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Dated: April 12, 2000.

William K. Hubbard,

Senior Associate Commissioner for Policy, Planning, and Legislation.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 98D-0969]

Risk Assessment of the Public Health Impact of Streptogramin Resistance in *Enterococcus faecium* Attributable to the Use of Streptogramins in Animals; Request for Comments and for Scientific Data and Information

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; request for comments and for scientific data and information.

SUMMARY: The Food and Drug Administration (FDA), Center for Veterinary Medicine (CVM), is announcing plans to develop a prototypic risk assessment (RA) model that accounts for the transfer of resistance determinants from bacteria in food-producing animals to bacteria in humans. The agency requests comments on their approach to the RA model and requests that scientific data and information relevant to the conduct of the RA be submitted. This model will be applied to assess the association between the development of streptogramin (quinupristin/dalfopristin (QD)) resistant *Enterococcus faecium* in humans and the use of virginiamycin in food-producing animals. The center will attempt to use the RA model to quantify the human health impact attributable both to direct acquisition of resistant *E. faecium* from food-producing animals and to the transfer of resistance determinants from *E. faecium* in food-producing animals to *E. faecium* in humans.

DATES: Submit written comments, scientific data, and information by June 19, 2000.

ADDRESSES: Single copies of "A 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" (hereinafter referred to as the Framework Document) is discussed in the **SUPPLEMENTARY INFORMATION** section of this document and may be obtained by writing to the Communications Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855. Send one self-addressed adhesive label to assist the office in processing your request. This document is also available through CVM's homepage on the Internet at <http://www.fda.gov/cvm/fda/mappgs/antitoc.html>. Submit written comments, scientific data, and information to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Nicholas E. Weber, Center for Veterinary Medicine (HFV-150), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-827-6986, FAX 301-594-2298, or e-mail nweber@cvm.fda.gov.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of January 6, 1999 (64 FR 887), FDA published a notice of availability of a discussion paper (the Framework Document). This Framework Document sets out a conceptual risk-based process for evaluating the microbial safety of antimicrobial drugs intended for use in food-producing animals. The proposed RA furthers the tenets of the Framework Document by developing a RA model to quantify the potential human health impact of resistant bacteria acquired from animals via food.

Thus, CVM proposes to conduct its second antimicrobial resistance RA. A draft of CVM's first antimicrobial resistance RA model and associated documents are available on CVM's homepage on the Internet at <http://www.fda.gov/cvm/fda/mappgs/ra/risk.html>. The first RA modeled the human health impact of fluoroquinolone resistant *Campylobacter* infections associated with the consumption of chicken. CVM proposes to develop a second RA that will account for both the acquisition of resistant bacteria and the transfer of resistance determinants from bacteria in food-producing animals to bacteria in humans. This model will be applied to assess the association between the

presence of streptogramin (QD) resistant *Enterococci faecium* in humans and the use of streptogramins (virginiamycin) in food-producing animals as an example of risk attributed to transference of resistance determinants.

In September 1999, FDA's Center for Drug Evaluation and Research approved Synercid™, a streptogramin (QD), for use in human medicine for treatment of vancomycin resistant *E. faecium* (VREF) bacteremias as well as for treatment of *Staphylococcus aureus* and *Streptococcus pyogenes* skin and soft tissue infections. At the current time, QD is considered to be the last line of therapy for VREF. Another streptogramin, virginiamycin, has been used in food-producing animals for 26 years. The initial approval was for chickens, but virginiamycin was subsequently approved for use in turkeys, swine, and most recently in cattle. This RA will seek to quantify the public-health risk attributable to the use of virginiamycin in food-producing animals. *Enterococcus faecium* that develop resistance due to exposure to virginiamycin also demonstrate reduced susceptibility to QD. These resistant strains of *E. faecium* can contaminate meat products and thereby enter the human intestine. It is thought that these resistant strains contaminating meat products may cause problems for the human in two major ways: By becoming host-adapted or by transferring resistance determinants to endogenous human *E. faecium*.

