured human health impact (H(x)). In such a situation, the current level would be considered unacceptable. If H(x) is already greater than T(x), it means the human health threshold has already been crossed.

The human health threshold (T(x)) is not a calculated value, but rather, is a value that is set by policy. Therefore, when running the calculations outlined in the threshold document, it must be assumed that T(x) is a known value. In contrast, the resistance threshold (t(x)) is a calculated value. We hope to obtain input at the public meeting on January 22-24, 2001, as to how to set a human health threshold (T(x)).

4. *Qt(x) appears to be determined by the same basic formula as Q. Is Qt(x) data from a later time period from Q? Generally how would the data to determine Qt(x) be obtained and how would it be related to the data collected to determine Q?*

The parameters, Q and $Q_t(x)$, were described in the threshold document primarily to help illustrate how the equation for calculating a resistance threshold was derived. In theory, when considering the continuum of food quantities (i.e., Q's), $Q_t(x)$ represents that quantity of food containing resistant bacteria that would be expected to be associated with human health effects at the threshold level (T(x)). As is illustrated with the derivation of Equation 4 in the threshold document, the parameter Q is defined as *total weight in pounds* × *proportion contaminated with bacteria* × *proportion resistant*. The *proportion resistant* parameter is termed (h) for current quantities (Q) and t(x) for threshold quantities ($Q_t(x)$). When solving for t(x), the *total weight in pounds* and *proportion contaminated with bacteria* parameters are cancelled. Therefore, the parameter that remains (for which data is needed) is the current proportion of animal-derived food containing resistant bacteria (i.e., h).

5. *The variable (h) can according to the threshold document be potentially obtained in several ways. What is the most likely source of the data to determine (h)? How is (h) different from the "proportion of samples from which resistant bacteria are isolated" used to determine Q and Qt(x)?*

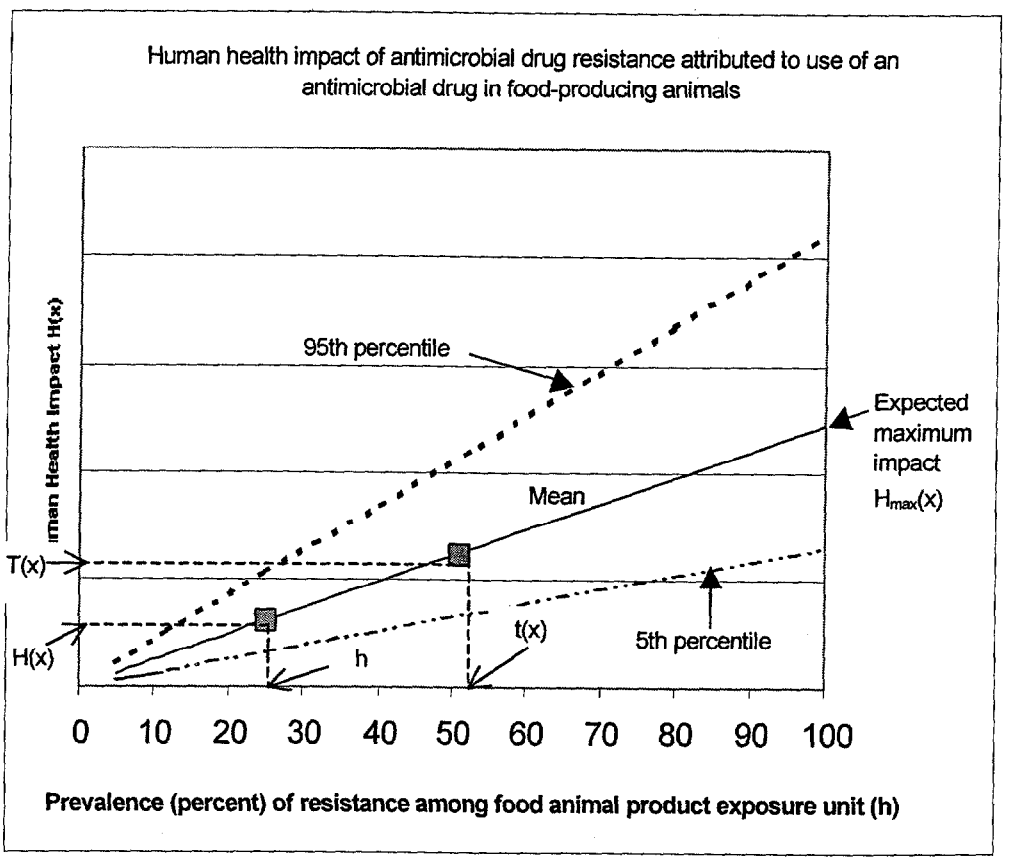
The variable (h) is a measure of the current prevalence of animal-derived foods containing resistant bacteria. The variable may be determined using USDA data to estimate bacterial contamination rates of food commodities and NARMS data to estimate prevalence of antimicrobial resistance. Alternatively, this parameter may also be estimated from other statistically-robust surveys of retail foods in cases where NARMS data is unavailable on a particular pathogen or drug.

