permanently retired from use, or otherwise permanently disposed of.

(b) A final distributor, upon sale or other distribution of a tracked device for use in or by the patient, shall promptly provide the manufacturer tracking the device with the following information:

(1) The name and address of the final distributor,

(2) The lot number, batch number, model number, or serial number of the device, or other identifier used by the manufacturer to track the device;

(3) The name, address, telephone number, and social security number (if available) of the patient receiving the device;

(4) The date the device was provided to the patient or for use in the patient;

(5) The name, mailing address, and telephone number of the prescribing physician;

(6) The name, mailing address, and telephone number of the physician regularly following the patient if different than the prescribing physician; and

(7) When applicable, the date the device was explanted and the name, mailing address, and telephone number of the explanting physician, the date of the patient's death, or the date the device was returned to the manufacturer, permanently retired from use, or otherwise permanently disposed of.

(c)(1) A multiple distributor shall keep written records of the following each time such device is distributed for use by a patient:

(i) The lot number, batch number, or model number, or serial number of the device, or other identifier used by the manufacturer to track the device;

(ii) The name, address, telephone number, and social security number (if available) of the patient using the device;

(iii) The location of the device;

(iv) The date the device was provided for use by the patient;

(v) The name, address, and telephone number of the prescribing physician;

(vi) The name, address, and telephone number of the physician regularly following the patient if different than the prescribing physician; and

(vii) When applicable, the date the device was permanently retired from use or otherwise permanently disposed of.

(2) Except as required by order under section 518(e), any person who is a multiple distributor subject to the recordkeeping requirement of paragraph (c)(1) of this section shall, within 5 working days of a request from the manufacturer or within 10 working days of a request from FDA for the information identified in paragraph (c)(1) of this section, provide such information to the manufacturer or FDA.

(3) A distributor, final distributor, or multiple distributor shall make any records required to be kept under this part available to the manufacturer of the tracked device for audit upon written request by an authorized representative of the manufacturer.

Subpart D—Records and Inspections

§ 821.50 Availability.

(a) Manufacturers, distributors, multiple distributors, and final distributors shall, upon the presentation by an FDA representative of official credentials and the issuance of Form FD 482 at the initiation of an inspection of an establishment or person under section 704 of the act, make each record and all information required to be collected and maintained under this part and all records and information related to the events and persons identified in such records available to FDA personnel.

(b) Records and information referenced in paragraph (a) of this section shall be available to FDA personnel for purposes of reviewing, copying, or any other use related to the enforcement of the act and this part. Records required to be kept by this part shall be kept within the United States.

§ 821.55 Confidentiality.

(a) Records and other information submitted to FDA under this part shall be protected from public disclosure to the extent permitted under part 20 of this chapter, and in accordance with § 20.63 of this chapter, information contained in such records that would identify patient or research subjects shall not be available for public disclosure except as provided in those parts.

(b) Patient names or other identifiers may be disclosed to a manufacturer or other person subject to this part or to a physician when the health or safety of the patient requires that such persons have access to the information. Such notification will be pursuant to agreement that the record or information will not be further disclosed except as the health aspects of the patient requires. Such notification does not constitute public disclosure and will not trigger the availability of the same information to the public generally.

§ 821.60 Retention of records.

Persons required to maintain records under this part shall maintain such records for the useful life of each tracked device they manufacture or distribute. The useful life of a device is the time a device is in use or in distribution for use. For example, a record may be retired if the person maintaining the record becomes aware of the fact that the device is no longer in use, has been explanted, returned to the manufacturer, or the patient has died.

Dated: May 26, 1992.

David A. Kessler,

Commissioner of Food and Drugs.

Louis W. Sullivan,

Secretary of Health and Human Services.

[FR Doc. 92–12623 Filed 5–28–92; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 821

[Docket No. 91N-0296]

Medical Devices; Device Tracking

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to establish a device tracking requirement for certain categories of medical devices under the Safe Medical Devices Act of 1990 (the SMDA). FDA first proposed such regulations in the **Federal Register** of March 27, 1992 (57 FR 10702). This action reflects the agency's initial review of certain comments received in response to the March 27, 1992, proposal. FDA is issuing this proposal to provide for orderly implementation of the tracking requirements. Elsewhere in this issue of the **Federal Register** is a document entitled "Medical Devices; Device Tracking; final rule, notification of status under the Safe Medical Devices Act; confirmation of effective date." That document describes how this proposed rule, by operation of the SMDA, will have the status of a final rule.

The promulgation of a device tracking regulation is required by the SMDA, which amended the Federal Food, and Drug, and Cosmetic Act (the act) to require that manufacturers of certain medical devices adopt a method of tracking that follows those devices through the distribution chain and then identifies and tracks the patients who receive them. The SMDA requires tracking by manufacturers of life-supporting or life-sustaining devices that are used outside a device user facility and of permanently implantable devices, if the failure of these devices would be reasonably likely to have serious adverse health consequences. The SMDA also gives FDA the authority to designate other devices which must be tracked by their manufacturers. The proposed regulation would also apply to devices that FDA designates for tracking. This proposal applies to all devices subject to tracking under the SMDA that are initially introduced into interstate commerce or presented for importation into the United States on or after March 1, 1993.

FDA is also announcing that it is withdrawing the March 1992, proposal. FDA requests comments on this proposed regulation. After closure of the comment period for this proposed rule and consideration of comments, FDA will, if necessary, take further action.

DATES: Written comments by July 28, 1992. The agency is proposing that any final rule that may issue based on this proposal become effective March 1, 1993. For further information on "Effective Date," see the document published elsewhere in this issue of the **Federal Register** entitled "Medical Devices; Device Tracking; final rule; notification of status under the Safe Medical Devices Act; confirmation of effective date."

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Joseph M. Sheehan, Center for Devices and Radiological Health (HFZ-84), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4874.

SUPPLEMENTARY INFORMATION:

I. Background

The SMDA (Pub. L. 101-629), which became law on November 28, 1990, added section 519(e) (21 U.S.C. 360i(e)) to the act as codified at 21 U.S.C. 321-393. Section 519(e) of the act requires that manufacturers track certain devices from the manufacturer through the distribution chain to the patient using the device. Under section 519(e) of the act, manufacturers must track life-supporting or life-sustaining devices that are used outside a device user facility and permanently implantable devices, if the failure of these devices would be reasonably likely to have serious adverse health consequences. Section 519(e) of the act also gives FDA the authority to designate other devices which must be tracked by their manufacturers.

Under section 3(a)(A)(ii) of the SMDA, FDA was to have issued proposed regulations implementing section 519(e) of the act within 9 months of enactment of the SMDA (by August 28, 1991). Under section 3(c)(2) of the SMDA, FDA is to issue final regulations not later than 18 months after the date of enactment of the SMDA (by May 28, 1992). However, section 3(c)(2) of the SMDA also provides that, if FDA does not promulgate final tracking regulations by May 28, 1992, that

> the Congress finds that there is good cause for the proposed regulations to be considered as the final regulations without response to comment because the implementation of * * * [section 519(e)] of the act [is] essential to protect the health of patients who use such devices. Consequently, in such event, the proposed regulations issued under paragraph (1) shall become final regulations as of the expiration of such 18 months. There shall be promptly published in the **Federal Register** notice of the new status of the proposed regulations.

(The SMDA, section 3(c)(2).)

On March 27, 1992 (57 FR 10702), FDA published a proposed rule in the **Federal Register** that outlined the recordkeeping and reporting requirements which FDA believed were necessary to ensure that tracking serves its purpose—ensuring that manufacturers can, after devices have been distributed, promptly locate the device and the user of the device if FDA orders a recall or patient notification due to serious adverse health consequences or unreasonable risks of substantial harm to the public health associated with the use of the device. To that end, the March 27, 1992, proposal applied to manufacturers and those persons involved in the distribution of tracked devices, including distributors, pharmacies, hospitals, and doctors.

The period for submitting comments in response to the March 27, 1992, proposal closed on May 26, 1992. By May 15, 1992, the agency had received over 400 comments. Comments have been received from physicians specializing in medical disciplines utilizing devices subject to tracking, large and small device manufacturers, distributors, durable medical equipment suppliers, hospitals, trade associations and attorneys representing business interests, and private citizens. The comments received thus far have raised significant issues, including the effective date of the proposed regulations; the applicability of tracking requirements to imported and exported devices; the prohibition on distributing to noncompliant distributors; alternative methods of tracking; devices subject to tracking; and reporting timeframes and costs. In addition, the agency expects to receive more comments before the close of the comment period on the March 27, 1992, proposal.

Given the statutory deadline, FDA does not have sufficient time to give full and careful consideration and response to all comments and issue final regulations by May 28, 1992, the date upon which proposed tracking regulations are to become final regulations under section 3(c)(2) of the SMDA. Nevertheless, FDA has been reviewing comments on the March 27, 1992, proposal as they are filed. In light of the comments filed and reviewed thus far, FDA has reconsidered aspects of the regulations proposed on March 27, 1992,

and has determined that some revisions of the proposed regulation are needed to ensure effective implementation of the statutory tracking requirements. Accordingly, FDA is incorporating the revisions that it has determined, based on comments reviewed thus far, are necessary and proposing a revised medical device tracking regulation that supersedes the March 27, 1992, proposal. To the extent still applicable, the basis, purpose, authority discussion, and other explanations in the preamble to that proposal apply to this proposal.

II. Effective Date

In the March 27, 1992 proposal, FDA proposed that the effective date of the regulation would be 30 days after date of the publication of the final rule or May 28, 1992, whichever occurred first. FDA also stated that section 519(e) of the act would go into effect on the date that final regulations go into effect or May 28, 1992, whichever occurs first. Many comments, however, explained that it would be impossible to comply with the rule by May 28, 1992, and requested that the agency extend by at least 6 months the effective date of the regulations. At least one comment pointed out that the SMDA provides only that section 519(e) of the act becomes effective on the effective date of final regulations and that nothing in the SMDA curtailed FDA's ability to provide for an effective date of the regulations after May 28, 1992. Many comments pointed out that numerous actions would have to be taken before May 28, 1992, to comply with all of the requirements of the regulations. Several comments noted that, in some cases, manufacturers would have to make changes to a tracked device or its manufacturing, packaging, or labeling in order to comply. The comments pointed out that some of these changes could require the submission of premarket notifications or premarket approval supplements for FDA clearance of the changes. Until a company received a response from FDA (which could take up to 90 days for a premarket notification and 180 days for an approval of a PMA supplement under the statutory timeframes), a company could not distribute the devices with the changes necessary to track its device. Comments noted that even if FDA clearance were not needed for a change, many necessary changes in manufacturing, packaging, or labeling could not be fully implemented by May 28, 1992.

Comments also noted that manufacturers needed more time to coordinate their tracking programs with the distributors, multiple distributors, and final distributors of their products and to educate these persons about the requirements and importance of tracking. In addition, comments explained that manufacturers could not, by May 28, 1992, draft the necessary standard operating procedures (SOP's), obtain and install the necessary computer systems, change pricing strategies, change distribution policies, change contractual agreements with distributors and hospitals, and hire and train employees to implement tracking systems.

According to the comments, manufacturers' inability to take all the steps by May 28, 1992, would disrupt the supply of devices critical to health. For example, the requirement that devices have a unique identifier for tracking purposes could result in devices being removed from inventory for repacking before shipment, while other devices might be taken off the market until their manufacturers had implemented their tracking systems.

FDA agrees with many of these comments. While FDA believes that tracking critical devices to ensure that notifications and recalls of such devices are promptly and effectively carried out is a significant public health tool, FDA also believes it is not in the public's interest for systems as complex and far-reaching as medical device tracking to be implemented in a piecemeal, unorganized, or careless manner. In order for tracking systems to perform as envisioned by Congress and FDA, FDA believes that affected parties do need more time so that they can implement tracking systems thoughtfully and carefully, taking into account factors related to the device itself, the distribution systems, and the users of the device.

Section 3(c) of the SMDA provides that, if FDA has not issued a final rule by May 28, 1992, the proposed rule will become the final rule on that date. However, FDA, upon reconsideration, agrees that the SMDA does not preclude FDA from providing for a delayed effective date for the regulations. Indeed, delaying the effective dates of final rules is a common practice in order to allow the regulated community adequate compliance time. As noted above, FDA has reconsidered the effective date in the March 27, 1992, proposal and has determined that it is appropriate, under the circumstances present here, to extend the effective date of the final rule until March 1, 1993. Under section 3(b)(3) of the SMDA, therefore, section 519(e) of the act will be effective on March 1, 1993.

Thus, on and after March 1, 1993, manufacturers and importers of devices subject to tracking will be required to have in place the written SOP's required under proposed § 821.25(c), and these SOP's should be made available to all who are responsible for implementing and maintaining the tracking system. FDA will regard the failure to have the required written SOP in place as a violation of sections 301 and 502 of the act.

Starting March 1, 1993, FDA also expects manufacturers and importers to make a good faith effort to comply with the remaining provisions of the proposed regulation. FDA, however, recognizes that for the first 6 to 12 months of tracking, manufacturers, distributors, multiple distributors, and final distributors will be fine-tuning their procedures for tracking based on their initial experiences. Thus, to determine "good faith," FDA will look at whether efforts to comply are documented after the first two audits and whether persons subject to tracking are taking immediate steps to correct any shortcomings identified by the first two audits. While FDA will not specifically schedule inspections for the purpose of reviewing a tracking system during the early stages of implementation, FDA will review tracking systems and records during regularly scheduled current good manufacturing practice (CGMP) inspections.

In the preamble to the proposed rule, the agency recognized there might be facets of device distribution, tracking, and patient followup whose impact upon the benefits, effectiveness, and cost of device tracking systems were not fully being taken into account in all respects by the agency (57 FR at 10702 at 10712 and 10713). Accordingly, FDA solicited comments in nine areas pertaining to: the number and kind of tracking systems presently in use by industry; how, to what degree, and at what cost existing tracking systems would have to be modified by manufacturers and distributors to accommodate the proposed device tracking requirements; and what business practices would be benefitted by the proposed tracking system requirements besides increased capabilities to track and recall devices and notify patients using certain devices.

FDA remains committed to the notice and comment process as the appropriate mechanism for informed decisionmaking on device tracking. The agency intends to review and consider all comments received in response to the proposed rule published on March 27, 1992 as well

as to review and consider all comments submitted by July 28, 1992, on the revisions to this proposed tracking rule.

A. Effective Date

As discussed above, FDA is revising § 821.1(c) of the proposed regulation, deleting the previous reference to May 28, 1992 as the latest date by which the manufacturer (repacker, initial foreign importer, and others) of a tracked device would be required to implement a method of tracking. Revised § 821.1(c) of the proposed rule requires the implementation of a method of tracking devices that are subject to section 519(e) of the act and that are manufactured, repacked, or presented for importation into the United States on or after March 1, 1993. Tracking will be required for finished devices initially introduced or delivered for introduction into interstate commerce and devices offered for importation on or after March 1, 1993.

B. Illustrative List

The majority of comments objected to the inclusion of one or more devices on the illustrative list of devices subject to the tracking requirements (§ 821.20(b)). As a result, FDA has reviewed the legislative history of the SMDA, the statutory language, the proposed definitions of the statutory terms, the specific comments already received about the purpose and contents of the list, and the intended uses, methods of operation, and safety records of the devices enumerated on the previous illustrative list. In so doing, FDA has been able to refine its understanding of the category of devices intended by Congress to be subject to tracking.

Preliminarily, FDA reiterates that the "[m]anufacturers have the responsibility to identify devices that meet the criteria for tracking and to initiate tracking." (proposed § 821.20(b)). The illustrative list, therefore, consists of those devices that, based upon information currently held by FDA with regard to approved intended uses, methods of operation, and extant agency safety records, FDA regards as subject to tracking under the criteria set forth in this regulation. Furthermore, if the intended uses or the methods of operation were to change, either because of changes in the use or manufacture or changes in knowledge about a device, the list might require further revision, either to include or exclude other devices. FDA solicits such comments for further evaluation.

The statutory algorithm for mandatory tracking requires the manufacturer to determine whether the device is either "permanently implantable" or "a life-sustaining or life-supporting device used outside a device user facility." (section 519(e)(1) of the act). If it is, the manufacturer must determine if the failure of the device would be "reasonably likely to have adverse health consequences." (section 519(e)(i) of the act). After reviewing the legislative history, FDA concluded that "permanently implantable" did not include all devices, which remain incorporated within the body, which would include all nonabsorbable suture material and similar devices. Rather, FDA concluded that the device must not only remain in the body, but must "continuously assist, restore, or replace the function of an organ system or structure of the human body throughout the useful life of the device." (proposed § 821.3(f)). Thus, the category of devices which are permanently implantable excludes those devices which, although they may remain permanently in the body, cease to perform the function for which they were designed after a known time period. The definition thus excludes nonabsorbable suture material. The category is designed to permit recalls, patient advisories, and/or explantation, of devices based upon new information of device failure related to device design or performance. Thus, FDA concluded that a device that serves only a temporary function, or ceases to perform the function for which it was designed, although it may remain in the body, was not intended by Congress to be tracked as a permanently implantable device.

Many comments brought to FDA's attention that many devices on the initial illustrative list for "permanently implanted" devices, although left in the body, only functioned temporarily when understood in light of their intended use and known method of function. To the extent that FDA has not completed the task of verification of such data submissions or to the extent that other parties may wish to submit further such information about devices currently on the illustrative list or devices that should be placed on such a list, FDA anticipates further revision.

Based upon review of the earlier published list of permanently implantable devices, FDA concludes that the following devices do not fall within the definition as the device does not continue to assist, restore or replace the function of an organ system or structure of the human body:

Vena Cava Clip
Cardiovascular Intravascular Filter
Intracardiac patch or pledget made of polypropylene, polyethylene terephthalate, polytetrafluoroethylene
Aneurysm clip
Artificial embolization device
Intravascular occluding catheter
Spinal interlaminal fixation orthosis
Spinal intervertebral body fixation orthosis

As FDA understands it, the vena cava clip and the cardiovascular intravascular filter serve to narrow the lumen of the inferior vena cava to preclude the passage of large emboli from the lower part of the body through the heart and into the lungs. The devices do not, generally, totally occlude blood flow, either because a smaller intraluminal passage remains or collateral circulation may develop around the device. However, the remaining blood flow is directed through smaller conduits that preclude passage of large emboli. These smaller conduits become permanent regardless of the permanence of the device. Device failure, based upon the newly identified design or performance questions, with resultant breakage and/or migration, is not likely to result in recurrence of susceptibility to large pulmonary emboli.

Aneurysm clips, intravascular occluding catheters, and artificial embolization devices are intended to restore normal circulatory function to a diseased, damaged, altered, or dysfunctional blood vessel by occluding the vessel at the appropriate point. After occlusion occurs, clot formation and organization and neointimal development replace the function of the device. The device remains in place only because removal is difficult or dangerous.

