DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

The Honorable Bart Stupak
Chairman
Subcommittee on Oversight and Investigations
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

SEP 2 8 2007

Dear Mr. Chairman:

Thank you for your letter of August 27, 2007, co-signed by John D. Dingell, Chairman, Committee on Energy and Commerce, concerning decisions made by the Food and Drug Administration (FDA or the Agency), regarding the use of carbon monoxide (CO) in modified atmosphere packaging (MAP) for meat products and "tasteless smoke" (which includes CO) for fish.

To provide some background on this matter, we note that under sections 201(s) and 409 of the Federal Food, Drug, and Cosmetic (FD&C) Act (Title 21, *United States Code* [U.S.C.] 321(s) and 348), any substance the intended use of which results or may reasonably be expected to result in its becoming a component of food, or otherwise affecting the characteristics of any food, is a food additive subject to premarket review and approval by FDA, unless the substance falls within one of the exclusions from the definition of "food additive" in section 201(s) or meets the exemption for investigational use in section 409(j) of the FD&C Act. Under section 201(s) of the FD&C Act, substances that are generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use (GRAS), are excluded from the definition of "food additive" and are not subject to the food additive petition process in section 409 of the FD&C Act. The FD&C Act does not provide a process or specific authority for FDA premarket approval of GRAS status.

Under FDA's voluntary GRAS notification program, an interested party may notify the Agency of its conclusion that a substance is GRAS under the intended conditions of use. FDA reviews whether the GRAS notice (GRN) provides a sufficient basis to support the party's GRAS self-determination and then responds to the notifier as to whether the Agency has any questions. Information in the notice corresponding to the substance and conditions of use that are the subject of the GRAS self-determination and FDA's response to the notice are readily available to the public by postings to the Agency's website that are updated regularly (*see http://www.cfsan.fda.gov/~rdb/opa-gras.html*).

As you noted in your letter, FDA responded to three GRAS notices for the use of CO in MAP systems for meat products (GRNs 83, 143, and 167) and one notice for the use of tasteless smoke in tuna (GRN 15). In the case of the GRAS notices concerning these uses of CO and tasteless smoke, FDA responded by stating that the Agency does not question the basis for the GRAS determinations. Therefore, the intended use of CO in MAP systems for meat and tasteless smoke for tuna, as described in the notices, would not be a food additive and would not require FDA premarket review and approval.

FDA has set out what constitutes general recognition of safety for GRAS status in Title 21, Code of Federal Regulations (CFR) 170.30. Importantly, the same quality and quantity of scientific data are needed to support a GRAS determination as are needed to support a food additive approval. However, there are additional criteria for the use of a GRAS ingredient. These criteria include a general availability (such as through publication in the scientific literature) of the data and information relied on to establish the safety of the ingredient and consensus among qualified experts about the safety of the ingredient for the intended use. These two facets (i.e., general availability and consensus) are necessary to establish general recognition.

A substance must be shown to be "generally recognized as safe" under the conditions of its intended use. Explicitly, GRAS is not an inherent property of a substance, rather, it is the specific conditions of use for the substance that is GRAS. The person asserting GRAS status, resulting in exclusion from the definition of "food additive" and exemption from the food additive premarket approval process, has the burden of proving that the use of the substance is "generally recognized as safe." To establish such recognition, the proponent must show that there is a consensus of expert opinion regarding the safety of the use of the substance. Unanimity among experts regarding safety of a substance is not required, and mere conflict among experts is not enough to preclude a finding of general recognition.

FDA has entered into a Memorandum of Understanding (MOU) with FSIS that establishes a process to review the joint listing of ingredients used in the production of meat and poultry products. Consistent with the terms of the MOU, FDA consulted with FSIS on the three GRAS notices for use of CO in MAP systems for meat products. The MOU with FSIS dated January 31, 2000, is enclosed at Tab A.

FDA and FSIS routinely consult to address our related, but separate, roles in the regulation of ingredients in meat. FDA has authority under the FD&C Act to determine the safety of ingredients used in food, while FSIS has separate authority for determining whether the intended use of an ingredient in meat is suitable under the Federal Meat Inspection Act (FMIA). Suitability relates to the effectiveness of an ingredient for its intended use and the assurance that the conditions of use will not result in an adulterated product or one that misleads consumers. Under the FMIA, FSIS also has authority regarding the labeling of meat products. FSIS has informed FDA that the use of CO in MAP systems, under the conditions specified in the GRAS notices, complies with the FMIA.

