PANTPA are, accordingly, beyond the scope of this rulemaking which deals with implementing the preferential tariff treatment and other customs-related provisions of the Act. Accordingly, it would be inappropriate for CBP to address the comment.

Conclusion

After further review of the matter, and in light of the one comment, CBP has determined to adopt as final, with no changes, the interim rule published in the **Federal Register** (78 FR 63052) on October 23, 2013.

Executive Order 12866

This document is not a regulation subject to the provisions of Executive Order 12866 of September 30, 1993 (58 FR 51735, October 1993), because it pertains to a foreign affairs function of the United States and implements an international agreement, as described above, and therefore is specifically exempted by section 3(d)(2) of Executive Order 12866.

Regulatory Flexibility Act

CBP Dec. 13–17 was issued as an interim rule rather than a notice of proposed rulemaking because CBP had determined that the interim regulations involve a foreign affairs function of the United States pursuant to § 553(a)(1) of the Administrative Procedure Act (APA). Because no notice of proposed rulemaking was required, the provisions of the Regulatory Flexibility Act, as amended (5 U.S.C. 601 *et seq.*), do not apply. Accordingly, this final rule is not subject to the regulatory analysis requirements or other requirements of 5 U.S.C. 603 and 604.

Paperwork Reduction Act

The collections of information contained in these regulations have previously been reviewed and approved by the Office of Management and Budget (OMB) in accordance with the requirements of the Paperwork Reduction Act (44 U.S.C. 3507) under control number 1651–0117, which covers many of the free trade agreement requirements that CBP administers, and 1651–0076, which covers general recordkeeping requirements. The collections of information in these regulations are in §§ 10.2003, 10.2004, and 10.2007 of title 19 of the Code of Federal Regulations (19 CFR 10.2003, 10.2004, and 10.2007). This information is required in connection with general recordkeeping requirements (§ 10.2007), as well as claims for preferential tariff treatment under the PANTPA and the Act and will be used by CBP to determine eligibility for tariff preference under the PANTPA and the Act. The likely respondents are business organizations including importers, exporters and manufacturers.

The estimated average annual burden associated with the collection of information in this final rule is 500 hours. Comments concerning the accuracy of this burden estimate and suggestions for reducing this burden should be directed to the Office of Management and Budget, Attention: Desk Officer for the Department of the Treasury, Office of Information and Regulatory Affairs, Washington, DC 20503. A copy should also be sent to the Trade and Commercial Regulations Branch, Regulations and Rulings, Office of International Trade, U.S. Customs and Border Protection, 90 K Street NE., 10th Floor, Washington, DC 20229–1177. Under the Paperwork Reduction Act, an agency may not conduct or sponsor and a person is not required to respond to a collection of information, unless it displays a valid OMB control number.

Signing Authority

This document is being issued in accordance with § 0.1(a)(1) of the CBP regulations (19 CFR 0.1(a)(1)) pertaining to the authority of the Secretary of the Treasury (or his/her delegate) to approve regulations related to certain CBP revenue functions.

List of Subjects

19 CFR Part 10

Alterations, Bonds, Customs duties and inspection, Exports, Imports, Preference programs, Repairs, Reporting and recordkeeping requirements, Trade agreements.

19 CFR Part 24

Accounting, Customs duties and inspection, Financial and accounting procedures, Reporting and recordkeeping requirements, Trade agreements, User fees.

19 CFR Part 162

Administrative practice and procedure, Customs duties and inspection, Penalties, Trade agreements.

19 CFR Part 163

Administrative practice and procedure, Customs duties and inspection, Exports, Imports, Reporting and recordkeeping requirements, Trade agreements.

19 CFR Part 178

Administrative practice and procedure, Exports, Imports, Reporting and recordkeeping requirements.

Amendments to the CBP Regulations

Accordingly, the interim rule amending parts 10, 24, 162, 163, and 178 of the CBP regulations (19 CFR parts 10, 24, 162, 163, and 178), which was published at 78 FR 63052 on October 23, 2013, is adopted as a final rule.

R. Gil Kerlikowske,

Commissioner.

Approved: May 14, 2014.

Timothy E. Skud,

Deputy Assistant Secretary of the Treasury.

[FR Doc. 2014–11576 Filed 5–20–14; 8:45 am]

BILLING CODE 9111–14–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 172

[Docket No. FDA–2009–F–0303]

Food Additives Permitted for Direct Addition to Food for Human Consumption; Advantame

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA or we) is amending the food additive regulations to provide for the safe use of advantame as a non-nutritive sweetener and flavor enhancer in foods generally, except meat and poultry. This action is in response to a petition filed by Ajinomoto Co., Inc.

DATES: This rule is effective May 21, 2014. See section IX for further information on the filing of objections. Submit either electronic or written objections and requests for a hearing by June 20, 2014. The Director of the Office of the Federal Register approves the incorporation by reference of certain publications listed in the rule as of May 21, 2014.

ADDRESSES: You may submit either electronic or written objections and requests for a hearing identified by Docket No. FDA–2009–F–0303, by any of the following methods:

Electronic Submissions

Submit electronic objections in the following way:

- *Federal eRulemaking Portal: http://www.regulations.gov.* Follow the instructions for submitting comments.

Written Submissions

Submit written objections in the following way:

• *Mail/Hand delivery/Courier (for paper submissions):* Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name and Docket No. FDA–2009–F–0303 for this rulemaking. All objections received will be posted without change to *http://www.regulations.gov,* including any personal information provided. For detailed instructions on submitting objections, see the ''Objections'' heading of the **SUPPLEMENTARY INFORMATION** section.

