DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 98D–0340]

Draft Guidance for Industry: Use of Antibiotic Resistance Marker Genes in Transgenic Plants; Report and Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance entitled ''Use of Antibiotic Resistance Marker Genes in Transgenic Plants: Guidance for Industry'' (the draft guidance) and report entitled ''Report on Consultations Regarding Use of Antibiotic Resistance Marker Genes In Transgenic Plants.'' The report summarizes FDA's recent consultations with outside experts on the use of antibiotic resistance marker genes in transgenic plants. The draft guidance is intended to provide information to crop developers that will assist them on the use of antibiotic resistance marker genes in the development of transgenic plants. In accordance with FDA's good guidance practices (GGP's) for Level 1 guidance, the agency is making the draft guidance available for public comment. The agency is also making the report available for public comment.

DATES: Written comments by December 7, 1998.

ADDRESSES: Submit written comments on the draft guidance and report to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit written requests for single copies of the draft guidance and report to the Division of Product Policy (HFS–206), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 200 C St. SW., Washington, DC 20204. Send two self-addressed adhesive labels to assist that office in processing your requests. Requests and comments should be identified with the docket number found in brackets in the heading of this document. The draft guidance, report, and received comments are available for public examination in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT:

Regarding human food issues: Nega Beru, Center for Food Safety and Applied Nutrition (HFS–206), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–418–3097.

Regarding animal feed issues: William D. Price, Center for Veterinary Medicine (HFV–200), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–827–6652.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of May 29, 1992 (57 FR 22984), FDA published a notice on a policy statement (the 1992 policy) regarding foods derived from new plant varieties, including those derived using genetic engineering techniques. In the 1992 policy statement, FDA specifically discussed antibiotic resistance selectable marker genes and noted that both the antibiotic resistance gene and the enzyme encoded by the gene, unless removed, are expected to be present in foods derived from plants developed using the markers. The agency acknowledged that, when present in food, enzymes that are encoded by selectable marker genes and that inactivate certain clinically useful antibiotics theoretically might reduce the therapeutic efficacy of antibiotics administered orally. Accordingly, FDA believes that it is important to evaluate such concerns with respect to commercial use of antibiotic resistance marker genes in food, especially those marker genes that will be widely used. In addition, the agency also believes that it is important to consider the possibility that resistance to antibiotics in microorganisms has the potential to spread through horizontal transfer of antibiotic resistance marker genes from plants (59 FR 26700, May 23, 1994). This second consideration was reflected in FDA's evaluation of the safety of the use of the kanamycin resistance (*kan*^{r}) gene product, aminoglycoside 3′-phosphotransferase II (APH(3′)II, also known as neomycin phosphotransferase II or nptII) when the agency amended the food additive regulations to permit the use of APH(3′)II in the development of transgenic tomato, cotton, and oilseed rape.

FDA received several comments from the public regarding the use of antibiotic resistance marker genes in transgenic plants in response to the 1992 policy, and in response to the agency's solicitation for comment regarding the request of Calgene, Inc., for an advisory opinion on the use of the *kan*^{r} gene as a selectable marker in the development of transgenic tomatoes (56 FR 20004, May 1, 1991). FDA responded to these comments when it issued the final rule permitting the use of APH(3′)II in the development of transgenic tomatoes, oilseed rape, and cotton (59 FR 26700 at 26706).

Since FDA's decision approving the use of the APH(3′)II in the development of transgenic tomatoes, cotton, and oilseed rape, the agency has continued to receive inquiries from crop developers as well as from the public regarding the safety and regulatory status of antibiotic resistance marker genes. Therefore, FDA sought to develop sound scientific principles regarding the safety of the use of antibiotic resistance marker genes in the development of transgenic plants intended for food use so as to provide sound scientific guidance to crop developers regarding the safe use of antibiotic resistance marker genes. Toward this end, FDA undertook several consultations with outside experts having expertise in relevant fields including gene transfer and antibiotic resistance. The purpose of the consultations was to determine whether circumstances exist under which FDA should recommend that a given antibiotic resistance gene not be used in crops intended for food use, and if so, to delineate the nature of those circumstances.

A team of scientists from FDA's Center for Food Safety and Applied Nutrition, Center for Veterinary Medicine, and Center for Drug Evaluation and Research held separate consultations with each expert. Following completion of all of the consultations, FDA prepared a report summarizing the discussions in each consultation. The report is entitled ''Report on Consultations Regarding Use of Antibiotic Resistance Marker Genes In Transgenic Plants.'' The agency is by this notice making this report available for comment.

In order to facilitate the consultations, the agency developed several questions to form the basis of the discussions with the outside experts. These questions, enumerated in the report, were not intended to be exhaustive but rather to initiate the discussions with the experts. The agency is aware that there may be relevant issues not covered by these questions, e.g., the likelihood of a mutation in a given antibiotic resistance gene giving rise to resistance to another antibiotic. In commenting on the draft guidance and report, the agency encourages comments on issues that may have not been covered.

With this notice, FDA is announcing the availability of the draft guidance. The draft guidance represents the agency's current thinking on the use of antibiotic resistance marker genes in transgenic plants. It does not create or confer any rights for or on any person and does not operate to bind FDA or the

public. An alternative approach may be used if such an approach satisfies the requirements of the applicable statute, regulations, or both. The draft guidance is being distributed for comment purposes in accordance with FDA's GGP's (62 FR 8961, February 27, 1997); the draft guidance has been designated as Level 1 guidance.