As you are aware, we have pending citizen petitions on this matter, and we continue to receive and review information relevant to the citizen petitions and to GRNs 15, 83, 143, and 167.

We have restated the specific questions posed in your letter below, in bold type, followed by FDA's response. Documents are provided as noted. FDA continues to search for additional responsive documents.

1. **Upon receiving Precept's purported GRAS notification, did FDA consider that the carbon monoxide in the Precept MAP system was a color additive and therefore not eligible for GRAS status? If not, why not?**

   Please provide all documents, including but not limited to, internal agency and inter-agency communications as well as external communications, relating to the legal determination that carbon monoxide in the Precept MAP system is not a color additive.

Response: Color additives require FDA premarket approval. FDA has previously concluded that substances used to fix the natural color of meats are considered to be color fixatives and not color additives. In 1982, a Federal district court agreed with FDA that nitrites fix rather than impart color in bacon and therefore are not color additives in bacon. The mechanism by which CO acts to stabilize the natural red color of myoglobin in muscle (meat) is well-known and described in the scientific literature (for example, "The storage life of beef and pork packaged in an atmosphere with low carbon monoxide and high carbon dioxide;" Meat Science; Sorheim, O., Nissen, H., and Nesbakken, T.; 52(157-164); 1999). FDA concluded that the use of CO, as described in the GRAS notices, (including the notice for the Precept Foods packaging system) is not a color additive because it does not impart color, but rather fixes the natural red color of myoglobin, the color that consumers associate with meat products.

Documents responsive to your request under this question are enclosed at Tab B.

2. a) **Was the safety risk associated with carbon monoxide's ability to mask indicators of microbial spoilage in fresh meat addressed in FDA's review of this use of carbon monoxide? If not, why not?**

   b) **In particular, did FDA consider the safety implications of consumption by at-risk populations such as the elderly, children, pregnant women, person taking immunosuppressant drugs, or AIDS patients of apparently fresh looking meat containing high levels of bacteria (>$1x10^7$ colony forming units per gram)?**

Response: FDA carefully considered the safety of using CO in MAP systems for meat packaging. Our analysis of the notices considered microbiological safety (i.e., level of contamination) and the data submitted assured us that use of CO in MAP systems would not result in an increased risk of foodborne illness to the consumer.

The color of meat is not a reliable indicator of microbiological safety; contamination of meat by pathogenic bacteria is not, in general, something that a consumer could visually detect. Additionally, CO-containing MAP systems (CO is used only up to 0.4 percent) will behave as other MAP systems do, and will not mask other signs of spoilage, such as off-odor, meat that is slimy or tacky to the touch, or packaging that is bulging because of gas formation from spoilage bacteria.

When FDA does a safety analysis of ingredients added to foods, we look at potential effects across the entire population. Our conclusion that the use of CO in MAP systems would not result in increased risk of foodborne illness applies to the general population because we have concluded that CO does not mask signs of spoilage.

We do not understand the source or relevance of your reference to "...meat containing high levels of bacteria ($>1x10^7$ colony forming units per gram)." We would need further explanation in order to understand the significance of this measurement to meat safety.

3. **a) Given the Agency's own experience with contaminated, decomposed imported fish appearing fresh and wholesome because of carbon monoxide coloring, please explain how FDA concluded that this use of carbon monoxide in fresh meat packaging is deemed GRAS.**

   b) Given the documented controversy and the European ban due to safety concerns, please explain how FDA analyzed this scientific literature under its GRAS standard and concluded that meat and fish treated with CO is "Generally Recognized as Safe."

   c) Did FDA consider the need for a food additive petition for the use of carbon monoxide in fresh meat packaging? If not, why not?

   Please provide all documents, including internal agency communications and notes that were not provided to the Committee in response to our February 9, 2006 request, addressing whether the data and other information in the Precept GRAS notification satisfied FDA's GRAS standard. In particular, please provide all documents relating to the agency's consideration of the European ban.

   Please also provide all records relating to the determination that fish processed using "tasteless smoke" or carbon monoxide is GRAS.

Response: First, to clarify what FDA reviewed, we note that FDA did not receive or review a GRN for the use of CO in fish. Regarding the Agency's review of the use of tasteless smoke, FDA reviewed the data presented in GRN 15 and found no reason to disagree with the conclusion that the use of tasteless smoke on raw tuna before it is frozen to preserve its taste, aroma, texture, and color is GRAS. In our response letter, we explained that if someone were to use tasteless smoke (or any other preservative) on partially decomposed fish, the fish would be adulterated. Additionally, the sale of contaminated fish, whether treated with tasteless smoke or not, is illegal because the product is adulterated.