Docket: For access to the docket to read background documents or objections received, go to *http://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Felicia M. Ellison, Center for Food Safety and Applied Nutrition (HFS–265), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740–3835, 240–402–1264.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Background

In a notice published in the **Federal Register** of July 21, 2009 (74 FR 35871), we announced that Ajinomoto Co., Inc., c/o Ajinomoto Corporate Services LLC, 1120 Connecticut Ave. NW., Suite 1010, Washington DC, 20036, had filed a food additive petition (FAP 9A4778). The petition proposed to amend the food additive regulations in part 172 *Food Additives Permitted for Direct Addition to Food for Human Consumption* (21 CFR part 172), to provide for the safe use of advantame as a non-nutritive sweetener in tabletop applications and powdered beverage mixes.

In a letter dated August 24, 2012, the petitioner informed us that the care of FAP 9A4778 had been transferred from Ajinomoto Corporate Services LLC to Ajinomoto North America, Inc., One Parker Plaza, 400 Kelby St., Fort Lee, NJ 07024.

In an amended notice published in the **Federal Register** of October 26, 2012 (77 FR 65340), we announced that Ajinomoto Co., Inc., c/o Ajinomoto North America, Inc., One Parker Plaza, 400 Kelby St., Fort Lee, NJ 07024, had amended its food additive petition to also provide for the safe use of advantame as a non-nutritive sweetener and flavor enhancer in foods generally, except in meat and poultry.

II. Evaluation of Safety of Advantame

Under section 409(c)(3)(A) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 348(c)(3)(A)), a food additive cannot be approved for a particular use unless a fair evaluation of the data available to FDA establishes that the additive is safe for that use. ''Safe'' or ''safety'' in the context of food additives means that there is ''a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use'' (21 CFR 170.3(i)). To establish with reasonable certainty that a food additive is not harmful under its intended conditions of use, we consider the projected human dietary exposure to the additive, the additive's toxicological data, and other relevant information (such as published literature) available to us. We compare an individual's estimated daily intake (EDI) of the additive from all food sources to an acceptable intake level established by toxicological data. The EDI is determined by projections based on the amount of the additive proposed for use in particular foods and on data regarding the amount consumed from all food sources of the additive. We commonly use the EDI for the 90th percentile consumer of a food additive as a measure of high chronic dietary intake.

A. Chemistry and Intake Considerations of Advantame

Advantame is the common or usual name for the chemical *N*-[*N*-[3-(3-hydroxy-4- methoxyphenyl)propyl]-α-aspartyl]-L-phenylalanine 1-methyl ester, monohydrate (CAS Reg. No. 714229–20–6). The additive is a white to yellowish crystalline powder that is an *N*-substituted derivative of the sweetener aspartame (21 CFR 172.804), with the amino nitrogen of aspartame alkylated with a 3-hydroxy-4-methoxy phenyl moiety. Advantame also is similar to the sweetener neotame, another *N*-substituted derivative of aspartame that is approved as a sweetener in foods generally, except meat and poultry, in accordance with current good manufacturing practice, in an amount not to exceed that reasonably required to accomplish the intended technical effect, in foods for which standards of identity established under section 401 of the FD&C Act (21 U.S.C. 341) do not preclude such use (21 CFR 172.829). Data in the petition show that advantame has a sweetening potency that is approximately 20,000 times that of sucrose, depending on its food application (Ref. 1). The petitioner has proposed the use of advantame in food at levels not in excess of that reasonably required to produce its intended technical effect. We have reviewed results from taste panel studies that investigated the sweetness profile of advantame as a function of concentration in a variety of foods, and these data demonstrate that advantame can be used at self-limiting levels in food (Refs. 1 and 2).

Based upon data from stability studies on advantame, we concluded that advantame is stable under normal storage and use conditions. The stability studies show that degradation of advantame is pH-, time-, and temperature-dependent and is more likely to occur from its use in low pH foods (i.e., acidic foods) during extended storage conditions. Under such extreme conditions, the principal degradation product is *N*-[*N*-[3-(3-hydroxy-4-methoxyphenyl)propyl]-α-aspartyl]-L-phenylalanine (ANS-acid), which is the de-esterified form of advantame. As is the case with neotame, the N-alkyl substituent effectively prevents the common dipeptide cyclization reaction that results in the formation of a diketopiperazine derivative (Refs. 1 to 3).

Further, there is no concern from exposure to these degradation products under either normal or extended storage and use conditions (Refs. 2 and 4).

The petitioner determined the eaters-only EDI of advantame (i.e., the EDI for the population of study subjects that consumed one or more of the foods containing the additive) from its proposed use as a general-purpose sweetener and flavor enhancer at the 90th percentile of consumption to be 10 milligrams per person per day (mg/p/d) for the total U.S. population (all ages) and 8.1 mg/p/d for children (3 to 11 years old). The corresponding mean estimated intakes are 4.9 mg/p/d and 4.6 mg/p/d, respectively. We concur with the petitioner's exposure estimate for advantame (Ref. 2).

We also estimated the eaters-only EDI of the principal degradation product

(ANS-acid), related impurities that may be formed during the manufacture of advantame, and related degradation products that may be formed under certain conditions in food. The eaters-only EDI of the principal degradation product, related impurities, and related degradation products at the 90th percentile of consumption is 0.10 mg/p/d, 0.15 mg/p/d, and 0.20 mg/p/d, respectively, for the total U.S. population (all ages); and 0.08 mg/p/d, 0.12 mg/p/d, and 0.16 mg/p/d, respectively for children (3 to 11 years old) (Ref. 2).

We also estimated the eaters-only dietary exposure to both advantame and its degradation products for other subpopulations, including various age groups of children, and have concluded that the exposure estimated for the U.S. population (all ages) represents the upper-bound cumulative dietary exposure to advantame and its degradation products from food (Ref. 2).