Pledgets serve to reinforce suture material placed through myocardial tissue. Much like suture material itself, the function of the pledget is replaced by natural processes of scar formation, neointimal and endothelial cell proliferation, and other processes of healing. These devices do not continue to function after that healing process is completed. These devices, therefore, do not "continuously * * * restore * * * the function of an organ system of the body throughout the useful life of the device," and FDA does not believe they are subject to tracking.

The spinal interlaminal and intervertebral body fixation devices are designed to provide an alternative to bony or ligamentous support after surgery to correct, repair, or treat various boney diseases or deformities of the spine. After the completion of healing by bone growth, spinal fusion, or other process, the device no longer serves as the primary support. Their removal at this stage is elective, but may be deferred based upon such considerations as the risk of further surgery. FDA here reiterates that we are

continuing to seek information regarding the potential adverse health consequences of these devices. FDA specifically solicits comments on whether deleting these devices from the list is appropriate. As noted in the preamble to the March 27, 1992 proposal, procedures exist for adding devices onto the list.

FDA notes, however, that FDA's current position on the two types of spinal fixation devices identified in the proposal, e.g., Harrington rod (21 CFR 888.3050) and Dwyer Wire (21 CFR 888.3060) does not reflect FDA's position on other devices that may be promoted and used for spinal fixation. Other devices have not yet been approved for spinal fixation or otherwise cleared for marketing as spinal fixation devices.

Finally, the agency has also reconsidered, based upon comments, the inclusion of the central nervous system fluid shunt ("CNS shunt") and components. Several comments noted that the Senate report, which referred to the "crucial concept" of "serious, adverse health consequences," stated that "injuries attributable to a device that are not significant in nature and are treatable and reversible by standard medical techniques, proximate in time to the injury, are not included within the term's definition." (See S. Rept. 513, 101st Cong., 2d sess. 19 (1990).) The comments noted that CNS shunt failure has always been a fairly common event and that there is no existing design that is free from such failure. Furthermore, the comments noted that shunt revision is a common and standard medical technique. Finally, the comments noted that shunt failure results in the slow reaccumulation of CNS fluid, at gradually-increasing pressure, during which time period symptoms of the original disease, which precipitated the primary CNS shunt insertion, slowly recur. FDA agrees. Complete CNS shunt failure is a common expected experience and existing medical standards and techniques have been developed so that CNS shunt revision is available on a timely and emergency basis to patients who have CNS shunts in place. Moreover, when such timely shunt revision is performed, reversal of the symptom complex occurs. FDA therefore concludes that CNS shunts are excluded from tracking based upon Congressional understanding of the terms, "serious adverse health consequences," which precludes application of tracking to devices for which timely, known, and well-recognized medical intervention would result in reversal of any medical complications due to expected device failure to function.

FDA notes, for the record and to assist manufacturers in identifying devices for which tracking is required, that timely intervention is unlikely to result in reversing complications for device failure when the device performs mandatory ventilatory, airway, or circulatory functions, which must be restored almost instantaneously if failure occurs.

Upon review, FDA concludes that the following device does not meet the statutory requirement that device failure "would be reasonably likely to have serious adverse health consequences": Central nervous system fluid shunt and components.

FDA also reviewed comments with regard to the second prong of mandatory tracking "Life-sustaining or Life-supporting devices used outside device user facilities." Several comments noted that devices included on the illustrative list were either (1) not intended for use to support or sustain life or (2) device failures were treatable and reversible by standard medical techniques, proximate in time to the injury. With regard to the second category of devices subject to tracking, FDA notes that these devices are not intended to be used along with attendant physician supervision and may be used in the home. FDA must consider, therefore, not whether the remedial techniques are standard medical techniques, but whether such techniques would be reasonably known and available to the user of the device.

FDA agrees with the comments that suggested and provided evidence that the following devices were not life-sustaining and life-supporting devices, within the intent of Congress, to be tracked:

Noncontinuous ventilator
Portable liquid oxygen unit
Portable oxygen generator, including oxygen concentrator

With respect to the ventilatory and oxygen devices, by their nature, these devices are not essential to sustaining ventilation or respiration. Patients who require ventilatory support to sustain or support life could not survive without continuous ventilation. Furthermore, while oxygen supplementation is frequently an adjunct to satisfactory home management of patients with respiratory disease, FDA believes that standard medical practice precludes the use of oxygen supplementation outside a user facility for patients who could not tolerate periods of room air breathing long enough to identify and obtain further supplemental oxygenation even if remediation required transport to a hospital facility.

FDA agrees with comments that suggested or provided evidence that the failure of the following devices would not be reasonably likely to have serious adverse health consequences because timely, simple, and well-known lay intervention would preclude irreversible injury:

Pressure regulator, including mechanical oxygen regulators
Tracheostomy tube and tube cuff
Portable liquid oxygen unit
Portable oxygen generator, including oxygen concentrator
Peritoneal dialysis system and accessories

With the exception of peritoneal dialysis systems and accessories, all of these devices are used for respiratory support for patients with impaired but functioning respiratory systems. FDA believes that both the nature of the devices and the nature of their use would preclude use of the devices outside a user facility without significant education and/or experience in the care and management of the devices. Furthermore, FDA believes that existing medical standards preclude the use of the device outside a user facility in circumstances where device failure would result in imminent death or permanent injury. Thus, FDA concludes that failure of these devices is not reasonably likely to have serious adverse health consequences. FDA would be receptive, however, to receipt of further information about the intended or actual use of such products that might prompt a reconsideration of this judgment.

FDA believes that failure of peritoneal dialysis systems would be easily recognized and remediated by the user in a sufficiently timely fashion to preclude serious adverse health consequences.

Electromechanical infusion pumps remain on the list, as devices not meeting the mandatory statutory criteria but as designated for tracking because their failure nonetheless presents the potential for serious adverse health consequences. Implantable infusion pumps remain on the list as meeting the definition of permanently implantable devices, the failure of which would be reasonably likely to have serious adverse health consequences. FDA has received reports that automated infusion pumps, either implantable or electromechanical, may fail either by ceasing function completely or by increasing the rate at which medication of fluid is delivered. While cessation of

administration or medication or fluid may be promptly recognized and remediated by the user, FDA has serious concerns as to whether the same is true for device failure that manifests by over-infusion or overdosage. Based upon the existing record of reported adverse events, not all of which have been life-threatening, and the belief that these automated products may not necessarily exhibit design or performance failures until long after marketing, FDA believes that these devices must be tracked to permit recalls and/or repair until a better safety record can be established.

As stated in the preamble to the March 27, 1992 proposal, as more information comes to its attention, FDA may add to or remove devices from the list in accordance with the procedures set forth in that preamble.

C. Exemptions/Variances; Alternative Systems

Many comments raised questions about the applicability of or need for certain tracking requirements of the proposed regulation with respect to specific devices. For example, some comments explained that there is no need for each device unit to a unique identifier to conduct an effective recall or notification of certain types of devices. Others stated that some devices may include disposable parts or accessories that do not need to be tracked all the way to the patient.

FDA agrees that it may be possible to effectively track certain devices without all of the information required under proposed § 821.25(a)(2) or § 821.25(a)(3). However, after reviewing the comments that raised this issue, FDA believes that whether this is true will depend on the particular device in question, its intended uses, and how and where it is distributed. FDA has concluded that such device-specific determinations are best handled on an individual basis. Thus, FDA is providing for exemptions or variances from proposed §§ 821.25 and 821.30 in certain cases and has included in the proposed rule a new proposed § 821.2 that sets out a procedure for petitioning FDA for such an exemption or variance from tracking requirements. Petitions for exemptions or variance must be submitted in accordance with § 10.30 (21 CFR 10.30) of FDA's administrative practice and procedure regulations. However, FDA will respond to such petitions in 90 days not the 180 days provided in § 10.30. The Director of the Office of Compliance and Surveillance, Center for Devices and Radiological Health will issue these responses. FDA notes that exemptions and variances from the requirements of proposed §§ 821.25 and 821.30 will not be granted lightly. Testing of the proposed alternative to demonstrate its viability will generally be necessary. Any person requesting an exemption will be required to demonstrate that the system that person proposes to meet the purposes of section 519(e) of the act and these proposed regulations will, in fact, ensure prompt and effective notifications and recalls under sections 518(a) and 518(e) of the act.

FDA recognizes the need to accommodate manufacturers who will be petitioning for exemptions or variances before the March 1, 1993 effective date. Thus, for those petitions received under proposed § 821.3 before November 1, 1992, FDA will extend the effective date of this part for the device in question, if FDA determines it needs more time to review the petition and issue its response. In this case, FDA, by February 1, 1993, will either approve or disapprove the petition, or extend the effective date to complete its review. Any extension that FDA grants to the effective date will be based upon the additional time FDA needs to complete its review of the petition.

D. Use of Social Security Number

At least one comment discussed in detail a proposal to use patients' social security numbers and information from Government data bases (from the Internal Revenue Service) as a primary method of tracking patients. The comment stated that this would be the most efficient and cost-effective method of tracking. The comment noted, however, that there were limitations to the proposal, most notably the fact that legislation is necessary to implement it because the permitted uses of such data bases are narrowly restricted by statute.

Under the Paperwork Reduction Act and implementing regulations, FDA has an obligation to inquire whether information required to be collected by manufacturers under a regulation is available from another source within the Federal Government.

FDA has not had time to fully evaluate this proposal. FDA will continue to explore the proposal because the agency, too, is interested in exploring the most efficient and cost effective methods for device tracking.

FDA agrees that it is desirable for Federal agencies to use other available Government data bases but disagrees with these comments' views that IRS's data base will meet FDA's need for device tracking. First, the device tracking regulation requires the collection of more than just patient name and current address. To ensure the effectiveness of recalls and health professional and patient notifications under sections 518(a) and 581(e) of the act, this tracking regulation also requires that manufacturers keep current distribution information and health professional information. FDA is not aware of any Government agency that keeps this information, and no comment has suggested that any Government agency currently collects this information.

With respect to IRS tax return information, the comment itself acknowledges that such information cannot be made available for use in tracking medical devices until section 6103 of the Internal Revenue Code (26 U.S.C. 6103) is amended to permit IRS to disclose this information. Under section 6103 of the Internal Revenue Code, IRS is prohibited from disclosing, even to another Government agency, any tax return information, including taxpayer identity, unless section 6103 specifically permits the disclosure. Section 6103 of the Internal Revenue Code contains no provision that would permit IRS to disclose taxpayer information to FDA (to any other person or agency) for purposes of locating patients with tracked devices.

The comment also submitted information concerning letter forwarding services provided by IRS. With respect to letter forwarding, FDA notes that manufacturers could use this service to supplement their efforts to keep in touch with patients or find patients lost to followup, but notes that the information in the comment states that it generally takes at least 90 days for IRS to process letter forwarding requests. FDA will work with the IRS to explore whether this time period could be shortened. As for relying on the existence of the IRS letter forwarding service to conduct notifications and recalls under sections 518(a) or 518(e) of the act (the purpose of tracking), a tracking system that relies on letter forwarding to conduct a recall or notification would not be effective because all the information necessary for effective recall or health professional and patient notification would not be available, and the information would not be available in a form that would permit effective recalls and health professional and patient notifications in accordance with the requirements of section 518(a) and 518(e) of the act.

Because of the agency's continuing interest in the subject of using existing data bases in device tracking, FDA invites further comments on this issue, and particularly on the issues discussed above.

E. Unique Identifiers

Several comments questioned the need for a unique identifier for each device subject to tracking. These comments generally pointed out that this requirement is neither necessary nor feasible in many cases. The comments further stated that, for many devices, problems would arise only by lot and, therefore, identification and tracking by lot number is sufficient. The comments also stated that the design of some devices would not allow for unique identifiers to be affixed to the device or the labeling.

FDA agrees that unique identification is not necessary in all cases. Therefore, FDA has revised proposed § 821.25 to allow for identification by lot number, batch number, model number, serial number, or any other identifier that would provide for an effective tracking system. FDA cautions, however, that the identification method should be tailored to the device and any recall or notification may be conducted in accordance with the size and scope of the identification system, e.g., by lot.

F. Premarket Clearance

Many comments stated that there may be a need to submit applications for premarket clearance under section 510(k) or 515 of the act cleared before implementing certain changes required to implement a tracking system. Generally these comments referred to the need to establish unique identifiers for certain devices. The comments stated that changes may be required in the device itself to provide for an identifier and such changes may be significant enough to require 510(k) or PMA clearance. The comments further pointed out that clearance could not be obtained in time to implement the changes before the May 28, 1992, effective date.

The problems addressed by these comments have been alleviated to a great extent by the delayed effective date, the changes in the requirements to provide a unique identifier, of each unit of device and the provisions for exemptions and variances. FDA believes that premarket clearance or approval generally should only be necessary for those changes that require physical alteration of the device that could significantly affect its safety or effectiveness as described in § 807.81(a)(3). Premarket clearance or approval is not required for changes in labeling to implement tracking, while changes in the sterilization process or changes requiring process validation will have to be accomplished in accordance with CGMP regulations (21 CFR Part 820), but do not need clearance or approval. Finally, FDA will provide for expedited review within 90 days of any 510(k)'s or PMA supplements that are required to comply with this regulation if the submission is made by November 1, 1992. These 510(k)'s should be marked clearly "Tracking 510(k)'s or PMA's."

G. Exported Devices

Several comments asked for clarification on whether the proposed regulation applied to exported devices, noting that there would be difficulties in applying the tracking requirements to exported devices. These comments stated that it would be difficult or impossible to track exported devices and tracking requirements may be contrary to patient confidentiality statues in some countries.

The proposed rule does not specifically address whether section 519(e) of the act applies to exported devices. FDA, however, agrees with the comments. FDA believes that tracking should not be required for devices after export from the United States. Devices must be tracked only until they leave the United States. Devices may also be exported without tracking if they are shipped in compliance with section 801(e)(1) of the act (21 U.S.C. 381(e)(1)) which governs the exportation of devices and states that a device intended for export shall be deemed not to be adulterated or misbranded under the act provided the device: (1) Meets the foreign purchaser's specification; (2) does not violate the laws of the foreign county to which the device is being imported; (3) is labeled as intended for export; and (4) is not sold or offered for sale in domestic commerce. Devices that are subject to section 519(e) of the act and are not tracked would be misbranded when introduced into interstate commerce unless they comply with the four requirements set out in section 801(e)(1). FDA emphasizes that it will not permit as an alternative method of disposition the export of devices subject to the tracking provisions of section 519(e) of the act that are offered for sale in the United States and that are seized because the manufacturer has not implemented a tracking system to track the devices. Such misbranded devices would not meet the requirement of section 801(e)(1)(D) of the act because they have been distributed in the United States. FDA advises that manufacturers that do not intend to track devices that are intended for export should label those devices "for export only" prior to any shipment from the manufacturing facility.

H. Prohibited Distribution

Proposed §§ 821.1(d) and 821.25(d) of the tracking rule prohibit shipment of a device to a distributor, final distributor, or multiple distributor when the manufacturer knows, should know, or becomes aware that such a person has not collected, maintained, or furnished required tracking records and information. Many comments objected to these provisions stating that they would unfairly burden manufacturers with enforcing distributor compliance with tracking requirements and responsibilities set forth for distributors by the proposed rule and would unfairly stop distribution of tracked devices to patients located in geographic areas serviced by a single distributor, doctor, hospital, or health care facility that fails to comply with distributor tracking requirements.

FDA agrees in part with the comments. Accordingly, in the proposed rule FDA is deleting § 821.1(d) of the proposed regulations. FDA is also revising § 821.25(d) of the March 27, 1992, proposed rule to remove the regulation's reference to manufacturer's obligation to cease distributing a tracked device to a noncompliant distributor when the manufacturer learns that a distributor, final distributor or multiple distributor has not complied with the tracking requirements to collect, maintain, or furnish required records or information. In accordance with the statute, the primary burden for ensuring that their tracking system works rests upon the manufacturer, who has a duty to encourage compliance with the requirements by distributors, e.g., through contractual agreements. Manufacturers thus must have taken all reasonable steps within their power to enforce compliance by distributors before notifying FDA. Proposed section 821.25(d) still requires manufacturers to notify the agency when a distributor, final distributor, or multiple distributor has not complied with the tracking requirements to collect, maintain, or furnish required records or information. When notifying FDA, the manufacturer should also provide a full list of all steps the manufacturer has taken to obtain compliance, as well as a fact-based assessment of the effect on supply of the device that will occur if the manufacturer ceases distribution to the person in question. FDA will then take any action necessary against that person.

I. Timeframes for Reporting

Several comments stated that the requirement that the information be

made available to FDA within 3 days of a request is infeasible and unnecessary. These comments stated that it would be impossible to gather the information in that timeframe and that it would not be needed so quickly.

FDA agrees in part with these comments. The purpose of the tracking regulation is to ensure that a manufacturer can, if ordered to do so by FDA, comply with sections 518(a) (health professional and patient notification) and 518(e) (recall) of the act in a prompt and complete manner. Under section 518(e) of the act (also added by the SMDA), if FDA determines that there is a reasonable probability that a device would cause serious adverse health consequences or death, FDA can initiate a mandatory recall by ordering appropriate persons to immediately cease distributing a device and to notify all health professionals and user facilities of the order and instruct them to cease use of the device. Under section 518(e) of the act, recall and notification to patients, however, will take place only after an opportunity for a hearing which is to occur within 10 days of the initial cease distribution and use order. Under section 518(a) of the act, FDA can order the notification of health professionals and patients if FDA determines: (1) That a device presents a substantial risk of harm to the public health; (2) that notification is necessary to eliminate the risk; and (3) that no more practicable means exist under the act to eliminate the risk. Such notification orders issue only after FDA has notified the relevant persons and given them the opportunity to consult with FDA (generally about 10 days).

FDA has thus revised the regulation (proposed § 821.25) to reflect these statutory timeframes. Proposed § 821.25 now provides for manufacturers to provide distributor information within 3 days and patient information within 10 working days. In addition, the proposed regulation has been revised (proposed § 821.30) to require multiple distributors to provide information to manufacturers within 5 working days of a request and to FDA within 10 working days.

FDA believes that these changes will allow for an effective tracking system, while still ensuring immediate response to a cease distribution and use order under section 518(e) of the act. FDA notes, however, that an order under section 518(e) of the act may require notification to distributors and users to begin in less than 3 days and that the recipient of a cease distribution and use order must comply with the timeframes in that order. The proposed regulation has been revised to reflect this fact.

J. Audit

Several comments questioned the extent of the audit provisions. The comments generally objected to what they perceived as a need to contact each patient every 6 months. The comments stated that this was unnecessarily burdensome and intrusive. Some comments also stated that distributors would not make their records available to manufacturers for audit.