Interested persons may, on or before December 7, 1998, submit written comments regarding the draft guidance and report to the Dockets Management Branch (address above). Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments and requests for copies are to be identified with the docket number found in brackets in the heading of this document. A copy of the draft guidance, report, and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. After consideration of any comments received in response to this notice, FDA will revise the draft guidance as appropriate and will announce its availability in the **Federal Register**.

An electronic version of the draft guidance and report are available on the Internet using the World Wide Web (WWW) at http://vm.cfsan.fda.gov under the heading ''Biotechnology.''

Dated: August 28, 1998.

William B. Schultz,

Deputy Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Care Financing Administration

[HCFA–1045–N]

RIN 0938–AJ16

Medicare Program: Request for Public Comments on Implementation of Risk Adjusted Payment for the Medicare+Choice Program and Announcement of Public Meeting

AGENCY: Health Care Financing Administration (HCFA), HHS.

ACTION: Solicitation of comments; announcement of meeting.

SUMMARY: This notice solicits further public comments on issues related to the implementation of risk adjusted payment for Medicare+Choice organizations. Section 1853(a)(3) of the Social Security Act (the Act) requires the Secretary to implement a risk adjustment methodology that accounts for variation in per capita costs based on health status and demographic factors for payments no later than January 1, 2000. The methodology is to apply uniformly to all Medicare+Choice plans. This notice outlines our proposed approach to implementing risk adjusted payment.

In order to carry out risk adjustment, section 1853(a)(3) of the Act also requires Medicare+Choice organizations, as well as other organizations with risk sharing contracts, to submit encounter data. Inpatient hospital data are required for discharges on or after July 1, 1997. Other data, as the Secretary deems necessary, may be required beginning July 1998.

The Medicare+Choice interim final rule published on June 26, 1998 (63 FR 34968) describes the general process for the collection of encounter data. We also included a schedule for the collection of additional encounter data. Physician, outpatient hospital, skilled nursing facility, and home health data will be collected no earlier than October 1, 1999, and all other data we deem necessary no earlier than October 1, 2000. Given any start date, comprehensive risk adjustment will be made about three years after the year of initial collection of outpatient hospital and physician encounter data. Comments on the process for encounter data collection are requested in that interim final rule. We intend to consider comments received in response to this solicitation as we develop the final methodology for implementation of risk adjustment.

This notice also informs the public of a meeting on September 17, 1998, to discuss risk adjustment and the collection of encounter data. The meeting will be held at the Health Care Financing Administration headquarters, located at 7500 Security Boulevard, Baltimore, MD, beginning at 8:30 a.m. Additional materials on the risk adjustment model will be available on or after October 15, 1998, and may be requested in writing from Chapin Wilson, Health Care Financing Administration, Department of Health and Human Services, 200 Independence Avenue, S.W., Room 435–H, Washington, DC 20201.

DATES: We request that comments be submitted on or before October 6, 1998.

ADDRESSES: Mail written comments (1 original and 3 copies) to the following address: Health Care Financing Administration, Department of Health and Human Services, Attention: HCFA–1045–N, P.O. Box 26688, Baltimore, MD 21207.

If you prefer you may deliver your written comments (1 original and 3 copies) to one of the following addresses:

Room 309–G, Hubert H. Humphrey Building, 200 Independence Avenue, SW., Washington, DC 20201, or

Room C5–09–26, 7500 Security Boulevard, Baltimore, MD 21244–1850

Because of staffing and resource limitations, we cannot accept comments by facsimile (FAX) transmission. In commenting, please refer to file code HCFA–1045–N. Comments received timely will be available for public inspection as they are received, generally beginning approximately 3 weeks after publication of a document, in Room 309–G of the Department's offices at 200 Independence Avenue, SW., Washington, DC, on Monday through Friday of each week from 8:30 a.m. to 5 p.m. (phone (202) 686–7890).

FOR FURTHER INFORMATION CONTACT: Cynthia Tudor, (410) 786–6499.

SUPPLEMENTARY INFORMATION:

I. Background

Since 1985, Medicare payments to risk contracting Health Maintenance Organizations (HMOs) for aged and disabled beneficiaries living in a given county have been based on actuarial estimates of the per capita cost Medicare incurs paying claims on a fee-for-service (FFS) basis in that county. (Medicare's costs in paying claims for beneficiaries with end-stage renal disease are not considered in these county estimates, but are treated separately on a statewide basis.) These county estimates have been adjusted for the demographic composition of that county (age, gender, Medicaid eligibility status, and institutional status) in order to produce a figure representing the costs that would be incurred by Medicare on behalf of an average Medicare beneficiary in the county. These county per capita payment rates, adjusted for the average beneficiary, have been published annually as the county rate book. Prior to January 1998, actual payments for a given HMO enrollee were based on this county rate book amount, adjusted by demographic factors associated with each enrollee. Again, the demographic factors have been age, gender, Medicaid eligibility, and institutional status. This methodology is known as the ''Adjusted Average Per Capita Cost'' (AAPCC) methodology, and HMOs with Medicare contracts under section 1876 of the Social Security Act (the Act) were paid on this basis between 1985 and 1997.