B. Overview of Advantame Safety Studies

In support of the safety of advantame, the petitioner submitted 37 preclinical (animal), clinical (human subjects), and specialty toxicology studies, along with several additional exploratory or screening studies. All pivotal preclinical studies were conducted in accordance with our Good Laboratory Practice (GLP) regulations appearing in 21 CFR part 58, or in accordance with other internationally accepted GLP standards.

The preclinical studies included *in vivo* short-term, sub-chronic, and chronic studies in the rat, mouse, rabbit, and dog, including reproductive and developmental studies in the rat and rabbit. The safety data also included neurotoxicity and immunotoxicity studies in the rat; pharmacokinetic studies in the mouse, rat, and dog; carcinogenicity studies in the mouse and rat; and a series of *in vitro* mutagenicity and genotoxicity studies. The petitioner also submitted studies assessing tolerance in the rabbit and dog, and palatability in the mouse.

In addition, the petitioner submitted four clinical studies that examined tolerance, absorption, distribution, metabolism, and excretion (ADME) of advantame in human subjects. Subjects in the ADME studies included healthy adult males and females, as well as adult males and females with type 2 diabetes.

C. Toxicology/Safety Assessment of Advantame

1. Pharmacokinetics and Metabolism of Advantame

The petitioner conducted pharmacokinetic and metabolism studies in the rat, dog, and humans to support the safety of advantame for human use. The studies were designed to address the metabolic fate (i.e., absorption, distribution, metabolism, and excretion) of advantame.

a. *Absorption of advantame.* Pharmacokinetic parameters estimated from advantame study data show that absorption of advantame and its metabolites occurs almost entirely in the small intestine, and that the amount absorbed can approach 15 percent in humans. Advantame absorption rates varied 2- to 4-fold between individuals. The rat and dog appeared to absorb less advantame than humans (8 to 15 percent as compared to humans). Absorption of advantame was limited by rapid intestinal hydrolysis of the methyl ester in all species.

b. *Distribution of advantame.* The petitioner conducted studies with radiolabelled advantame to identify which organs might accumulate advantame or its metabolites if absorbed. In the rat, the radiolabelled advantame was found primarily in the organs of absorption (gastrointestinal (GI) tract), metabolism (liver), and excretion (GI tract, kidneys, and urinary bladder). Low levels of radioactivity were observed in all other tissues. Distribution of radiolabelled advantame in the dog was studied after oral dosing and was dominated by high concentrations of radioactivity in the organs of absorption, followed by excretory organs, such as the liver and kidneys. There was very little radioactivity detected in other tissues. In a study using radiolabelled advantame in pregnant rats, low levels of radioactivity were observed in the placenta, with no radioactivity observed in the fetuses. Based on these findings, we conclude there is no concern for possible accumulation of advantame or its metabolites at expected human intake levels.

c. *Metabolism of advantame.* Data from metabolism studies using radiolabelled advantame in the rat, dog, and human volunteers showed five metabolites: (1) The methyl ester hydrolysis product (ANS9801-acid); (2) a sulfate conjugate of ANS9801-acid (ANS-a-SO4), *N*-[*N*-[3-(3-sulfoxy-4-methoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine; (3) de-methyoxylated metabolite of ANS9801-acid (RF–1), *N*-[*N*-[3-(3,4-dihydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine; (4) the phenylalanine cleavage product of ANS9801-acid (HF–1), *N*-[3-(3-hydroxy-4-methoxyphenyl)propyl]-L-α-aspartic acid; and (5) 3-(3-hydroxy-4-methoxyphenyl) propylamine (HU–1).

ANS9801-acid represented 40 percent or more of the excreted metabolic products in all species tested. HF–1 and HU–1 were other minor metabolites. These metabolites likely are derived from ANS9801-acid in the intestines. In humans, HF–1 and ANS9801-acid were the only metabolites identified in feces, at 30 ± 12 percent and 52 ± 13 percent of the dose, respectively. Other (uncharacterized) metabolites accounted for 0 to 3 percent of the dose in feces. ANS9801-acid represented 43 percent of urinary radioactivity, with HU–1 and HF–1 representing 35 percent and 19 percent of the urinary radioactivity, respectively. The remaining 2 to 3 percent of urinary radioactivity consisted of uncharacterized metabolites. Overall, 82 to 100 percent of the radioactivity was accounted for in these studies, which is within the acceptable range of recoveries for pharmacokinetic studies.

Methanol and phenylalanine both are released during the metabolism of advantame. The metabolism studies provided by the petitioner indicated that most advantame residues excreted in the feces and urine are in the form of the metabolite ANS9801-acid. At the EDI for advantame, it is unlikely that even 100 percent conversion of advantame to methanol or phenylalanine would affect physiological levels of methanol or phenylalanine. Therefore, we conclude that the amounts of methanol and phenylalanine released from metabolism of advantame do not represent a safety concern (Ref. 5).

d. *Excretion of advantame.* Advantame and its metabolites were rapidly eliminated from the rat and human. The findings were similar in dogs, with the exception of the excretion of the metabolite ANS-a-SO4, which was eliminated more slowly. Advantame has an approximate half-life (the amount of time required for a quantity of a substance to fall to half its initial value) of less than 60 minutes after absorption in humans. The metabolite ANS9801-acid has a half-life of 3 to 5 hours in humans. Ultimately, 90 to 95 percent of absorbed advantame is excreted in the feces and urine within 24 hours of absorption. Based on the review findings from the metabolism and pharmacokinetic studies on advantame, there is no indication that advantame or its metabolites will accumulate in humans. In addition,

given the rapid rates of excretion, there is no indication that advantame or its metabolites will accumulate in the body from the proposed uses of advantame (Ref. 3). The potential intake of the primary metabolite, the ANS9801-acid, as well as other minor metabolites is of no toxicological consequence. Therefore, we conclude that the metabolism and pharmacokinetic studies of advantame do not raise any safety concerns (Ref. 5).

