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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 192 and 592

[Docket No. 00N–1396]

RIN 0910–AC15

Premarket Notice Concerning Bioengineered Foods

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to require the submission to the agency of data and information regarding plant-derived bioengineered foods that would be consumed by humans or animals. FDA is proposing that this submission be made at least 120 days prior to the commercial distribution of such foods. FDA is taking this action to ensure that it has the appropriate amount of information about bioengineered foods to help to ensure that all market entry decisions by the industry are made consistently and in full compliance with the law. The proposed action will permit the agency to assess on an ongoing basis whether plant-derived bioengineered foods comply with the standards of the Federal Food, Drug, and Cosmetic Act (the act).

DATES: Submit written comments on the proposed rule by [*insert date 75 days after date of publication in the* **Federal Register**]. Submit written comments on the information collection provisions by [*insert date 30 days after date of publication in the* **Federal Register**].

See section XIV of this document for the proposed effective date of a final rule based on this document.

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ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit written comments on the information collection provisions to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT:

Regarding human food issues: Linda S. Kahl, Center for Food Safety and Applied Nutrition (HFS–206), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–418–3101.

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

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I. Background

A. The 1992 Policy

In the **Federal Register** of May 29, 1992 (57 FR 22984), FDA published its ''Statement of Policy: Foods Derived From New Plant Varieties'' (the 1992 policy). The 1992 policy clarified the agency's interpretation of the application of the act with respect to human foods and animal feeds derived from new plant varieties, including varieties that are developed using recombinant deoxyribonucleic acid (rDNA) technology. This proposal refers to foods derived from plant varieties that are developed using in vitro manipulations of DNA (generally referred to as rDNA technology) as ''bioengineered foods.''

The 1992 policy provided guidance to industry on scientific and regulatory issues related to plant-derived foods, including bioengineered foods. In developing the 1992 policy as it relates to bioengineered foods, FDA focused on modifications to foods that were likely to result in commercial products and did not attempt to predict future changes in foods that could result from technological advances. Instead, FDA intended to modify its policy as circumstances warranted (57 FR 22984 at 22985).

In announcing the 1992 policy, FDA invited interested persons to submit written comments. Comments received from the scientific community generally have supported the scientific guidance articulated in the 1992 policy, including the scientific guidance as it relates to bioengineered foods. In addition, the views expressed by the members of FDA's Food Advisory Committee (Ref. 1) and the joint meeting of FDA's Food Advisory Committee and Veterinary Medicine Advisory Committee (Ref. 2), generally supported the scientific guidance in the 1992 policy.

However, many consumers, a number of public interest groups, and some State officials have expressed concern about or opposed the regulatory guidance articulated in the 1992 policy, particularly regarding the ability of the regulated industry to make market entry decisions. Frequently, those comments suggested, as an important adjunct to the 1992 policy, that FDA require an administrative process, such as premarket notification, to ensure that the agency remains aware of new bioengineered foods entering commercial distribution.[1]

FDA is confident that the guidance articulated in the 1992 policy adequately addressed both the scientific and regulatory issues raised by the products that were approaching commercialization in 1992. FDA is aware, however, that rDNA technology continues to evolve and that it is not possible for the agency to anticipate all of the novel scientific and regulatory issues that may arise as the number and types of foods developed using this technology expands. As discussed more fully below, this proposed rule would modify the regulatory guidance laid out in the 1992

[1] This document defines "commercial distribution" as the introduction, or delivery for introduction, into interstate commerce for sale or exchange for consumption in any form by humans or other animals.

policy by requiring the submission to the agency of data and information regarding plant-derived bioengineered foods at least 120 days prior to the commercial distribution of such foods.

B. Consultations Under the 1992 Policy and the 1996 Procedures

In the 1992 policy, FDA explained that, under the act, developers of new foods have a responsibility to ensure that the foods they offer to consumers are safe and in compliance with all requirements of the act (57 FR 22984 at 22985). In light of this responsibility, FDA has long regarded it to be a prudent practice for producers who use new technologies in the manufacture or development of foods and food ingredients to work cooperatively with FDA to ensure that the products of these new technologies are safe and comply with all applicable legal requirements (57 FR 22984 at 22991). Historically, the food industry generally has initiated consultation with FDA during the pioneer stages of a new technology, even if there is no legal obligation to do so. These consultations have served to make FDA aware of foods and food ingredients before these products are distributed commercially, and have provided FDA with the information necessary to address any questions regarding the safety, labeling, or regulatory status of the food or food ingredient. As such, these consultations have provided assistance to both industry and the agency in exercising their mutual responsibilities under the act.

In the 1992 policy, FDA noted that the agency expected this practice of consultation to continue with respect to bioengineered foods (57 FR 22984 at 22991). One early example of such a consultation involved FLAVR SAVR™ tomatoes[2]. In developing FLAVR SAV™ tomatoes, Calgene used rDNA technology to introduce an antisense polygalacturonase gene, which was derived from tomatoes, and the kanamycin resistance gene (the *kan* ^{r} gene), which encodes the enzyme aminoglycoside-3′-phosphotransferase II (APH(3′)II). The enzyme APH(3′)II confers resistance to the clinically used antibiotics kanamycin and neomycin in the selection of new plant varieties developed using rDNA technology. The use of APH(3′)II raised several issues that had not previously been evaluated by the agency in the context of food safety. The initial consultation

[2] This consultation was concluded in May 1994 (59 FR 26647 at 26700, May 23, 1994).

between the agency and Calgene about the intended use of APH(3′)II, which in this instance resulted in the filing and approval of a food additive petition (59 FR 26700, May 23, 1994), was an effective mechanism to fully explore and resolve these issues.

The resolution of these and other scientific issues entailed the use of nontraditional approaches to the evaluation of food safety. For example, traditional evaluation of the safety of a food additive frequently includes toxicological tests conducted in accordance with the principles outlined in the agency's ''Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food'' (Redbook (Ref. 3)).[3] In addition to guidance on when certain tests may be appropriate, the Redbook includes specific recommendations on the protocols for conducting such tests.

In contrast, issues raised during the consultations on APH(3′)II and the FLAVR SAVR™ tomato required evaluation of data generated using procedures that had only rarely been used in the evaluation of food safety. For example, Calgene used ''Southern blots'' to determine which DNA sequences had been transferred to FLAVR SAVR™ tomatoes, ''Northern blots'' to demonstrate the intended technical effect in FLAVR SAVR™ tomatoes, and ''Western blots'' to determine the amount of APH(3′)II present in FLAVR SAVR™ tomatoes. The use of nontraditional strategies in the evaluation of food safety likely will become the norm as the use of rDNA technology expands, and further consultations between industry and the agency would foster the identification and design of reasonable test procedures to evaluate the composition and safety of whole foods.

Consultations are an appropriate forum for industry and the agency to address proactively issues that are relevant to bioengineered foods, and developers have actively consulted with FDA about their products since the issuance of the 1992 policy. In June 1996, FDA provided guidance

[3] In 1993, the Center for Food Safety and Applied Nutrition (CFSAN) released a revised Redbook for public comment (58 FR 16536, March 29, 1993). Following its evaluation of comments on each draft chapter of the Redbook, CFSAN is making revised chapters available on its Internet site (Ref. 4).

to industry on procedures for these consultations (the 1996 procedures (Ref. 5)).[4] Under that process, a developer who intends to commercialize a bioengineered food meets with the agency to identify and discuss relevant safety, nutritional, or other regulatory issues regarding the bioengineered food prior to marketing it. Depending on the experience the agency and the developer have with the kind of modification being considered, a developer may initiate such a consultation early or late in the development of the food. When the developer believes that it has accumulated adequate data or information to address any issues raised during the consultation, the developer begins the ''final consultation'' by submitting to FDA a summary of its scientific and regulatory assessment of the food. To date, the agency has completed its evaluation of data or other information from more than 45 such consultations (Ref. 6). FDA believes that, to date, all developers of bioengineered foods commercially marketed in the United States have consulted with the agency prior to marketing the food.

FDA continues to believe that the consultation process is appropriate for bioengineered foods. Accordingly, this proposed rulemaking includes FDA's recommendation that developers consult with the agency to identify and discuss relevant safety, nutritional, or other regulatory issues regarding a bioengineered food (see proposed § 192.10 and section VI of this document).

C. Public Meetings

In 1999, FDA announced that the agency would hold three public meetings, each in a different region of the United States (64 FR 57470, October 25, 1999). The purpose of those meetings was for the agency to share its current approach and experience over the past 5 years regarding bioengineered foods, to solicit views on whether FDA's policies or procedures should be modified, and to gather information to be used to assess the most appropriate means of providing information to the public about bioengineered products in the food supply. In the notice announcing the public

[4] In October 1997, FDA made administrative revisions to these procedures to reflect reorganizations within the Office of Premarket Approval, CFSAN, and the Center for Veterinary Medicine (CVM). In this document, FDA refers to these procedures as ''the 1996 procedures'' to reflect the year that the agency made them available.

meetings (64 FR 57470), FDA requested comments on specific questions regarding bioengineered foods. As a result of those meetings and the request for comments, the agency subsequently received more than 35,000 written comments about its policy regarding bioengineered foods.

At those meetings, and in the comments, FDA heard three messages very clearly. First, there does not appear to be any new scientific information that raises questions about the safety of bioengineered foods currently being marketed. Second, some of the public is concerned about FDA's existing guidance and regulatory approach to overseeing the safety of these products. These concerns include whether FDA's guidance and regulatory approach will be adequate for future developments and whether firms will continue to inform FDA about new bioengineered foods under the present program. In addition, there was a concern that the current regulatory process lacks transparency (e.g., because FDA discloses each consultation about a bioengineered food only at the end of the process). Third, there are very strongly held but divergent views as to whether bioengineered foods should bear special labeling. However, there was general agreement that providing more information to consumers about bioengineered foods would be useful[5] (Ref. 8).

II. Legal Authority

FDA is responsible for ensuring that all foods[6] in the American food supply conform to the applicable provisions of the law. The act provides FDA with broad authority to regulate the safety and wholesomeness of food. In particular, the act prohibits the adulteration of food under section 402 of the act (21 U.S.C. 342) and the misbranding of food under section 403 of the act (21 U.S.C. 343). The act also requires that all food additives (as defined by section 201(s) of the act (21 U.S.C. 321(s))) be approved by FDA before they are marketed (sections 409 and 402

[5] In May 2000, FDA announced that it intended to issue for public comment draft labeling guidance to aid manufacturers who wish to voluntarily label their products as made with or without the use of bioengineering or bioengineered ingredients (Ref. 7). The development of that draft guidance is outside the scope of this document.

[6] There are certain exceptions to this jurisdiction pertaining to meat, poultry, and egg products that are not relevant to this rulemaking.

of the act (21 U.S.C. 348(a) and 342(a)(2)(C))). FDA is authorized to seek sanctions against foods that do not adhere to the act's standards, through seizure of foods that violate the act under section 304 of the act (21 U.S.C. 334); the agency is also authorized to seek an injunction against, or criminal prosecution of, those responsible for introducing such foods into commerce under sections 302 and 303 of the act (21 U.S.C. 332 and 333).

All plant breeding techniques have the potential to alter food source crops in ways relevant to the legal status of food derived from such crops. However, rDNA technology greatly facilitates, relative to traditional breeding techniques, both the introduction of specific new substances into foods and the directed modification of the composition of foods. This is in part because the technology expands the range of sources of new substances that can be introduced into plants, relative to those that can be introduced with traditional techniques, due principally to rDNA technology's ability to permit the transfer to a food crop of genetic material from virtually any organism. Similarly, at the present time, information related to the genomes of many organisms is rapidly expanding, with the result that newly identified genes are now available to breeders. In addition, rDNA technology increases the speed by which traits can be introduced into food crops, by allowing the introduction of specific, well-characterized genetic material and by reducing the need for backcrossing to remove undesirable traits. Given the efficiencies of rDNA techniques, the advances in these techniques, and the rapidly expanding information related to genomes, FDA expects that these techniques are likely to be utilized to an increasingly greater extent by plant breeders and that the products of this technology are likely in some cases to present more complex safety and regulatory issues than seen to date.

Alterations in food source plants accomplished using rDNA technology, with resulting changes in the foods derived from such plants, can present a range of regulatory issues (57 FR 22984 to 23005). For example, such alterations may present questions as to the food additive status of the substances introduced into the food as a result of the genetic transformation. As noted, bioengineering permits the introduction into food of substances from any source, and the number

and types of genes available for use in rDNA technology are rapidly increasing. Thus, increasingly, substances may be introduced into food using rDNA techniques that cannot be introduced by traditional breeding. FDA noted in the 1992 policy that a nonpesticidal substance introduced into food by way of breeding is a food additive if the substance is not generally recognized as safe (GRAS) within the meaning of 21 U.S.C. 321(s). Because of the greater range of sources of substances that can be introduced into plants via rDNA technology, there is a greater likelihood that some of the new substances will be significantly different from substances that have a history of safe use in food or may otherwise not satisfy the GRAS standard in section 201(s) of the act(s). Thus, there is a greater potential for foods developed using rDNA technology to contain substances that are food additives.

The agency reiterates its view, as stated in the 1992 policy (57 FR 22990), that transferred genetic material can be presumed to be GRAS. Likewise, FDA is not altering its view, as set forth in the 1992 policy, that there is unlikely to be a safety question sufficient to question the presumed GRAS status of the proteins (typically enzymes) produced from the transferred genetic material, or of substances produced by the action of the introduced enzymes (such as carbohydrates, fats, and oils), when these proteins or other substances do not differ significantly from other substances commonly found in food and are already present at generally comparable or greater levels in currently consumed foods. However, FDA recognizes that because breeders utilizing rDNA technology can introduce genetic material from a much wider range of sources than previously possible, there is a greater likelihood that the modified food will contain substances that are significantly different from, or are present in food at a significantly higher level than, counterpart substances historically consumed in food. In such circumstances, the new substances may not be GRAS and may require regulation as food additives (57 FR 22990).

To date, FDA has not seen multiple examples of food additive substances introduced into food using rDNA technology. However, the agency recognizes that the potential for introducing such substances is real. There are, for example, certain plant-derived proteins that have a sweetening

effect but whose biochemical function is not known.[7] In addition, they are found in plants that have not been used for food. Thus, in contrast to other proteins introduced into foods by genetic engineering, which have been presumed GRAS, there is little or no apparent basis for a GRAS presumption for such substances. Genes encoding the protein sweetener could be introduced into a fruit to enhance sweetness. In such circumstances, FDA should be made aware of the intended marketing of the modified food and have access to relevant information to evaluate whether the protein sweetener is a food additive within the act's definition under section 201(s) of the act. If the protein sweetener is a food additive, premarket approval of the substance would be required under section 409 of the act before the altered food could be lawfully marketed.

Another potential consequence of transferring genetic material from one source into another is the possibility of introducing a food allergen that would not be expected to be in a particular food, a change that would be relevant to the legal status of such food. This is because genes code for proteins, and virtually all allergens are proteins (although only a small subset of proteins are allergens). Thus, by increasing the range of potential proteins that can be introduced into food over that possible by traditional breeding, there is an increased potential for introducing an allergen into a food developed using rDNA technology. Also, rDNA technology can be used to express proteins at higher concentrations than they would otherwise be expressed; these higher concentrations may increase the potential for such proteins to be allergenic.

One implication of being able to transfer genes between unrelated plants using rDNA techniques is that it is possible to transfer genes from one food plant to another quite unrelated food plant, thereby allowing the potential transfer of an allergen from the first plant to the second. In such a case, food from the bioengineered plant could have an allergenic characteristic completely different from that of its conventional counterpart. Such a change would not be evident to the consumer. For example, a gene from a Brazil nut plant was introduced into a soy plant to improve

[7] The proteins apparently do not make the plants more attractive to insects or animals, and thus would not likely function as natural sweeteners in plants in the wild.

the protein content of soy beans for use in animal feed. The seed was never commercialized, however, because when the company tested the soy beans for allergenicity, they found that people allergic to Brazil nuts were also allergic to the bioengineered soy (Refs. 9 and 10). Given the potential consequences to sensitive consumers of eating soy products containing a Brazil nut allergen, such a food would likely be considered misbranded within the meaning of sections 201(n) and 403(a)(1) of the act, unless the presence of the new allergen were disclosed to consumers.

Further, in certain circumstances, labeling may not be adequate or practical to ensure that consumers are aware of the presence of unexpected allergens. FDA would likely consider such food containing an unexpected allergen to be adulterated within the meaning of section 402(a)(1) of the act because the unexpected allergen rendered the food possibly injurious to health. With alterations of this type, FDA should be made aware of the modification and have an opportunity to assess whether and how the food could legally be marketed. Specifically, FDA should have the opportunity to consider whether any labeling proposed by the developer would ensure that the engineered food is not misbranded within the meaning of sections 201(n) and 403(a)(1) of the act, and whether, even with labeling, the food would be adulterated because it may be injurious to health within the meaning of section 402(a)(1) of the act.

Compositional changes in foods created through breeding may also present regulatory status issues. Although traditional breeding techniques can be used to alter significantly the compositional characteristics of food, rDNA technology enhances that ability because rDNA technology enables breeders to make targeted changes in plant components such as proteins and other constituents. For example, rDNA techniques would facilitate a breeder's ability to modify a soy plant so that the composition of oil derived from the plant would more closely resemble that of a tropical oil than that of conventional soy oil. In these circumstances, the name ''soy oil'' would likely not be suitable for the oil derived from the altered soy plant because the composition of the new oil is significantly different from what is customarily understood to be ''soy oil''. Thus, a new common or usual name would likely be required for this new oil to ensure that the oil is not

misbranded under section 403(i)(1) of the act. FDA should be made aware of compositional changes of this type so that the agency may consider whether a new common or usual name is required and, if so, what that new name should be.

Additionally, rDNA technology has recently begun to be used to introduce multiple genes to generate new metabolic pathways (Ref. 11). New metabolic pathways are intended to result in the synthesis of substances not normally present in the host plant. Such modifications may alter the composition of the food in a significant manner that may raise nutritional or safety issues or that would require use of a new common or usual name.

In addition to enabling breeders to introduce desired new characteristics into foods, all breeding methods used to develop new plant varieties have a potential for unintentionally introducing undesired new characteristics into foods (57 FR 22986). Broadly speaking, a breeding method's potential for introducing unintended changes to the characteristics of a food results either from bringing into a food plant extraneous genetic material encoding trait(s) additional to the desired trait(s), or from introducing mutations (such as deletions, amplifications, insertions, rearrangements, or DNA base-pair changes) into the plant's native genetic material that alter some characteristic(s) of the food.

The most commonly used breeding method is a ''narrow cross,'' which is hybridization between varieties of the same species. Hybridization between related species or genera that cannot be cross-fertilized is a ''wide cross.'' Wide crosses are useful for expanding the range of genetic source material that can be introduced into food crops, but are performed relatively infrequently because of technical and logistical difficulties. Both wide and narrow crosses will introduce into plants extraneous genetic material along with the genetic material encoding the desired traits. Breeders then attempt to remove any undesired traits through extensive backcrossing.

Plant breeders also use mutagenic techniques to modify plants. These techniques include random mutagenesis using a mutagenic agent and somaclonal variation. (Somaclonal variation refers to the process of growing a plant up from tissue culture and observing for phenotypic

changes, which are often due to chromosomal rearrangements or other mutations.) Both techniques can introduce undesirable mutations along with possible desirable mutations. As with hybridization, breeders perform backcrosses to eliminate any undesirable traits. Cell fusion poses similar issues to those posed by wide crosses (because it generally is performed between cells of different species of plants) and posed by somaclonal variation (because it involves growing a plant up from tissue culture).

Recombinant DNA technology greatly reduces the likelihood of introducing extraneous genetic material, as compared with hybridization, because it enables breeders to introduce only the gene or genes of interest, with little or no extraneous deoxyribonucleic acid (DNA). However, it shares with mutagenesis techniques a potential for introducing unintended effects through mutations. In part, this is because rDNA technology involves growing plants from tissue culture, which can exhibit somaclonal variation, and, more significantly, because breeders using this technology generally cannot control the location in the plant genome at which genetic material will insert when introduced into a plant. Thus, with rDNA technology, the introduced genetic segment may insert into a genetically active chromosomal location. Such insertion may disrupt or inactivate an important gene or a regulatory sequence that affects the expression of one or several genes, thereby potentially affecting adversely the safety of the food or raising other regulatory issues. Such an occurrence is referred to as an insertional mutation.

FDA believes that in the future, plant breeders will increasingly use rDNA techniques to achieve more complicated compositional changes to food, sometimes introducing multiple genes residing on multiple vectors to generate new metabolic pathways. FDA expects that with the increased introduction of multiple genes, unintended effects may become more common. For example, rice modified to express pro-vitamin A was shown to exhibit increased concentrations of xanthophylls (Ref. 11), and rice modified to reduce the concentration of a specific protein was found to exhibit an increased concentration of prolamine (Ref. 12).

FDA believes that the use of rDNA techniques in plant breeding may lead to unintended changes in foods that raise adulteration or misbranding questions. These unintended changes may cause a food to be adulterated because the food may be rendered injurious to health within the meaning of section 402(a)(1) of the act, or, in the absence of a new common or usual name, cause the food to be misbranded under section 403(i)(1) of the act. Because of its role in ensuring the safety of the U.S. food supply, FDA needs to be aware of the modifications to food source plants from the application of rDNA technology and any unintended effects in food that result so that the agency can evaluate whether the foods from such plants are adulterated or misbranded.