Although you state that "FDA e-mails and other documents indicate the Agency was well aware of the problem to many species including tuna," you identify only FDA's import bulletin on "Tuna Processed with Tasteless Smoke and/or Carbon Monoxide" issued on May 27, 1999. That import bulletin notes that tasteless smoke or CO may be used to preserve the natural red flesh color of tuna during frozen storage. The import bulletin pointed out concerns that tasteless smoke may be abused to enhance color, and that tuna so treated may not be labeled to indicate that fact. Our response letter to GRN 15, issued on March 10, 2000, clearly explains, as noted above, that abuse of tasteless smoke in a way that attempted to conceal signs of decomposition would render the fish adulterated and illegal. The letter went on to point out that abuse of tasteless smoke in a way that enhanced the color of the flesh so that the fish was made to appear of greater value than it was, would render the fish adulterated and illegal. Finally, the letter pointed out that the use of tasteless smoke to preserve the color of tuna upon freezing and thawing must be indicated in labeling in accordance with the FD&C Act. Thus the response letter to GRN 15 addressed the concerns about potential abuse described in the import bulletin. We note that the import bulletin had an expiration date of 90 days after issuance and that it was canceled on June 17, 2003.

FDA and FSIS reviewed the data presented in the notices for the use of CO in MAP systems for fresh meat. FDA found no reason to disagree with the conclusion that the use of CO in MAP systems for fresh meat is GRAS. As noted elsewhere, the uses described in the notices would not result in the masking of signs of spoilage, such as off-odor, meat that is slimy or tacky to the touch, or packaging that is bulging because of gas formation from spoilage bacteria. The agencies concluded that the uses of CO-containing MAP systems do not mask these signs of spoilage.

FDA is aware that the Scientific Committee on Food of the European Union has concluded that there is no health concern associated with the use of CO as a component in MAP systems for fresh meat provided the temperature during storage and transport does not exceed 4° Celsius. FDA agrees with the Scientific Committee on Food that storing products under inappropriate conditions may result in spoilage. However, FDA and FSIS considered this issue and concluded that under the conditions of use described in the GRAS notices, even at abusive temperatures, whether color is maintained or not, off-odors and slime will persist as indicators of spoilage in meat products. Also, we note that the proper storage and transport of foods is a requirement that all food producers must comply with under U.S. law.

As noted earlier, FDA found no reason to question the basis for the notifiers' conclusion that their use of CO-containing MAP packaging described in the notices is GRAS. Further, as noted earlier, GRAS substances are excluded from the definition of a "food additive" in section 201(s) of the FD&C Act and are therefore not subject to the food additive petition process in section 409 of the FD&C Act (21 U.S.C. 348) or to the requirement that a food additive regulation be promulgated prior to marketing of the product. Because FDA had no reason to question the asserted GRAS status of the substances, the Agency had no basis to consider requiring a food additive petition.

FDA is continuing to search for documents responsive to your request under this question.

4. **a) Did FDA recognize that consumers would presume that bright red color of carbon monoxide-treated meat was a sign that the meat was fresh and safe to eat?**

   b) Did FDA solicit from Precept or obtain from any other source, consumer perception data, to determine whether the unlabeled use of carbon monoxide could induce consumers to purchase and consume meat that is no longer fresh and may not be fit for human consumption? If not, why not?

   c) If FDA believes that color is not an ideal measure of meat freshness and safety, how would the agency advise consumers to select meat packaged in sealed MAP?

   d) Does FDA plan to conduct a consumer education campaign to train consumers away from their traditional reliance on meat color and appearance?

   Please provide all documents relating to FDA's consideration of consumer behavior in meat selection during the course of its review of the GRAS notifications for the use of carbon monoxide in fresh meat packaging. Please also provide all documents, including but not limited to, all internal notes or other memoranda, as well as correspondence with USDA's Food Safety and Inspection Service (FSIS), reflecting FDA's and FSIS's consideration of the ability of carbon monoxide to conceal the true freshness, quality, and safety of meat.