It is generally believed that the indigenous intestinal microflora of healthy humans inhibit colonization by bacteria from exogenous sources. In the case of illness requiring antibiotic therapy however, associated perturbations due to drug treatment may result in colonization by organisms not included in the flora of healthy individuals. This scenario could result in the intestinal colonization and proliferation of antibiotic resistant bacteria from the external environment. Enterococcal infections comprise 20 to 30 percent of over 2 million hospital-acquired infections per year in the United States (Ref. 1). VREF infections are almost exclusively hospital infections and account for about 14 percent of all enterococcal infections, although this varies widely (5 to 70 percent) from hospital to hospital, according to hospital vancomycin use, teaching versus nonteaching hospital status, and hospital size (number of beds) (Refs. 1 and 2). This translates to about 70,000 VREF infections per year which will most likely be treated with QD. Among VREF bacteremic patients treated with QD, emerging resistance

has been documented in about 4 percent of cases (Ref. 3).

QD is a mixture of streptogramin A (S_A) and streptogramin B (S_B) compounds. Resistance to Type B streptogramins is widespread among enterococci and other organisms. S_B resistance is due to hydrolysis of the antibiotic mediated by the *vgb* gene (Ref. 4), or more commonly, by ribosomal methylation mediated by the *ermB* gene product (Ref. 5). Expression of *erm* confers collateral resistance to macrolides, lincosamides, and streptogramin B (MLS_B) antimicrobials. Expression of S_B resistance determinants is not sufficient to confer resistance either to S_A or to the combination of compounds (Ref. 6). S_A resistance has been linked to two genes in *E. species*, *sata* (Ref. 7) and *satG* (Ref. 8). These genes encode related enzymes that inactivate the drug by acetylation, and expression imparts resistance to the mixture of S_A and S_B . Both genes have been found on plasmids and shown to be transferable *in vitro* to susceptible strains. However, a number of S_A resistant enterococci carry neither locus (Ref. 9), indicating that the complete complement of streptogramin resistance determinants has not been identified in enterococci.

Data on the prevalence of QD resistance in hospitals, the environment, and the community is sparse. QD-resistant *E. faecium* has been detected in the stools of healthy adults in the community. Because these individuals had not received QD therapy, some have assumed that the resistant strain entered the human population from an agricultural food production environment where virginiamycin is used or, possibly, following exposure to other drugs that conferred cross-resistance to streptogramins.

The prevalence of streptogramin resistant enterococci in the animal production environment and on animal derived food is largely unknown. For the purpose of this RA, data on human exposure to enterococci through the food supply and the rate at which these organisms possess determinants conferring resistance to streptogramin antibiotics is critical. Preliminary data collected on isolates from the poultry production environment suggest that about 65 percent of *E. faecium* are resistant to streptogramins (MIC \geq 4 μ g/ml) (Ref. 10). Data on the prevalence of these organisms and their antibiotic resistance phenotypes associated with retail products are very limited but critical to the RA process.

II. Objectives of the Risk Assessment

FDA is planning to conduct a RA of the potential harm to hospitalized patients by *E. faecium* resistant to the streptogramin combination drug (QD) associated with the use of virginiamycin in food-producing animals. A RA is a systematic and comprehensive collection and analysis of information that promotes an understanding of the interactions of various factors in a complex situation and provides a basis for making decisions. One goal of this RA is to organize a broad array of information and to study the complex set of interactions necessary to review the current uses of virginiamycin and their impact on public health in an effort to make sound science-based decisions. An underlying goal of this RA is to provide experience and a method for modeling risk involving transfer of resistance determinants from strains of bacteria found in food-producing animals to those found in people. It is anticipated that the RA will reveal data gaps and help guide the industry, FDA, and related agencies in setting research priorities.

III. Risk Assessment Plan

FDA's RA plan will attempt to determine the relationship between the use of virginiamycin in food-producing animals, and the development and dissemination of QD-resistant *E. faecium* in contaminated meat products. Examination of this relationship will be used to describe health effects in humans resulting from exposure to meat contaminated with QD resistant *E. faecium*. To accurately assess human exposure to QD-resistant *E. faecium* from contaminated meat, the RA will seek and analyze the following four types of information concerning the epidemiology of foodborne QD-resistant *E. faecium*. Information concerning the molecular epidemiology and associated carriage of resistance determinants of *E. faecium* with respect to the on-farm environment, carcass/retail meat contamination, other foods, and to the human community (both within and outside of the hospital setting) will be collected and analyzed.

1. Concerning the on-farm component of the RA, CVM will analyze epidemiological evidence pertaining to the following areas in each animal species studied: The prevalence of *E. faecium* colonization, the proportion of animals exposed to virginiamycin, the rate of selection of QD resistance in *E. faecium*, the emergence and dissemination of QD resistance determinants in virginiamycin exposed

live animals and in their environment (including the level of fecal shedding).

