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1703 '99 APR -7 P12:10

April 1, 1999

Dr. Margaret Miller
CVM/FDA
7500 Standish Place
Rockville, MD 20855

Dear Dr. Miller:

The following comments address the FDA document "Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals":

- For obvious personal reasons, none of us in the poultry industry want to see the effectiveness of antibiotics against infectious diseases in humans compromised. We share that goal with everyone who has paused to consider the possible consequences to us and to our loved ones. After all, we and our employees are the segment of society with the greatest direct occupational exposure to bacteria from poultry.

- We do not believe there are adequate data to conclude that the use of antibiotics in poultry is responsible for the presence of antibiotic-resistant bacteria in humans. Neither do we have the data to support the conclusion that the proper use of antibiotics in poultry does not promote the development of antibiotic resistance in some bacteria that could potentially cause foodborne illness. However, the temporal relationship between the licensing of an antibiotic for use in poultry and the recovery of antibiotic-resistant bacteria from a poultry species does not appear to be hard evidence that the two events are connected.

- It is understandable that those knowledgeable about antibiotics and their use are concerned about the frequent haphazard use of antibiotics in human medicine. It is not unusual that cultures and antibiotic sensitivity tests do not precede antibiotic therapy. Usually the most recent antibiotic on the market is selected for the type of clinical infection observed or for post-surgical prophylaxis. The inappropriate use of antibiotics in humans doubtless has a very significant role in the loss of the effectiveness of antibiotics in humans.

- The fluoroquinolone antibiotics were approved for use in dogs and cats long before they were approved for use in poultry. The close contact of owners and children with pets receiving such antibiotic therapy could result in human infections with animal-source antibiotic resistant bacteria. Foodhandlers receiving antibiotics could also spread bacteria to humans consuming that food. Health care workers in hospitals and similar institutions where multi-resistant bacteria are common can also be a source of human infections with resistant bacteria.

- Faced with continued antibiotic use, many bacteria will eventually develop increased levels of resistance to some antimicrobials. It happened with penicillin and the sulfonamides in the 1940's and higher dosages were needed to achieve the same level of effectiveness. These changes in bacterial susceptibility occurred long before it was economically feasible to use these drugs in animals.

- The food animal industry can probably survive without the availability of antibiotics. It will be costly to production efficiency, animal welfare and environmental concerns. The actual cost of animal-source foods to the consumer will doubtless increase as a result of any move to make antibiotics unavailable. No one really knows how much prices will have to increase and any figures circulating are pure speculation. Unfortunately, individuals at the bottom of the economic ladder view poultry as reasonably priced food they can afford to buy for their families. Even a small price increase could negatively impact the ability of some to maintain their current level of nutrition.

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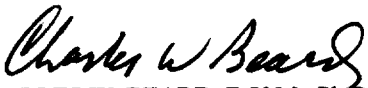
- Animal welfare issues will likely emerge as producers and veterinarians invariably find that they are unable to intervene when large numbers of poultry sicken and die from what would have been treatable diseases. To maintain the increasing food supply, it may be necessary to increase the number of production facilities beyond what would have been adequate with antibiotic availability. That likelihood and the requirement to dispose of the increased poultry mortality losses will make the current concerns over environmental impact even greater. These are high prices to pay for a regulatory action that is not founded on sound science and with no proven benefit to the public health.

- Both companies licensed to sell fluoroquinolones for use in poultry are required to submit results of post-approval monitoring for the development of antibiotic resistance to the FDA. The studies are ongoing. It seems inappropriate for CVM/FDA to require these studies and then ban the use of the antibiotics before the data are acquired and evaluated. It would be premature to push for a ban on the use of such antibiotics without evidence that their use has resulted in the development of unacceptable levels of antibiotic resistance.

In summary, restricting the use of antibiotics in poultry should be based on the scientific determination that such use poses an unacceptable risk to the public health. It should not be based on possibilities and speculation. The poultry industry has been built with the help of good science and it can accept a regulatory action on the antibiotic issue if it is founded in science. Without the science there should be no changes in allowable antibiotic uses. If direct connections can't be made between a suspected cause and effect, perhaps they aren't there.