2. Neurotoxicity and Immunotoxicity Assessment of Advantame

The petitioner investigated the potential neurotoxicity of advantame in rats. Within each of the standard toxicology studies submitted, the petitioner also reported physical, behavioral, and clinical observations for each animal, followed by extensive histological evaluations of brain, spinal cord, and peripheral nerves. Data on critical prenatal neurological development were examined in the *in utero* phase of the carcinogenicity/chronic toxicity studies in rats. No treatment-related neurotoxicological effects or abnormal behaviors were seen in animals that were exposed to advantame in these studies.

In addition to examining various general endpoints related to neurological systems within standard toxicology studies, the petitioner conducted a neurobehavioral study in which rats were fed diets containing 10, 100, or 1,000 milligrams per kilogram body weight (mg/kg bw) of advantame. One group of rats was fed a diet containing 3 mg/kg bw of amphetamine sulfate as a positive control. Locomotor activity of the rats was measured for 10 minutes at each dose interval beginning with the pre-dose period followed by measurements performed at 30, 60, 180, and 300 minutes post-dose. The study authors concluded that there were no significant effects of advantame on spontaneous locomotor activity at any dose level under the conditions of the study.

Based on the lack of effect on rat locomotor activity of advantame given at the highest dose, we concluded that the No Observed Effect Level (NOEL) under the conditions of this study was 1,000 mg/kg bw (Ref. 6). Given the lack of signs of neurotoxicity, as well as an absence of histopathological change in the central nervous system (brain and spinal cord) and peripheral nerves in any of the treated animals, we conclude that the neurotoxicity studies of advantame do not raise safety concerns (Ref. 4).

The petitioner presented data for two general, repeat-dose toxicology studies, a 4-week and a 13-week rat study, that evaluated the immunotoxicity potential of advantame. Findings related to various immune responses in these rat studies initially appeared to represent potential immunotoxicity responses (Ref. 7). After further evaluation, we determined that the lymphocyte reduction observed in the studies was due to individual animal variations and not to treatment with advantame. We also evaluated the reported low thymic weights in the high-dose groups of both sexes for the 4-week study and concluded that this change was consistent with a non-specific high-dose stress response because it was limited to the high-dose groups and affected only a few animals. We reviewed the seemingly dose-related degenerative changes in the thymuses of the 13-week female groups and determined that this change likely was incidental because it was not reported in either the 4-week or 2-year rat studies. Overall, we concluded that the immunological findings observed in the two rat studies did not have any toxicological significance as there was no evidence of a treatment-related immunotoxic response (Ref. 8). Based on these evaluations, we concluded that advantame did not cause immunotoxicological effects within the context of these rat studies (Ref. 4).

The petitioner conducted an additional immunotoxicity study in the same rat strain used in the 4-week and 13-week rat studies. In this study, rats were fed diets containing 0 mg/kg bw (control); 1,500 mg/kw bw; 5,000 mg/kg bw; and 15,000 mg/kg bw of advantame for 4 weeks. Groups of 10 rats of each sex were examined at the end of treatment, as well as after a 30-day recovery period. No treatment-related effects were detected in the various immunological parameters examined, including lymphocyte counts, thymus weights, immunophenotyping of lymphocytes, and lymphocyte proliferation assay, in the study. Based on these data, we concluded that advantame did not produce any immunotoxic effects under the conditions of this study (Ref. 9).

3. Human Clinical Studies

The petitioner submitted four human clinical studies as part of the safety data for advantame to demonstrate tolerance of the sweetener in humans. The first clinical study was conducted to investigate the tolerability of advantame when administered orally to healthy adult males at dose levels of 0.1 mg/kg bw, 0.25 mg/kg bw, and 0.35 mg/kg bw. The study also investigated the pharmacokinetic profile of advantame in the same volunteers. We concluded that the oral administration of advantame was tolerable in healthy adult male subjects when administered as a single dose at each dose level without the occurrence of any treatment-related adverse events during a subsequent 7-day observation period (Ref. 10). Based on this study, we concluded that advantame is well tolerated in healthy human males.

The second clinical study was conducted to characterize the metabolic profile of advantame in urine and feces in human subjects. This study investigated the absorption, metabolism, and excretion of radiolabelled advantame after a single oral dose at 0.25 mg/kg bw in six healthy adult male volunteers. In this study, systemic absorption of advantame was reported to be in the range of 9 to 30 percent (Ref. 10). We concluded that data on the pharmacokinetic profile of advantame from this study, although limited, was useful in our evaluation of the safety of advantame. Based on this study, we have no safety concerns with the absorption, metabolism, or excretion of advantame as it was well tolerated in human subjects.

The third clinical study was conducted to investigate the tolerability of repeated daily consumption of a 30 mg dose of advantame (equivalent to 0.375 mg/kg bw/day to 0.5 mg/kg bw/day) over a period of 4 weeks using six healthy subjects of each sex. The study also included a placebo control group consisting of six healthy subjects of each sex that received diets without advantame. Based on results of the study, we concluded that, although there were apparent small differences in blood plasma values of the main metabolite of advantame, ANS9801-acid, the differences were not due to randomization procedures of the study and, instead, were reflective of within-subject variability inherent in the subjects of the study (Ref. 10). We concluded advantame was well tolerated in these subjects and that there were no safety concerns.

The fourth clinical study was conducted as a double blind, placebo-controlled study in diabetic subjects designed to investigate the tolerability of repeated daily consumption of a 30 mg dose (equivalent to 0.375 mg/kg bw/day to 0.5 mg/kg bw/day) of advantame fed daily for 12 weeks, using 18 diabetic subjects of each sex per group. Diabetic subjects in the placebo-controlled group received diets without advantame. Based on the results of this study, we noted that there were no clinically significant changes identified. We concluded that advantame was tolerated

at daily doses up to 0.5 mg/kg bw/day in people with type 2 diabetes.