Because some rDNA-induced unintended changes are specific to a transformational event (e.g., those resulting from insertional mutagenesis), FDA believes that it needs to be provided with information about foods from all separate transformational events, even when the agency has been provided with information about foods from rDNA-modified plants with the same intended new trait and has had no questions about such foods. Similarly, the agency believes that it needs to be provided with information about foods from rDNA-modified plants whose intended change is the introduction of a pesticidal protein subject to oversight by the Environmental Protection Agency (EPA) rather than by FDA, because the transformational event that is used to introduce the pesticidal trait may also cause unintended changes to the food that would raise adulteration or misbranding questions subject to FDA jurisdiction.

In contrast, the agency does not believe that it needs to receive information about foods from plants derived through narrow crosses (including narrow crosses between different rDNA-modified lines). Narrow crosses, because they generally are performed between varieties that are themselves used in food or are very closely related to varieties used in food, are unlikely to introduce extraneous DNA that encodes traits that have not been in food before. In addition, plant lines used for narrow crosses generally have been subject to extensive backcrossing and field testing to ensure genetic stability (including lack of any active transposons that could cause insertional mutagenesis). Finally, because the plant lines are closely related to each other, crosses between

them will involve homologous recombination and thus are unlikely to be subject to insertional mutagenesis. Therefore, narrow crosses are unlikely to result in unintended changes to foods that raise safety or other regulatory questions.

The agency recognizes that unintended changes associated with other non-rDNA breeding methods may pose regulatory questions similar to those posed by rDNA methods. For example, wide crosses, especially between a food plant variety and an undomesticated nonfood plant variety, have much greater potential than do narrow crosses for introducing unintended traits that may alter the safety of the food; undomesticated plants frequently produce toxins at levels unsafe for human consumption, and may also produce substances not found in food. The agency has not found it necessary to assess routinely the safety of foods derived from such breeding methods, because over the last 50 to 60 years that some of these techniques have been used in plant breeding, breeders have used well-established practices successfully to identify and eliminate, prior to commercial use, plants that exhibit unexpected adverse traits. The agency is not aware of a basis for additional FDA oversight of foods derived from plants modified by such techniques, given that there has not been such a need in the past and that there do not appear to be any significant changes in breeders' use of such techniques that would warrant new FDA oversight. Rather, because of the technical advantages of rDNA methods over these other techniques, FDA anticipates that, in the future, breeders will likely use non-rDNA methods less frequently to introduce new characteristics into food plants as they increasingly utilize rDNA techniques. Likewise, despite the similar potential for unintended effects, FDA believes that declining to propose a requirement that the agency be notified about the commercialization of food source plants transformed using techniques other than rDNA is consistent with its current conclusion that, unexpected effects aside, rDNA techniques have a greater potential, relative to conventional methods of breeding, to result in the development of foods that present legal status questions. The agency therefore is not proposing to include foods from crops modified by methods other than rDNA techniques within the scope of this proposed notification rule. The agency requests comment as to whether it should

include foods from crops developed by wide crosses or other breeding methods in the scope of any final rule based upon this proposal.

FDA recognizes that whether there is a change in the legal status of a food resulting from a particular rDNA modification depends almost entirely on the nature of the modification, and that not every modification accomplished with rDNA techniques will alter the legal status of the food. In other words, many modifications will result in a food that does not contain an unapproved food additive, does not contain an unexpected allergen, and does not differ significantly in its composition compared with its traditional counterpart or otherwise require special labeling. For this reason, FDA is neither proposing to require premarket approval for all foods developed using rDNA technology nor is the agency proposing an across-the-board requirement that all such foods bear special labeling.

There is substantial basis to conclude, however, that there is greater potential for breeders, using rDNA technology, to develop and commercialize foods that are more likely to present legal status issues and thus require greater FDA scrutiny than those developed using traditional or other breeding techniques. It was in part for this reason that, in 1994, the agency initiated a consultation process. Since that time, developers have actively consulted with FDA regarding their new plant varieties; under this process, the agency has completed its evaluation of data and other information from some 45 consultations.

As noted, FDA believes that, to date, the developer of each rDNA variety commercially marketed in the United States has consulted with the agency prior to marketing food from the new variety. But these products represent only a small fraction of the potential products of rDNA technology. [8] Additionally, in general, the introduced traits have been agronomic in nature (i.e.,

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[8] For example, in the 45 consultations completed under the 1992 policy, only 11 different commodities are represented, including 12 consultations on corn, 7 on canola, 6 on tomatoes, 5 on cotton, and 4 on potatoes. Moreover, the 45 consultations do not represent 45 separate types of modifications; rather, these 45 consultations represent

Continued

directed at the characteristics of the plant and not at the characteristics of the food produced by the plant). However, this picture is rapidly changing. The current list, which is provided by the Animal and Plant Health Inspection Service (APHIS) in the U. S. Department of Agriculture (USDA), of field tests of plants being developed using rDNA technology shows that the plants under development have a broader variety of introduced traits (Ref. 13). Additionally, that list shows that many such traits are not simply agronomic, but are intended to modify the food itself, and thus would be more likely than in the past to raise regulatory issues falling under FDA's purview.[9] Finally, as noted previously, FDA believes that, given the efficiencies of rDNA techniques, the advances in these techniques, and the rapidly expanding information related to genomes, these techniques are likely to be utilized by plant breeders to an increasingly greater extent.

The confluence of the increasingly broader use of rDNA techniques to develop foods for human and animal use and the globalization of the world's food supply also suggest that FDA needs to be aware of the various foods developed using rDNA technology. Currently, approximately 45 percent of the United States' plant-derived food is imported, and that percentage continues to increase. The agency expects that rDNA techniques may, over time, be used increasingly by plant breeders and developers in countries that export foods to this country. In such circumstances, the accuracy of FDA's knowledge about the presence in the U.S. food supply of foods developed using rDNA techniques is likely to decrease. In addition, the awareness of particular food allergies is not uniform throughout the world because the diets of some populations do not contain sufficiently large amounts of a food such that the allergic potential has been demonstrated; in

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only 9 general types of modifications. These modifications were herbicide resistance, insect and virus resistance, delayed ripening or softening, male sterility or fertility restorer, high phosphorus availability, and modified oil.

[9] These include modifications for altered protein quality, increased carotenoid content, increased fruit solids, altered fiber quality, and increased fruit sweetness, among others.

these circumstances, it is particularly important that FDA be aware of imported foods modified using rDNA techniques that may unexpectedly contain a substance that is an allergen.

For all these reasons, FDA believes that the food products of rDNA technology are appropriately made subject to greater regulatory scrutiny by FDA in the form of enhanced agency awareness of all such foods intended for commercial distribution. This increased agency awareness will ensure that at this stage of this continuously evolving technology, all market entry decisions about new bioengineered foods, including those intended for import into the United States, are made consistently and in full compliance with the law. Similarly, in order for the agency to evaluate fully and consistently the possible regulatory consequences of the alterations made possible using rDNA technology, FDA must be made aware of the bioengineered foods entering commercial distribution.

Section 701(a) of the act (21 U.S.C. 371(a)) authorizes the Secretary of the Department of Health and Human Services (the Secretary) to issue regulations for the efficient enforcement of the act; under section 903(d)(2) of the act (21 U.S.C. 393(d)(2), the Secretary is responsible for executing the act, including section 701(a), through the Commissioner of Food and Drugs. The authority under section 701(a) of the act to issue regulations under the act extends to both regulations that supplement a specific statutory mandate as well as regulations that are justified by the statutory scheme as a whole. (See *National Confectioner's Association* v. *Califano*, 569 F.2d 690, 693 (D.C. Cir. 1978), citing *Toilet Goods Association* v. *Gardner*, 387 U.S. 158, 163 (1967).) In assessing a regulation issued under section 701(a), it is important to consider both the statutory purpose as well as the practical aspects of the situation, including the possible enforcement problems that may be encountered by FDA. (See *National Confectioner's Association* v. *Califano*, 569 F.2d 690, 693 (D.C. Cir. 1978), citing *Toilet Goods Association* v. *Gardner*, 387 U.S. 158, 163 (1967).)

To ensure that FDA has the maximum amount of information about foods from bioengineered plants, the agency has tentatively concluded that, prior to initiation of commercial distribution in

the United States of a bioengineered food, FDA must be notified of the intent to market such food, including foods intended for import into the United States. Notification will ensure that the agency is aware of all bioengineered foods entering commercial distribution that are subject to FDA's jurisdiction and will help to ensure that all market entry decisions by the industry are made consistently and in full compliance with the law. This will permit the agency to assess on an ongoing basis whether foods developed using rDNA technology comply with the standards of the act. FDA believes that it is essential that all those developing and marketing bioengineered foods participate fully and completely in the proposed notification program. Therefore, the agency is proposing that the notification program that is described in this document be mandatory.

Accordingly, for the reasons set forth above concerning the special circumstances of bioengineered foods, to enforce the act efficiently, and in particular, to administer efficiently the act's various provisions that relate to food as such provisions apply to bioengineered food, including section 301 of the act (21 U.S.C. 331) and sections 402, 403, and 409 of the act, FDA is proposing regulations to require that the agency be notified at least 120 days prior to the initiation of commercial distribution in the United States of a bioengineered food. The elements of FDA's proposed program are discussed in detail below.

III. Scope

FDA is proposing to require the submission to the agency of data and information regarding plant-derived bioengineered foods that would be consumed by humans or animals. FDA's proposal also includes a recommendation that prospective notifiers participate in a presubmission consultation program. The regulations regarding bioengineered foods that would be consumed by humans would be codified in new part 192. The regulations regarding bioengineered foods that would be consumed by animals would be codified in new part 592. The proposed regulations regarding bioengineered foods that would be consumed by animals parallel the proposed regulations regarding bioengineered foods that would be consumed by humans. For ease of discussion, in this proposed rule, FDA describes each of the regulations that would be codified in part 192,

without describing the parallel regulations in part 592. Following this discussion, FDA describes areas of importance in the proposed animal feed regulations (section XI of this document).

IV. Definitions

FDA is proposing to codify five definitions that are associated with the proposed notification program (proposed § 192.1). These terms are bioengineered food, commercial distribution, notifier, premarket biotechnology notice (PBN or notice), and transformation event. FDA invites comments on these proposed definitions. FDA is particularly interested in comments on the proposed definitions of bioengineered food and transformation event. Specifically, FDA is requesting comment on whether these proposed definitions are consistent with the agency's intent (described in section V of this document) that the proposed notification program apply to a particular subset of plant-derived foods. Such comments may result in a modification to the proposed definitions.

Under the proposed definitions, a required PBN may be submitted by any person who is responsible for the development, distribution, importation, or sale of a bioengineered food. Based on the agency's experience, FDA expects that it ordinarily will be the seed developers and purveyors who notify the agency about a bioengineered food.

V. Requirement for Premarket Biotechnology Notice

FDA is proposing to require a submission to the agency of data and information regarding a plant-derived bioengineered food at least 120 days prior to the commercial distribution of the food (proposed § 192.5). The proposed regulation would include a bioengineered food derived from a new plant variety modified to contain a pesticidal substance, and would exclude a bioengineered food that meets three specified criteria. The rationale for this proposed notification requirement is discussed in section II of this document. FDA specifically requests comment on the scope of the proposed notification requirement and on the proposed conditions for exclusion from the notification requirement. Such comments may result in a modification to the proposed regulation.

A. Foods That Are Subject to the Requirement

FDA is proposing that the notification requirement apply to a bioengineered food derived from a new plant variety modified to contain a pesticidal substance (proposed § 192.2(a)). Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (7 U.S.C. 136 *et seq.*), EPA has authority to regulate all pesticides, regardless of how they are made or their mode of action. Under the act, EPA has authority to regulate pesticide residues in foods and FDA has authority to regulate a nonpesticidal substance that may be introduced into a new variety and that is expected to become a component of food. Given this statutory framework, both FDA and EPA agree that any food safety questions beyond those associated with the pesticide, such as those raised by unexpected or unintended compositional changes, are under FDA's jurisdiction (57 FR 22984 at 23005). FDA's proposal to include in its notification program new plant varieties that contain a pesticidal substance will facilitate consultation between EPA and FDA on the scientific and regulatory issues that are not within the scope of EPA's authority under FIFRA and the act.

FDA is proposing to exclude from the notification requirement a bioengineered food that satisfies three conditions. The first condition is that the food derives from a plant line that represents a transformation event that has been addressed in a notice previously submitted to FDA (proposed § 192.5(a)(1)). Under § 192.5(a)(1), a separate notice would be required for distinct plant lines that are derived from separate transformed cells, even when those cells were transformed during a single transformation procedure. The second condition is that the use or application of the bioengineered food has been addressed in a notice previously submitted to FDA (proposed § 192.5(a)(2)). Under § 192.5(a)(2), a separate notice would be required, for example, if herbicide tolerance introduced into a variety of sweet corn that is used solely for human food is subsequently transferred, using traditional plant-breeding techniques, to a variety of field corn that would also be used in food intended for consumption by animals. The third condition is that a letter from FDA demonstrates that FDA has evaluated the use or application of the bioengineered food and has no questions about it (proposed § 192.5(a)(3)). Under § 192.5(a)(3), a notice would be required if, for example,

a prior notice about another use of a bioengineered food is still pending or if the agency's response to a prior notice demonstrates that FDA did not consider the prior notice as providing a basis to conclude that the bioengineered food was in compliance with all applicable requirements of the act.

As mentioned, FDA believes that all developers of bioengineered foods that already are commercially marketed in the United States have consulted with the agency prior to marketing the food. FDA believes that any legal status questions that pertain to the applicable bioengineered foods have been identified and resolved through that consultation process. Therefore, the notification requirement would not extend to bioengineered food obtained from a plant line (or series of plant lines) that derives from a particular transformation event, as long as both the applicable transformation and the use or application of the bioengineered food has been addressed satisfactorily in a completed consultation under the voluntary program.

It is likely that some final consultations received under the 1996 procedures would still be pending on the date of a final rule based on this proposal. The proposed regulations include no specific provisions regarding a bioengineered food that is the subject of a pending final consultation under the 1996 procedures. FDA specifically requests comment on how FDA should administer such submissions. FDA also specifically requests comment on whether the process for administering a final consultation that is pending on the date of a final rule based on this proposal should be included in these regulations. Such comments may result in a modification to the proposed regulation.

FDA specifically requests comment on the scope of proposed notification requirement and on the proposed conditions for exclusion from the notification requirement. Such comments may result in a modification to the proposed regulation.

B. Origin of Data and Information

FDA is proposing that the data or information that a notifier submits to FDA regarding a bioengineered food must be generated from a plant line whose derivation can be traced to the

transformation event that is the subject of the notice and that contains the genetic material introduced via the transformation event (proposed § 192.5(b)). As a practical matter, the proposed regulation will give flexibility to producers while providing the agency with relevant information concerning the nature of the bioengineered foods. FDA specifically requests comment on this proposed provision. Such comments may result in a modification to the proposed regulation.

C. Timing

FDA is proposing to require that a notifier submit a PBN at least 120 days before the bioengineered food is marketed (proposed § 192.5(c)). The proposed timeframe is consistent with contemporary expectations of the Congress for another notification program, the notification program for food contact substances (section 409(h) of the act).

FDA believes that it can, in most circumstances, complete its evaluation of a PBN within 120 days because, as discussed more fully below, FDA is recommending that prospective notifiers participate in a presubmission consultation program. The purpose of the presubmission consultation program is to enable a prospective notifier to identify and address relevant safety, nutritional, or other regulatory issues regarding the bioengineered food before submitting a PBN. Given this presubmission consultation program, FDA expects that a notifier will have sufficient information to prepare a notice that adequately addresses all issues and that scientific experts at the agency will be familiar with the issues raised by a particular bioengineered food when the agency receives the applicable PBN.[10]

VI. Recommendation for Presubmission Consultation

FDA is proposing to include in the regulation a recommendation that a prospective notifier consult with the agency, before submitting a PBN, to identify and discuss relevant safety,

[10] The consultation procedures do not identify a timeframe for FDA to complete its evaluation of a final consultation. As of April 2000, under that program the median time for FDA's response to a final consultation was approximately 155 days and the average time was approximately 175 days.

nutritional, or other regulatory issues regarding the bioengineered food (proposed § 192.10). The proposed recommendation describes procedures for requesting consultation and the public disclosure provisions that likely would apply to records that FDA maintains about the consultation. Under § 192.10(f), a notifier must state his view as to whether the fact that he is consulting with FDA, or any or all of the data or information that he submits to FDA, is exempt from disclosure under the Freedom of Information Act (FOIA) and must explain the basis for any such exemption claim. The recommendation to consult with FDA derives from the 1992 policy, the 1996 procedures, and FDA's experience under the 1996 procedures. FDA discusses the details of this proposed recommendation immediately below.

Using rDNA technology, bioengineered plants such as corn are now being developed for non-food uses. Examples of such applications include the transfer of genes that encode pharmaceutical proteins, oral vaccines, and enzymes that would be used for non-food industrial applications. In some cases, such as most of the pharmaceutical proteins, the final product would be a highly purified component of the plant commodity. In other cases, such as some oral vaccines, the final product would be a minimally processed plant commodity. In some cases, there may be a potential for a bioengineered plant commodity that is not intended for use in food to enter the food supply inadvertently. FDA encourages developers of bioengineered plants that are not intended for use in food or feed, but that theoretically could enter the food or feed supply, to participate in the consultation program described in this proposed rule. This participation would ensure that developers have given careful consideration to the procedures needed to ensure that their products do not inappropriately get into the food supply, and are aware of the legal implications if their products do.

A. Presubmission Consultation Program

FDA is proposing to recommend that a prospective notifier participate in a presubmission consultation program (proposed § 192.10(a)). Under the program (proposed § 192.10(b)), a prospective notifier would write to FDA and ask to consult about a bioengineered food. FDA

would establish an administrative file for each consultation and would meet with a prospective notifier upon request. Although FDA may provide written feedback during the consultation, that feedback would not release the prospective notifier from the proposed requirement to notify FDA about the bioengineered food at least 120 days before commercialization of the food. The proposed presubmission consultation program derives from the 1992 policy, the 1996 procedures, and FDA's experience under the 1996 procedures.

B. Public Disclosure

FDA is proposing to provide information about the availability for public disclosure of: (1) The fact that a developer is consulting with FDA (proposed § 192.10(c)) and (2) the data or information in the file that FDA would establish for a presubmission consultation (proposed § 192.10(d)). The regulations would inform all parties of the fact that FDA must act in response to a request under FOIA for information on presubmission consultations, and must disclose, or protect from disclosure, the applicable record(s) in accordance with § 20.61 (21 CFR 20.61) (proposed § 192.10(c)(2) and (d)(1)).

In light of the significant public interest in bioengineered foods and in FDA's oversight of these foods, FDA believes that it is important for developers to be informed that FOIA may entitle the public to know that the developer has provided data or information to FDA about a bioengineered food and to receive a copy of those data or information. Likewise, FDA believes that it is equally important for the public to know that the fact that a developer is consulting with FDA may be exempt from disclosure under FOIA and that some or all of the data or information that are submitted to FDA during a presubmission consultation could be exempt from public disclosure.

Under FOIA, data or information that are submitted to the Federal Government are available for public disclosure unless those data or information fall within an established exemption of FOIA. The exemption that is most relevant to data or information provided to FDA during a presubmission consultation is ''exemption 4,'' which applies to ''trade secrets and commercial or financial

information obtained from a person and privileged or confidential.'' (5 U.S.C. 552(b)(4)). FDA has issued regulations implementing exemption 4 of FOIA in § 20.61.

FDA believes that, in most cases, the fact that a developer is consulting with FDA would not constitute confidential commercial information. For example, most plants developed using rDNA technology are considered ''regulated articles'' under regulations of USDA's APHIS (7 CFR part 340), which regulates the introduction of certain ''genetically engineered'' plants. At some stage of research and development of a regulated article, a developer requests from APHIS a determination of the article's regulatory status, and, consistent with FOIA requirements, APHIS discloses that request. Thus, by virtue of the APHIS process, the fact that the developer is developing the plant and its food product would usually already be disclosed.

FDA also believes that, in most cases, most of the data or information provided to FDA during a presubmission consultation would not constitute a trade secret or confidential commercial information. For example, only a handful of the submissions that FDA has received under its current consultation program identified specific data or information that the developer claimed to be exempt under § 20.61. Neverthelesss, there could be circumstances where a developer initiates a presubmission consultation about a product that has not previously been disclosed to the public and has grounds to claim that the fact of the consultation should not be available for public disclosure. In such circumstances, disclosing any data or information in the applicable submission would reveal the existence of the submission. Thus, as long as the existence of the consultation is exempt from disclosure, all data or information in the submission would necessarily be exempt from disclosure.

C. Standard Procedures

FDA is proposing that a prospective notifier ask FDA in writing for an opportunity to consult about a bioengineered food (proposed § 192.10(e)). A written request would provide clarity about the subject of the consultation.