FDA notes that the audit requirement is not intended to keep the tracking data current. Rather, audits are to make sure that the tracking system implemented by a manufacturer works (i.e., generates current data). Each SOP should thus contain a sampling plan to audit the function of the tracking system from the manufacturer through the distribution chain to the end user. The extent of an audit depends on the type and adequacy of the system. Thus, it may not be necessary to contact every kind of distributor and patient every 6 months. For maintenance purposes, patients should be contracted as needed to ensure that the information in the system is current. It may only be necessary to contract a random statistically valid sampling of patients to assure that the system is working. Moreover, FDA notes that it may not be necessary to conduct audits every 6 months into perpetuity once the system is established. Therefore, FDA is revising the regulation to require that audits be conducted at least every 6 months for the first 3 years after distribution of a tracked device begins and at least annually in subsequent years. FDA has also added new § 821.30(d) to clearly require all distributors to make their tracking records available to affected manufacturers for audit.

K. Importers

One comment questioned whether foreign manufacturers must comply with the tracking requirements. The comment suggested that the rule should be revised to clarify foreign manufacturers must comply and appoint U.S. agents responsible for tracking. The comment points out that FDA has proposed a similar system in another regulation (56 FR 60024, November 26, 1991) for reporting deaths and serious injuries related to medical devices.

It is FDA's intent that imported devices be tracked by the initial importer who is required to register under section 510(k) of the act. FDA has proposed new § 821.4 to make this clear. FDA notes that the importer may then be a designated agent for purposes of the medical device reporting regulation.

L. Records

FDA has added a new requirement to proposed § 821.50(b) that records must be maintained within the United States.

M. Economic Impact

One comment questioned in detail FDA's economic analysis of the proposed rule and claimed that FDA had greatly underestimated the costs of the proposed rule. The comment said further that FDA needed to undertake more economic analysis to comply with Executive Order 12291 in that the comment estimates that the annual costs exceed $100 million, placing it in the category of a major rule under the Executive Order that requires further economic analysis.

If necessary, FDA will respond in detail to this comment at a later date. FDA believes that the annual costs of the proposed rule do not exceed $100 million. Furthermore, FDA notes that the revisions made in this proposed rule substantially reduce the costs of the rule.

III. Request for Comments

Interested persons may, on or before July 28, 1992, submit to the Docket Management Branch (address above) written comments regarding this proposal. 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 office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 821

Device tracking, Medical devices, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, FDA hereby withdraws the proposed rule that published in the **Federal Register** of March 27, 1992 (57 FR 10702). Further, FDA, proposes that 21 CFR Part 821 be added to read as follows:

PART 821—MEDICAL DEVICE TRACKING REQUIREMENTS

Subpart A—General Provisions

Sec.

Authority: Sec. 301, 501, 502, 510, 515, 518, 519, 701, and 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331, 351, 352, 360, 360e, 360h, 360i, 371, and 374).

Subpart A—General Provisions

§ 821.1 Scope.

(a) The regulations in this part implement section 519(e) of the Federal Food, Drug, and Cosmetic Act (the act) which requires the adoption of a method of device tracking by any person who registers under section 510 of the act and is engaged in the manufacture and distribution of devices the failure of which would be reasonably likely to have serious adverse health consequences if the devices are life-sustaining or life-supporting devices used outside of a device user facility or are permanently implantable devices. This part also applies to any other device that the Food and Drug Administration (FDA) designates as requiring a method of tracking to protect the public health. A device subject to this part either by statutory requirement or by FDA designation is referred to herein as a tracked device.

(b) These regulations are intended to ensure that tracked devices can be traced from the device manufacturing facility to the person for whom the device is indicated, that is, the patient. Effective tracking of devices from the manufacturing facility, through the distributor network (including distributors, retailers, rental firms and other commercial enterprises, device user facilities and licensed practitioners) and, ultimately, to any person for whom the device is intended is necessary for the effectiveness of remedies prescribed by the act, such as patient notification (section 518(a) of the act) or device recall (section 518(e) of the act). Although these regulations do not preclude a manufacturer from involving outside organizations in that manufacturer's device tracking effort, the legal responsibility for complying with this part rests with manufacturers who must register under section 510 of the act, and that responsibility cannot be altered, modified, or in any way abrogated by contracts or other agreements.

(c) Each manufacturer of a tracked device shall implement a method of tracking devices by March 1, 1993.

(d) The primary burden for ensuring that the tracking system works rests upon the manufacturer. A manufacturer or any other person, including a distributor, final distributor, or multiple distributor, who distributes a device subject to tracking who fails to comply with any applicable requirement of section 519(e) of the act or of this part, or any person who causes such failure, misbrands the device within the meaning of section 502(t)(2) of the act and commits a prohibited act within the meaning of sections 301(e) and 301(q)(1)(B) of the act.

(e) Any person subject to this part who permanently discontinues doing business is required to notify FDA at the time the person notifies any Government agency, court, or supplier, and provide FDA with a complete set of its tracking records and information. However, if a person ceases distribution of a tracked device but continues to do other business, that person continues to be responsible for compliance with this part unless another person, affirmatively and in writing, assumes responsibility for continuing the tracking of devices previously distributed under this part. Further, if a person subject to this part goes out of business completely, but other persons acquire the right to manufacture or distribute tracked devices, those other persons are deemed to be responsible for continuing the tracking responsibility of the previous person under this part.

§ 821.2 Exemptions and variances.

(a) A manufacturer, importer, distributor, or other interested person (including a trade association) may seek an exemption or variance from one or more requirements of this part.

(b) A request for an exemption or variance shall be submitted in the form of a petition under § 10.30 of this chapter and shall comply with the requirements set out therein, except that a response shall be issued in 90 days. The Director, Office of Compliance and Surveillance, Center for Devices and Radiological Health (CDRH), shall issue responses to requests under this section. The petition shall also contain the following:

(1) The name of the device and device class and representative labeling showing the intended use(s) of the device;

(2) The reasons that compliance with the tracking requirements of this part is unnecessary;

(3) A complete description of alternative steps that are available, or that the petitioner has already taken, to ensure that an effective tracking system is in place; and

(4) Other information justifying the exemption or variance.

(c) An exemption or variance is not effective until the Director, Office of Compliance and Surveillance, CDRH, approves the request under § 10.30(e)(2)(i) of this chapter.

(d) For petitions received under this section before November 1, 1992, FDA will, by February 1, 1993, approve or disapprove the petition or extend the effective date of this part for the device that is the subject of the petition. Any extension that FDA grants to the effective date will be based upon the additional time FDA needs to complete its review of the petition.

§ 821.3 Definitions.

The following definitions and terms apply to this part:

(a) *Act* means the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 321 *et seq.*, as amended.

(b) *Importer* means the initial distributor of an imported device who is required to register under section 510 of the act and § 807.20 of this chapter. *Importer* does not include anyone who only performs a service for the person who furthers the marketing, i.e., brokers, jobbers, or warehousers.

(c) *Manufacturer* means any person, including any importer, repacker, or relabeler, who manufactures, prepares, propagates, compounds, assembles, or processes a device or engages in any of the activities described in § 807.3(d) of this chapter.

(d) *Device failure* means the failure of a device to perform or function as intended, including any deviations from the device's performance specifications or intended use.

(e) *Serious adverse health consequences* means any significant adverse experience related to a device, including device-related events which are life-threatening or which involve permanent or long-term injuries or illnesses.

(f) *Permanently implantable device* means a device that is intended to be placed into a surgically or naturally formed cavity of the human body to continuously assist, restore, or replace the function of an organ system or structure of the human body throughout the useful life of the device. The term does not include any device which is intended and used for temporary purposes or which is intended for explanation.

(g) *Life-supporting or life-sustaining device used outside a device user facility* means a device which is essential, or yields information that is essential, to the restoration or continuation of a bodily function important to the continuation of human life that is intended for use outside a hospital, nursing home, ambulatory surgical facility, or diagnostic or outpatient treatment facility. Physicians' offices are not device user facilities and, therefore, devices used therein are subject to tracking if they otherwise satisfy the statutory and regulatory criteria.

(h) *Distributor* means any person who furthers the distribution of a device from the original place of manufacture to the person who makes delivery or sale to the ultimate user, i.e., the final or multiple distributor, but who does not repackage or otherwise change the container, wrapper, or labeling of the device or device package.

(i) *Final distributor* means any person who distributes a tracked device intended for use by a single patient over the useful life of the device to the patient. This term includes, but is not limited to, licensed practitioners, retail pharmacies, hospitals, and other types of device user facilities.

(j) *Distributes* means any distribution of a tracked device, including the charitable distribution of a tracked device. This term does not include the distribution of a device under an effective investigational device exemption in accordance with section 520(g) of the act and part 812 of this chapter or the distribution of a device for teaching, law enforcement, research, or analysis as specified in § 801.125 of this chapter.

(k) *Multiple distributor* means any device user facility, rental company, or any other entity that distributes a life-sustaining or life-supporting device intended for use by more than one patient over the useful life of the device.

(l) *Licensed practitioner* means a physician, dentist, or other health care practitioner licensed by the law of the State in which he or she practices to use or order the use of the tracked device.

(m) Any term defined in section 201 of the act shall have the same definition in this part.

§ 821.4 Imported devices.

For purposes of this part, the importer of a tracked device shall be considered the manufacturer and shall be required to comply with all requirements of this part applicable to manufacturers. Importers must keep all information required under this part in the United States.

Subpart B—Tracking Requirements

§ 821.20 Devices subject to tracking.

(a) A manufacturer of any device the failure of which would be reasonably likely to have a serious adverse health consequence, that is either a life-sustaining or life-supporting device used outside of a device user facility or a permanently implantable device, or a manufacturer of any other device that FDA, in its discretion, designates for tracking, shall track that device in accordance with this part.

(b) Manufacturers have the responsibility to identify devices that meet the criteria for tracking and to initiate tracking. By way of illustration and to provide guidance, FDA has set out below a list of example devices it regards as subject to tracking under the criteria set forth in this regulation.

(1) Permanently Implantable Devices.

21 CFR	Classification
870.3450	Vascular graft prosthesis of less than 6 millimeters diameter.
870.3460	Vascular graft prosthesis of 6 millimeters and greater diameter.
870.3545	Ventricular bypass (assist) device.
870.3610	Implantable pacemaker pulse generator.
870.3680	Cardiovascular permanent pacemaker electrode.
870.3800	Annuloplasty ring.
870.3925	Replacement heart valve.
(No cite)	Automatic implantable cardioverter/defibrillator.
878.3720	Tracheal prosthesis.
882.5820	Implanted cerebellar stimulator.
882.5830	Implanted diaphragmatic/phrenic nerve stimulator.
(No cite)	Implatable infusion pumps.

(2) Life-sustaining or life-supporting devices used outside device user facilities.

21 CFR	Classification
868.2375	Breathing frequency monitors (apnea monitors) (including ventilatory efforts monitors).
868.5895	Continuous ventilator.
870.5300	DC-defibrillator and paddles.

(c) FDA designates the following devices as subject to tracking. Manufacturers must track these devices in accordance with this part.

21 CFR	Classification
878.3530	Silicone inflatable breast prosthesis.
878.3540	Silicone gel-filled breast prosthesis.
876.3750	Testicular prosthesis, silicone gel-filled.
(No cite)	Silicone gel-filled chin prosthesis.
(No cite)	Silicone gel-filled angel chik reflux valve.
878.5725	Infusion pumps (Electromechanical only).

(d) FDA, when responding to premarket notification submissions and approving premarket approval applications, will notify the sponsor that FDA believes the device meets the criteria of section 519(e)(1) of the act and therefore should be tracked. FDA will also, after notifying the sponsor, publish a notice in the **Federal Register** announcing that FDA believes that a new generic type of device is subject to tracking and soliciting comment on FDA's position. If the device is a new generic type of device not already on the example list above, FDA will add it to this list.

§ 821.25 Device tracking system and content requirements: manufacturer requirements

(a) A manufacturer of a tracked device shall adopt a method of tracking for each such type of device that the manufacturer distributes that enables it to provide FDA with the following information in writing for each tracked device distributed:

(1) Except as required by order under section 518(e) of the act, within 3 working days of a request from FDA, prior to the distribution of a tracked device to a patient, the name, address, and telephone number of the distributor, multiple distributor, or final distributor holding the device for distribution and the location of the device;

(2) Within 10 working days of a request from FDA for life-sustaining or life-supporting devices used outside a device user facility that are intended for use by a single patient over the life of the device and permanent implant that are tracked devices, after distribution to or implantation in a patient:

(i) The lot number, batch number, model number or serial number of the device, or other identifier necessary to provide for effective tracking of the devices;

(ii) The date the device was shipped by the manufacturer;

(iii) The name, address, telephone number, and social security number (if available) of the patient receiving the device;

(iv) The date the device was provided to the patient;

(v) The name, mailing address, and telephone number of the prescribing physician;

(vi) The name, mailing address, and telephone number of the physician regularly following the patient if

different than the prescribing physician; and

(vii) If applicable, the date the device was explanted and the name, mailing address, and telephone number of the explanting physician; the date of the patient's death; or the date the device was returned to the manufacturer, permanently retired from use, or otherwise permanently disposed of.

(3) Except as required by order under section 518(e) of the act, within 10 working days of a request from FDA for life-sustaining or life-supporting devices used outside device user facilities that are intended for use by more than one patient and that are tracked devices, after the distribution of the device to the multiple distributor:

(i) The lot model number, batch number, serial number of the device, or other identifier necessary to provide for effective tracking of the device;

(ii) The date the device was shipped by the manufacturer;

(iii) The name, address, and telephone number of the multiple distributor;

(iv) The name, address, telephone number, and social security number (if available) of the patient using the device;

(v) The location of the device;

(vi) The date the device was provided for use by the patient;

(vii) The name, address, and telephone number of the prescribing physician; and

(viii) If and when applicable, the date the device was returned to the manufacturer, permanently retired from use, or otherwise permanently disposed of.

(b) A manufacturer of a tracked device shall keep current records in accordance with its standard operating procedure of the information identified in paragraphs (a)(1), (a)(2) and (a)(3)(i) through (a)(3)(iv) of this section on each tracked device released for distribution for as long as such device is in use or in distribution for use.

(c) A manufacturer of a tracked device shall establish a written standard operating procedure for the collection, maintenance, and auditing of the data specified in paragraphs (a) and (b) of this section. A manufacturer shall make this standard operating procedure available to FDA upon request. A manufacturer shall incorporate the following into the standard operating procedure:

(1) Data collection and recording procedures, which shall include a procedure for recording when data which is required under this part is missing and could not be collected and the reason why such required data is missing and could not be collected;

(2) A method of recording all modifications or changes to the tracking system or to the data collected and maintained under the tracking system, reasons for any modification or change, and dates of any modification or change. Modification and changes included under this requirement include modifications to the data (including termination of tracking), the data format, the recording system, and the file maintenance procedures systems; and

(3) A quality assurance program that includes an audit procedure to be run for each device product subject to tracking, at not less than 6-month intervals for the first 3 years of distribution and at least once a year thereafter. This audit procedure shall provide for statistically relevant sampling of the data collected to ensure the accuracy of data and performance testing of the functioning of the tracking system.

(d) When a manufacturer becomes aware that a distributor, final distributor, or multiple distributor has not collected, maintained, or furnished any record or information required by this part, the manufacturer shall notify the FDA district office responsible for the area in which the distributor, final distributor, or multiple distributor is located of the failure of such persons to comply with the requirements of this part. Manufacturers shall have taken reasonable steps to obtain compliance by the distributor, multiple distributor, or final distributor in question before notifying FDA.

Subpart C—Additional Requirements and Responsibilities

§ 821.30 Tracking obligations of persons other than device manufacturers: distributor requirements.

(a) A distributor, final distributor, or multiple distributor of any tracked device shall, upon purchasing or otherwise acquiring any interest in such a device, promptly provide the manufacturer tracking the device with the following information:

(1) The name and address of the distributor, final distributor or multiple distributor;

(2) The lot number, batch number, model number, or serial number of the device, or other identifier used by the manufacturer to track the device;

(3) The date the device was received;

(4) The person from whom the device was received;

(5) If and then applicable, the date the device was explanted, the date of the patient's death, or the date the device was returned to the distributor, permanently retired from use, or otherwise permanently disposed of.

(b) A final distributor, upon sale or other distribution of a tracked device for use in or by the patient, shall promptly provide the manufacturer tracking the device with the following information:

(1) The name and address of the final distributor,

(2) The lot number, batch number, model number, or serial number of the device, or other identifier used by the manufacturer to track the device;

(3) The name, address, telephone number, and social security number (if available) of the patient receiving the device;

(4) The date the device was provided to the patient or for use in the patient;

(5) The name, mailing address, and telephone number of the prescribing physician;

(6) The name, mailing address, and telephone number of the physician regularly following the patient if different than the prescribing physician; and

(7) When applicable, the date the device was explanted and the name, mailing address, and telephone number of the explanting physician, the date of the patient's death, or the date the device was returned to the manufacturer, permanently retired from use, or otherwise permanently disposed of.

(c)(1) A multiple distributor shall keep written records of the following each time such device is distributed for use by a patient:

(i) The lot number, batch number, or model number, or serial number of the device, or other identifier used by the manufacturer to track the device;

(ii) The name, address, telephone number, and social security number (if available) of the patient using the device;

(iii) The location of the device;

(iv) The date the device was provided for use by the patient;

(vi) The name, address, and telephone number of the prescribing physician;

(iv) The name, address, and telephone number of the physician regularly following the patient if different than the prescribing physician; and

(vii) When applicable, the date the device was permanently retired from use or otherwise permanently disposed of.

(2) Except as required by order under section 518(e) of the act, any person who is a multiple distributor subject to the recordkeeping requirement of paragraph (c)(1) of this section shall, within 5 working days of a request from the manufacturer or within 10 working days of a request from FDA for the information identified in paragraph

(c)(1) of this section, provide such information to the manufacturer or FDA.

(3) A distributor, final distributor, or multiple distributor shall make any records required to be kept under this part available to the manufacturer of the tracked device for audit upon written request by an authorized representative of the manufacturer.

Subpart D—Records and Inspections

§ 821.50 Availability.

(a) Manufacturers, distributors, multiple distributors, and final distributors shall, upon the presentation by an FDA representative of official credentials and the issuance of Form FD 482 at the initiation of an inspection of an establishment or person under section 704 of the act, make each record and all information required to be collected and maintained under this part and all records and information related to the events and persons identified in such records available to FDA personnel.

(b) Records and information referenced in paragraph (a) of this section shall be available to FDA personnel for purposes of reviewing, copying, or any other use related to the enforcement of the act and this part. Records required to be kept by this part shall be kept within the United States.

§ 821.55 Confidentiality.

(a) Records and other information submitted to FDA under this part shall be protected from public disclosure to the extent permitted under part 20 of this chapter, and in accordance with § 20.63 of this chapter, information contained in such records that would identify patient or research subjects shall not be available for public disclosure except as provided in those parts.