We raised concerns about the experimental design (e.g., sample size and the randomization procedures) in some of the clinical studies (Ref. 10). However, overall, we ultimately concluded that advantame was well-tolerated in healthy males when fed a single dose of advantame at dose levels of 0.1 mg/kg bw/day to 0.5 mg/kg bw/day. The third and fourth clinical studies showed that advantame was tolerated in healthy males and females and type 2 diabetic males and females when repeatedly fed a dose of 0.375mg/kg bw/day to 0.5 mg/kg bw/day for 4 weeks. The doses administered in the third and fourth studies were approximately 3-fold higher than the EDI for consumers of all ages at the 90th percentile of consumption (Ref. 10).

Pharmacokinetic evaluations of advantame were conducted on blood plasma samples from the human subjects that received single and repeat dose administrations of advantame. Data from these analyses showed that advantame was undetectable in plasma samples 4 hours after its administration. The repeat dosing studies showed variation in the plasma levels of ANS9801-acid for some subjects. The significance of this variability could not be determined because of the small number of subjects examined. However, the variable ANS9801-acid levels were not associated with any clinically significant, treatment-related toxicity in these subjects.

Clinically significant treatment-related toxicities or adverse events were not noted in the advantame-treated groups in any of these clinical studies. Overall, the clinical studies showed that oral administration of advantame was tolerated in humans fed up to 30 mg per day (Ref. 10).

4. Critical Toxicology Studies

We reviewed all studies and supplemental information submitted by the petitioner. During our review, we determined that certain studies were more pivotal in supporting a regulatory decision on the petitioned uses of advantame. We based our determination on the experimental design of the studies as well as the types of the studies' endpoints. We gave greater weight to the studies that examined the reproductive and developmental effects, long-term exposure, chronic toxicity, carcinogenicity potential, and investigations of specific toxicological issues presented by these studies. The critical studies were: (1) A two-generation reproduction study in rats; (2) a chronic (52-week) dog study; (3) a 104-week mouse carcinogenicity study, and (4) a combined 104-week rat carcinogenicity feeding study with *in utero* and chronic (52-week) phases.

a. *Two-generation reproduction study in the rat.* Reproductive performance and fertility were assessed over two generations in rats fed diets containing advantame at levels of 2,000 ppm, 10,000 ppm, or 50,000 ppm. The parental rats received the advantame diet for 10 weeks before pairing and during mating. Parental and first generation female rats continued to receive the advantame treatment throughout gestation, lactation, and until death. A control group of rats received the untreated basal diet for the same period of time. The first generation contained 25 male and 25 females from each of the parent groups and received advantame at the same dietary concentrations as their parents throughout the study until termination. Direct treatment of the first generation rats began at 4 weeks of age for 10 weeks before pairing and mating for the second generation litters. The first generation continued treatment until termination after the second generation litters were weaned.

Under the conditions of this study, advantame administration to rats did not produce any effects on mortality, body weight, estrous cycle, sperm motility, mating, fertility, duration of gestation, outcome of parturition, litter size, sex ratio, pup birth weights, survivability of pups, motor activity of pups, organ weights, or histopathology in either generation. However, at the 50,000 ppm dose level, statistically significant increased feed consumption in the advantame treated rats compared to the control rats during the maturation phases (before pairing) of parental males and first generation males and females was reported. This increased feed consumption, in the absence of any effect on feed conversion efficiency and body weight gain, was not considered toxicologically significant (Refs. 4 and 11). Based upon the findings, we established a No Observed Adverse Effect Level (NOAEL) at the 50,000 ppm dose for advantame-treated rats in this study.

b. *Chronic (52-week) study in dogs.* Chronic toxicity of advantame was evaluated in beagle dogs that were fed diets containing advantame at levels of 0 ppm, 2,000 ppm, 10,000 ppm, and 50,000 ppm over a 52-week period using four dogs/per sex/per group. Two additional dogs per sex were assigned to each dose group as part of a 6-week recovery phase without advantame. This study was performed to evaluate systemic toxicity of advantame in non-rodent species. The only clinical sign related to advantame treatment was the observation of pale feces in all high-dose and some mid-dose dogs of both sexes. We established a NOAEL for this study at the 50,000 ppm dose of advantame, the highest dose tested, equivalent to 2,058 mg/kg bw/day in male dogs and 2,139 mg/kg bw/day in female dogs (Refs. 4 and 12). We also concluded that systemic toxicity in the test animals associated with advantame administration was not apparent.

c. *The 104-week mouse carcinogenicity study.* The carcinogenicity potential of advantame was evaluated in mice (64/sex/group). The mice were fed diets containing advantame at levels of 0 ppm, 2,000 ppm, 10,000 ppm, or 50,000 ppm for 104 weeks beginning when they were approximately 6 weeks old. One hundred seventy-three male and 177 female mice died or were euthanized at the point of near death over the study period. A statistically significant effect of treatment on the distribution of deaths in the various dosing groups compared to the controls was not reported. The study's authors noted that the high death rate was not altered by the administration of advantame and that no specific factors that contributed to this rate were greater in number in the experimental groups compared to the control groups.

We noted a low survival rate of the test animals, a common finding in 2-year bioassays using the CD–1 mouse, and a number of various clinical signs in both the control and treated mice (Ref. 13). Our evaluation of the mouse survival data revealed no evidence of premature deaths that were due to treatment and none of the findings indicated a proliferative response as the cause of early death in these mice. We considered the data available up to the 92-week observation period and determined that 25 or more surviving animals per group was adequate to evaluate the carcinogenic potential for advantame. We concluded that none of the clinical signs observed correlated consistently with a histomorphological diagnosis or were an indication of treatment-related toxicity (Ref. 14).