FDA is proposing to require that a prospective notifier who initiates a consultation inform FDA whether, in his view, the fact of the consultation with FDA is confidential, and whether, in his view, any or all of the provided data or information is confidential (proposed § 192.10(f)(1)). FDA also is proposing to require that a prospective notifier who claims confidentiality for the existence or content of a presubmission consultation explain the basis for that claim (proposed § 192.10(f)(2)). FDA is proposing these requirements because of the significant public interest in bioengineered foods. These requirements would ensure that FDA is aware of the prospective notifier's position regarding the availability for public disclosure of the existence and content of the consultation. In addition, FDA believes that these requirements would alert a prospective notifier to the fact that the data or information contained in a submission to FDA are available for disclosure unless the applicable criteria for exemption are satisfied.

FDA is proposing to recommend that a prospective notifier send FDA a synopsis about the requested consultation (proposed § 192.10(f)(3)). The recommended synopsis would include the prospective notifier's name and address, the name of the bioengineered food and the plant species from which it is derived, a distinctive designation(s) that the notifier uses to identify the applicable transformation events, a list of the identity(ies) and source(s) of introduced genetic material, a description of the purpose or intended technical effect of the transformation event (including expected significant changes in the composition or characteristic properties of food derived from the plant as a result of the transformation event, regardless of whether these changes result from the insertion of new genes or from a modification in the expression of endogenous genes), a description of the applications or uses of the bioengineered food, and a description of any applications or uses of the bioengineered food that are not suitable for the bioengineered food. FDA is proposing to recommend this synopsis because the agency believes that the information in the synopsis is both necessary and sufficient to characterize the bioengineered food in a manner that will enable the agency to engage in a meaningful dialogue with the prospective notifier. For example, information about the identity and intended technical effect of the transformation event

would enable the agency to address the potential issue that the food would contain an unapproved food additive. A distinctive designation that the notifier uses to identify the applicable transformation event would enable the agency to efficiently locate other agency records regarding that transformation event. It would also facilitate discussions with APHIS and EPA, if sponsors use those same designations in information supplied to the other agencies. Information about the sources of the genetic material would enable the agency to identify issues associated with a known allergenic source. Information about expected significant changes in the composition of the food would enable the agency to discuss suggestions for an appropriate common or usual name for the bioengineered food. Information about the applications or uses of the food would enable the agency to identify applicable regulatory situations (e.g., whether the bioengineered food would likely be used in human food, animal feed, or both). Information about any applications or uses that the notifier believes would not be suitable for the bioengineered food would enable the agency to identify potential safety questions, if any, about such use of the bioengineered food.

FDA is proposing that a prospective notifier send a request for consultation regarding a bioengineered food to CFSAN (proposed § 192.10(g)). As necessary and appropriate, CFSAN would coordinate the consultation process with CVM. The proposed regulation is consistent with the approach in the 1996 procedures, which has worked well.

FDA is proposing that a prospective notifier should send an original and two paper copies of a written request for consultation and of any additional materials that are sent to FDA during the consultation process (proposed § 192.10(h)(1) and (h)(2)). FDA is proposing an original and two copies of these submissions for efficiency in providing information about the presubmission consultation to the agency's scientific reviewers.

Because it is likely the data or information in a presubmission consultation would be requested under FOIA by an outside party, FDA is proposing that a prospective notifier who claims that certain data or information provided to FDA during the presubmission consultation are exempt from disclosure should clearly identify, in each submission, the data or information at issue

(proposed § 192.10(h)(3)(i)). When this is the case, FDA also is proposing that the prospective notifier should provide an additional paper copy of the submission that does not contain such data or information (i.e., a redacted paper copy under proposed § 192.10(h)(3)(ii)). Providing a redacted copy would communicate very clearly which data or information the prospective notifier considers to be exempt. These recommendations are consistent with a practice that is commonly used by firms who send FDA a food additive petition that contains information that the petitioner claims to be confidential, a practice that has worked well. In addition, the practice of providing a redacted copy also has been used in a few cases under the 1996 procedures.

FDA is proposing that the redacted paper copy be prepared in a manner that clearly identifies the location and relative size of deleted information. This proposed regulation is consistent with FDA's proposed regulations (64 FR 60143, November 4, 1999) regarding implementation of the Electronic Freedom of Information Act Amendments of 1996 (EFOIA (Public Law 104–231)). EFOIA includes, among other things, provisions requiring agencies to inform requesters about the amount of information not being released to them.

FDA is proposing to specify the materials that the agency would place in an administrative file that it establishes for a presubmission consultation (proposed § 192.10(i)(1)). These materials include any correspondence between the prospective notifier and FDA, any written materials that the prospective notifier provides during the consultation process, and a memorandum of each meeting or significant phone call between FDA and the prospective notifier during the consultation. This part of the regulation would inform both prospective notifiers and outside parties of the materials that ordinarily would be in the administrative file of the consultation and thus potentially be subject to disclosure under FOIA.

FDA's proposal includes its commitment to discuss issues associated with a bioengineered food with any prospective notifier who asks to do so (proposed § 192.10(i)(2)). FDA is proposing to include this commitment to both remind and encourage prospective notifiers that the purpose of the recommended program is for a prospective notifier to engage FDA in a discussion about

the bioengineered food at an early stage of the food's development. However, the agency realizes that there may be circumstances where such a discussion would not be an efficient use of resources for either the prospective notifier or for FDA. For example, a prospective notifier may intend to notify FDA about bioengineered foods that derive from a series of plant lines that are the result of independent transformation events with the same genetic construct. After FDA has completed its evaluation of one of these bioengineered foods, the notifier likely would be aware of most or all of the applicable safety, nutritional, or other regulatory issues that could be associated with the food. Nevertheless, FDA would welcome the opportunity to be informed about the notifier's plans to submit additional notices because this information could help the agency to plan its workload.

The proposed regulation describes a flexible process for any discussion (e.g., by mentioning that the discussion could take place through a meeting or through a telephone conference). FDA is highlighting the opportunity to discuss the bioengineered food by a mechanism other than a face-to-face meeting to minimize the potential that a small business or academic research group would elect not to participate in the program due to the cost of travel. Given the agency's experience under the current consultation process, FDA is confident that a meaningful dialogue can often be accomplished without a face-to-face meeting.

VII. Premarket Biotechnology Notice: Administrative Information

FDA is proposing to codify certain administrative information that would apply to a PBN (proposed § 192.20). The proposed administrative information includes information about where to send a PBN, the number of copies to send, how to include information in a foreign language, how to refer to data or information that are already in FDA's files, how to obtain guidance on scientific issues, and the prerogative of a notifier to withdraw a PBN from FDA's consideration. Many of these administrative aspects of the proposed notification program are consistent with procedures already in place for the food additive petition program (§ 171.1 (21 CFR 171.1)). FDA

discusses the details of these administrative aspects of the proposed notification program immediately below.

A. Submissions to CFSAN for Use in Human Food, Animal Feed, or Both

FDA is proposing that a notifier send a PBN regarding a bioengineered food to CFSAN (proposed § 192.20(a)). As necessary and appropriate, CFSAN would coordinate FDA's evaluation of the PBN with CVM. The proposed regulation is consistent with the approach that FDA recommended in the 1996 procedures, an approach that has worked well.

B. Paper Copies

FDA is proposing that a prospective notifier send to the agency an original paper version and one paper copy of a PBN (including any amendments) (proposed § 192.20(b)(1)). A notifier would have an option to submit one additional paper copy or, under proposed 192.20(c)(1), to submit an electronic copy that is formatted in a manner that makes it suitable for FDA to use while evaluating the PBN. The number of paper copies required by the regulation is consistent with the number of paper copies that FDA currently requires for other premarket submissions, such as a food additive petition. A requirement for multiple paper copies generally serves the purpose of providing a copy of the submission to multiple scientific reviewers. However, as discussed below, FDA also is recommending that a notifier submit an electronic copy of a PBN that is formatted in a manner that makes it suitable for FDA to use in evaluating a PBN. Because scientific reviewers could accomplish their review by accessing the electronic copy, under the proposed rule, a notifier who submits an electronic evaluation copy would submit one less paper copy. FDA would retain the original paper version at CFSAN, while the paper copy would be retained at CVM. Comments may result in a modification to the proposed requirement to submit a single paper copy.

Under the regulation, the paper copy would be the official version at FDA. This provision would clarify the status of an electronic copy that FDA also is proposing to require [11] (see proposed § 192.20(c)(1) and section VII.C of this document).

FDA is proposing that a notifier who claims that specific data or information in the PBN are confidential must prepare and submit one paper copy of the PBN that does not contain any of those data or information (proposed § 192.20(b)(2)). Consistent with the EFOIA proposed rule, the notifier would prepare this redacted paper copy in a manner that clearly identifies the location and relative size of deleted information. As discussed previously regarding a presubmission consultation (see section VI.C of this document), the redacted copy would be very useful as it would communicate very clearly which data or information the notifier considers to be exempt from disclosure.

C. Electronic Copies

FDA is proposing to include in the regulation a recommendation that a notifier submit an electronic copy (the evaluation copy) that is formatted in a manner that makes it suitable for FDA to use while evaluating the PBN (proposed § 192.20(c)(1)). Because technology is advancing at a rapid pace, the regulation would inform notifiers how to obtain information about the appropriate format of the electronic copy rather than specify that format. Under the regulation, a notifier would provide such an electronic copy of both the original PBN and of any amendments to the PBN. FDA is recommending the submission of an electronic evaluation copy to take advantage of the fact that contemporary technology makes it possible for notifiers to send, and FDA to evaluate, submissions of data or information in electronic form, and the availability of an electronic evaluation copy has the potential to improve the efficiency of FDA's review. To encourage

[11] Under 21 CFR 11.1(c), an electronic record that meets the requirements of 21 CFR part 11 may be used in lieu of a paper record, unless paper records are specifically required. However, CFSAN is not prepared, at this time, to accept an electronic record as the official record because CFSAN does not yet have specific guidance for the submission of records only in electronic form.

manufacturers to submit an electronic evaluation copy, a notifier who submits such a copy would submit a total of two, rather than three, paper copies.

FDA also is proposing to require that a notifier submit an electronic copy (the disclosure copy) that is formatted in a manner that makes it suitable for FDA to use to make a PBN available to the public in an electronic reading room (proposed § 192.20(c)(2)). As would be the case with the electronic evaluation copy, the regulation would inform notifiers how to obtain information about the appropriate format of the electronic copy and a notifier would be required to provide such an electronic copy of both the original PBN and of any amendments to the PBN. Consistent with the EFOIA proposed rule, a notifier would delete data or other information claimed to be confidential from the electronic copy in a manner that clearly identifies the location and relative size of deleted information. FDA is proposing to require an electronic disclosure copy to facilitate the agency's compliance with EFOIA, which includes provisions regarding the availability of records in electronic form and the establishment of ''electronic reading rooms.'' As discussed in the EFOIA proposed rule, section 4 of EFOIA (5 U.S.C. 552(a)(2)(D)) adds a new category of records that agencies must make available in their public reading rooms. This new category consists of copies of records that have been released to any person under FOIA and that, because of their subject matter, the agency determines have become or are likely to become the subject of subsequent requests for substantially the same records. In light of the significant public interest in bioengineered foods and in FDA's oversight of these foods, FDA has tentatively concluded that it is likely that each submitted PBN would be requested under FOIA multiple times.

The preparation of an electronic copy formatted in a manner that makes it suitable for FDA to use to make a PBN available to the public in an electronic reading room will require use of computer technology. Although the use of this technology is widespread, it is possible that a firm that develops a bioengineered food would not have access to the particular technology that will be needed. For this reason, under the proposed regulation a notifier may request a waiver from

the requirement to submit an electronic disclosure copy. FDA would grant or deny the notifier's request on its merits.

FDA requests comments on its proposal to require an electronic disclosure copy of a PBN and to provide a notifier with an opportunity to request a waiver from this requirement. Such comments may result in a modification to the proposed requirement to submit such a copy.

D. English Language Translations, Incorporation by Reference, and Available Guidance Documents

FDA is proposing that a notifier who submits any material in a foreign language provide an English translation that is verified to be complete and accurate (proposed § 192.20(d)). This proposed regulation is necessary for the agency's efficient evaluation of a PBN and is consistent with other agency regulations regarding the submission of information in a foreign language (see e.g., § 171.1(a) and the agency's recent proposal for a premarket notification program for food contact substances (65 FR 43269, July 3, 2000)).

FDA is proposing that a notifier may incorporate by reference data or information that are already retained in FDA's files (proposed § 192.20(e)). The proposed regulation specifies that a notifier may simply incorporate by reference a file that the notifier previously submitted. If the notifier wishes to incorporate by reference a file that someone else previously submitted to FDA, the procedure to incorporate that file into the PBN depends on whether the file is publicly available (e.g., the file is in an electronic reading room or is otherwise available under FOIA). If the file is publicly available, a notifier may incorporate that file by referring FDA to it. If the file is not publicly available, a notifier may incorporate that file by referring FDA to it if the person who submitted the file authorizes the notifier to do so in a signed statement and the notifier includes that signed statement in the PBN. This proposed provision is similar to that described for incorporating previously submitted information into a food additive petition (§ 171.1(b)) and to that described in the agency's recent proposal for a premarket notification program for food-contact substances (65 FR 43269, July 13, 2000).

FDA is proposing to inform notifiers that they can obtain current guidance regarding specific technical issues by writing to FDA or by looking on FDA's site on the Internet (proposed § 192.20(f)). FDA is adding this provision to assist notifiers in addressing common technical issues, such as the estimation of dietary exposure to substances that are present in food. FDA expects that this provision will minimize the time spent, by the agency and the notifier, on routine technical issues.

E. Opportunity to Withdraw

FDA is proposing to codify a provision that a notifier may request, at any time during FDA's evaluation of a PBN, that FDA cease to evaluate that PBN (proposed § 192.30(g)). Under the regulation, the notifier could submit a future PBN about the same bioengineered food. FDA would retain the PBN in its files and would classify it as ''withdrawn.'' A notifier could choose to withdraw a notice for several reasons. For example, it is possible that discussions between the notifier and FDA would result in a decision by the notifier to substantially revise the notice to provide data or information that address the applicable legal status questions in a more thorough manner than the submitted PBN.

The proposed regulation is consistent with the provisions of the food additive premarket review program (§ 171.7). Although a notifier does not need explicit authorization to withdraw a notice, a notifier may not be aware of this fact. Likewise, a notifier may not be aware that a notice that is ''withdrawn'' remains an agency record that could be requested under FOIA. Thus, the regulation would both clarify a prerogative accorded to a notifier and inform the notifier of consequences associated with that prerogative.

VIII. Premarket Biotechnology Notice: Required Parts

FDA is proposing that a PBN be separated into seven parts (proposed § 192.25). These would include a letter (proposed § 192.25(a)); a synopsis (proposed § 192.25(b)); administrative statements about the status of review of the bioengineered food by other Federal agencies or by foreign

governments (proposed § 192.25(c)); data or information about the method of development (proposed § 192.25(d)); a discussion of any newly inserted genes that encode resistance to an antibiotic (proposed § 192.25(e)); data or information about substances introduced into, or modified in, the food (proposed § 192.25(f)); and data or information about the food (proposed § 192.25(g)). The proposed regulation fosters a case-by-case approach to addressing relevant scientific and regulatory issues rather than a single set of tests that likely would not be applicable in all circumstances. In general, the proposed requirements derive from the 1992 policy, the 1996 procedures, and FDA's experience under the 1996 procedures. In proposing these requirements, FDA also has drawn on its experience in administering a proposed notification program for GRAS substances (62 FR 18938, April 17, 1997).[12]

The proposed regulation reflects FDA's current judgment based on contemporary scientific methods for development of bioengineered foods and the types of bioengineered foods that are now under development. Accordingly, the proposed regulation focuses on modifications to foods that are likely to result in commercial products and does not attempt to predict future changes in foods that may result from technological advances. In this field of rapid scientific development, if circumstances warrant, FDA would propose to revise any regulation that results from this proposal. FDA requests comment on technological advances in rDNA technology that are likely to result in commercial products and that would not be addressed by the proposed submission requirements. Such comments may result in a modification to the proposed submission requirements.

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[12] FDA has not yet issued a final rule based on the GRAS proposal. However, in the GRAS proposal, FDA invited interested persons who determine that a use of a substance is GRAS to notify FDA of such GRAS determinations during the interim between the proposed and final rules (the interim period). During this interim period, FDA has received several dozen GRAS notices, which provided practical experience both with theoretical issues raised by that rulemaking and with practical issues associated with establishing an efficient program.

A. Part I: Letter

FDA is proposing to require that a responsible official of the notifier's organization, or the notifier's attorney or agent, date and sign a letter that informs FDA that the notifier is submitting a PBN under proposed § 192.25. In the letter, this official, attorney, or agent would state his position or title and attest to five statements.

1. Statements Regarding the Notifier's Responsibility and the Balanced Nature of the Notice

FDA is proposing to require that a notifier inform FDA that it is the notifier's view that the bioengineered food is as safe as comparable food and that the intended use of the bioengineered food is in compliance with all applicable requirements of the act (proposed § 192.25(a)(1)). Applicable requirements of the act would include, for example, the requirement under section 409(a) and 402(a)(2)(C) of the act for FDA review and approval of a food additive and the requirement under section 201(n) and 403 of the act that labeling for the food be appropriate. FDA also is proposing that a notifier state that to the best of the notifier's knowledge, the PBN is a representative and balanced submission that includes information, unfavorable as well as favorable, pertinent to the evaluation of the safety, nutritional, or other regulatory issues that may be associated with the bioengineered food (proposed § 192.25(a)(2)). FDA is proposing that the notifier attest to these statements because, under the act, developers of new foods have a responsibility to ensure that the foods they offer to consumers are safe and in compliance with all requirements of the act (57 FR 22984 at 22985).

FDA is proposing the standard ''as safe as'' because this is the standard that the agency currently uses to evaluate a notice that is submitted under the 1996 procedures. Because the proposed standard is a comparative standard (''as safe as''), it takes into account circumstances such as the existence of naturally occurring toxicants in many plants (e.g., solanine that occurs naturally in potatoes). As discussed below (see section VIII.G.1 and proposed § 192.25(g)(1)), FDA also is proposing that the notifier provide a justification for selecting a particular food or foods as the ''comparable food'' to which the notifier will compare the bioengineered food.

2. Statements Regarding the Availability of Data and Information for FDA's Review

FDA is proposing to require that a notifier agree to make relevant data or information that are not included in the PBN available to FDA upon request while FDA is evaluating the PBN or for cause (proposed § 192.25(a)(3)). FDA is proposing this requirement to ensure that the agency will have access to relevant data or other information if safety questions arise after the bioengineered food enters commercial distribution. This proposed requirement will also continue a practice that began under the 1996 procedures.

FDA also is proposing that a notifier agree to two procedures for making such data or information available to FDA (proposed § 192.25(a)(4)). The first procedure is to allow FDA to review and copy these data or information at a specified address during customary business hours. The second procedure is to send these data or information to FDA. FDA is proposing that a notifier agree to both of these two procedures to provide flexibility and efficiency to both the notifier and the agency.

3. Statement Regarding Public Disclosure

FDA is proposing that a notifier inform FDA as to whether the notifier claims that the existence of a PBN, or any or all of the data or information in the PBN, is exempt from disclosure under the FOIA and explain the basis for that claim (proposed § 192.25(a)(5)). FDA is proposing these requirements in light of the significant public interest in bioengineered foods. These requirements would ensure that FDA is aware of the notifier's position regarding the availability for public disclosure of the existence and content of a PBN. In addition, FDA believes that these requirements would alert a notifier that the data or information contained in a PBN are available for disclosure unless the applicable criteria for exemption are satisfied.

As discussed more fully below, this proposed rule assumes that the existence and content of a PBN is available for public disclosure unless the notifier establishes that the existence of the notice constitutes confidential commercial information or that specific data or information in the PBN constitute a trade secret or confidential commercial information. Thus, the proposed rule

acknowledges that there could be circumstances in which the existence or content (or a portion of the content) of a PBN would be eligible for an exemption from public disclosure.

B. Part II: Synopsis

FDA is proposing that the first section of a PBN be a synopsis (proposed § 192.25(b)) that includes the same information that FDA is recommending for inclusion in a presubmission consultation (see proposed § 192.10(f)(3) and section VI.C of this document). The synopsis would be a concise document that describes the bioengineered food in a manner that is suitable for preparing a publicly accessible list of PBN's (see proposed § 192.40(c)(1)(i) and section X.A of this document).

C. Part III: Status at Other Federal Agencies and Foreign Governments

FDA is proposing that a notifier inform FDA of the status of any prior or ongoing evaluation of the bioengineered plant, or food derived from such a plant, by USDA/APHIS and EPA (proposed § 192.25(c)(1) and (c)(2)). The proposed regulation is consistent with the recommendations in a report issued in April 2000 by the National Research Council (the 2000 NRC Report) (Ref. 14). That report recommended, among other things, that FDA, EPA, and USDA/APHIS establish a process to ensure appropriate and timely exchange of information between agencies about bioengineered pest-protected plants. Under the regulation, FDA would be aware of any issues still pending at those agencies, that are relevant to FDA's evaluation of the bioengineered food in question. When necessary and appropriate, FDA would contact APHIS, EPA, or both agencies about their evaluation of the bioengineered plant.