(b) Patient names or other identifiers may be disclosed to a manufacturer or other person subject to this part or to a physician when the health or safety of the patient requires that such persons have access to the information. Such notification will be pursuant to agreement that the record or information will not be further disclosed except as the health aspects of the patient requires. Such notification does not constitute public disclosure and will not trigger the availability of the same information to the public generally.

§ 821.60 Retention of records.

Persons required to maintain records under this part shall maintain such records for the useful life of each tracked device they manufacture or distribute. The useful life of a device is the time a device is in use or in distribution for use. For example, a record may be retired if the person maintaining the record becomes aware of the fact that the device is no longer in use, has been explanted, returned to the manufacturer, or the patient has died.

David A. Kessler,

Commissioner of Food and Drugs.

Dated: May 26, 1992.

Louis W. Sullivan,

Secretary of Health and Human Services.

[FR Doc. 92–12622 Filed 5–27–92; 8:45 am]

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Part IX

Department of Health and Human Services

Food and Drug Administration

Statement of Policy: Foods Derived From New Plant Varieties; Notice

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 92N-0139]

Statement of Policy: Foods Derived From New Plant Varieties

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is issuing a policy statement on foods derived from new plant varieties, including plants developed by recombinant deoxyribonucleic acid (DNA) techniques. This policy statement is a clarification of FDA's interpretation of the Federal Food, Drug, and Cosmetic Act (the act), with respect to new technologies to produce foods, and reflects FDA's current judgment based on new plant varieties now under development in agricultural research. This action is being taken to ensure that relevant scientific, safety, and regulatory issues are resolved prior to the introduction of such products into the marketplace.

DATES: Written comments by August 27, 1992.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Regarding Human Food Issues: James H. Maryanski, Center for Food Safety and Applied Nutrition (HFF-300), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-485-3617. Regarding Animal Feed Issues: William D. Price, Center for Veterinary Medicine (HFV-221), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-295-8724.

SUPPLEMENTARY INFORMATION:

Table of Contents

I. Background and Overview of Policy

New methods of genetically modifying plants are being used to develop new varieties that will be sources of foods. These methods, including recombinant DNA techniques and cell fusion techniques, enable developers to make genetic modifications in plants, including some modifications that would not be possible with traditional plant breeding methods. This policy discusses the safety and regulatory status of foods derived from new plant varieties, including plants developed by the newer methods of genetic modification.

FDA has received numerous inquiries from industry, government agencies, academia, and the public requesting clarification of the regulatory status of foods, such as fruits, vegetables, grains and their byproducts, derived from new plant varieties developed using recombinant DNA techniques. The questions that FDA has received center on issues such as whether the agency will conduct premarket review of these new foods, whether such foods introduced into interstate commerce would be challenged by FDA on legal grounds, which new plant varieties might come under the jurisdiction of FDA, what scientific information may be necessary to satisfy FDA that such foods are safe and comply with the law, whether petitions would be required by the agency, and whether special labeling would be required.

Representatives of the food biotechnology industry have expressed to FDA the need for strong but appropriate oversight by Federal agencies to ensure public confidence in foods produced by the new techniques. FDA has received several specific comments and suggestions from the industry and from the public concerning Federal oversight of foods developed through new methods of genetically modifying plants (Refs. 1 through 4). The agency has considered these and other documents, including scientific research papers, in developing this notice, and is setting forth this policy statement to clarify its interpretation of the act with respect to human foods and animal feeds [1] derived from new plant varieties, [2] including but not limited to plants developed by new methods of genetic modification.[3]

Under this policy, foods, such as fruits, vegetables, grains, and their byproducts, derived from plant varieties developed by the new methods of genetic modification are regulated within the existing framework of the act, FDA's implementing regulations, and current practice, utilizing an approach identical in principle to that applied to foods developed by traditional plant breeding. The regulatory status of a food, irrespective of the method by which it is developed, is dependent upon objective characteristics of the food and the intended use of the food (or its components). The method by which food is produced or developed may in some cases help to understand the safety or nutritional characteristics of the finished food. However, the key factors in reviewing safety concerns should be the characteristics of the food product,

[1] "Food" means (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 (section 201(f) of the act (21 U.S.C. 321(f))). "Food" includes human food, substances migrating to food from food-contact articles, pet food, and animal feed (21 CFR 170.3(m)). "Animal feed" means "an article which is intended for use for food for animals or other than man and which is intended for use as a substantial source of nutrients in the diet of the animal, and is not limited to a mixture intended to be the sole ration of the animal" (section 201(x) of the act (21 U.S.C. 321(x)).

[2] "Variety" is used here as a general term to describe subgroups (whether varieties or cultivars) of plants within a species developed for desirable traits.

[3] "Genetic modification" means the alteration of the genotype of a plant using any technique, new or traditional. "Modification" is used in a broad context to mean the alteration in the composition of food that results from adding, deleting, or changing hereditary traits, irrespective of the method. Modifications may be minor, such as a single mutation that affects one gene, or major alterations of genetic material that affect many genes. Most, if not all, cultivated food crops have been genetically modified.

rather than the fact that the new methods are used.

The safety of a food is regulated primarily under FDA's postmarket authority of section 402(a)(1) of the act (21 U.S.C. 342(a)(1)). Unintended occurrences of unsafe levels of toxicants in food are regulated under this section. Substances that are expected to become components of food as result of genetic modification of a plant and whose composition is such or has been altered such that the substance is not generally recognized as safe (GRAS) or otherwise exempt are subject to regulation as "food additives" under section 409 of the act (21 U.S.C. 348). Under the act, substances that are food additives may be used in food only in accordance with an authorizing regulation.

In most cases, the substances expected to become components of food as a result of genetic modification of a plant will be the same as or substantially similar to substances commonly found in food, such as proteins, fats and oils, and carbohydrates. As discussed in more detail in section V.C., FDA has determined that such substances should be subject to regulation under section 409 of the act in those cases when the objective characteristics of the substance raise questions of safety sufficient to warrant formal premarket review and approval by FDA. The objective characteristics that will trigger regulation of substances as food additives are described in the guidance section of this notice (section VII.).

The guidance section also describes scientific considerations that are important in evaluating the safety and nutritional value of foods for consumption by humans or animals, regardless of whether the food is regulated under section 402(a)(1) or section 409 of the act. The guidance section outlines a "decision tree" approach to safety assessment of foods derived from new plant varieties that FDA believes is compatible with current practice among scientists knowledgeable in this area. The guidance section also identifies certain scientific questions that may raise sufficient safety concern to warrant consultation with FDA.

Finally, this notice addresses FDA's responsibility under the National Environmental Policy Act (NEPA) and the food labeling provisions of the act as such provisions affect labeling of foods derived from new plant varieties.

This policy statement reflects FDA's current judgment based on the new plant varieties now under development in agricultural research. FDA invites comments on this document. Because scientific developments in this field are occurring rapidly, FDA will refine its policy, if circumstances warrant, in a future **Federal Register** notice. Additionally, FDA plans to announce in a future **Federal Register** notice a workshop to discuss specific scientific issues. FDA invites comment on topics that might be addressed at such a workshop.

II. Responsibility for Food Safety

FDA is the primary Federal agency responsible for ensuring the safety of commerical food and food additives, except meat and poultry products. FDA works closely on food safety matters with the U.S. Department of Agriculture (USDA), which regulates meat and poultry products, and with the U.S. Environmental Protection Agency (EPA), which regulates pesticides and sets tolerances for pesticide residues in food. FDA's authority is under the act, the Public Health Service Act, and FDA's implementing regulations codified in title 21 of the CFR. The act gives FDA broad authority to initiate legal action against a food that is adulterated or misbranded within the meaning of the act.

Producers of new foods have an obligation under the act to ensure that the foods they offer consumers are safe and in compliance with applicable legal requirements. Because in some cases the regulatory jurisdiction of a new food product including those produced using innovative methods may not be clear, producers can informally consult with FDA prior to marketing new foods to ensure that the safety and regulatory status of a new food is properly resolved.

Elsewhere in this issue of the **Federal Register**, FDA announces the filing of the first request by a producer for consultation with FDA concerning a new plant variety developed by recombinant DNA techniques. The request submitted by Calgene, Inc., (Calgene) concerns the FLAVR SAVR™ tomato, a new variety claimed to exhibit improved fruit ripening and other properties. Because Calgene made this request prior to the finalization of this policy statement, FDA advised the firm to submit the information about the tomato initially as a request for advisory opinion under § 10.85 (21 CFR 10.85) to permit the agency to consider the status of the new variety, and to utilize an evaluation process that is open to public comment and permits the agency to make its decision known to the public. Future requests for FDA consultation should be made consistent with the principles outlined in this notice. Thus, FDA does not anticipate that future requests of this nature will be filed under § 10.85

III. Scope of This Document

This notice discusses scientific and regulatory considerations for foods derived from new plant varieties. This notice does not address foods and food ingredients regulated by FDA that have been derived from algae, microorganisms, and other nonplant organisms, including: (1) Foods produced by fermentation, where microorganisms are essential components of the food (e.g., yogurt and single cell protein); (2) food ingredients produced by fermentation, such as many enzymes, flavors, amino acids, sweeteners, thickeners, antioxidants, preservatives, colors, and other substances; (3) substances produced by new plant varieties whose purpose is to color food, and (4) foods derived from animals that are subject to FDA's authority, including seafood. FDA is considering whether to address these issues in future **Federal Register** notices.

Finally, the principles discussed in this notice do not apply to "new drugs" as defined by section 201 (p) of the act (21 U.S.C. 321(p)), "new animal drugs" as defined by section 201(w) of the act (21 U.S.C. 321(w)), or to "pesticide chemicals" as defined by section 201(q) of the act. As discussed in section IX., EPA is responsible for pesticide chemicals, including those produced in plants as a result to genetic modification.

IV. Scientific Issues Relevant to Public Health

Plant breeding is the science of combining desirable genetic traits into a variety that can be used in agriculture. The desired traits can be broadly divided into two classes: Those that affect agronomic characteristics of the plant, and those that affect quality characteristics of the food. Agronomic characteristics include those affecting yield; resistance to diseases, insects, and herbicides; and ability to thrive under various adverse environmental conditions. Quality characteristics include those affecting processing, preservation, nutrition, and flavor.

The genetic modification techniques used to develop new plant varieties constitute a continuum. Traditional breeding typically consists of hybridization between varieties of the same species and screening for progeny with desired characteristics. Such hybridizations only can introduce traits found in close relatives. Breeders have developed or adopted a number of techniques to expand the range of

genetic variation available to them. These techniques introduce variation either by using mutagenesis to alter the genome or by introducing or modifying DNA segments, including DNA segments derived from other organisms.

Mutagenic techniques include both random mutagenesis, resulting from treatment with chemical and physical mutagens, and somaclonal variation, whereby, with the use of tissue culture techniques, plants are regenerated from callus or leaf tissue explants. The regenerated plants often have properties not found in the progenitor plant, reflecting both preexisting cellular genetic differences and tissue-culture induced mutations. The mutations range from single gene changes to chromosomal rearrangements. Mutagenesis techniques are limited, however, by their inability to target a desired trait. Somaclonal variants also frequently are unstable or infertile.

Techniques for gene transfer between plants that belong to different species or genera fall under the general heading of "wide crosses." These "crosses" have been accomplished using hybridization, and protoplast fusion. Traditional wide crosses involve hybridization between closely related species or genera, frequently requiring the use of special techniques such as embryo rescue and chromosome doubling to overcome physical or genetic barriers to the production of fertile progeny. They permit the transfer of genetic traits that are not present in close relatives of the modern plant varieties but are found in more distant wild relatives. Traits that confer resistance to a number of diseases have been introduced this way.

All of the techniques described above require extensive back crossing with the parent line [4] to eliminate mutations unlinked to that responsible for the desired phenotype and undesirable traits in extraneous genetic material introduced along with that encoding the desired trait.

Recombinant DNA techniques involve the isolation and subsequent introduction of discrete DNA segments containing the gene(s) of interest into recipient (host) plants. The DNA segments can come from any organism (microbial, animal, or plant). In theory, essentially any trait whose gene has been identified can be introduced into virtually any plant, and can be introduced without extraneous unwanted genetic material. Since these techniques are more precise, they increase the potential for safe, better-characterized, and more predictable foods.

DNA segments introduced using the new techniques insert semi-randomly into the chromosome, frequently in tandem multiple copies, and sometimes in more than one site on the chromosome. Both the number of copies of the gene and its location in the chromosome can affect its level of expression, as well as the expression of other genes in the plant. To ensure homozygosity and to enhance the stability of the line and the ability to cross the trait into other lines, the breeder will often perform a limited number of back crosses to ensure that the plant line has the new trait inserted in only one location in the chromosome.

Additionally, as with other breeding techniques, the phenotypic effects of a new trait may not always be completely predictable in the new genetic background of the host. Therefore, it is common practice for breeders using recombinant DNA techniques to cross the new trait into a number of hosts to find the best genetic background for expression of the new trait. Currently, for most crops only a few lines or varieties of any species are amendable to the use of recombinant DNA techniques. Once the desired trait is introduced into a line amenable to the technique, it must then be crossed by traditional means to other desired lines or varieties.

Regardless of the particular combination of techniques used, the development of a new plant variety typically will require many site-years (number of sites x number of years of plant testing) of performance trials before introduction into agricultural practice. These range from as few as 10 to 20 site-years for some plants to 75 to 100 site-years for others (some 5 to 10 years). The time of evaluation and the size and number of sites will vary as necessary to confirm performance; to reveal vulnerabilities to pests, diseases, or other production hazards; to evaluate stability of the phenotype; to evaluate characteristics of the food; to evaluate environmental effects; and to produce the required amount of seed before the new plant variety can be grown commercially by farmers. In the course of this intensive assessment, individual plants exhibiting undesirable traits are eliminated.

Recombinant DNA techniques are used to achieve the same types of goals as traditional techniques: The development of new plant varieties with enhanced agronomic and quality characteristics. Currently, over 30 different agricultural crops developed using recombinant DNA techniques are in field trials. Food crops have been developed using these techniques to exhibit improved resistance to pests and disease and to chemical herbicides. For example, a plant's ability to resist insect infestation reportedly has been improved by transferring bacterial genetic material that encodes proteins toxic to certain insects (e.g., *Bacillus thuringiensis delta* endotoxin). Other plants have been given viral coat-protein genes that confer cross-protection to viral pathogens.

Other new plant varieties have been developed that exhibit traits for improved food processing, improved nutritional content, or enhanced protection against adverse weather conditions. For example, genetic modifications of plant enzymes involved in fruit ripening may yield tomatoes with improved ripening characteristics, texture, and flavor. Scientists have used recombinant DNA techniques to transfer genetic material for the production of seed storage protein conferring improvements in nutritional balance of important amino acids in the new plant varieties. Scientists have also identified genes in certain fish that encode proteins that conferee increased resistance to cold. Copies of these genes have been introduced into agricultural crops with the goal of producing new plant varieties that show improved tolerance to cold weather conditions.

These examples illustrate only a few of the many improved agronomic and food processing traits currently being introduced into plants using recombinant DNA techniques. Any genetic modification technique has the potential to alter the composition of food in a manner relevant to food safety, although, based on experience, the likelihood of a safety hazard is typically very low. The following paragraphs describe some potential changes in composition that may require evaluation to assure food safety.

A. Unexpected Effects

Virtually all breeding techniques have potential to create unexpected (including pleiotropic [5] effects. For example, mutations unrelated to the desired modification may be induced; undesirable traits may be introduced along with the desired traits; newly introduced DNA may physically insert into a transcriptionally active site on the chromosome, and may thereby inactivate a host gene or alter control of

[4] A line is a group of individuals from a common ancestry. It is a more narrowly defined group than a variety. (Breeding Field Crops, J.M. Poehlman, Van Nostrand Reinhold, New York, 1987.

[5] Pleiotropic effects refer to multiple effects resulting from a single genetic change.

its expression; the introduced gene product or a metabolic product affected by the genetic change may interact with other cellular products to produce a deleterious effect. Plant breeders using well established practices have successfully identified and eliminated plants that exhibit unexpected, adverse traits prior to commercial use.

B. Known Toxicants

Plants are known to produce naturally a number of toxicants and antinutritional factors, such as protease inhibitors, hemolytic agents, and neurotoxins, which often serve the plant as natural defense compounds against pests or pathogens. For example, most cereals contain protease inhibitors, which can diminish the nutritive value of proteins. Many legumes contain relatively high levels of lectins and cyanogenic glycosides. Lectins, if not destroyed by cooking or removed by soaking, can cause severe nausea, vomiting, and diarrhea. Cyanogenic glycosides can be hydrolyzed by specific enzymes in the plant to release cyanide if food from the plant is improperly prepared. The levels of cyanogenic glycosides in cassava and some legumes can lead to death or chronic neurological disease if these foods are eaten uncooked. Cruciferae contain glucosinolates which may impair thyroid function. Squash and cucumber contain cucurbiticin, an acute toxicant. Chickpeas contain lathyrogens, which are neurotoxins.

Many of these toxicants are present in today's foods at levels that do not cause acuate toxicity. Others, such as in cassava and some legumes, are high enough to cause severe illness or death if the foods are not properly prepared. FDA seek to assure that new plant varieties do not have significantly higher levels of toxicants than present in other edible varieties of the same species.

Plants, like other organisms, have metabolic pathways that no longer function due to mutations that occurred during evolution. Products or intermediates of some such pathways may include toxicants. In rare cases, such silent pathways may be activated by mutations, chromosomal rearrangements, or new regulatory regions introduced during breeding, and toxicants hitherto not associated with a plant species may thereby be produced. Similarly, toxicants ordinarily produced at low levels in a plant may be produced at high levels in a new variety as a result of such occurrences. The likelihood of activation of quiescent pathways or increased expression from active pathways is considered extremely low in food plants with a long history of use that have never exhibited production of unknown or unexpected toxins, since the genetic changes that can lead to such events occur during growth and are induced with traditional breeding manipulations. In the few cases where toxicants have been raised to unsafe levels in a commercial plant variety, the toxicants were known to occur in significant levels in one of the parent species. Except in rare cases, plant breeders using well established practices have successfully identified and eliminated plants that express unacceptably high levels of toxicants prior to commercial use.

C. Nutrients

Another unintended consequence of genetic modification of the plant may be a significant alteration in levels of important nutrients. In addition, changes in bioavailability of a nutrient due to changes in form of the nutrient or the presence of increased levels of other constituents that affect absorption or metabolism of nutrients must be considered for potential nutritional impact.

D. New Substances

Because plant breeders using the new techniques are able to introduce essentially any trait or substance whose molecular genetic identity is known into virtually any plant, it is possible to introduce a protein that differs significantly in structure or function, or to modify a carbohydrate, fat or oil, such that it differs significantly in composition from such substances currently found in food.