2. The RA will also seek to collect and analyze information on the frequency of occurrence of post-slaughter contamination with QD resistant *E. faecium* to include carcass and retail sampling, and, where data are available, the impact of other agricultural sources of QD resistant *E. faecium* on food products destined for human consumption. Modeling may be used when data are collected at slaughter and retail outlets to estimate actual human exposure.

3. Human exposure is a function of QD-resistant *E. faecium* prevalence in the food supply and the consumption patterns of the population. The level of QD-resistant *E. faecium* contamination of meat destined for human consumption is very critical exposure information. Thus, the RA will evaluate information on the level of QD-resistant *E. faecium* in retail meat classes where data are available and combine this information with food consumption patterns. The RA will then produce estimates of QD-resistant *E. faecium* gut flora colonization likely given the levels of meat consumption by different subpopulations.

4. The RA will include an examination of the number of people who may enter the hospital colonized with QD-resistant *E. faecium*, and the proportion of those who are likely to develop VREF infections and require QD treatment. In addition, the RA will seek to evaluate the rate of emergence of QD-resistant *E. faecium* in the hospital environment and its dissemination within the hospital setting.

The RA process will seek to quantify the risk associated with virginiamycin use in animals utilizing data and information in a number of areas including: Prevalence of QD-resistant *E. faecium* pre- and post-slaughter contamination; molecular epidemiology of *E. faecium* carriage of resistance determinants in animal, community, and human clinical isolates; epidemiology of community and hospital sources of QD-resistant *E. faecium*; and prevalence of QD-resistant VREF infections, and molecular fingerprinting and epidemiology of QD resistance transfer to VREF in humans. All uncertainties and assumptions will be identified and documented. The RA process will also include an evaluation of the adequacy of current scientific knowledge, data, and information. This will be used to suggest where future research could be directed to reduce the uncertainty in the risk estimate.

IV. Data and Information Requested

FDA requests comments on the RA approach outlined in the RA plan and the submission of any information relevant to the RA. The purpose of the request for comments and data is to gather relevant information from a broad base of stakeholders to help the agency develop a science-based RA model. While some preliminary data are available, as indicated in section I of this document, the agency specifically requests data that would help to quantify the steps outlined in section III of this document. A list of requested information is presented below; however, the list is not exhaustive, and the agency encourages submission of any additional data relevant to this RA. The requested information includes, but is not limited to the following:

1. The prevalence of *E. faecium* and the prevalence of QD resistant *E. faecium* among all *E. faecium* in food-producing animals;
 2. Virginiamycin use information, including the proportion of food-producing animals in each class that receive virginiamycin;
 3. The prevalence of carcasses contaminated with *E. faecium* and among those, the prevalence of carcasses contaminated with QD-resistant *E. faecium*;
 4. Procedures during slaughtering and food processing which modify enterococcal contamination and load on the carcass or product;
 5. The prevalence and load of QD-resistant *E. faecium* in humans in the community acquired from contaminated meat products of each class;
 6. Consumption and food preparation patterns that would aid in apportioning potential *E. faecium* ingestion among chicken, turkey, pork, beef, and other sources;
 7. The prevalence of colonization by *E. faecium* and infection rates due to *E. faecium* in humans, for: (a) All *E. faecium*, (b) vancomycin resistant *E. faecium*, (c) QD-resistant *E. faecium*, and (d) QD-resistant/vancomycin resistant *E. faecium*;
 8. The rate at which QD resistance and vancomycin resistance will be transferred among *E. faecium* in humans;
 9. The enterococcal disease infection rate among humans harboring vancomycin resistant *E. faecium*;
 10. Genetic fingerprinting for molecular epidemiology of *E. faecium* strains and details of the mechanisms of associated resistance, including gene identification; and
 11. Other pertinent data.
- FDA's CVM requests that reports of data include a description of the

population from which samples were taken and a description of sampling and culture procedures used. All prevalence information or rates need to be provided with numerators and denominators. Likewise, count data is most useful if it is provided with information about the distribution of counts, such as with a range or with the mean and standard deviation. For the RA to become a useful regulatory tool for protection of public health in the United States, it must be based on good quality, contemporaneous data gathered in the United States, or from populations demonstrated to be representative of the U.S.-population.