Response: As stated in the MOU, under the FMIA and its implementing regulations, FSIS determines the suitability of the use of ingredients in the production of meat products. Suitability relates, among other things, to the effectiveness of an ingredient for its intended use and includes an assessment of whether the conditions of use will result in an adulterated product or one that misleads consumers. FSIS communicated its conclusions that Precept Foods, LLC's MAP system as set out in GRN 000143 was suitable and would not mislead consumers in FSIS' letter to FDA dated June 2, 2004. This letter was previously provided to Chairman Dingell by FDA in its letter of April 7, 2006. We also refer you to FSIS' letters to FDA setting out their conclusions on suitability and potential for consumer deception in their reviews of other MAP systems using CO in GRN 000083 and 000167. These letters were also previously provided in the April 7, 2006, letter. Therefore, we defer to FSIS to address these questions.

FSIS has authority under the FMIA for determining whether the intended use of an ingredient in meat is suitable, and suitability relates, among other things, to an assurance that the conditions of use will not result in a product that misleads consumers. Thus, the issues relevant to these questions are under the purview of FSIS, and we defer to FSIS to address them.

Documents responsive to your request under this question are enclosed at Tab C.

5. **a) Please explain how FDA addressed the fact that odor cannot be detected when purchased because the meat is sealed in MAP, and that governing law focuses on and prohibits adulteration and deception at the time of purchase.**

   b) Did FDA consider the sizable portion of the population whose sense of smell may be impaired, particularly among those who may also be most vulnerable to food borne illness because of impaired immune systems? If not, why not?

Response: As stated above, under the FMIA and its implementing regulations, FSIS determines the suitability of the use of ingredients in the production of meat products. We refer you to FSIS' conclusions from their review of the GRAS notices for MAP systems using CO on fresh meat in their letters to FDA, which were previously produced in our letter of April 7, 2006. Therefore, we defer to FSIS to answer these questions.

6. **a) FDA has stated that "use or freeze by" date labeling will provide information to consumers sufficient to ensure the safe use of carbon monoxide in fresh meat. Please provide all consumer behavior research or other evidence that supports this assertion, whether submitted in GRAS notifications or obtained independently by FDA.**

   b) Does FDA impose any prominence requirements to ensure that such "use or freeze by" date labeling is appropriately read and understood by consumers so that the inclusion of carbon monoxide in fresh meat MAP does not render the most unsafe? If not, why not?

Response: FSIS regulates the labeling of meat under the FMIA, including "use or freeze by" date labeling. Therefore, we defer to FSIS to answer these questions. Also, we refer you to FSIS' conclusions from their review of the GRAS notices for MAP systems with CO for use on fresh meat in their letters to FDA previously produced in our letter of April 7, 2006.

7. **a) To the extent that FDA considered "use or freeze by" date labeling sufficient to ensure the safe use of carbon monoxide in fresh meat, did the agency consider the fact that temperature abuse would render such date labeling meaningless as an assurance of meat freshness and safety?**

   b) Was FDA's consideration of the GRAS status of carbon monoxide in fresh meat packaging limited to information about use of carbon monoxide under laboratory conditions of ideal temperature control? If so, please explain why FDA disregarded the known prevalence of temperature abuse.

   c) Did FDA recognize that the fear of economic loss associated with meat "browning" has historically provided a strong incentive to assure adequate temperature control of meat throughout the chain of distribution, storage, and retail sale, and that such incentives would be eliminated by this use of carbon monoxide, which conceals evidence of mishandling?

Response: FSIS regulates the labeling of meat under the FMIA, including "use or freeze by" date labeling. FSIS' conclusions from their review of the GRAS notices for MAP systems with CO for use on fresh meat were communicated to FDA by letter and were previously produced in our letter of April 7, 2006. We defer to FSIS to answer the question in 7(a).

With regards to the questions in 7(b) and (c) concerning temperature abuse, FDA did not receive any specific data on temperature abuse as part of GRN 143 submitted by Precept on meats that are shipped in MAP systems. We note, moreover, that we have no information that suggests that meats shipped in MAP systems would behave any differently (e.g., the signs of spoilage would remain the same) than meats that are shipped not using a MAP system, even after temperature abuse.

8. a) How did FDA determine that the 35- and 28-day labeled shelf lives would be adequate to assure the safety and wholesomeness of carbon monoxide-treated meat under actual conditions of distribution, storage, retail sale, and consumer handling?

Given that the European Commission's Scientific Committee on Food concluded that carbon monoxide-treated meat could have a shelf life of 14 days for beef loin steaks and 11 days for ground beef, how did FDA conclude that carbon monoxide-treated meat with shelf lives up to 35 or 28 days was "Generally Recognized as Safe?"