E. Allergenicity

All food allergens are proteins. However, only a small fraction of the thousands of proteins in the diet have been found to be food allergens. FDA's principal concern regarding allergencity is that proteins transferred from one food source to another, as is possible with recombinant DNA and protoplast fusion techniques, might confer on food from the host plant the allergenic properties of food from the donor plant. Thus, for example, the introduction of a gene that encodes a peanut allergen into corn might make that variety of corn newly allergenic to people ordinarily allergic to peanuts.

Examples of foods that commonly cause an allergenic response are milk, eggs, fish, crustacea, molluscs, tree nuts, wheat, and legumes (particularly peanuts and soybeans). The sensitive population is ordinarily able to identify and avoid the offending food. However, if the allergen were moved into a variety of a plant species that never before produced that allergen, the susceptible population would not know to avoid food from that variety.

In some foods that commonly cause an allergic response, the particular protein(s) responsible for allergenicity is known, and therefore the producer may know whether the transferred protein is the allergen. However, in other cases, the protein responsible for a food's allergenicity is not known, and FDA considers it prudent practice for the producer initially to assume that the transferred protein is the allergen. Appropriate in vitro or in vivo allergenicity testing may reveal whether food from the new variety elicits an allergenic response in the potentially sensitive population (i.e., people sensitive to the food in which the protein is ordinarily found). Producers of such foods should discuss allergenicity testing protocol requirements with the agency. Labeling of foods newly containing a known or suspect allergen may be needed to inform consumers of such potential.

A separate issue is whether any new protein in food has the potential to be allergenic to a segment of the population. At this time, FDA is unaware of any practical method of predict or assess the potential for new proteins in food to induce allergenicity and requests comments on this issue.

F. Antibiotic Resistance Selectable Markers

In gene transfer experiments, only a small percentage of the recipient plant cells will actually take up the introduced genes, and many desirable traits (i.e., those that specify the intended technical effect) are not easy to detect before the plant has fully developed. Scientists, therefore, enhance their ability to isolate plant cells that have taken up and stably incorporated the desired genes by physically linking the desired gene to a selectable marker gene, such as a gene that specifies the production of a substance that inactivates antibiotics.

The kanamycin resistance gene is one of the most widely used selectable marker genes. The kanamycin resistance gene specifies the information for the production of the enzyme, aminoglycoside 3'-phosphotransferase II. The common name for this enzyme is kanamycin (or neomycin) phosphotransferase II. The kanamycin phosphotransferase II enzyme modifies aminoglycoside antibiotics, including kanamycin, neomycin, and geneticin (G418), chemically inactivating the antibiotic and rendering the cells that produce the kanamycin resistance gene product refractory or resistant to the

antibiotic. Plant cells that have received and stably express the kanamycin resistance gene survive and replicate on laboratory media in the presence of the antibiotic, kanamycin. Plant cells that did not take up and express the introduced kanamycin resistance gene will be killed by the antibiotic. By linking the selectable marker gene to another gene that specifies a desired trait, scientists can identify and select plants that have taken up and express the desired genes.

The kanamycin resistance gene has been used as a selectable marker in more than 30 crops to develop varieties that exhibit improved nutritional and processing properties, resistance to pests and diseases, tolerance to chemical herbicides, and other agronomic properties. Once the desired plant variety has been selected, the kanamycin resistance gene serves no further useful purpose, although it continues to produce the kanamycin phosphotransferase II enzyme in the plant tissues. Thus, while the kanamycin resistance gene is a research tool that is important for developing new plant varieties through the current recombinant DNA techniques of gene transfer, both the kanamycin resistance gene and its product, the kanamycin phosphotransferase II enzyme protein, are expected to be present in foods derived from such plants, unless removed through recently developed techniques (Ref. 5).

Selectable marker genes that produce enzymes that inactivate clinically useful antibiotics theoretically may reduce the therapeutic efficacy of the antibiotic when taken orally if the enzyme in the food inactives the antibiotic. FDA believes that it will be important to evaluate such concerns with respect to commercial use of antibiotic resistance marker genes in food, especially those that will be widely used. FDA is now evaluating this and other issues with respect to the use of the kanamycin resistance marker in food. (See 56 FR 20004, May 1, 1991.)

G. Plants Developed to Make Specialty Nonfood Substances

New genetic modification techniques may develop plants that produce nonfood chemicals, such as polymers and pharmaceuticals. In many cases, the plant will not subsequently be used for food. In such cases, the developer must ensure that food-use varieties of the crop do not cross with or become mixed with the nonfood-use varieties. This is not a new issue for breeders and growers. For example, some varieties of rapeseed oil are grown for industrial oil use, and have high levels of toxicants, such as erucic acid and glucosinylates, while other varieties are grown for food use and have low levels of these substances. Similarly, potatoes grown for industrial uses can have higher levels of solanine than those grown for retail food use. The producer of the oil or potato must ensure that the edible plant variety is not adulterated within the meaning of the act. Developers of crops designed to produce specialty nonfood substances have a comparable obligation.

If plants (or materials derived from plants) used to make nonfood chemicals are also intended to be used for food, producers should consult with FDA to determine whether the nonfood chemical would be a food additive requiring an authorizing regulation prior to marketing for food use.

H. Issues Specific to Animal Feeds

Unlike a food in the human diet, an animal feed derived from a single plant may constitute a significant portion of the animal diet. For instance, 50 to 75 percent of the diet of most domestic animals consists of field corn. Therefore, a change in nutrient or toxicant composition that is considered insignificant for human consumption may be a very significant change in the animal diet.

Further, animals consume plants, plant parts, and plant byproducts that are not consumed by humans. For example, animals consume whole cottonseed meal, whereas humans consume only cotton seed oil. Gossypol, a plant toxicant, is concentrated in the cotton seed meal during the production of cotton seed oil. Because plant byproducts represent an important feed source for animals, it is important to determine if significant concentrations of toxicants or other harmful plant constituents are present in new plant varieties.

Nutrient composition and availability of nutrients in feed are important safety considerations for animal health. For example, if a genetic modification in soybeans caused an increase in phytin content, the soybean feed may need to be supplemented with phosphorous to avoid problems of animal health.

V. Regulatory Status of Foods Derived From New Plant Varieties

A. The Statutory Framework for New Foods and Food Ingredients

The United States today has a food supply that is as safe as any in the world. Most foods derived from plants predate the establishment of national food laws, and the safety of these foods has been accepted based on extensive use and experience over many years (or even centuries). Foods derived from new plant varieties are not routinely subjected to scientific tests for safety, although there are exceptions. For example, potatoes are generally tested for the glycoalkaloid, solanine. The established practices that plant breeders employ in selecting and developing new varieties of plants, such as chemical analyses, taste testing, and visual analyses, rely primarily on observations of quality, wholesomeness, and agronomic characteristics. Historically, these practices have proven to be reliable for ensuring food safety. The knowledge from this past experience coupled with safe practices in plant breeding has contributed to continuous improvements in the quality, variety, nutritional value, and safety of foods derived from plants modified by a range of traditional and increasingly sophisticated techniques (Ref. 1 at xvi). Based on this record of safe development of new varieties of plants, FDA has not found it necessary to conduct, prior to marketing, routine safety reviews of whole foods derived from plants.

Nevertheless, FDA has ample authority under the act's food safety provisions to regulate and ensure the safety of foods derived from new plant varieties, including plants developed by new techniques. This includes authority to require, where necessary, a premarket safety review by FDA prior to marketing of the food. Under section 402(a)(1) of the act, a food is deemed adulterated and thus unlawful if it bears or contains an added poisonous or deleterious substance that may render the food injurious to health or a naturally occurring substance that is ordinarily injurious. Section 402(a)(1) of the act imposes a legal duty on those who introduce food into the market place, including food derived from new crop varieties, to ensure that the food satisfies the applicable safety standard. Foods that are adulterated under section 402(a)(1) of the act are subject to the full range of enforcement measures under the act, including seizure, injunction, and criminal prosecution of those who fail to meet their statutory duty.

FDA has relied almost exclusively on section 402(a)(1) of the act to ensure the safety of whole foods. Toxins that occur naturally in food and that render the food ordinarily injurious to health (such as poisons in certain mushrooms), and thus adulterated, rarely required FDA regulatory action because such cases are typically well known and carefully avoided by food producers.

FDA regards any substance that is not an inherent constituent of food or whose level in food has been increased by human intervention to be "added" within the meaning of section 402(a)(1) of the act. See *United States* v. *Anderson Seafoods, Inc.*, 622 F. 2d 157 (5th Cir. 1980). Added substances are subject to the more stringent "may render [the food] injurious" safety standard. Under this standard, the food is adulterated if, by virtue of the presence of the added substance, there is a "reasonable possibility" that consumption of the food will be injurious to health. *United States* v. *Lexington Mill & Elevator Co.*, 232 U.S. 399 (1914). The "may render injurious" standard would apply to a naturally occurring toxin in food if the level of the toxin in a new plant variety were increased through traditional plant breeding or some other human intervention. Section 402(a)(1) of the act would have been the legal basis under which FDA could have blocked marketing in the 1970's of a new variety of potato that had been found during its development to contain elevated and potentially harmful levels of solanine as a result of a cross with an inedible wild potato.

Section 402(a)(1) of the act is most frequently used by FDA to regulate the presence in food of unavoidable environmental contaminants such as lead, mercury, dioxin, and aflatoxin. FDA regulary establishes action levels and takes enforcement action to prevent the sale of foods that contain unacceptable levels of such unintended and undesired contaminants.

Section 402(a)(1) of the act was signed into law in 1938 and has its origins in a similar provision in the Federal Food and Drugs Act of 1906. Until 1958, this authority was the principal tool relied upon by FDA to regulate the safety of food and food ingredients. In 1958, in response to public concern about the increased use of chemicals in foods and food processing and with the support of the food industry, Congress enacted the Food Additives Amendment (the amendment) to the act. Among other provisions, the amendment established a premarket approval requirement for "food additives." The basic thrust of the amendment was to require that, before a new chemical additive (such as a preservative, antioxidant, emulsifier, or artificial flavor) could be used in food processing, its producer must demonstrate the safety of the additive to FDA. Congress recognized under this new scheme that the safety of an additive could not be established with absolute certainty or under all conditions of use. Congress thus provided for a science-based safety standard that requires producers of food additives to demonstrate to a reasonable certainty that no harm will result from the intended use of the additive. See 21 CFR 170.3(i). If FDA finds an additive to be safe, based ordinarily on data submitted by the producer to the agency in a food additive petition, the agency promulgates a regulation specifying the conditions under which the additive may be safely used. Food additives that are not the subject of such a regulation are deemed unsafe as a matter of law, and the foods containing them are adulterated under section 402(a)(2)(C) of the act (21 U.S.C. 342(a)(2)(C)) and are thus unlawful.

In enacting the amendment, Congress recognized that many substances intentionally added to food do not require a formal premarket review by FDA to assure their safety, either because their safety had been established by a long history of use in food or because the nature of the substance and the information generally available to scientists about the substance are such that the substance simply does not raise a safety concern worthy of premarket review by FDA. Congress thus adopted a two-step definition of "food additive." The first step broadly includes any substance the intended use of which results in its becoming a component of food. The second step, however, excludes from the definition of food additive substances that are GRAS. It is on the basis of the GRAS exception of the "food additive" definition that many ingredients derived from natural sources (such as salt, pepper, vinegar, vegetable oil, and thousands of spices and natural flavors), as well as a host of chemical additives (including some sweeteners, preservatives, and artificial flavors), are able to be lawfully marketed today without having been formally reviewed by FDA and without being the subject of a food additive regulation. The judgment of Congress was that subjecting every intentional additive to FDA premarket review was not necessary to protect public health and would impose an insurmountable burden on FDA and the food industry.

Congress' approach to defining food additives means, however, that companies developing new ingredients, new versions of established ingredients, or new processes for producing a food or food ingredient must make a judgment about whether the resulting food substance is a food additive requiring premarket approval by FDA. In many cases, the answer is obvious, such as when the ingredient is a man made chemical having no widely recognized history of safe use in food. Such an ingredient must be approved prior to its use by the issuance of a food additive regulation, based on information submitted to FDA in a food additive petition.

In other cases, the answer is less obvious, such as when an established ingredient derived from nature is modified in some minor way or produced by a new process. In such cases, the manufacturer must determine whether the resulting ingredient still falls within the scope of any existing food additive regulation applicable to the original ingredient or whether the ingredient is exempt from regulation as a food additive because it is GRAS. The GRAS status of some substances is recognized in FDA's regulations (21 CFR parts 182, 184, 186, 582, and 584), but FDA has not attempted to include all GRAS substances in its regulations.

FDA has traditionally encouraged producers of new food ingredients to consult with FDA when there is a question about an ingredient's regulatory status, and firms routinely do so, even though such consultation is not legally required. If the producer begins to market the ingredient based on the producer's independent determination that the substance is GRAS and FDA subsequently concludes the substance is not GRAS, the agency can and will take enforcement action to stop distribution of the ingredient and foods containing it on the ground that such foods are or contain an unlawful food additive.

FDA considers the existing statutory authority under sections 402(a)(1) and 409 of the act, and the practical regulatory regime that flows from it, to be fully adequate to ensure the safety of new food ingredients and foods derived from new varieties of plants, regardless of the process by which such foods and ingredients are produced. The existing tools provide this assurance because they impose a clear legal duty on producers to assure the safety of foods they offer to consumers; this legal duty is backed up by strong enforcement powers; and FDA has authority to require premarket review and approval in cases where such review is required to protect public health.

In the **Federal Register** of June 26, 1986 (51 FR 23302) (the June 1986 notice), FDA, in conjunction with the Office of Science and Technology Policy in the Executive Office of the President, described FDA's current food safety authorities and stated the agency's intention to regulate foods produced by

new methods, such as recombinant DNA techniques, within the existing statutory and regulatory framework. This notice reaffirms that intention. The following paragraphs explain briefly how the current framework will apply specifically to foods derived from new plant varieties, including plants developed by recombinant DNA techniques.

B. The Application of Section 402(a)(1) of the Act

Section 402(a)(1) of the act will continue to be FDA's primary legal tool for regulating the safety of whole foods, including foods derived from plants genetically modified by the new techniques. Section 402(a)(1) of the act will be applied to any substance that occurs unexpectedly in the food at a level that may be injurious to health. This includes a naturally occurring toxicant whose level is unintentionally increased by the genetic modification, as well as an unexpected toxicant that first appears in the food as a result of pleiotropic effects. Such substances are regarded by FDA as added substances whose presence adulterates the food if present at a level that "may render" the food injurious to health.

It is the responsibility of the producer of a new food to evaluate the safety of the food and assure that the safety requirement of section 402(a)(1) of the act is met. In section VII., FDA provides guidance to the industry regarding prudent, scientific approaches to evaluating the safety of foods derived from new plant varieties, including the safety of the added substances that are subject to section 402(a)(1) of the act. FDA encourages informal consultation between producers and FDA scientists to ensure that safety concerns are resolved. However, producers remain legally responsible for satisfying section 402(a)(1) of the act, and they will continue to be held accountable by FDA through application of the agency's enforcement powers.

C. The Application of Section 409 of the Act

When Congress enacted the amendment in 1958, it did not explicitly address the possible application of the food additive approval process to foods derived from new plant varieties. As previously discussed, such foods have historically been regulated successfully under section 402(a)(1) of the act. The new methods of genetic modification have focused attention, however, on the possibility that intended changes in the composition of food resulting from genetic modification might be of a nature sufficient as a legal and public health matter to trigger regulation of a component of the food under section 409 of the act.

As discussed above, the food additive definition broadly encompasses any substance that has an intended use in food, unless the substance is GRAS. It was on this basis that the June 1986 notice indicated that, in some cases, whole foods derived from new plant varieties, including plants developed by new genetic modification techniques, might fall within the scope of FDA's food additive authority. Indeed, FDA's regulations have long recognized that it might be appropriate in some circumstances to review the GRAS (and implicitly food additive) status of foods or substances of natural biological origin that have a history of safe use but which subsequently have had "significant alteration by breeding and selection." (See 21 CFR 170.30(f).) As already discussed, however, FDA has rarely had occasion to review the GRAS status of foods derived from new plant varieties because these foods have been widely recognized and accepted as safe.

FDA has reviewed its position on the applicability of the food additive definition and section 409 of the act to foods derived from new plant varieties in light of the intended changes in the composition of foods that might result from the newer techniques of genetic modification. The statutory definition of "food additive" makes clear that it is the intended or expected introduction of a substance into food that makes the substance potentially subject to food additive regulation. Thus, in the case of foods derived from new plant varieties, it is the transferred genetic material and the intended expression product or products that could be subject to food additive regulation, if such material or expression products are not GRAS.

In regulating foods and their byproducts derived from new plant varieties, FDA intends to use its food additive authority to the extent necessary to protect public health. Specifically, consistent with the statutory definition of "food additive" and the overall design of FDA's current food safety regulatory program, FDA will use section 409 of the act to require food additive petitions in cases where safety questions exist sufficient to warrant formal premarket review by FDA to ensure public health protection.

With respect to transferred genetic material (nucleic acids), generally FDA does not anticipate that transferred genetic material would itself be subject to food additive regulation. Nucleic acids are present in the cells of every living organism, including every plant and animal used for food by humans or animals, and do not raise a safety concern as a component of food. In regulatory terms, such material is presumed to be GRAS. Although the guidance provided in section VII. calls for a good understanding of the identity of the genetic material being transferred through genetic modification techniques, FDA does not expect that there will be any serious question about the GRAS status of transferred genetic material.

FDA expects that the intended expression product or products present in foods derived from new plant varieties will typically be proteins or substances produced by the action of protein enzymes, such as carbohydrates, and fats and oils. When the substance present in the food is one that is already present at generally comparable or greater levels in currently consumed foods, there is unlikely to be a safety question sufficient to call into question the presumed GRAS status of such naturally occurring substances and thus warrant formal premarket review and approval by FDA. Likewise, minor variations in molecular structure that do not affect safety would not ordinarily affect the GRAS status of the substances and, thus, would not ordinarily require regulation of the substance as a food additive.

It is possible, however, that the intended expression product in a food could be a protein, carbohydrate, fat or oil, or other substance that differs significantly in structure, function, or composition from substances found currently in food. Such substances may not be GRAS and may require regulation as a food additive. For example, if a food derived from a new plant variety contains a novel protein sweetener as a result of the genetic modification of the plant, that sweetener would likely require submission of a food additive petition and approval by FDA prior to marketing. FDA invites comments on substances, in addition to proteins, carbohydrates, and fats and oils, that in the future may be introduced into foods by genetic modification.

Section VII. of this notice provides guidance to producers of new foods for conducting safety evaluations. This guidance is intended to assist producers in evaluating the safety of the food that they market, regardless of whether the food requires premarket approval by FDA. This guidance also includes criteria and analytical steps that producers can follow in determining whether their product is a candidate for food additive regulation and whether consultation with FDA should be pursued to determine the regulatory

status of the product. Ultimately, it is the food producer who is responsible for assuring safety.