The variable (h) is the same as the quantity referred to in the threshold document as the "proportion of samples from which resistant bacteria are isolated" used to estimate Q. As noted in the response to #4 above, the other two factors (*total weight in pounds* and *proportion contaminated with bacteria)* used to estimate Q were cancelled when solving for t(x) in Equation 4.

6. *The variable t(x) appears to be representing a level of resistance prevalence in food either at slaughter or at retail. Can you make clear, conceptually, how the ratio of the current measured prevalence H(x) and the unacceptable prevalence T(x) multiplied by the proportion of resistant isolates (h) independently yields a value for t(x) that establishes a threshold which is related to T(x) or is based on a relationship of resistance prevalence in humans and animals.*

To illustrate how the ratio of the current measured prevalence H(x) and the unacceptable prevalence T(x) multiplied by the proportion of resistant isolates h independently yields a value for t(x), refer to the graph below (similar to Figure 4 in the threshold document). The slope of the line is defined by H(x)/h or T(x)/t(x). Therefore the ratio H(x)/h must equal the ratio T(x)/t(x). Rearranging the terms to solve for t(x) yields the following equation:

$$t(x) = \frac{T(x)*h}{H(x)}$$



7. *How can you introduce t(x) into the denominator of the expanded version of the equation T(x)/Q(x)? Is t(x) really a calculated value or is it a result of a policy decision of what is an acceptable level of resistance in animal or food isolates?*

   As noted in the response to Question #4 above, t(x) was introduced into the denominator in order to define Q as *total weight in pounds* × *proportion contaminated with bacteria* × *proportion resistant.* The *proportion resistant* parameter was then designated as (h) for current quantities (Q) and t(x) for threshold quantities ($Q_t(x)$).

   $$\frac{H(x)}{Q} = \frac{H(x)}{\text{total weight in pounds} * \text{proportion contaminated with bacteria} * h} \quad \text{and,}$$

   $$\frac{T(x)}{Q(x)} = \frac{T(x)}{\text{total weight in pounds} * \text{proportioncontaminated with bacteria} * t(x)}$$

   Therefore, when solving for t(x), the proportion (prevalence) of resistance that is associated with the threshold, T(x), the *total weight in pounds* and *proportion contaminated with bacteria* parameters are cancelled. The resulting equation is:

   $$t(x) = \frac{T(x) \times h}{H(x)}$$

   As noted in the response to Question #3, the human health threshold (T(x)) is a value that is set by policy and is not calculated. In contrast, the resistance threshold (t(x)) is a value that is calculated using the relationship defined in the equation above.

If you would like to discuss these questions further, or have any additional questions, please contact me, at 301-827-7570.

Sincerely yours,

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