In addition, as discussed previously in this notice, the purpose of this notification program is to provide FDA with the information necessary to determine whether there are legal status questions concerning a bioengineered food so as to permit FDA to carry out its enforcement responsibilities. This would include its responsibilities to enforce section 402(a)(2)(B) of the act,

which addresses foods containing illegal pesticide residues.[13] If the EPA regulatory process regarding the bioengineered food is not yet complete and a tolerance or exemption from tolerance has not been established, the food would not be in full compliance with the law. Accordingly, in these circumstances, FDA would inform a notifier that the agency does not consider the notifier's PBN to satisfy the requirement for premarket notice (see proposed § 192.30(e) and section IX.C.5 of this document).

FDA also is proposing that a notifier inform FDA as to whether the bioengineered food is or has been the subject of review by any foreign government and, if so, describe the status of that review (proposed § 192.25(c)(3)). Foreign countries have instituted various regulatory requirements for bioengineered foods. Information about the status of a notifier's submission(s) to foreign countries could be pertinent to FDA's review. For example, some issues raised by a foreign country could be relevant to the legal status of the bioengineered food under the act.

D. Part IV: Method of Development

FDA is proposing that a PBN include data or information about the method of development (proposed § 192.25(d)). Specifically, FDA is proposing that the data or information that a notifier provides regarding the method of development include: (1) Characterization of the parent plant including scientific name, taxonomic classification, mode of reproduction, and pertinent history of development (proposed § 192.25(d)(1)); (2) construction of the vector used in the transformation of the parent plant, with a thorough characterization of the genetic material intended for introduction into the parent plant and a discussion of the transformation method, open reading frames, and

[13] Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), EPA registers pesticides, including those introduced into food via bioengineering; under section 408 of the act (21 U.S.C. 346a), EPA sets a tolerance or grants an exemption from a tolerance for pesticide residues in food. FDA has the statutory responsibility to enforce these tolerances or exemptions; under section 402(a)(2)(B), a food is adulterated if it contains a pesticide residue that exceeds an established tolerance or for which there is no tolerance or exemption from the requirement for a tolerance.

regulatory sequences (proposed § 192.25(d)(2)); (3) characterization of the introduced genetic material, including the number of insertion sites, the number of gene copies inserted at each site, and information on DNA organization within the inserts; and information on potential reading frames that could express unintended proteins in the transformed plant (proposed § 192.25(d)(3)); and (4) data or information related to the inheritance and genetic stability of the introduced genetic material (proposed § 192.25(d)(4)). The proposed requirement derives from the 1992 policy, the 1996 procedures, and FDA's experience under the 1996 procedures. FDA requests comment on technological advances in rDNA technology that are likely to result in commercial products and that would not be addressed by the proposed submission requirements. Such comments may result in a modification to the proposed submission requirements.

FDA also is proposing to require that a notifier include a discussion, as necessary, of other relevant data or information about the method of development (proposed § 192.25(d)(5)). This requirement would cover any issues about the method of development that are not explicitly addressed in proposed § 192.25(d)(1), (d)(2), (d)(3), and (d)(4). FDA expects that such issues would be identified during presubmission consultations on specific products.

E. Part V: Antibiotic Resistance

In September 1998, FDA issued for public comment a draft guidance document regarding the use of antibiotic resistance markers in bioengineered plants (the 1998 draft antibiotic resistance

guidance (Ref. 15)).[14],[15] Consistent with the thinking presented in that document, FDA is proposing to require that a PBN include a discussion about any newly inserted genes that encode resistance to an antibiotic (proposed § 192.25(e)). Because scientific methods to assess this issue are evolving, in the proposed regulation FDA is recommending that a notifier contact FDA about the agency's current thinking on this topic.

F. Part VI: Substances in the Food

FDA is proposing that a PBN include data or information about substances introduced into, or modified in, the food (proposed § 192.25(f)). These data or information would include data or information about the identity and function of these substances (proposed § 192.25(f)(1)), the level of these substances in the bioengineered food (proposed § 192.25(f)(2)), dietary exposure to these substances (proposed § 192.25(f)(3)), the potential that a protein introduced into the food will be an allergen (proposed § 192.25(f)(4)), and a discussion of other safety issues that may be associated with these substances (proposed § 192.25(f)(5)). In general, the proposed requirements derive from the 1992 policy, the 1996 procedures, and FDA's experience under the 1996 procedures. FDA requests comment on these proposed submission requirements. Such comments may result in a modification to the proposed submission requirements.

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[14] In the 1992 policy, FDA discussed the role of genes that encode resistance to an antibiotic as part of the development of some bioengineered foods (57 FR 22984 at 22987). In the APH(3')II final rule, FDA approved the use of the enzyme expressed by one such gene, the kan^r gene encoding resistance to kanamycin, in the development of new varieties of cotton, oilseed rape, and tomatoes. Between November 1996, and February 1997, FDA had several discussions with outside experts 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. Based on these discussions, FDA issued for public comment the 1998 draft antibiotic resistance guidance. FDA intends to issue final guidance in the near future.

[15] A report that describes the consultations that FDA relied on in developing this draft guidance is available (Ref. 16).

1. Covered Substances

FDA is proposing that a notifier provide data or information about substances introduced into, or modified in, the food (proposed § 192.25(f)). Under the regulation, a ''modified substance'' would include a substance that is present in the bioengineered food at an increased level relative to comparable food. Because pesticidal substances are regulated by EPA, the proposed regulation regarding data and information about substances introduced into the plant excludes data and information about pesticidal substances.

As discussed previously (section II of this document), a nonpesticidal substance introduced into food by way of breeding is a food additive if the substance is not GRAS within the meaning of 21 U.S.C. 321(s). Thus, the legal status issues raised by bioengineered foods include the potential that the food would contain an unapproved food additive. In the 1992 policy, FDA expressed its view that there is unlikely to be a safety question sufficient to question the presumed GRAS status of the expression products of the transferred genetic material when the expression products do not differ significantly from other substances commonly found in food and are already present at generally comparable or greater levels in currently consumed foods (57 FR 22984 at 22990). In the 1992 policy, FDA identified proteins, carbohydrates, and fats and oils as substances commonly found in food because those were the substances that were being considered in products under development in 1992.[16] As discussed, rDNA technology has recently begun to be used to introduce multiple genes to generate new metabolic pathways (Ref. 11). As with proteins, carbohydrates, and fats and oils, it is FDA's view that the substances produced by the new pathways would be presumed to be GRAS if they do not differ significantly from other substances that are currently present at generally comparable or greater levels in food and, as such, are safely consumed.

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[16] As discussed in the 1992 policy, FDA has presumed that transferred nucleic acids would be GRAS (57 FR 22990). Under the proposed regulation, a notifier provides data or other information about transferred nucleic acids in Parts IV (method of development) and V (genes that encode resistance to an antibiotic).

2. Identity, Function, Level, and Dietary Exposure

FDA is proposing that a PBN include data or information about the identity and function of substances introduced into, or modified in, the food (proposed § 192.25(f)(1)) and the level in the bioengineered food of these substances (proposed § 192.25(f)(2)). The proposed regulation derives from the fact that the quantity and quality of scientific evidence required to establish that the use of a substance is safe vary considerably depending upon the chemical, physical, and physiological properties of the substance and its estimated dietary exposure.

FDA is proposing that a notifier include either: (1) An estimate of dietary exposure to substances introduced into, or modified in, the food (proposed § 192.25(f)(3)(i)); or (2) a statement that explains the basis for the notifier's conclusion that an estimate of dietary exposure to these substances is not needed to support safety (proposed § 192.25(f)(3)(ii)). As discussed in the 1992 policy (57 FR 22984 at 22998), many substances that would be introduced into, or modified in, a bioengineered food would be present in the bioengineered food at a relatively low level. For example, since 1994, developers have completed more than 45 consultations about bioengineered foods, most of which contain newly introduced or modified enzymes (Ref. 6). In most cases, an estimate of dietary exposure to these enzymes was not critical to the safety assessment. However, this is not always the case, even for enzymes that would be present in food at a low level. For example, in the case of the enzyme APH(3′)II, FDA relied, in part, on the estimated dietary exposure to APH(3′)II in concluding that active APH(3′)II in food would not interfere with the clinical efficacy of the orally administered antibiotic, kanamycin (59 FR 26700 at 26703). Thus, the particular circumstances will determine whether an actual estimate of dietary exposure to a substance that is introduced into a food plant is needed to support the notifier's view that the bioengineered food is as safe as comparable food.

3. Allergenicity

FDA is proposing that a notifier include a discussion of the available data or information that address the potential that a protein introduced into the food will be an allergen (proposed

§ 192.25(f)(4)). The proposed regulation is consistent with the 1996 procedures, which recommend that a notifier provide FDA with information regarding any known or suspected allergenicity and a discussion of the available information about the potential for the bioengineered food to induce an allergic response. Because scientific methods to assess this issue are evolving, in the proposed regulation FDA is recommending that a notifier contact FDA about the agency's current thinking on this topic.

FDA is developing guidance for evaluating the potential allergenicity of proteins introduced into bioengineered foods and intends to make that draft guidance available for public comment in the near future. The draft guidance will be based in part on recommendations made by scientific experts who attended a public scientific conference on food allergy and bioengineered foods that FDA, EPA, and USDA jointly hosted on April 18 and 19, 1994 (the 1994 allergenicity conference (Ref. 17)).[17]

4. Other Safety Issues

It is impracticable for FDA to either anticipate all classes of substances that could be introduced into food or provide specific guidance about each of those classes of substances.

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[17] The goal of the 1994 allergenicity conference was to foster a scientific dialogue to assess information that was available at that time regarding the characteristic properties of food allergens and the methods that are available to assess allergenicity. The scientists who participated in this conference noted that serum from an individual who is sensitive to a known allergenic source can be used to assess the allergenic potential of proteins derived from that source. These scientists acknowledged that there are no direct methods to assess allergenicity of proteins from sources that are not known to produce food allergy. However, they suggested that the possibility that a new protein will cause an allergic reaction can, to some degree, be evaluated by comparing its similarity to characteristics of known food allergens. If a protein does not have characteristics of known food allergens, the potential that the protein would cause an allergic reaction is minimized. Because exceptions have been reported for the observed characteristics of allergens, and no one factor is fully predictive, the scientists recommended that an assessment of allergenicity be based on all available information.

Therefore, FDA is proposing that a notifier provide a discussion of data or information relevant to other safety issues that may be associated with the substances introduced into, or modified in, the food (proposed § 192.25(f)(5)). This requirement would cover any issues that are not explicitly addressed in proposed § 192.25(f)(1), (f)(2), (f)(3), and (f)(4) regarding substances introduced into, or modified in, the food. Such issues could include, for example, the digestibility or toxicity of an introduced protein. FDA expects that such issues would be identified during presubmission consultations on specific foods.

G. Part VII: Data and Information About the Food

FDA is proposing that a notifier provide data or information about the bioengineered food (proposed § 192.25(g)). These data or information would include a justification for selecting a particular food(s) as ''comparable food'' (proposed § 192.25(g)(1)); a discussion of historic uses of the comparable food(s) (proposed § 192.25(g)(2)); data or information comparing the composition and characteristics of the bioengineered food to those of comparable food(s), with emphasis on significant nutrients, naturally occurring toxicants and antinutrients, and any intended changes to the composition of the food (proposed § 192.25(g)(3)); any other information relevant to the safety, nutritional, or other regulatory assessment of the bioengineered food (proposed § 192.25(g)(4)); and a narrative that explains the basis for the notifier's view that the bioengineered food is as safe as comparable food(s) and that the bioengineered food is otherwise in compliance with all applicable requirements of the act (proposed § 192.25(g)(5)). In general, the proposed requirements derive from the 1992 policy, the 1996 procedures, and FDA's experience under the 1996 procedures. FDA discusses the details of this proposed regulation immediately below. FDA requests comment on the proposed submission requirements regarding the food. Such comments may result in a modification to the proposed submission requirements.

1. Comparable Food

FDA is proposing that the notifier provide a justification for selecting a particular food or foods as the ''comparable food'' to which the notifier will compare the bioengineered food (proposed § 192.25(g)(1)). The proposed requirement is based on the 1992 policy and FDA's experience under the 1996 procedures.

Ordinarily, the comparable food would be the parental variety or commonly consumed varieties of the parent plant (57 FR 22984 at 22996 and Ref. 5)). However, when the intended effect of the transformation is to change the composition of the food, it may be appropriate to also compare the composition and characteristics of the bioengineered food to that of another commonly consumed food. For example, if an oilseed crop is modified to produce an oil that has a higher content of a particular fatty acid than commonly consumed varieties, it may be appropriate to also compare the composition and characteristics of the bioengineered food to that of a food that contains that fatty acid. FDA expects that any issues associated with the appropriate selection of comparable food(s) would be identified during presubmission consultations on specific products.

2. Historic Uses of the Comparable Food

FDA is proposing that the notifier provide a discussion of historic uses of the comparable food(s) to which the notifier will compare the bioengineered food (proposed § 192.25(g)(2)). Several notifiers who have consulted with FDA under the 1996 procedures have included such a discussion (e.g., as part of their description of the applications or uses of the bioengineered food). FDA has found that such a discussion is particularly helpful in identifying the potential uses of the bioengineered food, regardless of whether those uses are specifically targeted by the notifier.

3. Comparing the Composition and Characteristics of the Bioengineered Food to That of Comparable Food

Consistent with the 1992 policy, the 1996 procedures, and FDA's experience under the 1996 procedures, FDA is proposing that a notifier provide data or information comparing the composition and characteristics of the bioengineered food to those of comparable food(s), with emphasis on changes in the levels of significant nutrients and naturally occurring toxicants and antinutrients (proposed § 192.25(g)(3)(i) and (g)(3)(ii)). Such changes could raise legal status questions such as whether the name of the food adequately describes the food or whether the food is adulterated within the meaning of section 402(a)(1) of the act.

Consistent with the 1992 policy, the 1996 procedures, and FDA's experience under the 1996 procedures, FDA is proposing that a notifier provide data or information about any intended changes to the composition or characteristics of the food (proposed § 192.25(g)(3)). Such changes could raise legal status questions such as the appropriate common or usual name for the food. For example, FDA has been notified about a modification to a canola variety of rapeseed to produce an oil with a modified fatty acid composition. Because the name that is most often used to describe oil derived from the parent plant (i.e., canola oil) did not accurately reflect the characteristic properties of the bioengineered oil, the notifier suggested a new name for the oil.

Intended changes to the composition or characteristics of the food also could raise safety questions about the food. For example, it is possible that a developer could modify corn so that the corn becomes a significant dietary source of the nutrient folic acid. Folic acid is used to fortify many foods, including breakfast cereals, because of the relationship between consumption of folic acid and a reduced risk of neural tube defects (21 CFR 101.79). However, excess folic acid in the diet can mask the signs of vitamin B_{12} deficiency. Thus, an increased level of folic acid in a food such as corn, which is commonly used in breakfast cereals, could raise safety or other regulatory issues.

Under proposed § 192.25(g)(3), intended changes to the composition of food include modifications that are intended to reduce the level of a substance in food. For example, it is possible that a modification would be intended to decrease the level of a substance that is considered undesirable, such as the phytate that naturally occurs in soybeans. It also is possible that a modification would be intended to reduce the fat content of a food. As with intended increases in the level of substances already in food, changes that decrease the level of substances already in food could raise legal status questions such as the appropriate common or usual name for the food.

4. Other Relevant Information

Consistent with the 1992 policy, the 1996 procedures, and FDA's experience under the 1996 procedures, FDA is proposing that a notifier provide a discussion of any other information relevant to the safety, nutritional, or other regulatory assessment of the bioengineered food (proposed § 192.25(g)(4)). This requirement would cover any legal status issues about the food that are not explicitly addressed in proposed § 192.25(g)(1), (g)(2), and (g)(3). For example, under proposed § 192.25(g)(4), a notifier could discuss the basis for proposing a specific common or usual name for a bioengineered food, or any other proposed labeling that would accompany the bioengineered food. FDA expects that such issues would be identified during presubmission consultations on specific foods.

FDA requests comment on whether this rule should also include a requirement that a premarket notice for a bioengineered food include methods by which the food could be detected. In particular, the agency is interested in comments on the circumstances under which such methods should or should not be required, and the rationale for any such requirement (e.g., the modification to the crop makes the food acceptable for animal feed but unacceptable for human food). The agency is also interested in comments on whether any such required methods should be for raw agricultural commodities, representative finished foods likely to contain the modified food, or both; and whether any such required methods should contain sufficient information, such as primer sequences, to

enable technically-proficient non-government laboratories to use them; and what other criteria, if any, there should be for required methods (e.g., cost). Such comments may result in a modification to the proposed submission requirements.

5. Narrative

FDA is proposing to require that a notifier provide a narrative that explains the basis for the notifier's view that the bioengineered food is as safe as comparable food and that the bioengineered food is otherwise in compliance with all applicable requirements of the act (proposed § 192.25(g)(5)). The narrative would provide an integrated discussion of the data and information submitted in a PBN. FDA is proposing this requirement because the notifier has the responsibility for determining that the intended use of the bioengineered food is as safe as comparable food and is otherwise lawful. Absent an integrated discussion of the underlying data and information, the basis for the notifier's conclusion about the legal status of the bioengineered food may not be apparent.

IX. Agency Administration of a Premarket Biotechnology Notice

A. Filing Decision

FDA is proposing to do an initial evaluation of the notice within 15 working days to see whether the notice appears to include all elements required under §§ 192.20 and 192.25 (proposed § 192.30(a)). FDA also is proposing to file a PBN that appears to include all required elements, and to contact a notifier to explain what is missing if the PBN does not appear to include all required elements. FDA is proposing this ''filing decision'' because the timeframe for the agency's response to the notifier (i.e., 120 days (see proposed § 192.5(c) and section V.C of this document) is relatively short. To enable the agency to complete its evaluation in this period, it is essential that the agency have a complete notice when the 120-day period begins.

The proposed timeframe for the filing decision (i.e., within 15 working days) is consistent with the timeframe for the filing decision for a food additive petition (§ 171.1(i)(1)). The proposed

process that ''FDA will inform the notifier'' provides flexibility for the mechanism whereby FDA contacts a notifier. FDA expects to contact the notifier by telephone or possibly by electronic mail and expects that a notifier would provide the missing material promptly. However, should circumstances warrant (e.g., FDA is unable to reach a notifier by telephone, or the notifier does not provide the materials promptly), under the regulation, FDA could send a letter or telefax to the notifier explaining that the agency had received, but not filed, the PBN and the reasons therefor.

Under proposed § 192.30(a)(1), CFSAN will inform CVM about any PBN that it files. Regardless of whether the bioengineered food would be used in human food, food for animals, or both, this inter-Center communication will ensure that both Centers are aware of all bioengineered foods that are nearing commercialization.

B. Acknowledgment Letter

FDA is proposing to send, within 15 working days of filing a notice, a letter to the notifier (or, when applicable, the notifier's agent) informing the notifier of the date on which FDA filed the PBN (proposed § 192.30(b)). As a practical matter, such a letter would acknowledge receipt as well as inform the notifier of the date of filing.

C. Response Letter

FDA is proposing to respond to a notifier within 120 days of filing a notice (proposed § 192.30(c)). Because all submissions will be sent to CFSAN, CFSAN would issue the response to the notifier, regardless of whether the intended use of the bioengineered food is in human food, food for animals, or both. A response from CFSAN would make clear that CFSAN was aware of, and thus had been notified about, all bioengineered foods, regardless of their intended use.

As with any correspondence, the particular circumstances will determine the full text of the agency's letter. However, the agency believes that a letter would likely fall into one of four general categories (proposed § 192.30(d)(1), (d)(2), (d)(3), and (d)(4)). FDA discusses each of these four categories immediately below.

1. General Categories for FDA's Response

a. *Letter that extends FDA's evaluation.* FDA is proposing that the agency could inform a notifier that the agency is extending its evaluation of the premarket notice by 120 days (proposed § 192.30(d)(1)). Under the regulation, in this letter FDA would also inform the notifier that the agency expects that the bioengineered food will not be marketed during the extended evaluation period.

Ordinarily, FDA expects to send a final response to a notifier within 120 days, particularly if a prospective notifier discusses relevant scientific and regulatory issues with FDA, prior to submitting a PBN about a bioengineered food (see proposed § 192.10 and section VI of this document). However, there are several circumstances that could prevent the agency from completing its evaluation within that time period. For example, FDA may need to extend the review time if a notifier did not participate in the presubmission consultation program; the issues raised by a particular bioengineered food could be particularly novel and complex; parts of a submission could require clarification, amplification, or correction; or the submission could be poorly written or be of such poor scientific quality that it precludes timely evaluation by the agency.

As discussed previously, FDA is issuing this proposed rule to ensure that it has the appropriate amount of information about bioengineered foods and to help to ensure that all market entry decisions by the industry are made consistently and in full compliance with the law. The goal of this rulemaking would not be achieved if a bioengineered food entered commercial distribution before FDA had completed its evaluation of the applicable notice.

b. *Letter that the notice does not provide a basis.* FDA is proposing that the agency have an option to inform a notifier that the premarket notice does not provide a basis for the notifier's view that the bioengineered food is as safe as comparable food or is otherwise lawful (proposed § 192.30(d)(2)). In so doing, FDA would inform the notifier of the reasons for this conclusion. Under the regulation, in this letter FDA would also inform the notifier that the agency expects that the bioengineered food will not be marketed.