FDA believes that the credibility and validity of the RA requires that the process for the conduct of the RA be transparent, and all data and information evaluated in the context of the RA and utilized in the RA should be publicly available. Accordingly, any data or information submitted in response to this document should be in a form that permits public disclosure. Submitters of data and information should not mark any information as "Confidential" and should fully expect that any data or information submitted will be made available to the public. Questions regarding the public availability of data and information submitted in response to this document, including questions on maintaining confidentiality while maximizing the utility of the data, should be directed to the contact person above.

As noted, the purpose of this request for data is to gather relevant information to facilitate a valid RA of the human health impact attributable both to direct acquisition of resistant *E. faecium* from food-producing animals and to the transfer of resistance determinants from *E. faecium* in food-producing animals to *E. faecium* in humans. The larger goal is the development of a prototype quantitative RA model that incorporates a segment modeling the transfer of resistance determinants from animal bacteria to human bacteria. This model along with CVM's first quantitative antimicrobial RA model for acquisition of resistant food-borne bacteria will be used to help the agency make appropriate risk management decisions about the use of antimicrobials in food-producing animals. Accordingly, it is acceptable that data submitted in response to this document be "blinded" in the sense that the data need not identify the particular manufacturer, animal producer, or processor that was the source of the samples underlying the results. However, the agency must be assured of the validity of the study design and data.

The RA team plans to present a summary of responses to this document as part of the completed RA document.

Comments and scientific data and information should be addressed to the Dockets Management Branch (address above) and identified with the docket number found in brackets in the heading of this document. Received materials may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

V. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. The Centers for Disease Control and Prevention National Nosocomial Infections Surveillance (NNIS) System, NNIS Report, data summary from October 1986 to April 1996, issued May 1996, *American Journal of Infection Control*, 24(5), pp. 380-388, 1996.
2. Moellering, R. C., P. K. Linden, J. Reinhardt, E. A. Blumberg, et al., "The Efficacy and Safety of Quinupristin/dalfopristin for the Treatment of Infections Caused by Vancomycin-resistant *Enterococcus faecium*," Synercid Emergency Use Study Group, *Journal of Antimicrobial Chemotherapy*, 44(2), pp. 251-261, 1999.
3. Huycke, M., D. Sahm, and M. Gilmore, "Multiple-Drug Resistant Enterococci: The Nature of the Problem and an Agenda for the Future," *Emerging Infectious Diseases*, 4(2), pp. 239-249, 1998.
4. Jensen, L. B., A. M. Hammerum, F. M. Agerstrup, A. E. Van Den Gofaard, and E. E. Stobberingh, "Occurrence of *satA* and *vgb* Genes in Streptogramin-resistant *Enterococcus faecium* Isolates of Animal and Human Origins in The Netherlands," *Antimicrobial Agents and Chemotherapy*, vol. 42, pp. 3330-3331, 1998.
5. Leclercq, R., and P. Courvalin, "Bacterial Resistance to Macrolide, Lincosamide, and Streptogramin Antibiotics by Target Modification," *Antimicrobial Agents and Chemotherapy*, 35(7), pp. 1267-1272, 1991.
6. Bozdogan, B., and R. Leclercq, "Effects of Genes Encoding Resistance to Streptogramins A and B on the Activity of Quinupristin-Dalfopristin Against *Enterococcus faecium*," *Antimicrobial Agents and Chemotherapy*, 43(11), pp. 2720-2725, 1999.
7. Rende-Fournier, R., R. Leclercq, M. Galimand, J. Duval, and P. Courvalin, "Identification of the *satA* Gene Encoding a Streptogramin A Acetyltransferase in *Enterococcus faecium* BM4145," *Antimicrobial Agents and Chemotherapy*, 37(10), pp. 2119-2125, 1993.
8. Werner, G., and W. Witte, "Characterization of a New Enterococcal Gene, *satG*, Encoding a Putative Acetyltransferase Conferring Resistance to Streptogramin A Compounds," *Antimicrobial Agents and Chemotherapy*, 43(7), pp. 1813-1814, 1999.

9. Soltani, M., D. Beighton, J. Philpott-Howard, N. Woodford, "Mechanisms of Resistance to Quinupristin-dalfopristin among Isolates of *Enterococcus Faecium* from Animals, Raw Meat, and Hospital Patients in Western Europe," *Antimicrobial Agents and Chemotherapy*, 44(2), pp. 433-436, 2000.