FDA has long regarded it to be a prudent practice for producers of foods using new technologies to work cooperatively with the agency to ensure that the new products are safe and comply with applicable legal requirements. It has been the general practice of the food industry to seek informal consultation and cooperation, and this practice should continue with respect to foods produced using the newer techniques of genetic modification.

VI. Labeling

FDA has received several inquiries concerning labeling requirements for foods derived from new plant varieties developed by recombinant DNA techniques. Section 403(i) of the act (21 U.S.C. 343(i)) requires that a producer of a food product describe the product by its common or usual name or in the absence thereof, an appropriately descriptive term (21 U.S.C. part 101.3) and reveal all facts that are material in light of representations made or suggested by labeling or with respect to consequences which may result from use (21 U.S.C. 343(a); 21 U.S.C. 321(n)). Thus, consumers must be informed, by appropriate labeling, if a food derived from a new plant variety differs from its traditional counterpart such that the common or usual name no longer applies to the new food, or if a safety or usage issue exists to which consumers must be alerted.

For example, if a tomato has had a peanut protein introduced into it and there is insufficient information to demonstrate that the introduced protein could not cause an allergic reaction in a susceptible population, a label declaration would be required to alert consumers who are allergic to peanuts so they could avoid that tomato, even if its basic taste and texture remained unchanged. Such information would be a material fact whose omission may make the label of the tomato misleading under section 403(a) of the act (21 U.S.C. 343(a)).

FDA has also been asked whether foods developed using techniques such as recombinant DNA techniques would be required to bear special labeling to reveal that fact to consumers. To date, FDA has not considered the methods used in the development of a new plant variety (such as hybridization, chemical or radiation-induced mutagenesis, protoplast fusion, embryo rescue, somaclonal variation, or any other method) to be material information within the meaning of section 201(n) of the act (21 U.S.C. 321(n)). As discussed above, FDA believes that the new techniques are extensions at the molecular level of traditional methods and will be used to achieve the same goals as pursued with traditional plant breeding. The agency is not aware of any information showing that foods derived by these new methods differ from other foods in any meaningful or uniform way, or that, as a class, foods developed by the new techniques present any different or greater safety concern than foods developed by traditional plant breeding. For this reason, the agency does not believe that the method of development of a new plant variety (including the use of new techniques including recombinant DNA techniques) is normally material information within the meaning of 21 U.S.C. 321(n) and would not usually be required to be disclosed in labeling for the food.

The guidance section (section VII.) of this notice discusses certain circumstances where questions may arise about the proper labeling of foods derived from new plant varieties. FDA requests comments on the labeling of foods derived from new plant varieties, including plants developed with recombinant DNA techniques.

VII. Guidance to Industry for Foods Derived From New Plant Varieties

A. Introduction

This guidance section describes many of the scientific considerations for evaluating the safety and nutritional aspects of food from new plant varieties derived by traditional methods (such as hybridization or mutagenesis), tissue culture methods (such as somaclonal variation and protoplast fusion), and recombinant DNA methods. Although some of the safety considerations are specific to individual technologies, many safety considerations are similar regardless of the technology used. This guidance section does not attempt to delineate acceptable practices for each specific technology. FDA expects plant breeders to adhere to currently accepted scientific standards of practice within each technology. This guidance section is based on existing practices followed by the traditional plant breeders to assess the safety and nutritional value of new plant varieties and is not intended to alter these long-established practices, or to create new regulatory obligations for them.

This guidance section describes food safety and nutritional concerns, rather than performance characteristics for which the new plant varieties may have been developed. However, this guidance section cannot identify all safety and nutritional questions that could arise in a given situation and, while comprehensive, should not be viewed as exhaustive. In some cases, additional factors may need to be considered, while in other situations, some of the factors may not apply. Therefore, this guidance section also describes situations in which producers should consult with FDA on scientific issues, the design of appropriate test protocols, requirements for labeling, and whether a food additive petition may be required.

Genetic modifications of plants can have unintended or unexpected effects on the phenotype of the plant, such as poor growth or reduced tolerance to conditions of environmental stress, that are readily apparent and can be effectively managed by appropriate selection procedures. However, effects such as an alteration in the concentration of important nutrients, increases in the level of natural toxicants, or the transfer of allergens from one species to another may not be readily detected without specific test procedures. FDA believes that a scientific basis should exist to establish that new plant varieties do not exhibit unacceptable effects with respect to toxicants, nutritional value, or allergens. In cases where the host plant has little or no history of safe use, the assessment of new plant varieties should include evidence that unknown toxicants are not present in the new plant variety at levels that would be injurious to health.

In addition, by using recombinant DNA techniques, plant breeders are now capable theoretically of introducing essentially any trait (and thus substance) whose molecular genetic identity is known into virtually any plant due to the increased power and precision of recombinant DNA techniques. This guidance section, however, discusses only proteins, carbohydrates, and fats and oils, in the belief that these are the principal substances that are currently being intentionally modified or introduced into new plant varieties. Using the new techniques, it is possible to introduce a gene that encodes a protein that differs significantly in structure or function, or to modify a carbohydrate, or fat or oil, such that it differs significantly in composition from such substances currently found in food. FDA believes that plant breeders must carefully evaluate the potential for adverse effects that could result from the presence of these substances in new plant varieties.

Theoretically, genetic modifications have the potential to activate cryptic

pathways synthesizing unknown or unexpected toxicants, or to increase expression from active pathways that ordinarily produce low or undetectable levels of toxicants. However, this potential has been effectively managed in the past by sound agricultural practices. The agency believes that the use of host plants with a history of safe use, coupled with a continuation of sound agricultural practice, will minimize the potential for adverse public health consequences that may arise from increased levels of unknown or unexpected toxicants.

This guidance section provides a basis for determining whether new plant varieties are as safe and nutritious as their parental varieties. The assessment scheme focuses on characteristics of the new plant variety, based on characteristics of the host and donor species, the nature of the genetic change, the identity and function of newly introduced substances, and unexpected or unintended effects that accompany the genetic change. The assessment focuses on the following considerations:

1. Toxicants known to be characteristic of the host and donor species;

2. The potential that food allergens will be transferred from one food source to another;

3. The concentration and bioavailability of important nutrients for which a food crop is ordinarily consumed;

4. The safety and nutritional value of newly introduced proteins; and

5. The identity, composition and nutritional value of modified carbohydrates, or fats and oils.

The scientific concepts described in this guidance section are consistent with the concepts of substantial equivalence of new foods discussed in a document under development by the Group of National Experts on Safety in Biotechnology of the Organization for Economic Cooperation and Development (OECD). This guidance section is also consistent with the principles for food safety assessment discussed in the Report of a Joint Food and Agriculture Organization/World Health Organization Consultation (Ref. 6).

B. Flow Charts

The flow charts presented in sections VII.D. through VII.F. (Figures 2 through 6) outline a series of questions related to the safety and nutritional value of foods derived from the new plant variety, and are intended to provide general guidance to breeders and developers. FDA intends that these flow charts be used in conjunction with other information and practices that breeders and developers rely on to develop new plant varieties. These reflect the current state of scientific information and are not intended as regulatory requirements. As new information is developed, FDA anticipates that the flow charts may require modification.

The summary flow chart (Figure 1) presented in this section is a synopsis of FDA's safety assessment process. It describes, in a general way, the assessment for unexpected or unintended effects that may arise as a result of the specific characteristics that are associated with the host plant and donor(s), as well as the assessment of the expected or intended effects. Because Figure 1 is a summary, it should not be relied upon for a safety assessment. The boxes labeled Figure 2, Figure 3, Figure 4, and Figures 5 and 6, respectively, refer to more specific flow charts that describe, in appropriate detail, the safety assessment from the perspective of the host, donor, and new substances that are introduced into the new plant variety.

Sections VII.D. through VII.F. address the scientific considerations pertaining to the host plant, donor(s), and new substances in more detail. Each section describes information that relates to the safety assessment, presents a flow chart that summarizes the safety assessment, discusses each of the questions in that flow chart, and describes the endpoints that are reached in that flow chart.

There are three endpoints in the flow charts in this notice: (1) No concerns, (2) new variety not acceptable, and (3) consult FDA. The notes to each individual flow chart discuss the interpretation of these endpoints in relation to that particular flow chart. In general, the interpretation of "no concerns" or "new variety not acceptable" is similar for each flow chart. The endpoint "consult FDA" means that producers may need to consult FDA on regulatory questions, such as whether a food additive petition or special labeling is needed, or on technical questions, such as appropriate testing protocols or specific scientific issues.

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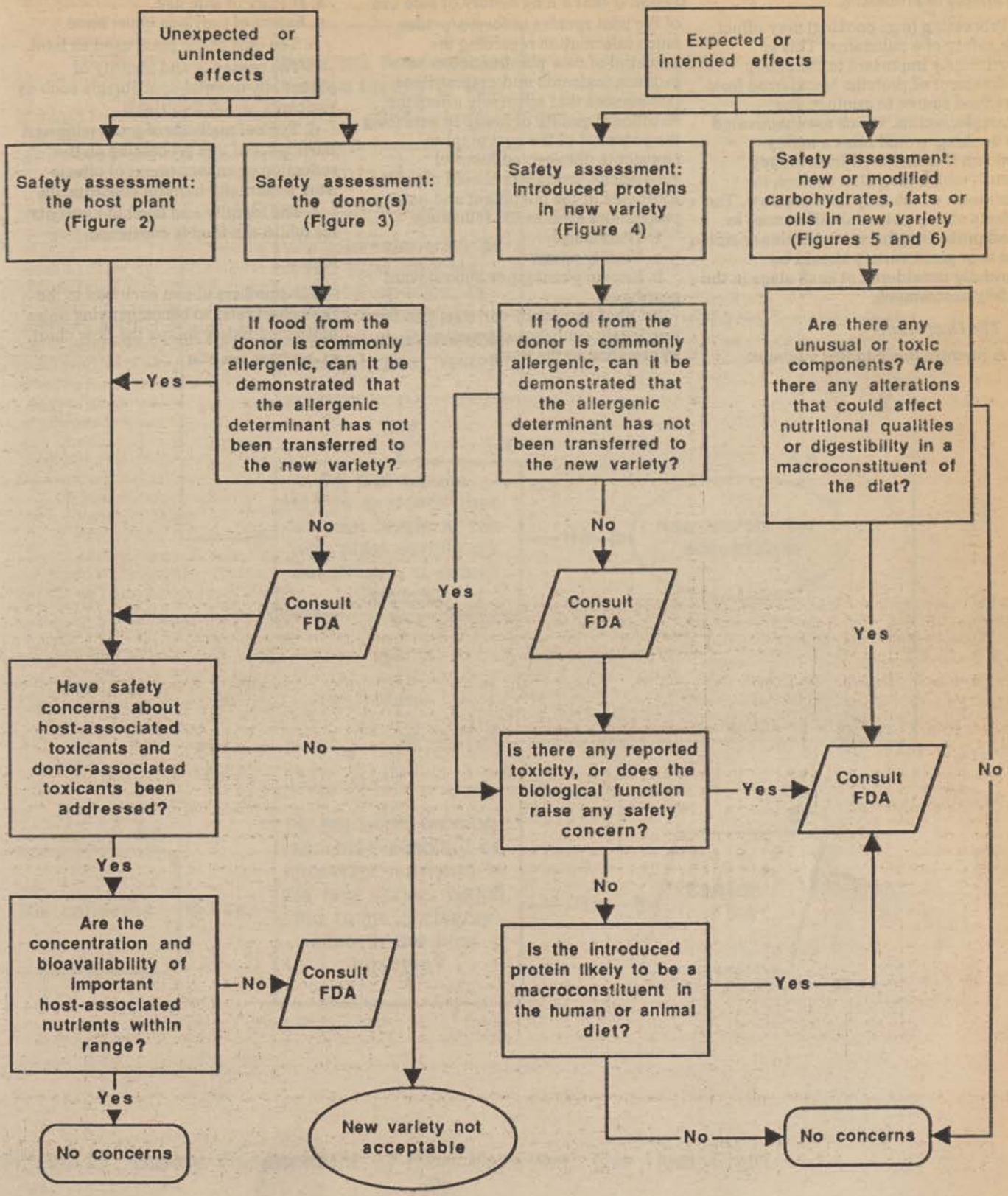

Figure 1. Safety Assessment of New Varieties: Summary

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C. Effects of Processing

Processing (e.g., cooking) may affect the safety of a substance. This is particularly important in the safety assessment of proteins transferred from one food source to another. For example, lectins, which are inactivated by cooking, would raise a safety concern if transferred from kidney beans, which are eaten cooked, to tomatoes, which may be eaten raw. The effects of any potential differences in food processing between the donor and the new plant variety should be carefully considered at each stage in the safety assessment.

D. The Host Plant

A premise basic to this guidance section is that a long history of safe use of the host species in food provides much information regarding the potential of new plant varieties to produce toxicants and antinutrients (substances that adversely affect the nutritional quality of food). In assessing the potential of the host plant to contribute unexpected harmful substances, producers should consider attributes of the host plant and its progenitors such as the following:

1. Taxonomy.
   a. Variety name.
   b. Known phenotypes and relevant genotypes.
2. Other species or varieties that have previously contributed genetic information to the host.
3. History of safe use.
   a. Extent of previous experience.
   b. The part of the plant used as food.
   c. The presence and identity of potentially harmful constituents such as toxicants and antinutrients.
   d. Typical methods of processing and the impact of this processing on the reduction or enhancement of effects from potentially harmful constituents.
4. The identity and level of nutrients for which the food is consumed.

Figure 2

The numbers above each box in the flow chart refer to accompanying notes that immediately follow the flow chart.

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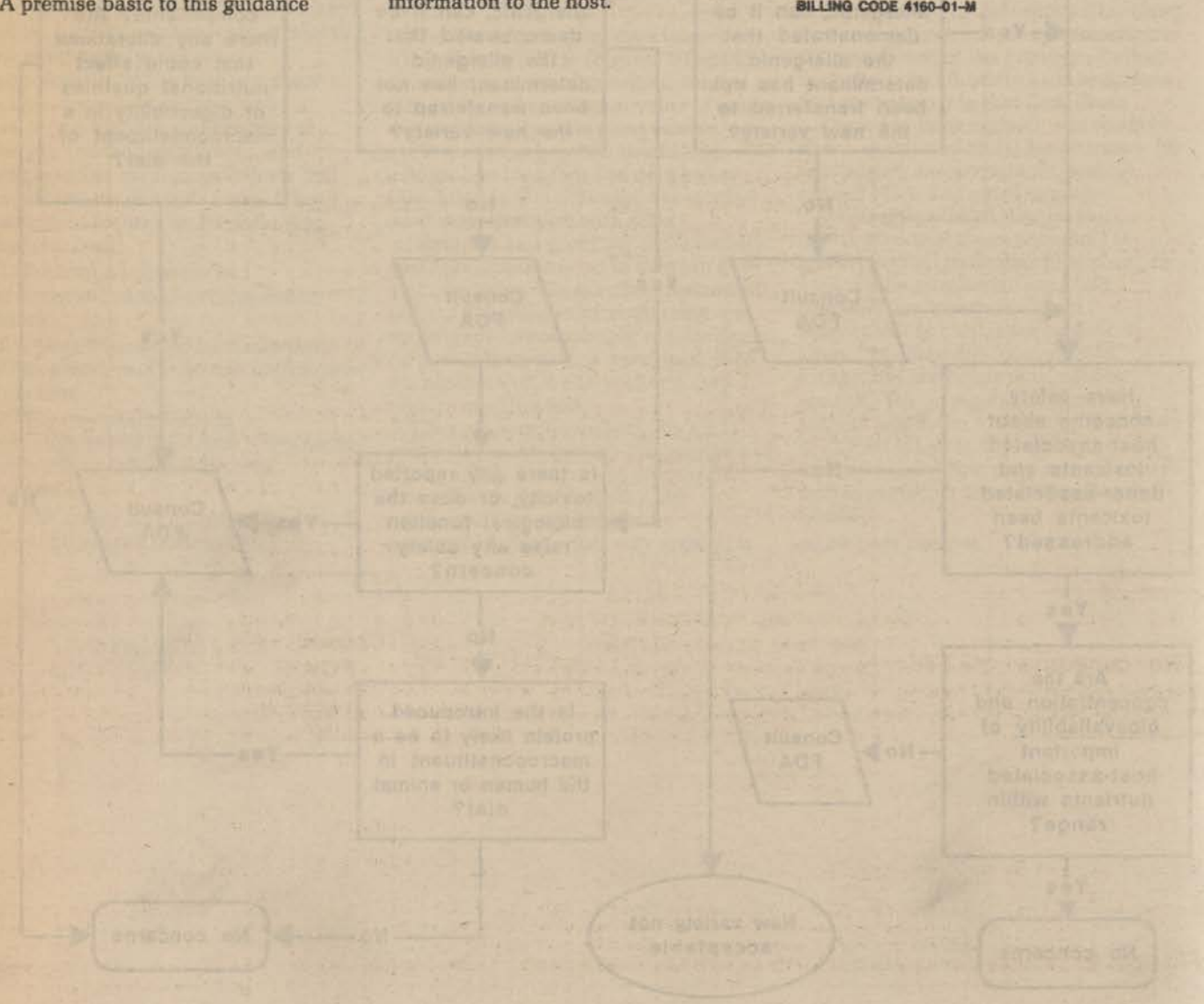

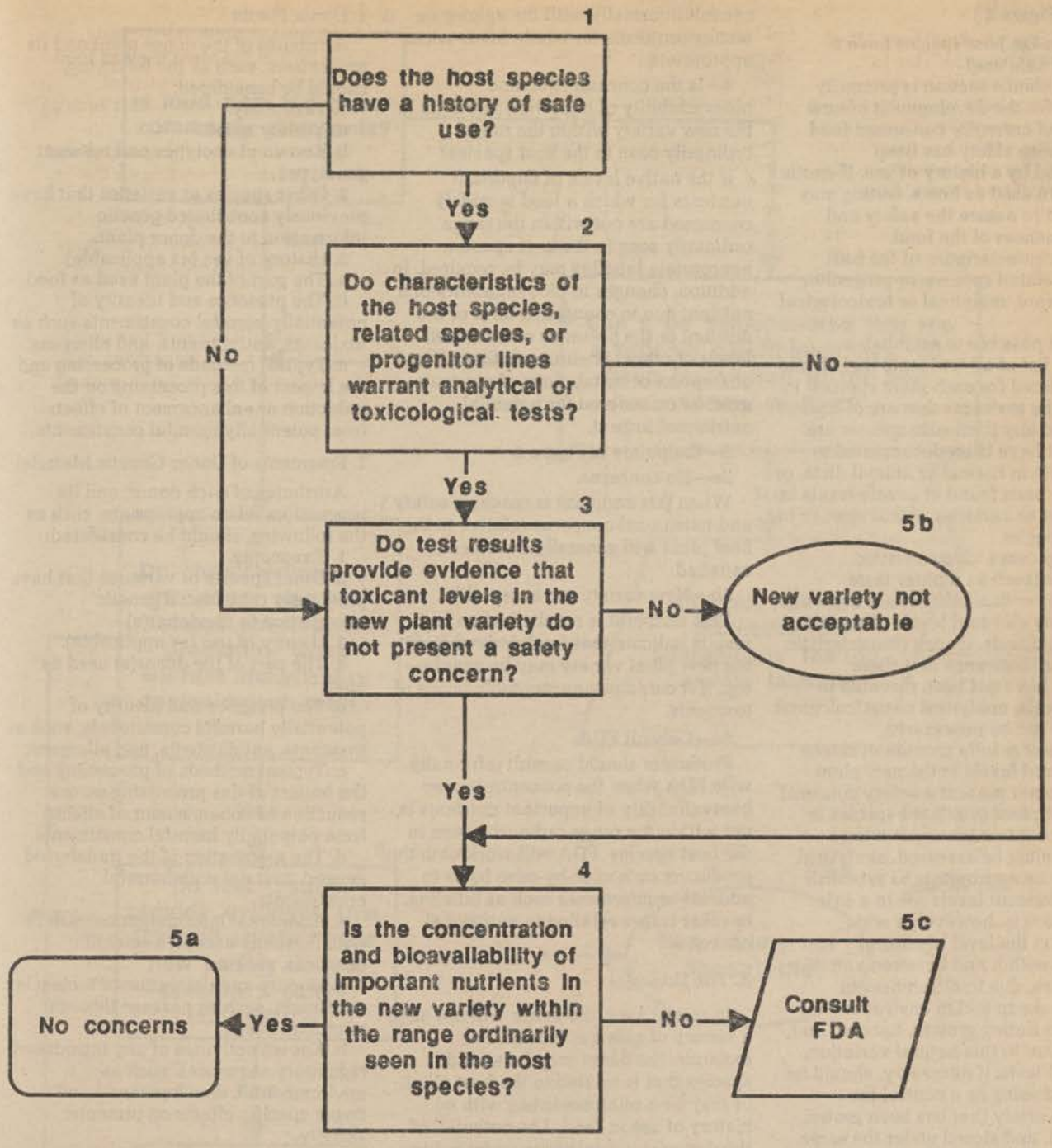

Figure 2. Safety Assessment of New Varieties: The Host Plant

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Notes to Figure 2

1—Does the host species have a history of safe use?