FDA has had experience with another food program, the proposed notification program for GRAS substances, in which some submitted notices do not provide a basis for the notifier's view that the intended use of a substance is lawful (Ref. 18). The underlying reasons why the applicable notices have not provided a basis for a GRAS determination have been quite varied. Likewise, there could be various reasons why a premarket notice does not provide a basis for the notifier's view that the bioengineered food is as safe as comparable food or is otherwise lawful. For example, the notice may not provide a basis for the notifier's view that a substance introduced into the bioengineered food is not an unapproved food additive or that the bioengineered food would not be misbranded. As another example, the notice may not provide a basis to conclude that a bioengineered food that contains an unusually high level of a naturally occurring toxicant would not be adulterated. As a third example, if the poor quality of a notice makes it difficult for the agency to fully evaluate the notice, regardless of the time period available, FDA may inform the notifier of the inadequacies of the notice rather than extend its evaluation of the notice for another 120 days.

If a notice about a bioengineered food does not provide a basis to conclude that a bioengineered food is as safe as comparable food or is otherwise lawful, that food could be adulterated or misbranded and should not be marketed. If a notifier initiates commercial distribution of a bioengineered food after being informed that the applicable notice is not adequate, FDA will carefully and completely review the legal status of the applicable food and will use all available options to ensure that the food is fully in compliance with all provisions of the act. In particular, in such circumstances, the agency fully intends to bring to bear the complete range of its authorities and resources, including its authority under section 704 of the act (21 U.S.C. 374) to conduct inspections and investigations, collect samples, and perform analyses, as well as its authority under sections 705 and 903 of the act (21 U.S.C. 375 and 393) to engage in publicity and public education. When the agency concludes through the application of these resources that a food is adulterated, misbranded, or otherwise not in full compliance with the act, FDA will utilize the

act's legal sanctions, as appropriate, including in rem seizure of violative foods and injunction proceedings against, or criminal prosecution of, those responsible for distributing such foods.

c. *Letter that FDA has no questions*. If, based on its evaluation of a notice, FDA has no questions regarding the notifier's view that the bioengineered food is as safe as comparable food and is otherwise lawful, FDA would inform a notifier of that fact (proposed § 192.30(d)(3)). Because the evaluation of food safety is a time-dependent judgment that is based on general scientific knowledge as well as specific data and information about the food, FDA would qualify its statement to clarify that the agency has no questions ''at this time.'' This proposed response is similar to the letters that FDA has issued in response to submissions received under the 1996 procedures.

d. *Letter that a notifier has withdrawn the notice*. Under proposed § 192.20(g), if a notifier requests that FDA cease to evaluate a PBN, FDA would retain the PBN in its files and classify the PBN as ''withdrawn.'' In such a circumstance, FDA would bring the notification process to closure by sending the notifier a letter acknowledging that the agency had received a withdrawal letter and had ceased to evaluate the PBN, effective on the date that FDA received the letter (proposed § 192.30(d)(4)). This proposed response is similar to responses issued by FDA under the proposed notification program for GRAS substances when the notifier requests that FDA cease to evaluate a GRAS notice (Ref. 18).

2. Status of the Bioengineered Food at EPA

If the bioengineered food contains a pesticidal substance, FDA is proposing that FDA's response letter will describe the status of the bioengineered food at EPA (proposed § 192.30(e)). If all applicable regulatory processes at EPA have come to closure (proposed § 192.30(e)(1)), FDA would say so and would respond as described above. As discussed above, if regulatory processes at EPA regarding the bioengineered food are still pending, FDA would inform the notifier that FDA does not consider the PBN to satisfy the requirement for premarket notice (proposed § 192.30(e)(2)).

X. Public Disclosure

FDA is proposing to inform notifiers about: (1) The public disclosure provisions that apply to the existence and content of a PBN; (2) procedures that a notifier should use to inform FDA of the notifier's view about whether the existence or content of a PBN is exempt from public disclosure; and (3) the criteria that FDA uses to evaluate the notifier's view (proposed § 192.40(a) through (d)). FDA also is proposing the procedures that FDA will use to disclose the agency's evaluation of, and response to, each PBN (proposed § 192.40(e)). This part of the regulation would ensure that both notifiers and the interested public have information about provisions that derive from the FOIA. FDA requests comment on these proposed provisions. Such comments may result in a modification to the proposed requirements.

A. Existence of the Notice

FDA is proposing that the existence of a filed PBN ordinarily is available for public disclosure on the date that FDA files it (proposed § 192.40(a)(1)). Under the regulation, a notifier who believes that the existence of a PBN is exempt from disclosure would be responsible for asserting that claim (proposed § 192.40(a)(2)). If a notifier claims that the existence of a PBN is confidential, FDA would evaluate that claim and would disclose the existence of the PBN, unless FDA determines that the criteria for exemption from disclosure in § 20.61 are satisfied (proposed § 192.40(a)(3)). If FDA determines that the existence of a PBN is confidential at the time that the agency files it, the existence of the PBN would become available for public disclosure, in accordance with § 20.61, when the criteria for exemption from disclosure are no longer satisfied (proposed § 192.40(a)(4)).

FDA has previously discussed the FOIA, and the exemption from public disclosure that the FOIA provides for trade secrets and confidential commercial information, with respect to data or information that a developer submits to FDA during a presubmission consultation (section VI.B of this document). Consistent with that discussion, FDA believes that, in most cases, the fact that a notifier had submitted a PBN would not constitute confidential commercial information.

Nevertheless, there could be circumstances in which a notifier submits a PBN and has grounds to claim that the existence of the PBN should not be available for public disclosure.

FDA is proposing to make a list of filed PBN's easily accessible to the public (e.g., by placing the information on the Internet or in a paper or electronic file that is available at FDA for public review and copying) (proposed § 192.40(b)). FDA expects that the list of PBN's would include most or all of the information in the synopsis of the PBN. Consistent with current procedures for updating an easily accessible inventory of notices received for another foods program (i.e., the GRAS notification program; see Ref. 18), FDA expects to update the list of filed PBN's on an approximately monthly basis. The proposed regulation to make this information easily accessible to the public is responsive to the input that FDA received at the public meetings that it convened in 1999, and to the comments that FDA received as a result of those meetings.

B. Content of the Notice

FDA is proposing that the data or information in a PBN ordinarily are available for public disclosure on the date that FDA files the PBN (proposed § 192.40(c)(1)). Under the regulation, a notifier who believes that some or all of the content of a PBN is exempt from disclosure would be responsible for asserting that claim (proposed § 192.40(c)(2)). If a notifier claims that some or all of the content of a PBN is confidential, FDA would evaluate that claim. FDA would disclose the content of the PBN, unless FDA determines that the criteria for exemption from disclosure in § 20.61 are satisfied (proposed § 192.40(c)(3)). If FDA determines that some or all of the content of a PBN is confidential at the time that the agency files it, the data or information in question would become available for public disclosure, in accordance with § 20.61, when the criteria for exemption from disclosure are no longer satisfied (proposed § 192.40(c)(4)).[18]

[18] Section 20.61 describes both criteria for exemption from disclosure and procedures that apply in circumstances where FDA disagrees with the view of a person who submits data or information that some or all of those data or information satisfy the criteria for exemption from disclosure.

Consistent with the agency's discussion of its view regarding the disclosability of the data or information provided to FDA during a presubmission consultation (section VI.B of this document), FDA believes that, in most cases, most of the data or information in a PBN would not constitute a trade secret. For example, very few of the submissions that FDA has received under its current consultation program identify specific data or information that the developer claims to be exempt under § 20.61. However, when the existence of the PBN is exempt from disclosure, all data and information in the submission would necessarily be exempt from disclosure.

FDA anticipates that the PBN will be easily accessible to the public. Under EFOIA and FDA's proposed rule to implement EFOIA, frequently requested records, or records that are likely to be requested frequently, are placed in an ''electronic reading room.'' As discussed above (see section VII.C of this document), FDA has tentatively concluded that it is likely that each submitted PBN would be requested under FOIA multiple times. Therefore, these records will be easily accessible to the public because they will be available electronically (proposed § 192.40(d)).

C. Disclosure of FDA's Evaluation of, Response to, a Notice

FDA is proposing to make two agency records associated with a PBN easily accessible to the public (e.g., by placing the information on the Internet or in a paper or electronic file that is available at FDA for public review and copying) (proposed § 192.40(e)(1)). The applicable records include the text of the letter issued by the agency in response to each PBN, and the text of the agency's completed evaluation of each PBN.

The proposed regulation commits to make available the ''text'' of the agency's letter and the agency's memorandum, rather than a ''copy'' of these records, to enable FDA to satisfy the regulations by a mechanism other than providing a physical copy of these records (e.g., by providing an electronic copy on the Internet). Consistent with current procedures for updating an easily accessible inventory of notices received for another foods program (i.e., the GRAS notification program; see Ref. 18), FDA expects to add the text of applicable agency letters and memoranda to the easily accessible file on an approximately monthly basis. The proposed regulation

to make this information easily accessible to the public is responsive to the input that FDA received at the public meetings that it convened in 1999, and to the comments that FDA received as a result of those meetings.

As discussed previously (proposed § 192.30(c)(1) and section IX.C.1 of this document), a notifier could receive a letter that informs the notifier that FDA is extending its evaluation of the premarket notice by 120 days. Under the proposed regulation to make the agency's response to a PBN easily accessible to the public, such an extension letter would be easily accessible to the public. When FDA issues a final letter regarding the applicable notice, it is likely that the agency would replace the extension letter with the final letter rather than making both letters easily accessible. The fact that the notifier had received an extension letter would still be readily apparent (e.g., because the date of the final response letter would be more than 120 days from the date of the extension letter). In addition, it is likely that FDA's final response letter would acknowledge the fact that the agency had sent a letter extending its evaluation.

XI. Proposed Regulations Regarding Bioengineered Foods That Would Be Used in Animal Feed

FDA is proposing to require the submission to the agency of data and information regarding bioengineered plant-derived foods that would be used in animal feed. FDA's proposal also includes a recommendation that prospective notifiers participate in a presubmission consultation program. In general, these proposed regulations regarding bioengineered foods intended to be fed to animals (proposed part 592) parallel the agency's proposed regulations for human food (proposed part 192). The following discussion addresses areas of importance in the proposed animal feed regulations (proposed part 592).

The number of different species encompassed by the term ''animal,'' as used in the act, is extraordinarily broad. CVM has regulatory authority over the food consumed by all nonhuman species, ranging from those raised in aquaculture, such as lobster and fish, to pets, birds, and the traditional classes of farm animals like cattle, swine, and horses. These animals may consume

parts of a bioengineered plant that are not eaten by people. For example, cattle and other herbivores eat the forage portion of the corn plant (stalk and leaves), which has no human food applications. In addition, animals may eat the byproducts or residues left over from the production of human foods. For example, soybean meal, which is a source of dietary protein widely used in animal diets, is a byproduct from the production of soybean oil, which is primarily used in human foods. As another example, broken rice, which is not desirable for human food, is a major pet food ingredient.

Undesirable substances can concentrate in the byproducts or residues left over from the production of human foods. For example, gossypol, a naturally occurring toxicant in cotton, concentrates in cottonseed meal, which is a byproduct obtained during the manufacture of cottonseed oil. The presence of gossypol limits the use of cottonseed meal in animal feed. As another example, some substances that can cause enlargement of the thyroid naturally occur in rapeseed plants and are concentrated in the meal (commonly called canola meal) that is a byproduct obtained during the manufacture of low erucic acid rapeseed oil (comonly called canola oil). These compounds must remain at a low level for the canola meal to be useful in animal feed.

In some cases, bioengineered foods could make up most of an animal's diet, which the animal could consume for its entire lifespan. For example, in a single year a high-producing dairy cow could eat as much as 6,000 pounds of a nutritional supplement containing added energy and protein. This supplement could contain up to 80 percent corn grain and 20 percent soybean meal. The same dairy cow could also consume as much as 4,380 pounds of fermented corn forage and ears (i.e., whole plant corn silage in that same year). Fattening beef cattle could eat a diet based on 10 percent whole plant corn silage, 80 percent corn grain, and 9 percent soybean meal. A typical swine diet contains 74 percent corn grain and 23 percent soybean meal, while broiler chicks might eat a ration that is 58 percent corn grain and 35 percent soybean meal. Because these foods may comprise such a large percentage of an animal's diet, an undesirable substance that is introduced

into a bioengineered food, even at a low level, has the potential to adversely affect an animal that eats the food.

Because of these factors, notifiers in assembling a PBN to address bioengineered foods to be consumed by animals should pay particular attention to the intended use of the bioengineered food, including the species expected to consume it; the function and level of all introduced or modified substances; and any changes in the composition and characteristics of the food. FDA has concluded that the notices should contain adequate information about any potential safety issues for all substances introduced into, or modified in, the food. Concerns associated with any changes in the composition or characteristics of the bioengineered food should also be addressed. Notifiers should be aware that in some cases, animal diets are formulated using different nutritional parameters than those used by human nutritionists. For example, when a diet is formulated for cattle, nutritionists utilize parameters such as neutral detergent fiber and acid detergent fiber in evaluating the suitability of a potential ingredient. Notices for bioengineered plants intended to be fed to animals should incorporate these differences in how ingredients are evaluated for their nutritional content.

XII. Paperwork Reduction Act

This proposed rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501–3520). A description of these provisions is given below with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

FDA invites comments on: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance

the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Premarket Notice Concerning Bioengineered Food

Description: Section 701 of the act sets forth authority to issue regulations for the efficient enforcement of the act. Section 201 of the act defines terms utilized within the act. Food is defined by section 201 of the act to mean: ''(1) articles used for food or drink for man or other animals, (2) chewing gum, and (3) articles used for components of any such article.'' Thus, the act clearly incorporates animal feed and drink into its definition of food.

Section 403 of the act prohibits the misbranding of food. Section 402 of the act prohibits the adulteration of food. Section 409 of the act establishes a premarket approval requirement for ''food additives.'' Section 201(s) of the act provides a two-step definition of ''food additive.'' The first step broadly includes any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of food, which under section 201(f) of the act includes animal food. The second step, however, excludes from the definition of food additive substances that are GRAS by qualified experts.

In this proposed rule, FDA is proposing to require the submission to the agency of data and information regarding plant-derived bioengineered foods. The proposed rule refers to foods derived from plant varieties that are developed using rDNA technology as ''bioengineered foods.'' FDA is proposing that this submission be made at least 120 days prior to the commercial distribution of such foods. The notice would include data and information about the bioengineered food and a narrative that provides an integrated discussion of those data and information. The notifier would maintain a record of relevant data and information that are not included in the notice. FDA would make the existence of the notice, and the agency's evaluation of and response to the notice, easily accessible to the public. The content of the notice would be publicly available consistent with

the FOIA and other federal disclosure statutes. FDA is also proposing to include in the regulation a recommendation that prospective notifiers consult with the agency to identify and discuss relevant safety, nutritional, or other regulatory issues regarding a bioengineered food.

Description of Respondents: Developers, manufacturers, distributors, or importers of food.

FDA estimates the burden of this collection of information as follows:

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
192.10(e) through (g)	20	1	20	4	80
192.10(h)(1)	20	1	20	0.5	10
192.10(h)(2)	20	1	20	8	160
192.10(h)(3)(i)	2	1	2	2	4
192.10(h)(3)(ii)	2	1	2	5	10
192.20(b)(2)(i)	2	1	2	2	4
1192.20(b)(2)(ii)	2	1	2	5	10
192.20(c)(1)	20	1	20	8	160
192.20(c)(2)	20	1	20	8.4	168
192.20(d)	0.5	1	0.5	20	10
192.20(e)	0.5	1	0.5	2	1
192.20(g)	0.5	1	0.5	1	0.5
192.20(a) through (b)(1) and 192.25	20	1	20	190	3,800
Total					4,417.50

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

TABLE 2.—ESTIMATED ANNUAL RECORDKEEPING BURDEN[1]

21 CFR Section	No. of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Recordkeeper	Total Hours
192.25(a)(2)	20	1	20	19	380
Total					380

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

Under the proposed rule, a notifier sends a notice regarding a bioengineered food to CFSAN regardless of whether the intended use is in human food, food for animals, or both. Because FDA routinely issues separate regulations regarding human food and animal feed, the regulations associated with the notice are codified in two parts of title 21: part 192 and part 592. Both CFSAN and CVM have been consulting with developers of bioengineered foods, and have received submissions of data and information about such foods. Since 1994, FDA has received, on average, eight submissions about bioengineered foods that are ready for commercialization per year. However, given the efficiencies of rDNA techniques, the advances in these techniques, and the rapidly expanding information related to genomes, FDA expects that these techniques are likely

to be utilized to an increasingly greater extent. Thus, for the purpose of this analysis FDA is estimating that the agency would receive 20 PBN's per year.

In this analysis, FDA is assuming that all notices about bioengineered foods will encompass both human food and food for animals. FDA is making this assumption because this was the case in approximately 70 percent of submissions that FDA has received since 1994. Because some 30 percent of notices may not encompass both human food and food for animals, FDA's assumption results in a conservative estimate of the reporting and recordkeeping burden.

Because FDA's analysis assumes that all notices will encompass both human food and food for animals, and because all notices are submitted to CFSAN, regardless of the intended use, FDA is estimating the recordkeeping and reporting burden only for the regulations issued in Part 192. FDA is making no separate estimate of the recordkeeping and reporting burden for the regulations issued in Part 592 because this burden is subsumed within the burden estimated for part 192.

A. Hourly Burden to Prepare a Report (Proposed §§ 192.20(a) through (b)(1) and § 192.25)

FDA contacted five firms that had made one or more submissions under FDA's existing procedures, which are summarized in a guidance first issued in 1996 (the 1996 procedures (Ref. 5)). FDA asked each of these firms for an estimate of the hourly burden to prepare a submission under the current process. Three of these firms subsequently provided the requested information. Based on this information, FDA is estimating that the average time to prepare a submission under the 1996 procedures is 150 hours.

The proposed rule would include some reporting requirements that are not described in the 1996 procedures. After considering the amount of time that firms need, on average, to prepare a submission under the 1996 procedures, and after considering the relative contribution of the additional parts, FDA is estimating that a firm would need 32 to 48 additional hours to prepare the additional sections. For the purpose of this analysis, FDA selected the average of these estimates (i.e., 40 additional hours).

FDA is estimating that the hourly burden to prepare a PBN is the sum of the hours that a firm currently spends, on average, to prepare a submission under the 1996 procedures and the additional hours that a firm would spend, on average, to prepare a submission that addresses requirements that are not described under the 1996 procedures. This sum is 150 hours plus 40 hours, or 190 hours.

B. Hourly Reporting Burden Associated With Confidential Information in a Report (Proposed § 192.20(b)(2)(i) and (b)(2)(ii)

FDA expects that most of the data or information in a PBN will be available for public disclosure. However, a few firms that made submissions under the 1996 procedures included information that they considered to be confidential. To ensure that FDA is aware of confidential information, under the proposed rule a notifier must identify any confidential information in the PBN. FDA is estimating that two PBN's per year would contain confidential information and that it would take a notifier 2 hours to identify this information. Under the proposed rule, a notifier who includes confidential information must prepare and submit an additional paper copy that has been edited to delete confidential information (i.e., a redacted copy). FDA is estimating that it would take a notifier 5 hours to prepare the redacted copy. FDA's estimates of the hourly reporting burden associated with confidential information are based on its familiarity with submissions received under the 1996 procedures, including the content and organization of those submissions. In most cases, the confidential information is present in limited locations within a given submission.

C. Hourly Reporting Burden Associated With Electronic Copies of the Report (Proposed §§ 192.20(c)(1) and (c)(2)

Under the proposed rule, a notifier ordinarily would submit an electronic copy that would be in a format that is suitable for FDA to use to make the PBN available in an electronic reading room (e.g., html format). FDA is estimating that it would take 8 hours to format the electronic disclosure copy. Because a notifier who includes confidential information must redact this copy,

FDA is estimating that it would take an additional 4 hours to do the redacting and that this would occur in 2 of the 20 notices submitted per year. Thus, FDA is estimating that it would take a total of 8.4 hours, on average, to prepare the electronic disclosure copy. FDA's estimate of the hourly reporting burden associated with an electronic copy is based on its understanding of the attributes of commonly used software programs that likely would be used to prepare the electronic copy.

Under the proposed rule, a notifier may request a waiver from the proposed requirement to submit an electronic disclosure copy, e.g., because the notifier does not have access to the technology that is needed to prepare such a copy. Because a notifier who requests a waiver need only write an explanation of why he is requesting the waiver, FDA estimates that it would take 0.5 hours to request a waiver. Because most firms who have already consulted with FDA regarding bioengineered foods are large firms who likely would have access to the appropriate technology, FDA is assuming that a request for a waiver will be a rare event, and may not happen at all. Therefore, in this estimate of the hourly burden to prepare a notice, FDA is making the conservative assumption that all firms will submit an electronic disclosure copy, with an hourly burden of 8 hours, and that no firms will request a waiver, which would have a reduced burden of only 0.5 hours.