Thank you for allowing this association to comment on this critically important issue.

Sincerely,



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Vice President, Research and Technology
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CB/jcs

p. 5, lines 123-124

The level of impurities should be assessed by comparing three postmodification batches to the range of historical data from ten premodification commercial batches.

This sentence should be changed to read, "The level of impurities should be assessed by comparing three postmodification batches to the range of historical data from ~~ten~~ **three** premodification commercial batches.

Rationale - Ten recent premodification batches may be difficult to obtain for small sales products. These low volume, occasionally produced products may have limited historical data. Since data may be obtained from three postmodification batches, then data from three premodification batches should be used for comparison.

p. 5, lines 137-138

1.b. Existing impurities, including residual organic solvents, are at or below the upper statistical limit of historical data.

This sentence should be changed to read, "Existing impurities, including residual organic solvents, are **within specifications or, if not specified,** are at or below the upper statistical limit of historical data.

Rationale -- Specifications are developed from historical data for the product prior to the change and then applied to the product after a change. Also, this statement is similar to p. 6, lines 149-151.

p. 5, lines 139-140

1.c. ***Total*** *impurities are at or below the upper statistical limit of historical data.*

This sentence should be changed to read, "Total impurities are **within specifications or, if not specified,** are at or below the upper statistical limit of historical data.

Rationale -- See rationale under p. 5, lines 137-138 above.

p. 6, lines 149-150

2.b. Existing impurities, including residual organic solvents, are within the stated limits or, if not specified, at or below the upper statistical limit of historical data.

This sentence should be changed to read, "Existing impurities, including residual organic solvents, are within ~~the stated limits~~ **specifications** or, if not specified, at or below the upper statistical limit of historical data."

Rationale -- See rationale under p. 5, lines 137-138 above.

p. 6, lines 152-153

2.b. Total impurities are within the stated limits or, if not specified, are at or below the upper statistical limit of historical data.

This sentence should be changed to read, "Total impurities are within the stated limits specifications or, if not specified, are at or below the upper statistical limit of historical data."

Rationale -- See rationale under p. 5, lines 137-138 above.

p. 6, lines 170-172

When equivalence cannot be demonstrated at commercial scale, the reviewing division should be contacted.

This sentence should be deleted.

Rationale -- The responsibility for contacting the Agency is on the ANDA holder and not the drug substance manufacturer.

p. 7, lines 173-177

Additional purification procedures (or repetition of an existing procedure on a routine basis) to achieve equivalence with prechange material after the final intermediate are not covered under BACPAC I. However, modified purification procedures prior to the final intermediate can be filed under BACPAC I (see section IV. C for process changes and section IV. D for multiple changes).

This paragraph should be changed to read, "Additional purification procedures, **modified purification procedures,** or repetition of an existing procedure on a routine basis to achieve equivalence with prechange material after the final intermediate ~~are not~~ can be covered under BACPAC I. ~~However, modified purification procedures prior to the final intermediate can be filed under BACPAC I~~ (see section IV. C for process changes and section IV. D for multiple changes).

Rationale -- These changes more clearly explains what changes may be covered under BACPAC I.

p. 7, line 200

- *Conforms to historical particle size distribution profile.*

This sentence should be changed to read, **"Is within the stated specifications or, if not specified,** conforms to historical particle size distribution profiles."

Rationale -- See rationale under p. 5, lines 137-138 above.

p. 7, lines 201-203

NAPM feels that the Decision Tree developed by the PhRMA BACPAC Work Group published in an article entitled, PhRMA Bulk Active Postapproval Changes (BACPAC) Decision Tree, *Pharmaceutical Technology*, pp. 68-76, September, 1998 is more appropriate than the Decision Tree that appears in this guidance. (A copy of this article is attached).

p. 8, lines 219-221

The new site, which may be within a single facility, within a contiguous campus, or in a different campus, should have similar environmental controls.

This sentence should be deleted.

Rationale -- Environmental controls may be different at different manufacturing sites. Environmental controls are considered on p 8, lines 225-226 which states that the manufacturing facilities should operate according to current GMPs.

p. 8, lines 227-229

Site changes within a single facility that fall within the scope of sections IV. A and IV. A. 1 need not be filed with the Agency, and equivalence testing as described in this document need not be carried out.