Response: FSIS regulates the labeling of meat under the FMIA, including "use or freeze by" date labeling. Therefore, we defer to FSIS to answer these questions.

9. Please explain whether FDA now disagrees with its own regulation at 21 CFR 173.350 or considers it no longer operative. If so, why has FDA not addressed the matter through notice and comment rulemaking?

Response: FDA considers 21 CFR 173.350 to be in effect and the Agency would enforce this regulation against a violative product if necessary. However, it is important to note that 21 CFR 173.350 does not apply to CO-containing MAP systems for meat products. These systems are not "combustion gas" and therefore, while it is true that under 21 CFR 173.350 combustion gas is not permitted to be used on meats, this regulation does not apply. Thus, there is no reason to consider amending 21 CFR 173.350.

10. a) Please explain how this use of carbon monoxide differs from FDA's regulatory example of chemical preservatives used "to promote color retention," which must be labeled under 21 U.S.C. 343 (k) and 21 C.F.R. 101.22 (j).

b) Please explain why the use of carbon monoxide in fresh meat packaging, which makes the meat red indefinitely, regardless of age or temperature abuse, does not need to be disclosed on the label, as would appear to be the case to comply with 21 U.S.C. 343 (a) and 321 (n).

Response: As noted previously, FSIS regulates the labeling of meat under the FMIA. FSIS set out its conclusions in letters to FDA previously provided to Chairman Dingell in our letter of April 7, 2006. These questions are under the purview of FSIS, and we defer to FSIS to address them.

11. Did FDA deem the carbon monoxide in the Precept MAP system to be a processing aid? If so, please explain how the carbon monoxide in that system satisfies FDA's regulatory definition of a processing aid.

Please provide all records, including but not limited to, internal notes, memoranda, and communications with Precept and FSIS, addressing labeling of the carbon monoxide in Precept's MAP system, including whether it met FDA's definition of a processing aid. To the extent not otherwise requested, please provide all records, including but not limited to, internal notes, memoranda, and inter-agency communications relating to all contacts with FSIS personnel regarding GRN 000143.

Response: FDA did not consider whether the carbon monoxide in the Precept MAP system was a processing aid because, as noted above, FSIS regulates the labeling of meat under the FMIA. However, FDA did consider labeling of tasteless smoke when it considered the use of this CO-containing product to preserve the color of tuna on freezing. In that case, FDA determined that the tasteless smoke was acting as a preservative, and thus must be declared under 21 CFR 101.22(j).

FDA is continuing to search for documents responsive to your request under this question.

12. a) Did FDA consider the labeling requirements for "tasteless smoke" to be a sufficient safeguard to ensure that the use of carbon monoxide "tasteless smoke" did not deceive consumers into purchasing or consuming tuna that may have become unsafe while remaining fresh-looking?

b) If so, what steps has FDA taken to ensure that treated tuna is consistently and appropriately labeled, whether it is pre-packaged or sold by weight in the retail fish case, so that consumers are not deceived by tuna that may appear fresher or safer than it is?

Response: FDA did not impose the labeling requirements as a "safeguard" for the use of tasteless smoke. Rather, requirements for the labeling of tasteless smoke are a means to communicate material facts. FDA's response on the GRAS status of tasteless smoke was limited to the specific conditions of use asserted by the notifier -- that is, that tasteless smoke is GRAS for use on raw tuna, before it is frozen, to preserve its taste, aroma, texture, and color. FDA considered that this use of tasteless smoke would constitute use as a preservative. Products containing a preservative may not be labeled "fresh" (21 CFR 101.95). This regulation is intended to communicate material facts to help ensure that consumers are not deceived.

FDA evaluated all safety concerns regarding the use of tasteless smoke to preserve raw tuna before it is frozen. Under the conditions of use described in GRN 15, we found no reason to disagree with the notifier's conclusion that this use of tasteless smoke is GRAS. We have no evidence that tasteless smoke represents a public health hazard, or that it promotes economic deception when used responsibly and lawfully. Under the FD&C Act, a company must comply with all labeling requirements or the product is, by definition, misbranded and not legal for sale.

Thank you again for your interest in this matter. We hope this information is helpful. Please do not hesitate to contact us if we can provide assistance in the future.

Sincerely,

Stephen R. Mason
Acting Assistant Commissioner
for Legislation

Enclosures