In addition, in the proposed rule FDA is recommending that a notifier submit an electronic copy that would be formatted in a manner that is suitable for FDA to use to evaluate the PBN (e.g., portable document format (PDF)). A notifier who submits an electronic evaluation copy would submit one less paper copy. FDA is estimating that it would take 8 hours to format the electronic evaluation copy.

D. Hourly Reporting Burden Associated With English Language Translations, Authorization to Incorporate Information by Reference, and Withdrawal (Proposed § 192.20(d), (e), and (g)

Under the proposed rule, a notifier who includes information in a foreign language must include an English translation that is verified to be accurate and complete. Based on its experience,

FDA is estimating that it would take 20 hours to prepare such a translation and that this would happen very rarely (i.e., once every 2 years). However, FDA has limited experience with the hourly burden associated with English language translations and specifically requests comment on this estimate.

Under the proposed rule, a notifier who wishes to incorporate by reference a submission made by another party must include a signed statement from that party, authorizing the notifier to incorporate the information by reference, unless the referenced submission is publicly available (e.g., under the FOIA). FDA is estimating that it would take 2 hours to obtain the signed statement and that this would happen very rarely (i.e., once every 2 years). FDA's estimate is based on its experience with incorporation by reference in another food program (i.e., the food additives program).

Under the proposed rule, a notifier who wishes to withdraw a PBN from FDA's consideration must do so in writing. Because this can be done by a simple letter, FDA is estimating that it would take 1 hour. FDA also is estimating that this would happen very rarely (i.e., once every 2 years).

E. Hourly Reporting Burden Associated With a Voluntary Presubmission Consultation Program (Proposed § 192.10(e) through (g), (h)(2), (h)(3)(i), and (h)(3)(ii)

In the proposed rule, FDA is recommending that prospective notifiers participate in a presubmission consultation program. Accordingly, FDA has estimated the hourly burden to notifiers who choose to participate.

Under the proposed rule, a prospective notifier who requests consultation prepares a single submission to address potential uses of the bioengineered food in both human food and food intended for animals. The prospective notifier would send multiple paper copies of the submission to CFSAN, who would contact CVM when the bioengineered food would be consumed by animals. Based on its experience under the 1996 procedures, FDA is estimating that it would take 0.5 hours to prepare the multiple copies that would be submitted for each request for consultation.

Since 1994, FDA has received on average approximately seven requests per year for consultation about bioengineered foods that are under development (i.e., before the foods are ready for commercialization). However, given the efficiencies of rDNA techniques, the advances in these techniques, and the rapidly expanding information related to genomes, FDA expects that these techniques are likely to be utilized to an increasingly greater extent. For the purpose of this analysis FDA is estimating that the agency would receive 20 requests for consultation per year about bioengineered foods. Based on its experience under the 1996 procedures, FDA is estimating that it would take 4 hours to prepare written materials that accompany the original request for consultation and 8 hours to prepare one or several additional written submissions as the consultation proceeds.

To ensure that FDA is aware of confidential information, a notifier who submits confidential information must both identify the confidential information and prepare and submit an additional paper copy that does not contain such information. FDA is estimating that it would take 2 hours to identify such information in both the original and additional submissions and that it would take 5 hours to prepare redacted copies of these submissions. FDA also is estimating that approximately 2 of 20 requests for consultation would include confidential information. FDA's estimates are based on its familiarity with requests for consultation under the 1996 procedures, including the content and organization of written materials that accompanied those requests.

F. Hourly Recordkeeping Burden (Proposed § 192.25(a)(2))

Under the proposal, notifiers must retain the data and other information that provides the basis for their conclusions about the bioengineered food. FDA is assuming that notifiers would establish and maintain an administrative file that contains these data and information. Based on its experience with the content of submissions received under the 1996 procedures, FDA is estimating that the one-time process of establishing such a file would equal 10 percent of the hourly burden already estimated for preparing a PBN (i.e., 10 percent of 190 hours, or 19 hours).

In compliance with the PRA, the agency has submitted the information collection provisions of this proposed rule to OMB for review. Interested persons must submit written comments regarding information collection by [*insert date 30 days after date of publication in the* **Federal Register**], to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Desk Officer for FDA.

XIII. Analysis of Economic Impacts

A. Cost-Benefit Analysis

FDA has examined the economic implications of this proposed rule as required by Executive Order 12866. Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Executive Order 12866 classifies a rule as significant if it meets any one of a number of specified conditions, including: having an annual effect on the economy of $100 million, adversely affecting a sector of the economy in a material way, adversely affecting competition, or adversely affecting jobs. A regulation is also considered a significant regulatory action if it raises novel legal or policy issues. The Office of Management and Budget has determined that this proposed rule is a significant regulatory action as defined by Executive Order 12866.

B. Background

Bioengineered foods have the potential to offer multiple benefits such as: Improved yield, drought resistance, disease resistance, improved flavor, longer shelf life, increased nutrition, and reduced need for pesticides, among others. Consumers have expressed concern, however, about possible risks that can accompany bioengineered foods. From a public health perspective, the main concerns are allergenicity and toxicity. To ensure that bioengineered foods are as safe as their conventional counterparts, FDA instituted a consultation process with industry to review the

development of new bioengineered foods (57 FR 22984 at 22991 and (Ref. 5)). Since then, food producers have completed some 45 consultations about bioengineered foods. To the best of our knowledge all bioengineered foods on the market have gone through FDA's process before they have been marketed.

Under the current process, a developer who intends to commercialize a bioengineered food meets with the agency prior to marketing to identify and resolve relevant safety, nutritional, or other regulatory issues regarding the bioengineered food. When the developer believes that it has accumulated adequate data or information to address and resolve any potential safety or other regulatory issues, the developer submits to FDA a summary of its assessment of these issues. Agency scientists evaluate that summary to determine whether any safety or other regulatory issues are resolved. This process ensures that developers of bioengineered foods are aware of and address safety and other issues prior to marketing.

However, because the consultation process is voluntary, food producers could choose not to notify FDA. Additionally, as food producers in countries that export foods to the United States begin to adopt bioengineered varieties, they may choose not to participate in the voluntary consultation process. Requiring premarket notification for bioengineered foods ensures that FDA will continue to have the opportunity to discuss safety and other regulatory issues with developers before new bioengineered foods go on the market, thereby putting an additional check in place for bioengineered foods.

1. Benefits

Although the current consultation process has been successful in that the agency believes that it has reviewed all of the bioengineered foods that have reached the market, a firm could bypass the current review process. In so doing, the firm may market a product that presents safety or other regulatory issues that would otherwise have been identified and resolved through consultation with the agency. For example, the food may contain an unexpected allergen or an unapproved

food additive, or may be so significantly different from its conventional counterpart that special labeling would be required to enable consumers to identify the difference.

Bioengineering enables developers to expand greatly the range of sources of genes to introduce into foods. Genes code for proteins, and virtually all known food allergens are proteins. Therefore, by transferring a gene from one foodplant to another (and thereby essentially transferring a protein from one food to another) one may transfer the allergenic properties of the first food to the second. Because food allergies can result in serious harm, including anaphylactic shock and death, it is important to know the allergenic profile of food from a plant that is to be used as the source of a gene to be transferred to another foodplant.

It is also possible for a protein that has never been in food before to become an allergen once people become exposed to it in the diet. Therefore, it is also important to know whether a protein from a traditionally nonfood source has characteristics associated with allergenic proteins.

Similarly, because bioengineering enables developers to introduce genetic material from a wider range of sources than has traditionally been possible, there is a greater likelihood that a developer using bioengineering to modify a foodplant may introduce genetic material whose expression results in a substance that is significantly different from substances historically consumed in food. Such a substance may require premarket approval as a food additive because it may not be GRAS.

It is also possible with bioengineering that the newly introduced genetic material may be inserted into the chromosome of a foodplant in a location that causes the food derived from the plant to have higher levels of toxins than normal, or lower levels of a significant nutrient. In the former case, the food may not be safe to eat, or may require special preparation to reduce or eliminate the toxic substance. In the latter case, the food may require special labeling, so that consumers would know that they were not receiving the level of nutrients they would ordinarily expect from consuming a comparable food. It is important therefore for developers to evaluate

bioengineered foods from new plant varieties to determine whether the composition of the food has been altered.

The additional provisions of the proposed rule, beyond what was requested by the 1996 procedures, aid in ensuring that relevant safety questions are addressed by the developer. The submission of a narrative of the developer's reasons for concluding that the bioengineered food is as safe as comparable food and its justification of the choice of comparable foods by the notifier will aid in ensuring that all potential safety issues have been considered. Discussion of unsuitable uses will provide FDA the opportunity to ensure that foods that would not be suitable for particular applications are not marketed for those applications. Submission of a redacted copy will aid the agency in protecting confidential information in the notice and in responding to FOIA requests. Submission of an electronic disclosure copy would facilitate the agency's making the PBN available in an electronic reading room.

2. Costs

For developers who would have gone through FDA's consultation process, the costs associated with the proposed required process would include only costs of the additional provisions of the proposed rule. The required process will be modeled on the experience and knowledge gained from the current consultation process, but there will be a number of new provisions that will have costs for notifiers. First, the rule would require a narrative explaining how the notifier concluded the bioengineered food is as safe as comparable food and that the food is in compliance with the act. Second, notifiers who inform FDA about a bioengineered food that contains a gene that encodes resistance to an antibiotic must specifically discuss the issues associated with the use of that gene. Although this provision was not in the 1992 policy or the 1996 procedures, in 1998 FDA released draft guidance for public comment. Since 1998, most notifiers who are in this situation have included this discussion in their submissions; in addition, many plant varieties are being developed without genes that encode resistance to an antibiotic. Therefore, FDA is considering that the requirement to discuss genes that encode resistance to an antibiotic be a cost

of the proposed rule for only one submission per year (that is, FDA is estimating that only one relevant submission would have omitted this discussion without the rule). Third, notifiers must submit a written justification of their choice of foods that are comparable to the bioengineered food and the historic uses of these comparable foods. Fourth, if the bioengineered food is unsuitable for any applications or uses, notifiers must submit a description of these applications or uses. Because inappropriate uses are seldom an issue, FDA is considering that this issue would arise approximately once every 3 years. Fifth, if the submission includes confidential information, notifiers must submit redacted copies. Because very few submissions under the current process have included confidential information, FDA is considering that approximately one or two copies per year will contain confidential materials. Sixth, notifiers must ordinarily would submit an electronic copy suitable for making the PBN available in an electronic reading room, but could request a waiver if they have access to the technology that would be needed to prepare the copy.

FDA contacted five firms that had made one or more submissions under the 1996 procedures. FDA asked each of these firms for an estimate of the hourly cost associated with preparing a submission under the current process. Three of these firms subsequently provided the requested information. One firm estimated an average cost of $125 per hour; another firm estimated an average cost of $48 per hour; a third firm estimated an average cost of $60 per hour. Based on this information, FDA is estimating that the average cost to prepare a submission under the 1996 procedures is approximately $78 per hour.

The agency estimated the cost of a notice as the time needed multiplied by $78, the average cost associated with the person responsible for preparing a notice. Since 1994, FDA has received approximately eight submissions per year, but the agency expects this number of submissions to increase because of the increasing use of the technology. Because most firms who have consulted with FDA under the current process are large firms who likely would have access to the technology that would be needed to prepare an electronic disclosure copy, in this analysis FDA is estimating that no firms would request a waiver from the proposed requirement to submit such a copy.

Therefore, total costs for these additional provisions are expected to be between $16,604 and $67,444 per year.

TABLE 3.

	Number of submissions per year	Time costs per submission (hours)	Cost per submission	Total annual cost
Narrative	8 to 20	8 to 16	$624 to $,1248	$4992 to $24960
Antibiotic resistance	1 to 2	8 to 16	$624 to $1248	$624 to $2496
Comparable foods	8 to 20	8 to 16	$624 to $1248	$4992 to $24960
Unsuitable uses	⅓	8 to 16	$624 to $1248	$208 to $416
Electronic disclosure copy	8 to 20	8.4	$655	$5242 to $13104
Redacted paper copy	1 to 2	7	$546	$546 to $1092

For developers who would not have chosen to notify FDA, the cost of the proposed rule would be higher. Regardless of whether they choose to consult with FDA, food producers are statutorily prohibited from marketing misbranded or adulterated foods. To ensure that the new food is not adulterated or misbranded, the developer must generate similar information to what would be required under the proposed notification requirement. Therefore, for these developers, the cost of the proposed notification requirement would be the submission of paperwork documenting the generation of the needed information, not the information itself. FDA's estimate of the time required to prepare a notice is discussed previously (section XII of this document). According to that analysis, the average submission would require 255.5 hours of preparation. Additionally, maintaining records of the notice would require 19 hours by the firm. At an average hourly cost of $78, the total cost of preparation and recordkeeping for a submission would be $21,411 (hourly cost x 274.5 hours).

As discussed above, FDA has requested comment on whether this rule should also include a requirement that a premarket notice for a bioengineered food include methods by which the food could be detected. As part of its analysis of impacts, FDA requests comments on the technical feasibility and if feasible, the costs of requiring such methods in a PBN. In particular, FDA requests comments on the feasibility and costs of requiring methods of detection in all circumstances and in a limited set of circumstances, such as foods whose use is restricted in some way. FDA also requests comments on the costs of supplying methods for detection of the bioengineered food in crops and in finished food products.

C. Regulatory Flexibility Act

FDA has examined the economic implications of this proposed rule as required by the Regulatory Flexibility Act (5 U.S.C. 601–612). If a rule has a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would lessen the economic effect of the rule on small entities.

Businesses in Agricultural Services are considered small if they have fewer than 500 employees, and in Commercial Physical and Biological Research (SIC 8731) if they have less than $5 million in annual receipts. Companies engaged in the development of bioengineered food may fit into either of these categories. Since 1994, more than 45 biotechnology submissions have been completely evaluated by FDA; these submissions were made by 11 distinct companies and 3 universities. Most of these companies are multinationals with hundreds of millions of dollars in annual sales and do not meet the criteria for a small entity. However, at least one of the companies that has notified FDA would meet the small entity definitions.

For firms that would not have notified FDA, the cost may be $21,411. FDA finds that this proposed rule would have a significant economic impact on a substantial number of small entities.

FDA considered a number of options to ease the burden on small businesses. Extra flexibility for small businesses meeting with FDA was considered. However, the proposed rule as written already includes flexibility for meeting with FDA, allowing phone meetings in lieu of meeting in person. Additional guidance was another option considered. However, the recommended presubmission consultation provides an opportunity for small businesses to get guidance from FDA about regulatory and safety concerns and how they can be dealt with by a small business. Thus, FDA has tentatively determined there is adequate flexibility written into the rule to accommodate the special needs of small businesses.

D. Unfunded Mandates Reform Act

Section 202(a) of the Unfunded Mandates Reform Act of 1995 (Public Law 104–4) requires that agencies prepare a written statement of anticipated costs and benefits before proposing any

rule that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million in any one year (adjusted annually for inflation). FDA has tentatively determined that this proposed rule is not a significant action as defined in the Unfunded Mandates Reform Act and will not have an effect on the economy that exceeds $100 million adjusted for inflation in any one year. The correct inflation-adjusted statutory threshold is $107 million.

XIV. Effective Date

FDA proposes that any final rule that may issue based on this proposal become effective 60 days after the date of publication of the final rule in the **Federal Register**.

XV. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environment assessment nor an environmental impact statement is required.

XVI. Comments

Interested persons may submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, written comments regarding this proposal by [*insert date 75 days after date of publication in the* **Federal Register**]. Submit written comments on the information collection provisions by [*insert date 30 days after date of publication in the* **Federal Register**]. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

XVII. References

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

1. Transcript of the Meeting of FDA's Food Advisory Committee, Herndon, VA, April 6, 7, and 8, 1994.

2. Transcript of the Joint Meeting of FDA's Food Advisory Committee and Veterinary Medicine Advisory Committee, November 2 and 3, 1994.

3. Table of Contents, ''Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food'' (Also known as ''Redbook I''), FDA, Bureau of Foods (Now CFSAN), 1982. May be Purchased From: National Technical Information Services (NTIS), 5285 Port Royal Rd., Springfield, VA 22161, 703–487–4650, NTIS Order Number PB83–170696.

4. Table of Contents, ''Toxicological Principles for the Safety of Food Ingredients; Redbook 2000,'' available at http://vm.cfsan.fda.gov.

5. ''Guidance on Consultation Procedures: Foods Derived From New Plant Varieties,'' available at http://vm.cfsan.fda.gov.

6. ''Foods Derived From New Plant Varieties Derived Through Recombinant DNA Technology; Final Consultations Under FDA's 1992 Policy,'' available at http://vm.cfsan.fda.gov.

7. Press Release, U.S. Department of Health and Human Services, ''FDA to Strengthen Pre-market Review of Bioengineered Foods,'' May 3, 2000, available at http://vm.cfsan.fda.gov.

8. Transcripts from Public Meetings Held on November 18, 1999, Chicago, IL, November 30, 1999, Washington, DC, and December 13, 1999, Oakland, CA; at http://www.fda.gov.

9. Nordlee, J. A. et al., ''High Methionine Brazil Nut Protein Binds Human IgE,'' *Journal of Allergy and Clinical Immunology*, vol. 93, number 1, part 2, p. 209, 1994.

10. Nordlee, J. A. et al., ''Identification of Brazil-Nut Allergen in Transgenic Soybeans,'' *New England Journal of Medicine*, vol. 334, pp.688–728, 1996.

11. Ye, X. et al., ''Engineering the Provitamin A (Beta-Carotene) Biosynthetic Pathway into (Carotenoid-Free) Rice Endosperm,'' *Science* vol. 287: pp. 303–05, 2000.

12. Kubo, Tomoaki, ''Potential of Foods From Which Unfavorable Component Have Been Removed,'' Topic 10, Joint FAO/WHO Expert Consultation on Foods Derived from Biotechnology, Biotech 00/12, 29 May-2 June 2000, available at www.who.int/fsf/GMfood/consultation) May2000/biotech) 00) 12.pdf.

13. Agriculture Biotechnology: Permitting, Notification, and Deregulations, U.S. Department of Agriculture, Animal Plant Health and Inspection Service, available at http://www.aphis.usda.gov.

14. Genetically Modified Pest-Protected Plants: Science and Regulation. Committee on Genetically Modified Pest-Protected Plants, Board on Agriculture and Natural Resources, National Research Council, National Academy Press, Washington, DC 20055, available at http://www.nap.edu/.

15. ''Guidance for Industry: Use of Antibiotic Resistance Marker Genes in Transgenic Plants,'' available at http://vm.cfsan.fda.gov.

16. ''Report on Consultations Regarding Use of Antibiotic Resistance Marker Genes in Transgenic Plants,'' available at http://vm.cfsan.fda.gov.

17. Transcript of ''Conference on Scientific Issues Related to Potential Allergenicity in Transgenic Food Crops,'' Annapolis, MD, April 18 and 19, 1994, Document TR–1, summary available at http:// vm.cfsan.fda.gov.

18. Inventory of GRAS Notices, available at http://vm.cfsan.fda.gov.

List of Subjects

21 CFR Part 192

Administrative practice and procedure, Food additives, Food labeling, Foods, Reporting and recordkeeping requirements.

21 CFR Part 592

Administrative practice and procedure, Animal feeds, Animal foods, Food additives, Food labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that Title 21 CFR, Chapter I be amended as follows:

1. Add part 192 to read as follows:

PART 192—PREMARKET NOTICE CONCERNING BIOENGINEERED FOOD

Sec.

192.1 Definitions: What terms do I need to know?

192.5 Requirement for premarket biotechnology notice.

192.10 Recommendation for presubmission consultation.

192.20 Premarket biotechnology notice: Administrative information.

192.25 Premarket biotechnology notice- required parts. What must I include in a premarket biotechnology notice?

192.30 FDA evaluation and response: What will I get back from FDA and how long will it take?

192.40 Public disclosure.

Authority: 21 U.S.C. 331, 342, 343, 348, 371.

PART 192—PREMARKET NOTICE CONCERNING BIOENGINEERED FOOD

§ 192.1 Definitions: What terms do I need to know?

(a) A *bioengineered food* means food derived from a plant that is developed using a transformation event.

(b) *Commercial distribution* means introduction, or delivery for introduction, into interstate commerce for sale or exchange for consumption in any form by humans or other animals.

(c) A *notifier* is the person who submits a premarket biotechnology notice under this part. Any person who is responsible for the development, distribution, importation, or sale of a bioengineered food may be a notifier.

(d) A *premarket biotechnology notice* (PBN) is a submission to FDA regarding a bioengineered food that is intended to enter commercial distribution. Under this part, a PBN includes all data and information in the original submission and in any amendments to the original submission.

(e) *Transformation event* means the introduction into an organism of genetic material that has been manipulated in vitro. For the purpose of this part, ''organism'' refers to plants.

§ 192.5 Requirement for premarket biotechnology notice.