The Center for Food Safety and Applied Nutrition's Cancer Assessment Committee (CAC) evaluated data from the 104-week mouse study for the carcinogenic potential of advantame. The CAC concluded that oral administration of advantame at doses up to 50,000 ppm for 104 weeks did not produce any treatment-related tumors or any evidence of increased incidences of tumors in mice (Ref. 15). We established a NOEL for female mice of 10,000 ppm

advantame in the diet (based on decreased weight gain at 50,000 ppm) and a NOEL of 50,000 ppm advantame in the diet for male mice, equivalent to 5,693 mg/kg bw/day (Ref. 16).

d. *Combined 104-week rat carcinogenicity study with in utero phase and toxicity phase.* This study included three phases: (1) An *in utero* reproduction phase; (2) a 52-week chronic toxicity phase; and (3) a 104-week oral carcinogenicity phase. In each of the study phases, rats were fed diets containing advantame at levels of 2,000 ppm, 10,000 ppm, or 50,000 ppm. The control groups of rats received a similar diet without advantame for the same period of time. The *in utero* reproduction phase of this study was designed to generate and assess populations of rats that had been exposed to advantame prior to mating, during mating, and throughout gestation and lactation up to weaning and the start of the main chronic and carcinogenicity studies. Four-week-old offspring produced during the parent mating were used to populate the first generation that was subsequently used in the 104-week carcinogenicity study and in the 52-week chronic toxicity rat study. Offspring that did not meet the survival criteria or had abnormal bodyweights were not used, and where possible, the numbers of surviving offspring per litter were reduced by random selection to four males and four females per litter. Adult parent males were killed after mating; adult parent females were killed after litters were weaned. Body weights, feed consumption, and survival rates were evaluated in the parent rats. The abilities to mate and give birth also were evaluated in the parent rats. The numbers of offspring, sex ratios, and litter weights were recorded for the first generation offspring.

Results from the *in utero* phase of the rat study showed that: (1) Fertility, growth, and survival in the parent rats was unaffected by advantame treatment; (2) body weights and feed consumption in the treated parent groups were similar to that seen in the control rats; and (3) initial body weights of the first generation rats that were selected for either the carcinogenicity study or the 52-week toxicity study were not affected by exposure to advantame during preconception, *in utero,* or during weaning.

The chronic toxicity phase of this study consisted of three advantame treatment groups of first generation rats selected from the *in utero* study, with 20 of each sex per group. The rats were fed diets containing advantame at levels of 2,000 ppm, 10,000 ppm, and 50,000 ppm. A group of untreated first generation rats not exposed to advantame was selected to serve as controls for this 52-week phase of the study. An additional 10 rats of each sex were added to the control group and the 10,000 ppm and 50,000 ppm treatment groups to provide animals for a 6-week recovery phase without advantame following their initial advantame exposure period (week 0 to week 52).

The study's authors reported no effect of the administration of advantame on mortality, maternal body weight gain and feed consumption, fertility, or on the growth and survival of offspring during the *in utero* phase. (''*In utero,*'' in this context, refers to the exposure of the developing embryo-fetus within the womb (uterus) of the mother (Parental F0 females).) Two animals died during the course of the treatment phase. These deaths, however, were not dose related. One male in the high-dose group died during the recovery phase.

The CAC evaluated data from the 104-week rat carcinogenicity study for the carcinogenic potential of advantame. The CAC concluded that oral administration of advantame at doses up to 50,000 ppm for 104 weeks did not produce any treatment-related tumors or any evidence of increased incidences of tumors in rats (Ref. 15). We established a NOAEL for this study of 50,000 ppm advantame in the diet, equivalent to an achieved dose of 3,279 and 4,025 mg/kg bw/day in males and females, respectively (Ref. 16). We also concluded that advantame treatment did not result in an increased incidence of tumors in rats.

Based on our review of the previously mentioned critical studies, we concluded that there is no cause for concern regarding the carcinogenicity potential of advantame as proposed for its use as a non-nutritive sweetener and flavor enhancer in foods.

D. Estimating an Acceptable Daily Intake of Advantame

In determining an acceptable daily intake (ADI) for a new ingredient, we rely on a comprehensive evaluation of all relevant studies and information submitted by the petitioner. Four studies had the greatest impact in our reaching a safety decision. These studies are highlighted in table 1.

TABLE 1—SUMMARY OF STUDY DATA PERTINENT TO ESTABLISHING AN ACCEPTABLE DAILY INTAKE VALUE FOR ADVANTAME

Study	Dose range (ppm)	Pivotal [1] Endpoint	NOEL [2] (ppm)	NOAEL [3] (ppm)
Rat two-generation reproductive study	0, 2,000, 10,000, 50,000	ND	10,000	50,000
Dog 52-week study	0, 2,000, 10,000, 50,000	ND	10,000	50,000
Mouse 2-year bioassay	0, 2,000, 10,000, 50,000	ND	10,000	50,000
Rat 2-year bioassay with in utero and 1-year chronic phase.	0, 2,000, 10,000, 50,000	ND	10,000	50,000

[1] ND = None Detected.
[2] NOEL = No Observed Effect Level.
[3] NOAEL = No Observed Adverse Effect Level.

Based on our review of the studies summarized in table 1, we determined the most appropriate study for establishing an ADI for advantame was the combined 104-week rat carcinogenicity study with *in utero* and chronic (52-week) phases. This study was of sufficient length and overall complexity to produce information on chronic exposure, potential toxicity, and potential carcinogenicity of advantame. Therefore, the data from the 1-year chronic phase of this study was chosen to determine the ADI. The primary reasons for selecting it were its length (52-weeks) and the inclusion of a 6-week recovery phase (control, 10,000 ppm, and 50,000 ppm dose groups), the total number of animals in each dose group (20 animals of each sex per group for the chronic phase with 10 additional animals of each sex for groups in the recovery phase), and the high overall animal survival rate. In addition, the results from the 2-year phase showed no indication that advantame is carcinogenic.