This guidance section is primarily designed for the development of new varieties of currently consumed food plants whose safety has been established by a history of use. If exotic species are used as hosts, testing may be needed to assure the safety and wholesomeness of the food.

2—Do characteristics of the host species, related species, or progenitor lines warrant analytical or toxicological tests?

It is not possible to establish a complete list of all toxicants that should be considered for each plant species. In general, the toxicants that are of highest concern in any particular species are those that have been documented to cause harm in normal or animal diets, or that have been found at unsafe levels in some lines or varieties of that species or related species.

In many cases, characteristic properties (such as a bitter taste associated with alkaloids) are known to accompany elevated levels of specific natural toxicants. If such characteristic provide an assurance that these toxicants have not been elevated to unsafe levels, analytical or toxicological tests may not be necessary.

3—Do test results provide evidence that toxicant levels in the new plant variety do not present a safety concern?

If a host plant or related species is known to contain toxicants whose presence must be assessed, analytical tests may be appropriate to establish that the toxicant levels are in a safe range. There is, however, a wide variation in the level of natural toxicants within and between varieties of a species, due to differences in genetic makeup and in environmental conditions during growth, harvest, and storage. Due to this natural variation, analytical tests, if necessary, should be performed using as a control the parental variety that has been grown, harvested, and stored under the same conditions as the new plant variety.

In some cases, analytical methods alone may not be available, practical, or sufficient for all toxicants whose levels are needed to be assessed. In such situations, comparative toxicological tests on the new and parental plant varieties may provide assurance that the new variety is safe. FDA encourages producers of new plant varieties to consult informally with the agency on testing protocols for whole foods when appropriate.

4—Is the concentration and bioavailability of important nutrients in the new variety within the range ordinarily seen in the host species?

If the native levels of important nutrients for which a food is widely consumed are not within the range ordinarily seen in the host species, appropriate labeling may be required. In addition, changes in bioavailability of a nutrient due to changes in form of the nutrient or the presence of increased levels of other constitutents that affect absorption or metabolism of nutrients must be considered for potential nutritional impact.

5—Endpoints in Figure 2.

5a—No concerns.

When this endpoint is reached, safety and nutritional concerns relative to the host plant will generally have been satisfied.

5b—New variety not acceptable.

This endpoint is reached when test results indicate that food derived from the new plant variety may be unsafe—e.g., if it contains unacceptable levels of toxicants.

5c—Consult FDA.

Producers should consult informally with FDA when the concentration or bioavailability of important nutrients is not within the range ordinarily seen in the host species. FDA will work with the producers on a case-by-case basis to address requirements such as labeling, or other issues relating to nutritional concerns.

E. The Donor(s)

In some cases, the donor will not have a history of safe use in food. For example, the donor may be a wild species that is related to the host plant, or may be a microorganism with no history of use in food. The potential of the donor(s) to contribute undesirable characteristics to the new plant variety should be assessed. In assessing the potential of the donor to contribute unexpected harmful substances, producers should consider attributes of the donor plant, or of fragments of genetic material from one or multiple donors, to the extent that such information is available (see Figure 3).

1. Donor Plants

Attributes of the donor plant and its progenitors, such as the following, should be considered:

1. Taxonomy.

a. Variety name.

b. Known phenotypes and relevant genotypes.

2. Other species or varieties that have previously contributed genetic information to the donor plant.

3. History of use (as applicable).

a. The part of the plant used as food.

b. The presence and identity of potentially harmful constituents such as toxicants, antinutrients, and allergens.

c. Typical methods of processing and the impact of this processing on the reduction or enhancement of effects from potentially harmful constituents.

2. Fragments of Donor Genetic Material

Attributes of each donor, and its progenitors when appropriate, such as the following, should be considered:

1. Taxonomy.

2. Other species or varieties that have previously contributed genetic information to the donor(s).

3. History of use (as applicable).

a. The part of the donor(s) used as food.

b. The presence and identity of potentially harmful constituents, such as toxicants, antinutrients, and allergens.

c. Typical methods of processing and the impact of this processing on the reduction or enhancement of effects from potentially harmful constituents.

d. The association of the transferred genetic material with harmful constituents.

4. Additional information consistent with currently accepted scientific practices, such as:

a. History and derivation of molecular constructs, such as passage through microbial hosts.

b. Known activities of any introduced regulatory sequences, such as environmental, developmental and tissue-specific effects on promoter activity.

c. The presence of extraneous open reading frames, and the potential for transcription and expression of these additional open reading frames.

Figure 3

The numbers above each box in the flow chart refer to accompanying notes that immediately follow the flow chart.

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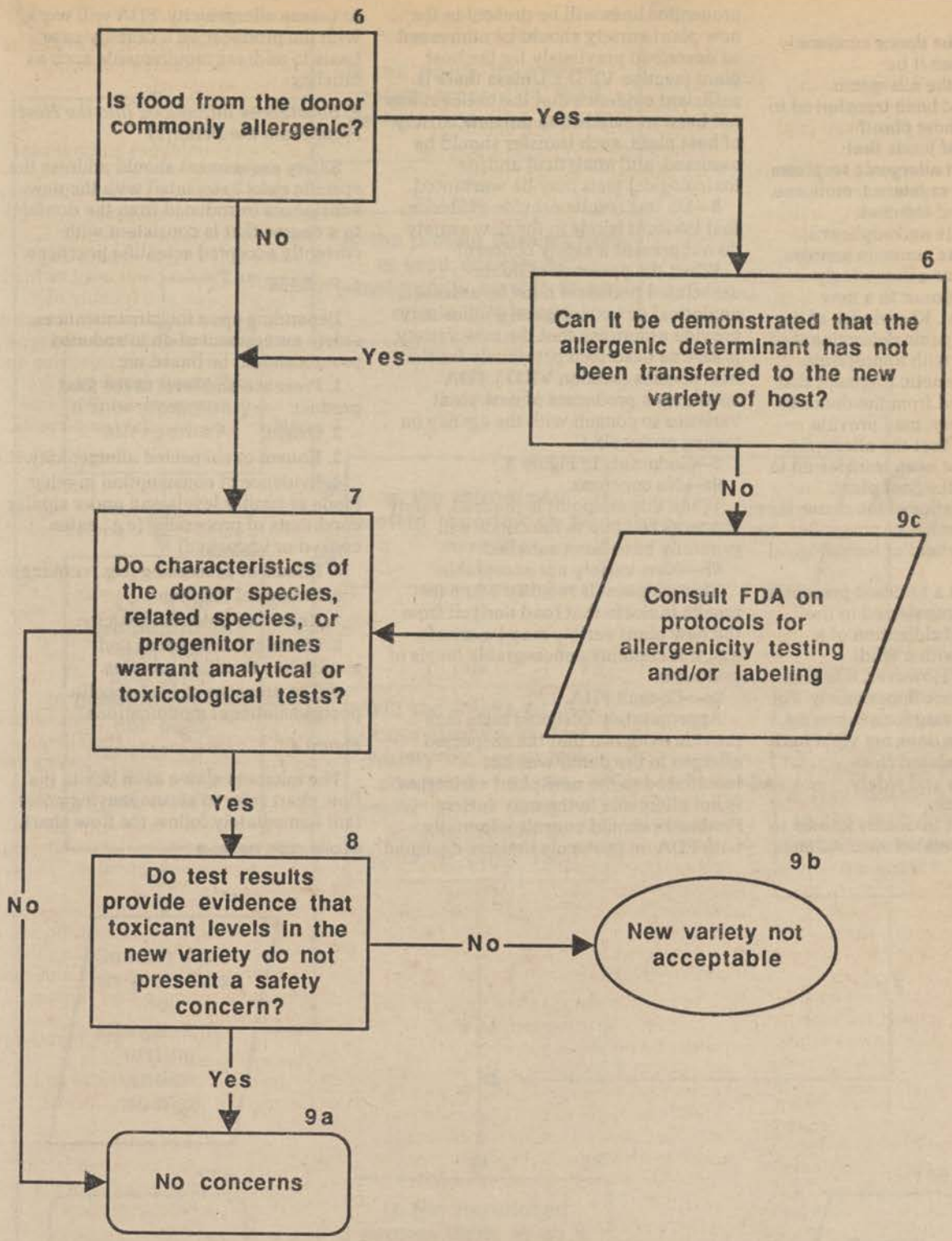

Figure 3. Safety Assessment of New Varieties: The Donor(s)

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Notes to Figure 3

6—Is food from the donor commonly allergenic? If yes, can it be demonstrated that the allergenic determinant has not been transferred to the new variety of host plant?

Some examples of foods that commonly cause an allergenic response are milk, eggs, fish, crustacea, molluscs, tree nuts, wheat, and legumes (particularly peanuts and soybeans). Allergens from these common sources may be knowingly or unknowingly transferred from a donor to a new variety of host plant. Knowledge of the identity of the allergenic determinant of the donor, coupled with appropriate knowledge of the genetic fragment that has been transferred from the donor to the new plant variety, may provide sufficient evidence that the allergenic determinant has not been transferred to the new variety of the host plant.

7—Do characteristics of the donor species, related species, or progenitor lines warrant analytical or toxicological tests?

It is possible that a toxicant present in the donor may be transferred to the host, e.g., during hybridization of a cultivated variety with a wild, poisonous relative. However, it is also possible to use a toxic donor safely. For example, a gene coding for an enzyme that is not toxic and does not yield toxic products may be isolated from pathogenic bacteria and safely transferred to a plant.

The potential that toxicants known to exist in the donor, related species, or progenitor lines will be present in the new plant variety should be addressed as described previously for the host plant (section VII.D.). Unless there is sufficient evidence that the toxicant has not been transferred to the new variety of host plant, such transfer should be assumed, and analytical and/or toxicological tests may be warranted.

8—Do test results provide evidence that toxicant levels in the new variety do not present a safety concern?

When the presence of donor-associated toxicants must be assessed, analytical or toxicological studies may provide assurance that the new variety is safe as described previously for the host species (section VII.D.). FDA encourages producers of new plant varieties to consult with the agency on testing protocols.

9—Endpoints in Figure 3.

9a—No concerns.

When this endpoint is reached, safety concerns relative to the donor will generally have been satisfied.

9b—New variety not acceptable.

This endpoint is reached when test results indicate that food derived from the new plant variety may be unsafe, e.g., if it contains unacceptable levels of toxicants.

9c—Consult FDA.

Appropriately designed tests may provide evidence that the suspected allergen in the donor was not transferred to the new plant variety, or is not allergenic in the new variety. Producers should consult informally with FDA on protocols that are designed to assess allergenicity. FDA will work with the producer on a case-by-case basis to address requirements such as labeling.

F. Substances Introduced Into the Host Plant From the Donor(s)

Safety assessment should address the specific risks associated with the new substances introduced from the donor(s) to a degree that is consistent with currently accepted scientific practices.

1. Proteins

Depending upon the circumstances, safety assessment of an introduced protein should be based on:

1. Presence and level in the food product.
2. Origin.
3. Known or suspected allergenicity.
4. Evidence of consumption in other foods at similar levels and under similar conditions of processing (e.g., eaten cooked or uncooked).
5. Effects of processing (e.g., cooking).
6. Biological function.
7. Known or potential toxicity.
8. Chemical differences and similarities to edible proteins.
9. The presence of host-specific posttranslational modifications.

Figure 4

The numbers above each box in the flow chart refer to accompanying notes that immediately follow the flow chart.

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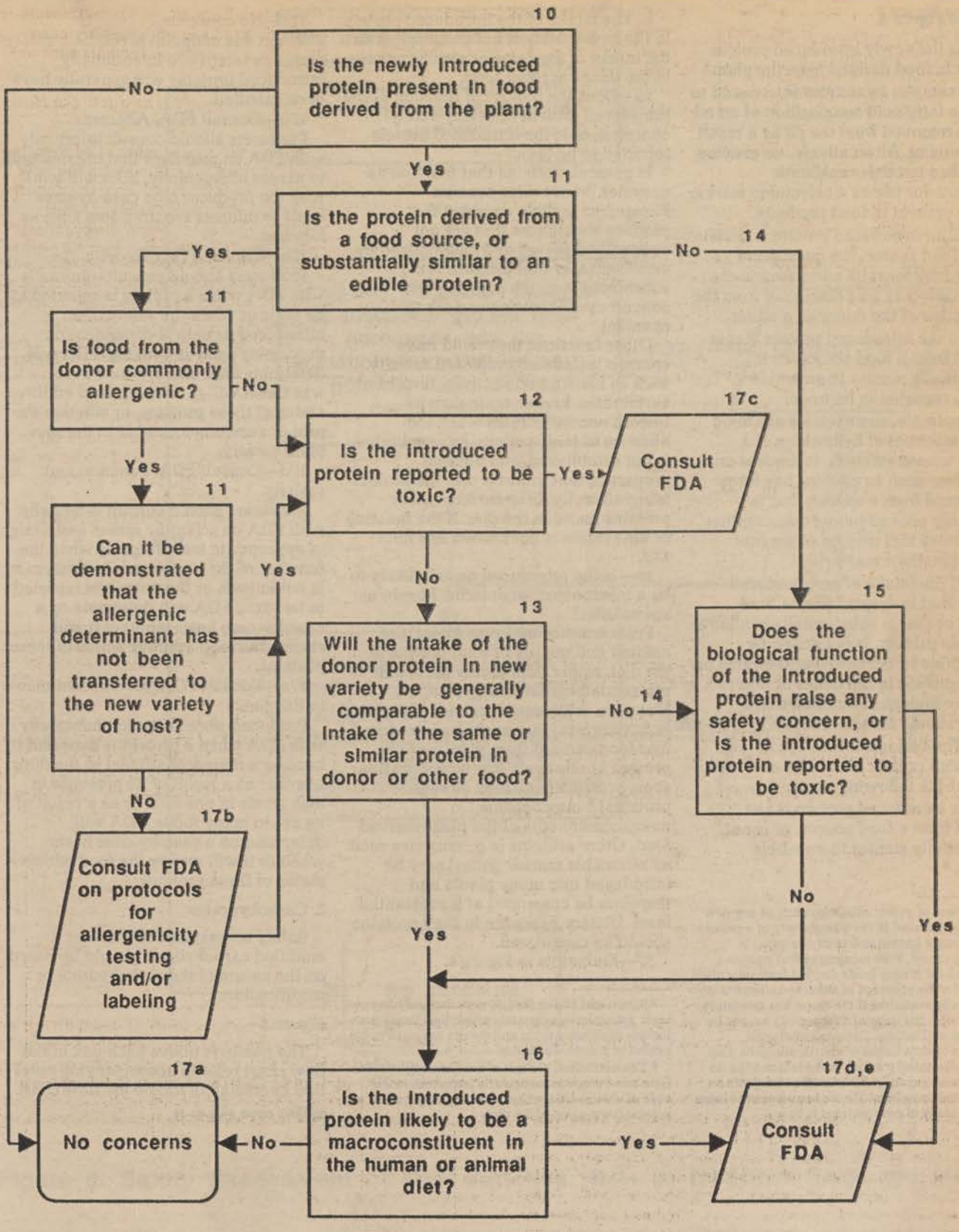

Figure 4. Safety Assessment of New Varieties: Proteins Introduced from Donor(s)

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Notes to Figure 4

10—Is the newly introduced protein present in food derived from the plant?

For example, an enzyme introduced to alter the fatty acid composition of an oil may be removed from the oil as a result of processing. Alternatively, an enzyme introduced to confer antibiotic resistance for use as a selectable marker may be present in food products.

11—If an introduced protein is derived from a food source, the question of allergenicity must be addressed in the same fashion as was discussed from the perspective of the donor as a whole.

12—Is the introduced protein that is derived from a food source, or is substantially similar to an edible protein, reported to be toxic?

For example, some lectins are toxic unless inactivated by cooking. If a protein whose safety is dependent on processing such as cooking has been transferred from a species that is commonly cooked before consumption to a species that may be eaten raw, safety questions may arise.

13—If the intake of an introduced protein that is derived from a food source, or that is substantially similar to an edible protein, is not generally comparable to the intake of the same or similar protein in the donor or other food, the biological function of the protein should be assessed.

14—The biological function of the introduced protein should be assessed if either of the following occur:

a. The introduced protein is not derived from a food source, or is not substantially similar to an edible protein; [6]

b. The intake of the introduced protein in the new variety is not comparable to the intake of the same or similar protein in the donor or other food.

15—Does the biological function of the introduced protein raise any safety concerns, or is the introduced protein reported to be toxic?