(a) *What foods must I notify FDA about*? You must notify FDA about any bioengineered food, including a bioengineered food derived from a new plant variety modified to contain a pesticidal substance, that will enter commercial distribution unless all of the following conditions are satisfied:

(1) The bioengineered food derives from a plant line that represents a transformation event that has been addressed in a PBN previously submitted to FDA;

(2) The use or application of the bioengineered food has been addressed in a notice previously submitted to FDA; and

(3) A letter from FDA demonstrates that FDA has evaluated the use or application of the bioengineered food and has no questions about it. This would include a letter issued between May 1, 1994, and the effective date of this rule.

(b) *Must the data or other information that I submit to support my PBN be generated from a particular plant line*? The data or other information that you submit to FDA regarding a bioengineered food must be generated from a plant line whose derivation can be traced to the transformation event that is the subject of the notice and that contains the genetic material introduced via the transformation event.

(c) *When do I submit my PBN*? You must submit your PBN at least 120 days before the bioengineered food is marketed.

§ 192.10 Recommendation for presubmission consultation.

(a) *Is there a program that provides an opportunity for me to consult with FDA about a bioengineered food before I submit a PBN*? FDA has established a presubmission consultation program to enable a prospective notifier to identify and discuss relevant safety, nutritional, or other issues regarding a bioengineered food before submitting a PBN about that food. FDA recommends that you participate in this program.

(b) *How does the presubmission consultation program work*? In this program, you inform FDA about the bioengineered food. FDA encourages you to discuss with us safety, nutritional, or other issues that may be associated with the bioengineered food. FDA will establish an administrative file for your consultation. Although FDA may provide written feedback during the consultation, that feedback would not release you from the requirement in § 192.5 to notify FDA about the bioengineered food as described in §§ 192.20 and 192.25.

(c) *Would the fact that I am consulting with FDA be confidential*? (1) In most cases, the fact that you are consulting with FDA would not be confidential.

(2) If you claim that the fact that you are consulting with FDA is confidential, FDA will evaluate your claim. If FDA is asked, under the Freedom of Information Act (FOIA), about whether you are consulting with us, FDA will disclose that fact unless we determine that your claim demonstrates that the criteria for exemption from disclosure in § 20.61 of this chapter are satisfied.

(d) *Would any of the data or other information in the administrative file of my consultation be disclosed to the public*? (1) If the fact that you are consulting with FDA is not confidential, then the data or other information in the administrative file of your presubmission consultation would be available for public disclosure in accordance with § 20.61 of this chapter.

(2) As long as the fact that you are consulting with FDA is confidential, then the data or other information in the administrative file of your presubmission consultation would not be available for public disclosure.

(e) *How do I get started*? To participate in the presubmission consultation program, write to FDA and tell us that you want to consult about a bioengineered food.

(f) *If I participate, what do I provide to FDA*? (1) You must state your view as to whether the fact that you are consulting with FDA, or any or all of the data or other information that you submit to FDA, is exempt from disclosure under the FOIA (i.e., is confidential).

(2) If you claim that the fact that you are consulting with FDA, or that any or all of the data or other information that you submit to FDA is confidential, you must explain the basis for your claim.

(3) We recommend that you send us the following synopsis about the requested consultation:

(i) Your name and address;

(ii) The name of the bioengineered food that is the subject of the presubmission consultation and the plant species from which it is derived;

(iii) The distinctive designation(s) that you use to identify the applicable transformation event(s);

(iv) A list of the identity(ies) and source(s) of introduced genetic material;

(v) A description of the purpose or intended technical effect of the transformation event. This includes expected significant changes in the composition or characteristic properties of food derived from the plant as a result of the transformation event, regardless of whether these changes result from the insertion of new genes or from a modification in the expression of endogenous genes;

(vi) A description of the intended applications or uses of the bioengineered food; and

(vii) A description of any applications or uses that are not suitable for the bioengineered food.

(g) *Where do I send my written request for consultation*? Send your written request for consultation about a bioengineered food to the Office of Premarket Approval (HFS–200), Center for Food Safety and Applied Nutrition, 200 C St. SW., Washington, DC 20204. As necessary and appropriate, the Center for Food Safety and Applied Nutrition (CFSAN) will coordinate FDA's

evaluation of your request with the Office of Surveillance and Compliance, Center for Veterinary Medicine (CVM).

(h) *What copies do I send*? (1) You should send an original and at least two paper copies of your written request for consultation.

(2) If you submit additional written information to FDA (i.e., after your original written request), you should send an original and at least two paper copies of each additional submission.

(3) If you claim that any specific data or other information that you provide to FDA during the consultation are confidential, you should:

(i) Clearly identify, in each submission, the data or other information that you claim are confidential;

(ii) Prepare and submit a ''redacted'' paper copy of the submission (i.e., a copy that does not contain any of those data or information).

(iii) Prepare this redacted paper copy in a manner that clearly identifies the location and relative size of deleted information.

(i) *What will FDA do with my written request for consultation*? (1) FDA will establish an administrative file for your consultation and will place the following materials in that file:

(i) Any correspondence between you and FDA;

(ii) Any written materials that you provide during the consultation process; and

(iii) A memorandum of each meeting or significant phone call that you have with FDA regarding the subject of your consultation.

(2) If you ask FDA to discuss the bioengineered food with you, we will do so (e.g., at a meeting at its offices or via a telephone conference).

§ 192.20 Premarket biotechnology notice: Administrative information.

(a) *Where do I send my PBN*? Send a PBN regarding a bioengineered food to the Office of Premarket Approval (HFS–200), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 200 C St. SW., Washington, DC 20204. As necessary and appropriate, the Center

for Food Safety and Applied Nutrition (CFSAN) will coordinate FDA's evaluation of your PBN with the Office of Surveillance and Compliance, Center for Veterinary Medicine (CVM).

(b) *What paper copies do I send*? (1) At a minimum, you must submit an original paper version and one paper copy of a PBN (including any amendments that you make to your PBN). The original paper version will be the official version at FDA. If, under paragraph (c)(1) of this section, you choose not to send an electronic evaluation copy of your PBN, then you must submit one additional paper copy, for a total of three paper copies.

(2) If you claim that specific data or other information in the PBN are confidential, you must:

(i) Clearly identify, in each submission, the data or information that you claim are confidential;

(ii) Prepare and submit a ''redacted'' paper copy of the PBN (i.e., a copy that does not contain any of those data or information); and

(iii) Prepare this redacted paper copy in a manner that clearly identifies the location and relative size of deleted information.

(c) *What electronic copies do I send*? (1) *Evaluation copy*. FDA recommends that you submit an electronic copy that is formatted in a manner that makes it suitable for FDA to use while evaluating your PBN. If you do so, you should submit such an electronic copy of your original PBN and of any amendments that you make to your PBN. To obtain current information about the technical format of this evaluation copy, contact the Office of Premarket Approval (OPA) at the address listed previously or look on OPA's home page on the Internet.

(2) *Disclosure copy*. (i) Unless waived under paragraph (c)(2)(ii) of this section, you must submit an electronic copy that is formatted in a manner that makes it suitable for FDA to use to make your PBN available to the public in an electronic reading room. This includes an electronic copy of your original PBN and of any amendments that you make to your PBN. If you claim that specific data or other information in the PBN are confidential, you must remove such data or information from the disclosure copy in a manner that clearly identifies the location and relative size of deleted information. To obtain current information about the technical format of this

disclosure copy, write to OPA at the address listed previously or look on OPA's home page on the Internet.

(ii) You may request that FDA waive the requirement for an electronic disclosure copy, e.g., if you do not have access to the appropriate technology for formatting such a copy. FDA will grant or deny your request according to its merits.

(d) *May I submit any data or other information, such as a reprint of a published scientific article, in a foreign language*? If you submit any material in a foreign language, you must provide an English translation that is verified to be complete and accurate.

(e) *May I incorporate data or other information that are already retained in FDA's files by referring to them*? (1) If you previously submitted a file to FDA, you may incorporate that file by referring FDA to it.

(2) If someone else previously submitted a file to FDA, the procedure that you may use to incorporate that file into your PBN depends on whether the file is publicly available (e.g., the file is in an electronic reading room or is otherwise available under FOIA).

(i) If the file is publicly available, you may incorporate that file by referring FDA to it.

(ii) If the file is not publicly available, you may incorporate that file by referring FDA to it if the person who submitted the file authorizes you to do so in a signed statement and you include that signed statement in your PBN.

(f) *How can I get additional information that will help me to prepare a PBN*? You can obtain current guidance regarding specific technical issues by writing to OPA at the address listed previously or by looking on OPA's home page on the Internet.

(g) *May I withdraw a PBN from FDA consideration after I send it*? (1) At any time during FDA's evaluation of a PBN, you may request that FDA cease to evaluate it. Your request would not preclude you from submitting a future PBN about the same bioengineered food.

(2) If you request that FDA cease to evaluate your PBN, FDA will retain your PBN in its files and classify your PBN as ''withdrawn.''

§ 192.25 Premarket biotechnology notice- required parts; What must I include in a premarket biotechnology notice?

A PBN has seven parts. You must include all of the information described in each part, or explain why it does not apply to the bioengineered food.

(a) *Part I.* In your PBN, you must provide a letter that a responsible official of your organization, or your attorney or agent, dates and signs. In this letter, you inform FDA that you are submitting a PBN under § 192.25, state your position or title, and attest to the following:

(1) It is your view that:

(i) The bioengineered food is as safe as comparable food; and

(ii) The intended use of the bioengineered food is in compliance with all applicable requirements of the Federal Food, Drug, and Cosmetic Act (the act).

(2) You agree to make relevant data or other information that are not included in your PBN available to FDA upon request, either while FDA is evaluating your PBN or for cause.

(3) You agree to two procedures for making relevant data or other information that are not included in your PBN available to FDA by:

(i) Allowing FDA to review and copy these data or information at a specified address during customary business hours; or

(ii) Sending a copy of these data or information to FDA.

(4)(i) Your view as to whether the existence of your PBN, or any or all of the data or other information in your PBN, is exempt from disclosure under the FOIA (i.e., is confidential); and

(ii) If you claim that the existence of the PBN, or any or all of the data or other information in the PBN, is confidential, you must explain the basis for your claim.

(5) To the best of your knowledge, the PBN is a representative and balanced submission that includes information, unfavorable as well as favorable, pertinent to the evaluation of the safety, nutritional, or other regulatory issues that may be associated with the bioengineered food.

(b) *Part II.* In your PBN, you must provide the following synopsis:

(1) *Section 1.* Your name and address;

(2) *Section 2*. The name of the bioengineered food that is the subject of the PBN and the plant species from which it is derived;

(3) *Section 3*. The distinctive designation(s) that you use to identify the applicable transformation event(s);

(4) *Section 4*. A list of the identity(ies) and source(s) of introduced genetic material;

(5) *Section 5*. A description of the purpose or intended technical effect of the transformation event. This includes expected significant changes in the composition or characteristic properties of food derived from the plant as a result of the transformation event, regardless of whether these changes result from the insertion of new genes or from a modification in the expression of endogenous genes;

(6) *Section 6*. A description of the applications or uses of the bioengineered food; and

(7) *Section 7*. A description of any applications or uses that are not suitable for the bioengineered food.

(c) *Part III*. In your PBN, you must describe the status of the bioengineered food at other Federal agencies and foreign governments.

(1) *Status at the U.S. Department of Agriculture, Animal and Plant Health Inspection Service (APHIS)*. A statement as to whether the bioengineered food plant has been the subject of an initiated or completed authorization, or petition for nonregulated status by APHIS, under 7 CFR 340.

(2) *Status at the U.S. Environmental Protection Agency (EPA)*. A statement as to whether any plant pesticide residue in the bioengineered food is or has been the subject of a consultation with, or review by, EPA and, if so, a description of the status of that consultation or review.

(3) *Status at foreign governments*. A statement as to whether the bioengineered food is or has been the subject of review by any foreign government and, if so, a description of the status of that consultation or review.

(d) *Part IV*. In your PBN, you must provide the following data or other information about the method of development of the food:

(1) *Section 1*. Characterization of the parent plant including scientific name, taxonomic classification, mode of reproduction, and pertinent history of development.

(2) *Section 2*. Construction of the vector used in the transformation of the parent plant. This includes a thorough characterization of the genetic material intended for introduction into the parent plant and a discussion of the transformation method, open reading frames, and regulatory sequences.

(3) *Section 3*. Characterization of the introduced genetic material, including the number of insertion sites, the number of gene copies inserted at each site, information on deoxyribonucleic acid (DNA) organization within the inserts, and information on potential reading frames that could express unintended proteins in the transformed plant.

(4) *Section 4*. Data or other information related to the inheritance and genetic stability of the introduced genetic material.

(5) *Section 5*. A discussion, as necessary, of other relevant data or other information about the method of development.

(e) *Part V*. In your PBN, you must discuss any newly inserted genes that encode resistance to an antibiotic. FDA recommends that you contact FDA about the agency's current thinking on this topic.

(f) *Part VI*. In your PBN, you must provide the following data or other information about substances (other than DNA, ribonucleic acid (RNA), or pesticidal substances) introduced into, or modified in, the food (including substances that you expect to be present in the bioengineered food at an increased level relative to comparable food):

(1) *Section 1*. Data or other information about the identity and function of substances introduced into, or modified in, the food;

(2) *Section 2*. Data or other information relating to the level in the bioengineered food of substances introduced into, or modified in, the food;

(3) *Section 3*. (i) An estimate of dietary exposure to substances introduced into, or modified in, the food; or

(ii) A statement that explains the basis for your conclusion that an estimate of dietary exposure to these substances is not needed to support your view that the bioengineered food is as safe as comparable food.

(4) *Section 4*. A discussion of the available data or other information that address the potential that a protein introduced into the food will be an allergen. FDA recommends that you contact FDA about the agency's current thinking on this topic.

(5) *Section 5*. A discussion of data or other information relevant to other safety issues that may be associated with the substances introduced into, or modified in, the food.

(g) *Part VII*. In your PBN, you must provide the following data or other information about the food:

(1) *Section 1*. Justification for selecting a particular food(s) as the comparable food to which you will compare the bioengineered food.

(2) *Section 2*. A discussion of historic uses of the comparable food(s) to which you will compare the bioengineered food.

(3) *Section 3*. Data or other information comparing the composition and characteristics of the bioengineered food to those of comparable food(s), with emphasis on:

(i) Levels of significant nutrients;

(ii) Levels of naturally occurring toxicants and antinutrients; and

(iii) Any intended changes to the composition of the food.

(4) *Section 4*. Any other information relevant to the safety, nutrition, or other assessment of the bioengineered food.

(5) *Section 5*. A narrative that explains the basis for your view that the bioengineered food is as safe as comparable food and that the bioengineered food is otherwise in compliance with all applicable requirements of the act.

§ 192.30 FDA evaluation and response; What will I get back from FDA and how long will it take?

(a) Within 15 working days of receipt, FDA will do an initial evaluation of your PBN to determine whether it appears to include all elements required under §§ 192.20 and 192.25.

(1) If your PBN appears to include all required elements, the Center for Food Safety and Applied Nutrition (CFSAN) will file it and will inform the Center for Veterinary Medicine (CVM) of the filing.

(2) If your PBN does not appear to include all required elements, FDA will inform you of that fact and explain what is missing.

(b) Within 15 working days of filing a notice, FDA will send you (or your agent) a letter that informs you of the date on which FDA filed the PBN.

(c) Within 120 days of filing a notice, FDA will send you (or your agent) a letter about its evaluation of your premarket notice.

(d) In general, FDA will respond as follows:

(1) FDA is extending its evaluation of your premarket notice by 120 days and expects that the bioengineered food will not be marketed during that evaluation; or

(2) FDA has completed its evaluation of your premarket notice. Based upon this evaluation, and as discussed in this letter, the premarket notice does not provide a basis for your view that the bioengineered food is as safe as comparable food or is otherwise in compliance with all applicable requirements of the act. Therefore, the agency expects that the bioengineered food will not be marketed; or

(3) FDA has completed its evaluation of your premarket notice. Based upon this evaluation, the agency has no questions, at this time, regarding your view that the bioengineered food is as safe as comparable food and is otherwise in compliance with all applicable requirements of the act; or

(4) FDA has received a letter in which you withdrew your PBN from its consideration without prejudice to a future filing. Given your letter, FDA ceased to evaluate your PBN on the date that we received your letter.

(e) If your PBN is about a bioengineered food that contains a plant pesticide, FDA will describe the status of the bioengineered food at EPA.

(1) If all applicable regulatory processes at EPA have come to closure, FDA will say so and will respond as described in paragraph (d) of this section.

(2) If regulatory processes at EPA regarding the bioengineered food are still pending, FDA will inform you that FDA does not consider your PBN to satisfy the requirement for premarket notice.

§ 192.40 Public disclosure.

(a) *When could anyone else find out that I sent a PBN to FDA*? (1) Ordinarily, the existence of your PBN is available for public disclosure on the date that FDA files it.

(2) If you believe that the existence of your PBN is confidential, it is your responsibility to say so. The way to do this is by making a claim for confidentiality in the letter that you send in Part I of your PBN (§ 192.25(a)(4)).

(3) If you claim that the existence of your PBN is confidential, FDA will evaluate your claim. FDA will disclose the existence of your PBN, unless FDA determines that your claim demonstrates that the criteria for exemption from disclosure in § 20.61 of this chapter are satisfied.

(4) If FDA determines that the existence of your PBN is confidential at the time that we file it, the existence of your PBN will become available for public disclosure, in accordance with § 20.61 of this chapter, when the criteria for exemption from disclosure in § 20.61 of this chapter are no longer satisfied.

(b) *How could anyone else find out that I sent a PBN to FDA*? (1) FDA will make a list of filed PBN's easily accessible to the public (e.g., by placing the information on the Internet or in a paper or electronic file that is available at FDA for public review and copying).

(2) In general, FDA will use the information submitted in Part II of each PBN (i.e., the information described in § 192.25(b) of this part) to prepare this list and will update this list on an approximately monthly basis.

(c) *Would the data or other information in my PBN (including an amendment to my PBN, or any data or information that I incorporate by reference) be available to the public*? (1) Ordinarily, the data or other information in your PBN are available for public disclosure, in accordance with § 20.61 of this chapter, as of the date that FDA files the PBN.

(2) If you believe that any or all of the data or other information in your PBN is confidential, it is your responsibility to say so. The way to do this is in the letter that you send in Part I of your PBN (§ 192.25(a)(4)). In addition, under § 192.20(b) and (c), it is your responsibility to provide copies of your PBN that do not contain any data or other information that you claim are confidential.

(3) If you claim that any or all of the data or other information in your PBN is confidential, FDA will evaluate your claim. FDA will disclose the data or information in your PBN unless FDA determines that your claim demonstrates that the criteria for exemption from disclosure in § 20.61 of this chapter are satisfied.

(4) If FDA determines that any or all of the data or other information in your PBN is confidential as of the date that we file it, those data or information would be available for public disclosure, in accordance with § 20.61 of this chapter, when the criteria for exemption from disclosure in § 20.61 of this chapter are no longer satisfied.

(5) As long as the existence of your PBN is confidential, then the data or other information in your PBN would not be available for public disclosure.

(d) *How could the public obtain disclosable data and information in my PBN*? Under the FOIA, the public could obtain the disclosable data or other information in your PBN or an amendment to your PBN, or that you incorporate by reference into your PBN, by looking for

these data and information in FDA's electronic reading room or by asking FDA to send them a copy of these data and information.

(e) *Would the agency's evaluation of my PBN be available to the public*? FDA will make the following information easily accessible to the public (e.g., by placing the information on the Internet or in a paper or electronic file that is available at FDA for public review and copying):

(1) The text of any letter issued by the agency under § 192.30(c).

(2) The text of the agency's completed evaluation of any notice submitted under this part.

2. Add part 592 to read as follows:

PART 592—PREMARKET NOTICE CONCERNING BIOENGINEERED FOOD

Sec.

592.1 Definitions: What terms do I need to know?

592.5 Requirement for premarket biotechnology notice.

592.10 Recommendation for presubmission consultation.

592.20 Premarket biotechnology notice: Administrative information.

592.25 Premarket biotechnology notice- required parts; What must I include in a premarket biotechnology notice?

592.30 FDA evaluation and response; What will I get back from FDA and how long will it take?

592.40 Public disclosure.

Authority: 21 U.S.C. 331, 341, 343, 348, 371.

§ 592.1 Definitions. What terms do I need to know?

(a) *A bioengineered food* means food derived from a plant that is developed using a transformation event.

(b) *Commercial distribution* means introduction, or delivery for introduction, into interstate commerce for sale or exchange for consumption in any form by humans or other animals.

(c) A *notifier* is the person who submits a premarket biotechnology notice under this part. Any person who is responsible for the development, distribution, importation, or sale of a bioengineered food may be a notifier.

(d) *A premarket biotechnology notice* (PBN) is a submission to FDA regarding a bioengineered food that is intended to enter commercial distribution. Under this part, a PBN includes all data and information in the original submission and in any amendments to the original submission.

(e) *Transformation event* means the introduction into an organism of genetic material that has been manipulated in vitro. For the purpose of this part, ''organism'' refers to plants.

§ 592.5 Requirement for premarket biotechnology notice.