Based on the NOAEL for the 1-year chronic toxicity study, we concluded that the appropriate ADI for advantame is 1,970 mg/p/d (Ref. 4). This level is significantly higher than the EDI for advantame of 10 mg/p/d for humans of all ages at the 90th percentile.

III. Comments

We received two comments in response to the advantame food additive petition. One comment merely expressed support for the petitioned use of advantame, providing that safety is shown and the substance is properly declared when used as an ingredient in food. The other comment stated that they did not object to the petition, but rather to the use of advantame as a flavoring substance in food prior to a premarket approval for use as a sweetener and flavor enhancer without declaring advantame as an ingredient on the food label. Because this comment is not relevant to the safety of advantame, it has no bearing on our evaluation of the advantame petition.

IV. Conclusion

We have evaluated the data and other information submitted by the petitioner in support of the safe use of advantame as a general-purpose sweetener and flavor enhancer in food and conclude that there is a reasonable certainty that the substance is not harmful under the petitioned conditions of use. Therefore, we conclude that the food additive regulations should be amended as set forth in this document.

V. Public Disclosure

In accordance with § 171.1(h) (21 CFR 171.1(h)), the petition and the documents that we considered and relied upon in reaching our decision to approve the petition will be made available for public disclosure (see **FOR FURTHER INFORMATION CONTACT**). As provided in § 171.1(h), we will delete from the documents any materials that are not available for public disclosure.

VI. Environmental Impact

We have carefully considered the potential environmental effects of this action and have concluded that it will not have a significant impact on the human environment, and that an environmental impact statement is not required. FDA's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Division of Dockets Management (see **ADDRESSES**) between 9 a.m. and 4 p.m., Monday through Friday.

VII. Paperwork Reduction Act of 1995

This final rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VIII. Section 301(*ll*) of the FD&C Act

Our review of this petition was limited to section 409 of the FD&C Act. This final rule is not a statement regarding compliance with other sections of the FD&C Act. For example, the Food and Drug Administration Amendments Act of 2007, which was signed into law on September 27, 2007, amended the FD&C Act to, among other things, add section 301(*ll*) of the FD&C Act (21 U.S.C. 331(*ll*)). Section 301(*ll*) of the FD&C Act prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FD&C Act (21 U.S.C. 355), a biological product licensed under section 351 of the Public Health Service Act (42 U.S.C. 262), or a drug or biological product for which substantial clinical investigations have been instituted and their existence has been made public, unless one of the exemptions in section 301(*ll*)(1) to (*ll*)(4) of the FD&C Act applies. In our review of this petition, we did not consider whether section 301(*ll*) of the FD&C Act or any of its exemptions apply to food products containing this food additive. Accordingly, this final rule should not be construed to be a statement that a product containing this food additive, if introduced or delivered for introduction into interstate commerce, would not violate section 301(*ll*) of the FD&C Act. Furthermore, this language is included in all food additive final rules that pertain to food and therefore should not be construed to be a statement of the likelihood that section 301(*ll*) of the FD&C Act applies.

IX. Objections

If you will be adversely affected by one or more provisions of this regulation, you may file with the Division of Dockets Management (see **ADDRESSES**) either electronic or written objections. You must separately number each objection, and within each numbered objection you must specify with particularity the provision(s) to which you object, and the grounds for your objection. Within each numbered objection, you must specifically state whether you are requesting a hearing on the particular provision that you specify in that numbered objection. If you do not request a hearing for any particular objection, you waive the right to a hearing on that objection. If you request a hearing, your objection must include a detailed description and analysis of the specific factual information you intend to present in support of the objection in the event that a hearing is held. If you do not include such a description and analysis for any particular objection, you waive the right to a hearing on the objection.

It is only necessary to send one set of documents. Identify documents with the docket number found in brackets in the heading of this document. Any objections received in response to the regulation may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at *http://www.regulations.gov.*

X. References

The following references have been placed on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at *http://www.regulations.gov.*

1. Memorandum from H. Lee, Division of Petition Review, CFSAN, FDA to F. Ellison, Division of Petition Review, CFSAN, FDA, July 28, 2009.
2. Memorandum from H. Lee, Division of Petition Review, CFSAN, FDA to F. Ellison, Division of Petition Review, CFSAN, FDA, December 26, 2012.
3. Memorandum from H. Lee, Division of Petition Review, CFSAN, FDA to F. Ellison, Division of Petition Review, CFSAN, FDA, November 24, 2009.
4. Memorandum from T. S. Thurmond, Division of Petition Review, CFSAN, FDA to F. Ellison, Division of Petition Review, CFSAN, FDA, May 14, 2013.
5. Memorandum from W. Roth, Division of Food Contact Notification, CFSAN, FDA to F. Ellison, Division of Petition Review, CFSAN, FDA, January 22, 2013.
6. Memorandum from T. Walker, Division of Petition Review, CFSAN, FDA to F. Ellison, Division of Petition Review, CFSAN, FDA, December 8, 2011.
7. Memorandum from S.K. Park, Division of Petition Review, CFSAN, FDA to F. Ellison, Division of Petition Review, CFSAN, FDA, April 18, 2011.
8. Memorandum from S. Francke-Carroll and S. Mog, Senior Science and Policy Staff, CFSAN, FDA to T.S. Thurmond, S.K. Park, and C. Whiteside, Division of Petition Review, CFSAN, FDA, March 17, 2011.
9. Memorandum from S. Francke-Carroll and S. Mog, Senior Science and Policy Staff, CFSAN, FDA to C. Whiteside, T.S. Thurmond, and S.K. Park, Division of Petition Review, CFSAN, FDA, March 1, 2013.
10. Memorandum from C. Whiteside, Division of Petition Review, CFSAN,