Change this sentence to read, "Site changes within a single facility **or contiguous campus** that fall within the scope of sections IV. A and IV. A. 1 need not be filed with the Agency, and equivalence testing as described in this document need not be carried out.

Rationale -- The addition of "or contiguous campus" makes the sentence more inclusive.

p. 9, lines 248-250

Delete the phrase, *"if relevant to the finished dosage form performance."*

Rationale -- The drug substance manufacturer does not have the responsibility to determine the relevance to the finished dosage form performance. The finished dosage form manufacturer is responsible for the performance for the drug product.

p. 9, lines 254-255

When equivalence is not established, the need for qualification of impurities and studies to ensure bioequivalence of the dosage form should be considered.

This sentence should be changed to read. "When equivalence is not established, the need for qualification of impurities and studies to ensure bioequivalence of the dosage form should be considered **by the applicant**.

Rationale -- The drug substance manufacturer does not have the responsibility for considering the need to perform a bioequivalence study. The finished dosage form manufacturer is responsible for this determination.

p. 9, lines 255-257

The additional data that should be submitted will depend on the individual case, and the appropriate review division(s) should be contacted for guidance.

This sentence should be changed to read. "The additional data that should be submitted **by the applicant** will depend on the individual case, and the appropriate review division(s) should be contacted for guidance.

Rationale -- The responsibility for notifying the Agency should be on the ANDA holder and not the drug substance manufacturer. Any additional data should be filed by the applicant.

p. 9, line 261, Filing Documentation

The guidance does not indicate whether the drug substance manufacturer or the finished dosage form manufacturer (i.e, ANDA holder) is responsible for filing documentation.

p. 10, lines 295-296

Delete the phrase, *"if relevant to the finished dosage form performance."*

Rationale -- The drug substance manufacturer does not have the responsibility to determine the relevance to the finished dosage form performance. The finished

dosage form manufacturer is responsible for the performance for the drug product.

p. 10, lines 305-306

NAPM does not understand how the outsourced intermediate is affected by the scale change. Does the drug substance manufacture need to report to the Agency if the outsource supplier has scaled up? Normally, a certificate of analysis is obtained from the outsource supplier.

p. 10, line 323

`The term, *"significant change,"* needs to be defined in this document.

p. 13, lines 371-373
p. 15, lines 414-416
p. 16, lines 453-455
p. 18, lines 507-509

This sentence needs further clarification as to the type of data required in the report. In addition, the guidance does not state where and when the report must be filed.

p. 13, lines 381-382
p. 15, lines 429-430
p. 16, lines 469-470
p. 18, lines 524-525

Delete the phrase, *"if relevant to the finished dosage form performance."*

Rationale -- The drug substance manufacturer does not have the responsibility to determine the relevance to the finished dosage form performance. The finished dosage form manufacturer is responsible for the performance for the drug product.

p. 15, lines 433-435
p. 16, lines 472-474
p. 18, lines 528-530

When equivalence is not established, the need for qualification of impurities and studies to ensure bioequivalence of the dosage form should be considered.

This sentence should be changed to read. "When equivalence is not established, the need for qualification of impurities and studies to ensure bioequivalence of the dosage form should be considered **by the applicant**.

Rationale -- The drug substance manufacturer does not have the responsibility for considering the need to perform a bioequivalence study. The finished dosage form manufacturer is responsible for this determination.

p. 17, lines 477-478

- *A Certificate of Analysis from the supplier for each outsourced intermediate affected by the process change.*

As discussed under p. 10, lines 305-306, NAPM does not understand how the outsourced intermediate is affected by the scale change. Normally, a certificate of analysis is obtained from the outsource supplier.

p. 18, lines 503-505

A change-control protocol is a current GMP/SOP issue.

p 22, Attachment B

A definition for the term, "raw materials" should be added to this section.

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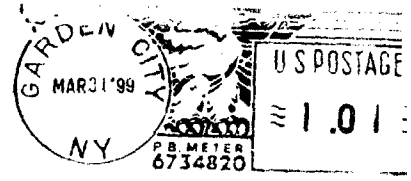

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