10. English, L. L., J. R. Hayes, D. G. White, S. W. Joseph, L. E. Carr, and D. D. Wagner, "Antibiotic Susceptibility Profiles of *Enterococcus* Isolates from the Poultry Production Environment," Abstract J17, 2000 *FDA Science Forum FDA and the Science of Safety: New Perspectives*, p. 73, 2000.

Dated: April 11, 2000.

Margaret M. Dotzel,

Acting Associate Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket Nos. 00D-1086, 00D-1087, 00D-1088, 00D-1089, 00D-1090, and 00D-1091]

Guidance Documents for Premarket Notification (510(k)) Submissions for Six Devices; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of six guidance documents. These six guidance documents are intended to serve as special controls for six devices that FDA has proposed previously to reclassify from class III (premarket approval) to class II (special

controls). Elsewhere in this issue of the **Federal Register**, FDA is reopening the comment period on the proposed reclassification of the six devices and one other device. FDA is now inviting comment on these guidance documents because they were not available for comment at the time of the publication of the proposed reclassification (64 FR 12774, March 15, 1999).

DATES: Submit written comments by July 18, 2000.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Comments should be identified with the docket number for the appropriate guidance document found in the **SUPPLEMENTARY INFORMATION** section. Submit written requests for single copies on a 3.5" diskette of one or more of these guidance documents to the Division of Small Manufacturers Assistance (HFZ-220), Center for Devices and Radiological Health, Food and Drug Administration, 1350 Piccard Dr., Rockville, MD 20850. Send two self-addressed adhesive labels to assist that office in processing your request, or fax your request to 301-443-8818. See the **SUPPLEMENTARY INFORMATION** section for information on electronic access to the guidance documents.

FOR FURTHER INFORMATION CONTACT: Joseph M. Sheehan, Center for Devices and Radiological Health (HFZ-215), Food and Drug Administration, 1350 Piccard Dr., Rockville, MD 20850, 301-827-2974.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of March 15, 1999, FDA published a proposed rule to reclassify 38 preamendments class III devices into class II and to establish special controls for these devices. FDA invited interested persons to comment on the proposed rule by June 14, 1999.

FDA received one request to reopen the comment period for six devices. The request noted that FDA had not made the guidance documents that were proposed as special controls for these six devices available for comment through FDA's Good Guidance Practices (GGP's) (62 FR 8961, February 27, 1997). The request further noted that it was impossible to comment on the proposed reclassification without the guidance documents being available. Therefore, the requester asked that FDA extend the comment period until at least 90 days after the guidance documents are publicly available. FDA agreed with the request. FDA also identified three additional devices for which the agency had not issued the guidance documents proposed as special controls in accordance with the GGP policy.

The agency is announcing the availability of the following six guidance documents (each with a separate docket number) for six of these nine devices. In the near future, FDA will announce the availability of two guidance documents that will address the other three devices.

The six guidance documents, with their docket numbers, and Facts-on-Demand (FOD) numbers are as follows:

Guidance document	Docket No.	FOD No.	21 CFR Section	Device name
Guidance for the Submission of Research and Marketing Applications for Permanent Pacemaker Leads and for Pacemaker Lead Adaptor 510(k) Submissions.	00D-1086	372	870.3260	Pacemaker lead adaptor.
Guidance Document for Vascular Prostheses 510(k) Submissions.	00D-1087	1357	870.3450	Vascular graft prosthesis of less than 6 millimeter diameter.
Guidance for Annuloplasty Rings 510(k) Submissions.	00D-1088	1358	870.3800	Annuloplasty ring.
Guidance for Extracorporeal Blood Circuit Defoamer 510(k) Submissions.	00D-1089	1632	870.4230	Cardiopulmonary bypass defoamer.
Guidance for Cardiopulmonary Bypass Arterial Line Blood Filter 510(k) Submissions.	00D-1090	1622	870.4260	Cardiopulmonary bypass arterial line blood filter.
Guidance for Cardiopulmonary Bypass Oxygenators 510(k) Submissions.	00D-1091	1361	870.4360	Cardiopulmonary bypass oxygenators.

These guidance documents represent the agency's current thinking on premarket notifications for these devices. These guidance documents do

not create or confer any rights for or on any person and do not operate to bind FDA or the public. An alternative approach may be used if such approach

satisfies the applicable statute, regulations, or both. Under FDA's GGP policy, each of these guidance documents is a Level 2 guidance.