FDA to F. Ellison, Division of Petition Review, CFSAN, FDA, February 7, 2013.
11. Memorandum from A. Khan, Division of Petition Review, CFSAN, FDA to F. Ellison, Division of Petition Review, CFSAN, FDA, June 22, 2010.
12. Memorandum from T. Walker, Division of Petition Review, CFSAN, FDA to F. Ellison, Division of Petition Review, CFSAN, FDA, December 27, 2011.
13. Memorandum from I. Chen, Division of Petition Review, CFSAN, FDA to F. Ellison, Division of Petition Review, CFSAN, FDA, May 24, 2010.
14. Memorandum from S. Francke-Carroll and S. Mog, Senior Science and Policy Staff, CFSAN, FDA to C. Whiteside and A. Khan, Division of Petition Review, CFSAN, FDA, March 17, 2011.
15. Memorandum from A. Khan, Division of Petition Review, CFSAN, FDA to F. Ellison, Division of Petition Review, CFSAN, FDA, March 3, 2012.
16. CFSAN Cancer Assessment Committee Full Committee Review, Carcinogenicity Evaluation of Advantame, April 27, 2012.

List of Subjects in 21 CFR Part 172

Food additives, Incorporation by reference, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 172 is amended as follows:

PART 172—FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION

■ 1. The authority citation for 21 CFR part 172 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 342, 348, 371, 379e.

■ 2. Add § 172.803 to subpart I to read as follows:

§ 172.803 Advantame.

(a) Advantame is the chemical *N*-[*N*-[3-(3-hydroxy-4-methoxyphenyl)propyl]-α-aspartyl]-L-phenylalanine 1-methyl ester, monohydrate (CAS Reg. No. 714229–20–6).

(b) Advantame meets the following specifications when it is tested according to the methods described or referenced in the document entitled ''Specifications and Analytical Methods for Advantame'' dated April 1, 2009, by the Ajinomoto Co. Inc., Sweetener Department 15–1, Kyobashi 1-chome, Chuo-ku, Tokyo 104–8315, Japan. The Director of the Office of the Federal Register approves this incorporation by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the Office of Food Additive Safety (HFS–200), Center for Food Safety and Applied Nutrition, 5100 Paint Branch Pkwy., College Park, MD 20740. Copies may be examined at the Food and Drug Administration's Main Library, 10903 New Hampshire Ave., Bldg. 2, Third Floor, Silver Spring, MD 20993, 301–796–2039, or at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202–741–6030 or go to: *http://www.archives.gov/federal-register/cfr/ibr-locations.html*.

(1) Assay for advantame, not less than 97.0 percent and not more than 102.0 percent on a dry basis.

(2) Free *N*-[*N*-[3-(3-hydroxy-4-methoxyphenyl)propyl]-α-aspartyl]-L-phenylalanine, not more than 1.0 percent.

(3) Total other related substances, not more than 1.5 percent.

(4) Lead, not more than 1.0 milligram per kilogram.

(5) Water, not more than 5.0 percent.

(6) Residue on ignition, not more than 0.2 percent.

(7) Specific rotation, determined at 20 °C $[\alpha]_D$: −45.0 to −38.0° calculated on a dry basis.

(c) The food additive advantame may be safely used as a sweetening agent and flavor enhancer in foods generally, except in meat and poultry, in accordance with current good manufacturing practice, in an amount not to exceed that reasonably required to achieve the intended technical effect, in foods for which standards of identity established under section 401 of the Federal Food, Drug, and Cosmetic Act do not preclude such use.

(d) If the food containing the additive purports to be or is represented to be for special dietary use, it must be labeled in compliance with part 105 of this chapter.

Dated: May 15, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2014–11584 Filed 5–19–14; 11:15 am]

BILLING CODE 4160–01–P

DEPARTMENT OF DEFENSE

Office of the Secretary

[DOD–2012–OS–0105]

RIN 0720–AB58

32 CFR Part 199

TRICARE Revision to CHAMPUS DRG-Based Payment System, Pricing of Hospital Claims

AGENCY: Office of the Secretary, Department of Defense.

ACTION: Final rule.

SUMMARY: This Final rule changes TRICARE's current regulatory provision for inpatient hospital claims priced under the DRG-based payment system. Claims are currently priced by using the rates and weights that are in effect on a beneficiary's date of admission. This Final rule changes that provision to price such claims by using the rates and weights that are in effect on a beneficiary's date of discharge.

DATES:

Effective Date: This Final rule is effective June 20, 2014.

Applicability Date: This rule applies to claims with a discharge date of October 1, 2014, or later from hospitals paid by TRICARE under the Inpatient Prospective Payment System/Diagnosis-Related Groups-based payment system.

FOR FURTHER INFORMATION CONTACT: Ms. Amber Butterfield, TRICARE Management Activity, Medical Benefits and Reimbursement Office, telephone (303) 676–3565.

SUPPLEMENTARY INFORMATION:

I. Dates

The effective date above is the date that the policies herein take effect and are considered to be officially adopted. The applicability date, which is different than the effective date, is the date on which the policies adopted in this rule shall apply to claims from hospitals paid by TRICARE under the Inpatient Prospective Payment System/Diagnosis-Related Groups-based payment system, and must be implemented.

II. Executive Summary and Overview

A. Purpose of the Final Rule

1. Need for the Regulatory Action

This Final rule amends the TRICARE/CHAMPUS regulatory provision (32 CFR 199.14(a)(1)(i)(C)(3)) of pricing inpatient hospital claims that are reimbursed under the DRG-based payment system from the beneficiary's date of admission, to pricing such