(a) *What foods must I notify FDA about*? You must notify FDA about any bioengineered food, including a bioengineered food derived from a new plant variety modified to contain a pesticidal substance, that will enter commercial distribution unless all of the following conditions are satisfied:

(1) The bioengineered food derives from a plant line that represents a transformation event that has been addressed in a PBN previously submitted to FDA;

(2) The use or application of the bioengineered food has been addressed in a notice previously submitted to FDA; and

(3) A letter from FDA demonstrates that FDA has evaluated the use or application of the bioengineered food and has no questions about it. This would include a letter issued between May 1, 1994, and the effective date of this rule.

(b) *Must the data or other information that I submit to support my PBN be generated from a particular plant line*? The data or other information that you submit to FDA regarding a bioengineered food must be generated from a plant line whose derivation can be traced to the transformation event that is the subject of the notice and that contains the genetic material introduced via the transformation event.

(c) *When do I submit my PBN*? You must submit your PBN at least 120 days before the bioengineered food is marketed.

§ 592.10 Recommendation for presubmission consultation.

(a) *Is there a program that provides an opportunity for me to consult with FDA about a bioengineered food before I submit a PBN*? FDA has established a presubmission consultation program to enable a prospective notifier to identify and discuss relevant safety, nutritional, or other issues regarding a bioengineered food before submitting a PBN about that food. FDA recommends that you participate in this program.

(b) *How does the presubmission consultation program work*? In this program, you inform FDA about the bioengineered food. FDA encourages you to discuss with us safety, nutritional, or other issues that may be associated with the bioengineered food. FDA will establish an administrative file for your consultation. Although FDA may provide written feedback during the consultation, that feedback would not release you from the requirement in § 592.5 to notify FDA about the bioengineered food as described in §§ 592.20 and 592.25.

(c) *Would the fact that I am consulting with FDA be confidential*? (1) In most cases, the fact that you are consulting with FDA would not be confidential.

(2) If you claim that the fact that you are consulting with FDA is confidential, FDA will evaluate your claim. If FDA is asked, under the Freedom of Information Act (FOIA), about whether you are consulting with us, FDA will disclose that fact unless we determine that your claim demonstrates that the criteria for exemption from disclosure in § 20.61 of this chapter are satisfied.

(d) *Would any of the data or other information in the administrative file of my consultation be disclosed to the public*? (1) If the fact that you are consulting with FDA is not confidential, then the data or other information in the administrative file of your presubmission consultation would be available for public disclosure in accordance with § 20.61 of this chapter.

(2) As long as the fact that you are consulting with FDA is confidential, then the data or other information in the administrative file of your presubmission consultation would not be available for public disclosure.

(e) *How do I get started*? To participate in the presubmission consultation program, write to FDA and tell us that you want to consult about a bioengineered food.

(f) *If I participate, what do I provide to FDA*? (1) You must state your view as to whether the fact that you are consulting with FDA, or any or all of the data or other information that you submit to FDA, is exempt from disclosure under the FOIA (i.e., is confidential).

(2) If you claim that the fact that you are consulting with FDA, or that any or all of the data or other information that you submit to FDA, is confidential, you must explain the basis for your claim.

(3) We recommend that you send us the following synopsis about the requested consultation:

(i) Your name and address;

(ii) The name of the bioengineered food that is the subject of the presubmission consultation and the plant species from which it is derived;

(iii) The distinctive designation(s) that you use to identify the applicable transformation event(s);

(iv) A list of the identity(ies) and source(s) of introduced genetic material;

(v) A description of the purpose or intended technical effect of the transformation event. This includes expected significant changes in the composition or characteristic properties of food derived from the plant as a result of the transformation event, regardless of whether these changes result from the insertion of new genes or from a modification in the expression of endogenous genes;

(vi) A description of the intended applications or uses of the bioengineered food; and

(vii) A description of any applications or uses that are not suitable for the bioengineered food.

(g) *Where do I send my written request for consultation*? Send your written request for consultation about a bioengineered food to the Office of Premarket Approval (HFS-200), Center

for Food Safety and Applied Nutrition, 200 C St. SW. Washington, DC 20204. As necessary and appropriate, the Center for Food Safety and Applied Nutrition (CFSAN) will coordinate FDA's evaluation of your request with the Office of Surveillance and Compliance, Center for Veterinary Medicine (CVM).

(h) *What copies do I send*? (1) You should send an original and at least two paper copies of your written request for consultation.

(2) If you submit additional written information to FDA (i.e., after your original written request), you should send an original and at least two paper copies of each additional submission.

(3) If you claim that any specific data or other information that you provide to FDA during the consultation are confidential, you should:

(i) Clearly identify, in each submission, the data or other information that you claim are confidential; and

(ii) Prepare and submit a ''redacted'' paper copy of the submission (i.e., a copy that does not contain any of those data or information).

(iii) Prepare this redacted paper copy in a manner that clearly identifies the location and relative size of deleted information.

(i) *What will FDA do with my written request for consultation*? (1) FDA will establish an administrative file for your consultation and will place the following materials in that file:

(i) Any correspondence between you and FDA;

(ii) Any written materials that you provide during the consultation process; and

(iii) A memorandum of each meeting or significant phone call that you have with FDA regarding the subject of your consultation.

(2) If you ask FDA to discuss the bioengineered food with you, we will do so (e.g., at a meeting at its offices or via a telephone conference).

§ 592.20 Premarket biotechnology notice: Administrative information.

(a) *Where do I send my PBN*? Send a PBN regarding a bioengineered food to the Office of Premarket Approval (HFS–200), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 200 C St. SW., Washington, DC 20204. As necessary and appropriate, the Center for Food Safety and Applied Nutrition (CFSAN) will coordinate FDA's evaluation of your PBN with the Office of Surveillance and Compliance, Center for Veterinary Medicine (CVM).

(b) *What paper copies do I send*? (1) At a minimum, you must submit an original paper version and one paper copy of a PBN (including any amendments that you make to your PBN). The original paper version will be the official version at FDA. If, under paragraph (c)(1) of this section, you choose not to send an electronic evaluation copy of your PBN, then you must submit one additional paper copy, for a total of three paper copies.

(2) If you claim that specific data or other information in the PBN are confidential, you must:

(i) Clearly identify, in each submission, the data or information that you claim are confidential;

(ii) Prepare and submit a ''redacted'' paper copy of the PBN (i.e., a copy that does not contain any of those data or information); and

(iii) Prepare this redacted paper copy in a manner that clearly identifies the location and relative size of deleted information.

(c) *What electronic copies do I send*?

(1) *Evaluation copy*. FDA recommends that you submit an electronic copy that is formatted in a manner that makes it suitable for FDA to use while evaluating your PBN. If you do so, you should submit such an electronic copy of your original PBN and of any amendments that you make to your PBN. To obtain current information about the technical format of this evaluation copy, contact the Office of Premarket Approval (OPA) at the address listed previously or look on OPA's home page on the Internet.

(2) *Disclosure copy*.

(i) Unless waived under paragraph (2)(ii) of this section, you must submit an electronic copy that is formatted in a manner that makes it suitable for FDA to use to make your PBN available

to the public in an electronic reading room. This includes an electronic copy of your original PBN and of any amendments that you make to your PBN. If you claim that specific data or other information in the PBN are confidential, you must remove such data or information from the disclosure copy in a manner that clearly identifies the location and relative size of deleted information. To obtain current information about the technical format of this disclosure copy, write to OPA at the address listed previously or look on OPA's home page on the Internet.

(ii) You may request that FDA waive the requirement for an electronic disclosure copy, e.g., if you do not have access to the appropriate technology for formatting such a copy. FDA will grant or deny your request according to its merits.

(d) *May I submit any data or other information, such as a reprint of a published scientific article, in a foreign language*? If you submit any material in a foreign language, you must provide an English translation that is verified to be complete and accurate.

(e) *May I incorporate data or other information that are already retained in FDA's files by referring to them*? (1) If you previously submitted a file to FDA, you may incorporate that file by referring FDA to it.

(2) If someone else previously submitted a file to FDA, the procedure that you may use to incorporate that file into your PBN depends on whether the file is publicly available (e.g., the file is in an electronic reading room or is otherwise available under FOIA).

(i) If the file is publicly available, you may incorporate that file by referring FDA to it.

(ii) If the file is not publicly available, you may incorporate that file by referring FDA to it if the person who submitted the file authorizes you to do so in a signed statement and you include that signed statement in your PBN.

(f) *How can I get additional information that will help me to prepare a PBN*? You can obtain current guidance regarding specific technical issues by writing to OSC at the address listed previously or by looking on CVM's home page on the Internet.

(g) *May I withdraw a PBN from FDA consideration after I send it?* (1) At any time during FDA's evaluation of a PBN, you may request that FDA cease to evaluate it. Your request would not preclude you from submitting a future PBN about the same bioengineered food.

(2) If you request that FDA cease to evaluate your PBN, FDA will retain your PBN in its files and classify your PBN as ''withdrawn.''

§ 592.25 Premarket biotechnology notice- required parts; What must I include in a premarket biotechnology notice?

A PBN has seven parts. You must include all of the information described in each part, or explain why it does not apply to the bioengineered food.

(a) *Part I.* In your PBN, you must provide a letter that a responsible official of your organization, or your attorney or agent, dates and signs. In this letter, you inform FDA that you are submitting a PBN under § 192.25 and attest to the following:

(1) It is your view that:

(i) The bioengineered food is as safe as comparable food; and

(ii) The intended use of the bioengineered food is in compliance with all applicable requirements of the the Federal Food, Drug, and Cosmetic Act (the act).

(2) You agree to make relevant data or other information that are not included in your PBN available to FDA upon request, either while FDA is evaluating your PBN or for cause.

(3) You agree to two procedures for making relevant data or other information that are not included in your PBN available to FDA by:

(i) Allowing FDA to review and copy these data or information at specified address during customary business hours; or

(ii) Sending a copy of these data or information to FDA.

(4)(i) Your view as to whether the existence of your PBN, or any or all of the data or other information in your PBN, is exempt from disclosure under the FOIA (i.e., is confidential); and

(ii) If you claim that the existence of the PBN, or any or all of the data or other information in the PBN, is confidential, you must explain the basis for your claim.

(5) To the best of your knowledge, the PBN is a representative and balanced submission that includes information, unfavorable as well as favorable, pertinent to the evaluation of the safety, nutritional, or other regulatory issues that may be associated with the bioengineered food.

(b) *Part II*. In your PBN, you must provide the following synopsis:

(1) *Section 1*. Your name and address;

(2) *Section 2*. The name of the bioengineered food that is the subject of the PBN and the plant species from which it is derived;

(3) *Section 3*. The distinctive designation(s) that you use to identify the applicable transformation event(s);

(4) *Section 4*. A list of the identity(ies) and source(s) of introduced genetic material;

(5) *Section 5*. A description of the purpose or intended technical effect of the transformation event. This includes expected significant changes in the composition or characteristic properties of food derived from the plant as a result of the transformation event, regardless of whether these changes result from the insertion of new genes or from a modification in the expression of endogenous genes;

(6) *Section 6*. A description of the applications or uses of the bioengineered food; and

(7) *Section 7*. A description of any applications or uses that are not suitable for the bioengineered food.

(c) *Part III*. In your PBN, you must describe the status of the bioengineered food at other Federal agencies and foreign governments.

(1) *Status at the U.S. Department of Agriculture, Animal and Plant Health Inspection Service (APHIS)*. A statement as to whether the bioengineered food plant has been the subject of an initiated or completed authorization, or petition for nonregulated status by APHIS, under 7 CFR part 340.

(2) *Status at the U.S. Environmental Protection Agency (EPA).* A statement as to whether any plant pesticide residue in the bioengineered food is or has been the subject of a consultation with, or review by, EPA and, if so, a description of the status of that consultation or review.

(3) *Status at foreign governments.* A statement as to whether the bioengineered food is or has been the subject of review by any foreign government and, if so, a description of the status of that consultation or review.

(d) *Part IV.* In your PBN, you must provide the following data or other information about the method of development of the food:

(1) *Section 1.* Characterization of the parent plant including scientific name, taxonomic classification, mode of reproduction, and pertinent history of development.

(2) *Section 2.* Construction of the vector used in the transformation of the parent plant. This includes a thorough characterization of the genetic material intended for introduction into the parent plant and a discussion of the transformation method, open reading frames, and regulatory sequences.

(3) *Section 3.* Characterization of the introduced genetic material, including the number of insertion sites, the number of gene copies inserted at each site, information on deoxyribonucleic acide (DNA) organization within the inserts, and information on potential reading frames that could express unintended proteins in the transformed plant.

(4) *Section 4.* Data or other information related to the inheritance and genetic stability of the introduced genetic material.

(5) *Section 5.* A discussion, as necessary, of other relevant data or other information about the method of development.

(e) *Part V.* In your PBN, you must discuss any newly inserted genes that encode resistance to an antibiotic. FDA recommends that you contact FDA about the agency's current thinking on this topic.

(f) *Part VI.* In your PBN, you must provide the following data or other information about substances (other than DNA, ribonucleic acid (RNA), or pesticidal substances) introduced into,

or modified in, the food (including substances that you expect to be present in the bioengineered food at an increased level relative to comparable food):

(1) *Section 1*. Data or other information about the identity and function of substances introduced into, or modified in, the food;

(2) *Section 2*. Data or other information relating to the level in the bioengineered food of substances introduced into, or modified in, the food;

(3) *Section 3*. (i) An estimate of dietary exposure to substances introduced into, or modified in, the food; or

(ii) A statement that explains the basis for your conclusion that an estimate of dietary exposure to these substances is not needed to support your view that the bioengineered food is as safe as comparable food.

(4) *Section 4*. A discussion of the available data or other information that address the potential that a protein introduced into the food will be an allergen. FDA recommends that you contact FDA about the agency's current thinking on this topic.

(5) *Section 5*. A discussion of data or other information relevant to other safety issues that may be associated with the substances introduced into, or modified in, the food.

(g) *Part VII*. In your PBN, you must provide the following data or other information about the food:

(1) *Section 1*. Justification for selecting a particular food(s) as the comparable food to which you will compare the bioengineered food.

(2) *Section 2*. A discussion of historic uses of the comparable food(s) to which you will compare the bioengineered food.

(3) *Section 3*. Data or other information comparing the composition and characteristics of the bioengineered food to those of comparable food(s), with emphasis on:

(i) Levels of significant nutrients;

(ii) Levels of naturally occurring toxicants and antinutrients; and

(iii) Any intended changes to the composition of the food.

(4) *Section 4*. Any other information relevant to the safety, nutrition, or other assessment of the bioengineered food.

(5) *Section 5*. A narrative that explains the basis for your view that the bioengineered food is as safe as comparable food and that the bioengineered food is otherwise in compliance with all applicable requirements of the act.

§ 592.30 FDA evaluation and response: What will I get back from FDA and how long will it take?

(a) Within 15 working days of receipt, FDA will do an initial evaluation of your PBN to determine whether it appears to include all elements required under §§ 592.20 and 592.25.

(1) If your PBN appears to include all required elements, the Center for Food Safety and Applied Nutrition (CFSAN) will file it and will inform the Center for Veterinary Medicine (CVM) of the filing.

(2) If your PBN does not appear to include all required elements, FDA will inform you of that fact and explain what is missing.

(b) Within 15 working days of filing a notice, FDA will send you (or your agent) a letter that informs you of the date on which FDA filed the PBN.

(c) Within 120 days of filing a notice, FDA will send you (or your agent) a letter about its evaluation of your premarket notice.

(d) In general, FDA will respond as follows:

(1) FDA is extending its evaluation of your premarket notice by 120 days and expects that the bioengineered food will not be marketed during that evaluation; or

(2) FDA has completed its evaluation of your premarket notice. Based upon this evaluation, and as discussed in this letter, the premarket notice does not provide a basis for your view that the bioengineered food is as safe as comparable food or is otherwise in compliance with all applicable requirements of the act. Therefore, the agency expects that the bioengineered food will not be marketed; or

(3) FDA has completed its evaluation of your premarket notice. Based upon this evaluation, the agency has no questions, at this time, regarding your view that the bioengineered food is as safe as comparable food and is otherwise in compliance with all applicable requirements of the act; or

(4) FDA has received a letter in which you withdrew your PBN from its consideration without prejudice to a future filing. Given your letter, FDA ceased to evaluate your PBN on the date that we received your letter.

(e) If your PBN is about a bioengineered food that contains a plant pesticide, FDA will describe the status of the bioengineered food at EPA.

(1) If all applicable regulatory processes at EPA have come to closure, FDA will say so and will respond as described in paragraph (d) of this section.

(2) If regulatory processes at EPA regarding the bioengineered food are still pending, FDA will inform you that FDA does not consider your PBN to satisfy the requirement for premarket notice.

§ 592.40 Public disclosure.

(a) *When could anyone else find out that I sent a PBN to FDA*? (1) Ordinarily, the existence of your PBN is available for public disclosure on the date that FDA files it.

(2) If you believe that the existence of your PBN is confidential, it is your responsibility to say so. The way to do this is by making a claim for confidentiality in the letter that you send in Part I of your PBN (§ 592.25(a)(4)).

(3) If you claim that the existence of your PBN is confidential, FDA will evaluate your claim. FDA will disclose the existence of your PBN, unless FDA determines that your claim demonstrates that the criteria for exemption from disclosure in § 20.61 of this chapter are satisfied.

(4) If FDA determines that the existence of your PBN is confidential at the time that we file it, the existence of your PBN will become available for public disclosure, in accordance with

§ 20.61 of this chapter, when the criteria for exemption from disclosure in § 20.61 of this chapter are no longer satisfied.

(b) *How could anyone else find out that I sent a PBN to FDA*?

(1) FDA will make a list of filed PBN's easily accessible to the public (e.g., by placing the information on the Internet or in a paper or electronic file that is available at FDA for public review and copying).

(2) In general, FDA will use the information submitted in Part II of each PBN (i.e., the information described in § 192.25(b) of this chapter) to prepare this list and will update this list on an approximately monthly basis.

(c) *Would the data or other information in my PBN (including an amendment to my PBN, or any data or information that I incorporate by reference) be available to the public*? (1) Ordinarily, the data or other information in your PBN are available for public disclosure, in accordance with § 20.61 of this chapter, as of the date that FDA files the PBN.

(2) If you believe that any or all of the data or other information in your PBN is confidential, it is your responsibility to say so. The way to do this is in the letter that you send in Part I of your PBN (§ 592.25(a)(4)). In addition, under § 592.20(b) and (c), it is your responsibility to provide copies of your PBN that do not contain any data or other information that you claim are confidential.

(3) If you claim that any or all of the data or other information in your PBN is confidential, FDA will evaluate your claim. FDA will disclose the data or information in your PBN, unless FDA determines that your claim demonstrates that the criteria for exemption from disclosure in § 20.61 of this chapter are satisfied.

(4) If FDA determines that any or all of the data or other information in your PBN is confidential as of the date that we file it, those data or information would be available for public disclosure, in accordance with 20.61 of this chapter, when the criteria for exemption from disclosure in § 20.61 of this chapter are no longer satisfied.

(5) As long as the existence of your PBN is confidential, then the data or other information in your PBN would not be available for public disclosure.

(d) *How could the public obtain disclosable data and information in my PBN*?

Under the FOIA, the public could obtain the disclosable data or other information in your PBN or an amendment to your PBN, or that you incorporate by reference into your PBN, by looking for these data and information in FDA's electronic reading room or by asking FDA to send them a copy of these data and information.

(e) *Would the agency's evaluation of my PBN be available to the public*?

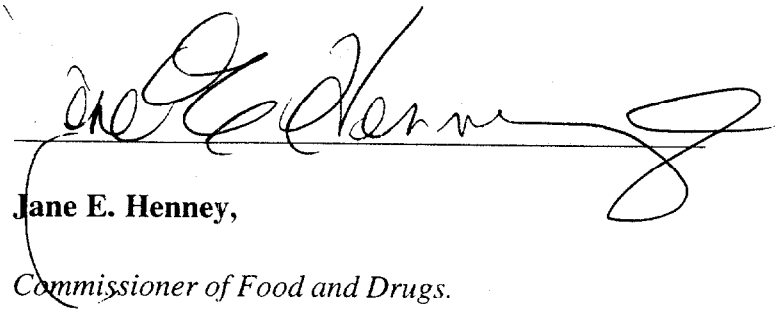
FDA will make the following information easily accessible to the public (e.g., by placing the information on the Internet or in a paper or electronic file that is available at FDA for public review and copying):

(1) The text of any letter issued by the agency under § 192.30(c) of this chapter.

(2) The text of the agency's completed evaluation of any notice submitted under this part.

SEP 22 2000

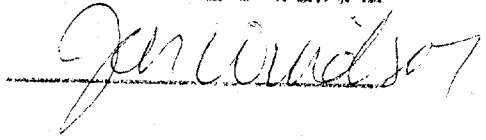
Dated: _____

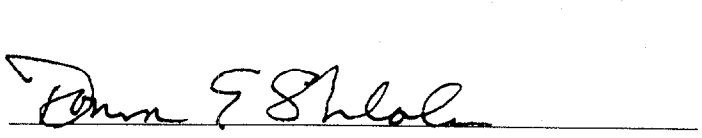


Jane E. Henney,

Commissioner of Food and Drugs.

CERTIFIED TO BE A TRUE COPY OF THE ORIGINAL





Donna E. Shalala,

Secretary of Health and Human Services.

[FR Doc. 00–???? Filed ??–??–00; 8:45 am]

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