In general, proteins that function as enzymes do not raise concern [7] Exceptions include enzymes that produce substances that are not ordinarily digested and metabolized by vertebrates, or that produce toxic substances (e.g., the enzymes that convert cyanogenic glycosides to cyanide).

Other functions that could raise concern include any reported toxicity, such as known toxic activity toward vertebrates, known toxic activity toward nonvertebrates when the absence of toxic activity to vertebrates is not established, and unusual properties that indicate that the protein is significantly different from other proteins found in the diet. If the function of the protein is not known, see note 17d.

16—Is the introduced protein likely to be a macroconstituent in the human or animal diet?

From a nutritional standpoint, the amount and quality of total protein in the diet, rather than of any particular protein, is of greatest significance. However, while most individual proteins (e.g., enzymes) that might be introduced into food derived from plants will be present at relatively low concentrations, some proteins (e.g., seed storage proteins) [8] may become macroconstituents of the plant-derived food. Other proteins (e.g., enzymes used as selectable marker genes) may be introduced into many plants and therefore be consumed at a substantial level. Dietary exposure to such proteins should be considered.

17—Endpoints in Figure 4.

17a—No concerns.

When this endpoint is reached, safety concerns relative to intentionally introduced proteins will generally have been satisfied.

17b—Consult FDA: Allergens.

Producers should consult informally with FDA on protocols that are designed to assess allergenicity. FDA will work with the producer on a case-by-case basis to address requirements such as labeling.

17c—Consult FDA: Toxicity.

Producers should consult informally with FDA when a protein is reported to be toxic or when the safety of an introduced protein is dependent on processing such as cooking. FDA will determine on a case-by-case basis whether it will review the food additive status of these proteins, or whether the proteins are unacceptable in the new plant variety.

17d—Consult FDA: Function and toxicity.

Producers should consult informally with FDA on scientific issues and design of appropriate test protocols when the function of the protein raises concern or is not known, or the protein is reported to be toxic. FDA will determine on a case-by-case basis whether it will review the food additive status of these proteins.

17e—Consult FDA: Macroconstituents in the diet.

Producers should consult informally with FDA when a protein is expected to become a macroconstituent of the diet, whether as a result of its presence in high levels in one food or as a result of its use in many foods. FDA will determine on a case-by-case basis whether it will review the food additive status of these proteins.

2. Carbohydrates

Safety assessment of a new or modified carbohydrate should be based on the nature of the carbohydrate or modification.

Figure 5

The numbers above each box in the flow chart refer to accompanying notes that immediately follow the flow chart.

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[6] The issue of potential allergenicity of any new protein (as opposed to the allergenicity of a protein derived from a known source of allergens) is frequently raised. FDA recognizes that routine procedures for testing foods derived from new plant varieties for the presence of unknown allergens are not currently available. If the donor has no history of use in food, the issue of allergenicity cannot be addressed at this time. Comparison of gene sequences to data banks of known allergens may become increasingly useful as the information on such proteins expands. FDA invites comments on methods that may be available to address the issue of allergenicity of new proteins in foods.

[7] Pariza and Foster (Ref. 7) note that very few toxic agents have enzymatic properties. Exceptions include diphtheria toxin and certain enzymes in the venom of poisonous snakes.

[8] The nutritional content of seed storage proteins from some crops is particularly important in the case of animal feed, where one crop may furnish a substantial portion of the diet.

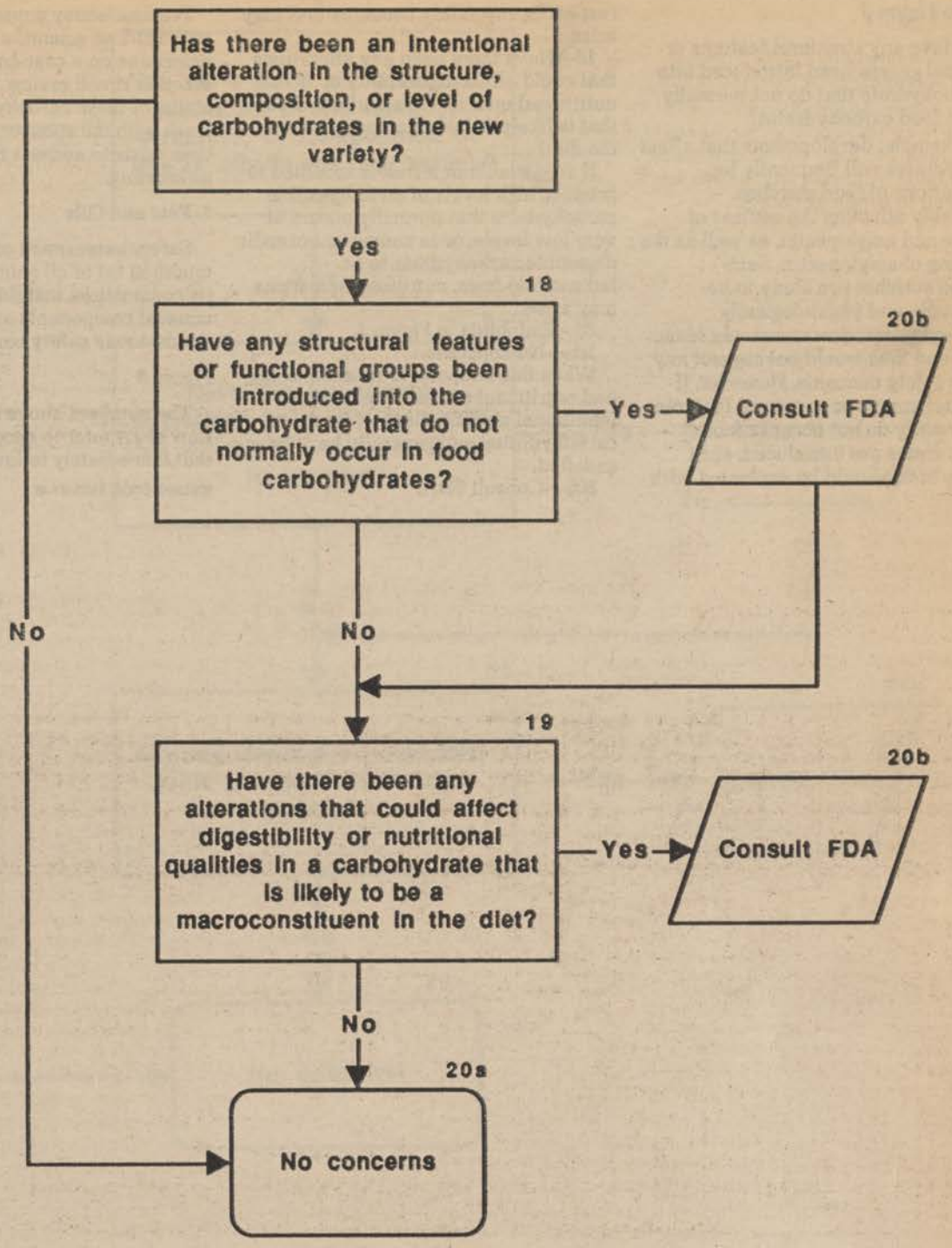

Figure 5. Safety Assessment of New Varieties: New or Modified Carbohydrates

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Notes to Figure 5

18—Have any structural features or functional groups been introduced into the carbohydrate that do not normally occur in food carbohydrates?

For example, developments that affect carbohydrates will frequently be modifications of food starches, presumably affecting the content of amylose and amylopectin, as well as the branching of amylopectin. Such modified starches are likely to be functionally and physiologically equivalent to starches commonly found in food and thus would not suggest any specific safety concerns. However, if functional groups or structural features that normally do not occur in food carbohydrates are introduced, such modifications should be evaluated with respect to any safety concerns that may arise.

19—Have there been any alterations that could affect digestibility or nutritional qualities in a carbohydrate that is likely to be a macroconstituent in the diet?

If a vegetable or a fruit is modified to produce high levels of an indigestible carbohydrate that normally occurs at very low levels, or to convert a normally digestible carbohydrate to an indigestible form, nutritional questions may arise.

20—Endpoints in Figure 5.

20a—No concerns.

When this endpoint is reached, safety and nutritional concerns relative to intentional modifications of food carbohydrates will generally have been satisfied.

20b—Consult FDA.

Producers may consult informally with FDA on scientific issues. FDA will determine on a case-by-case basis whether it will review the food additive status of these carbohydrates, and will work with the sponsor on a case-by-case basis to address requirements such as labeling.

3. Fats and Oils

Safety assessment of a new or modified fat or oil should be based on its composition and the presence of any unusual components at levels that would cause safety concern.

Figure 6

The numbers above each box in the flow chart refer to accompanying notes that immediately follow the flow chart.

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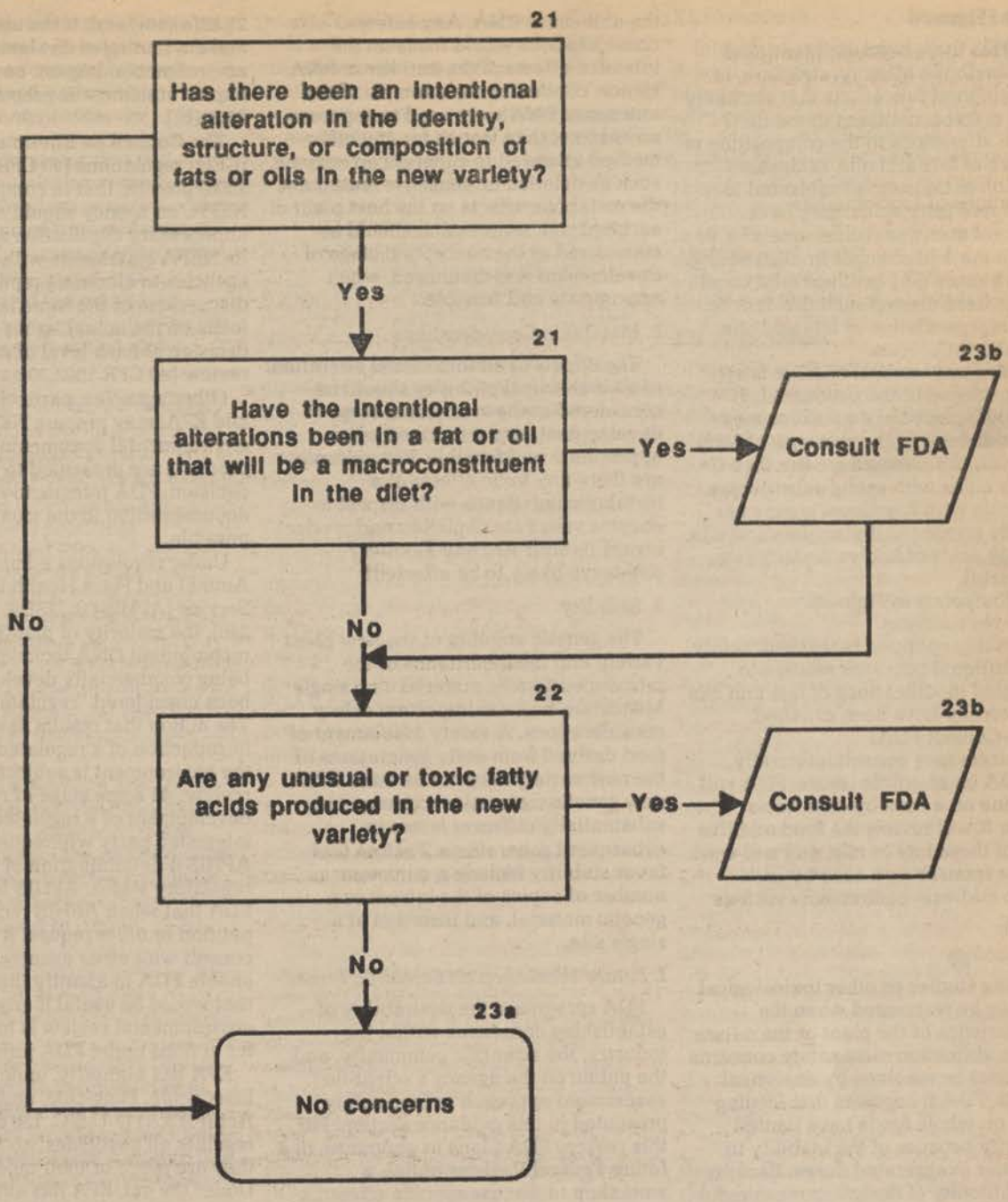

Figure 6. Safety Assessment of New Varieties: New or Modified Fats or Oils

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Notes to Figure 6

21—Has there been an intentional alteration in the identity, structure, or composition of fats or oils that are likely to be a macroconstituent in the diet?

Some alterations in the composition or structure of fats and oils, such as an alteration in the ratio of saturated to unsaturated fatty acids, may have significant nutritional consequences, or result in marked changes in digestibility. Other changes may produce a fat or oil that has been altered such that it is no longer representative of fats and oils from the host species.

22—Are any unusual or toxic fatty acids produced in the new variety?

For example, safety questions may arise as a result of the presence of fatty acids with chain length greater than C–22, fatty acids with cyclic substituents, fatty acids with functional groups not normally present in dietary fats and oils, and fatty acids of known toxicity (e.g., erucic acid).

23—Endpoints in Figure 6.

23a—No concerns.

When this endpoint is reached, safety and nutritional concerns relative to intentional modifications of fats and oils will generally have been satisfied.

23b—Consult FDA.

Producers may consult informally with FDA on scientific issues. FDA will determine on a case-by-case basis whether it will review the food additive status of these fats or oils, and will work with the sponsor on a case-by-case basis to address requirements such as labeling.

G. Toxicology

Feeding studies or other toxicological tests may be warranted when the characteristics of the plant or the nature of the modification raise safety concerns that cannot be resolved by analytical methods. FDA recognizes that feeding studies on whole foods have limited sensitivity because of the inability to administer exaggerated doses. Because of the difficulty of designing meaningful studies, FDA encourages companies to consult informally with the agency about test protocols.

H. Other Information

The information described below is not directly addressed in the flow charts but should be considered during the development of new plant varieties.

1. Nucleic Acids

Introduced nucleic acids, in and of themselves, do not raise safety concerns. Thus, for example, the introduction of a gene encoding an anti-sense ribonucleic acid (RNA) would not raise concerns about either the gene or the anti-sense RNA. Any safety considerations would focus on the intended effects of the anti-sense RNA. Hence, continuing the example, if the anti-sense RNA were used to suppress an enzyme, then just as for any other method intended to suppress an enzyme, such as deletion or nonsense mutations, the metabolic effects on the host plant of such enzyme suppression should be considered at the conceptual stage of development and monitored, when appropriate and feasible.

2. Metabolic Considerations

The effects of an intentional alteration of a biochemical pathway should be considered at the conceptual stage of development, and monitored when appropriate and feasible. For example, are there any toxic effects of a metabolic imbalance with respect to enzyme substrate depletion and product accumulation? Are any auxiliary pathways likely to be affected?

3. Stability

The genetic stability of the new plant variety and the inheritance of the introduced genetic material as a single Mendelian trait are important safety considerations. A safety assessment of food derived from early generations of the new variety may not be valid if the new genetic material is expressed at substantially different levels in subsequent generations. Factors that favor stability include a minimum number of copies of the introduced genetic material, and insertion at a single site.

I. Future Workshop on Scientific Issues

FDA recognizes the desirability of establishing consensus within the industry, the scientific community, and the public on the agency's scientific assessment approach to food safety presented in this guidance section. For this reason, FDA plans to announce, in a future **Federal Register** notice, a workshop to discuss specific scientific issues. The notice announcing the workshop will include a description of the scientific issues to be discussed. FDA invites comment on topics that might be addressed at such a workshop.

VIII. Environmental Consideration: Applicability of NEPA

NEPA requires FDA to consider in its decisionmaking the environmental impact of its major Federal actions that significantly affect the quality of the human environment. The promulgation of a food additive regulation is an agency action that ordinarily triggers the NEPA requirement for development of an environmental assessment (21 CFR 25.22(a)(10)) and, if the agency does not make a finding of no significant environmental impact, an environmental impact statement is prepared (21 CFR 25.21(b)).

The Council on Environmental Quality (CEQ) regulations (40 CFR 1500 through 1508) provide that in complying with NEPA, an agency should avoid unnecessary duplication and should tier its NEPA statements with those of other agencies to eliminate repetitive discussions of the same issues and to focus on the actual issues ripe for decision at each level of environmental review (40 CFR 1502.20 and 1508.28).

Other agencies, particularly USDA and EPA, may prepare NEPA and other environmental documentation before products are presented to FDA for a decision. FDA intends to rely on such documentation to the maximum extent possible.

Under regulations administered by the Animal and Plant Health Inspection Service (APHIS) in USDA (7 CFR part 340), the majority of plants developed by recombinant DNA techniques that are being commercially developed have been considered "regulated articles." The action that results in a permit for introduction of a regulated article into the environment is subject to NEPA review. At some stage of research and development of a regulated article, an interested party will request from APHIS a determination of the article's regulatory status. APHIS has informed FDA that when APHIS receives a petition or other request it intends to consult with other agencies. This should enable FDA to identify the type of data that would be useful if any subsequent environmental review is to be prepared for actions under FDA jurisdiction.

EPA has authority, under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (7 U.S.C. 136 *et seq.*), to regulate all pesticides, no matter how they are made or their mode of action. Under the act, EPA has authority to regulate pesticide residues in foods. Any relevant review that EPA conducts under FIFRA, the act, or any other of its statutes, involving an assessment of potential effects on human health and the environment will be available to FDA.

FDA intends to work closely with USDA and EPA to minimize duplication of environmental reviews. The agency will, to the extent possible, invoke the tiering provisions in the CEQ regulations and, in FDA's environmental assessments, rely on APHIS NEPA reviews and other such documents, as well as relevant environmental documents considered by EPA. Further,

FDA will provide informal guidance on environmental issues to assist individuals who are preparing food additive petitions to meet FDA's requirements for environmental assessments.

FDA does not consider that the activities it may undertake with respect to foods from new plant varieties other than promulgation of food additive regulations, such as consultation with producers on safety issues and providing advice on the regulatory status of foods from new plant varieties, will constitute agency action under NEPA.

IX. Coordination With EPA: Pesticide Considerations

Questions have been raised concerning whether FDA or EPA would have jurisdiction when plants are modified to express pesticidal substances. FDA and EPA are agreed that substances that are pesticides as defined by FIFRA (7 U.S.C. section 136(u)), are subject to EPA's regulatory authority. The agencies also agree that FDA's authority under the act extends to any nonpesticide substance that may be introduced into a new plant variety and that is expected to become a component of food.

EPA and FDA are aware that there may be cases in which the jurisdictional responsibility for a substance is not clear. Because pesticides, as defined by FIFRA, are subject to EPA's jurisdiction, the agencies encourage producers who have such questions to contact EPA. FDA and EPA intend to consult closely on such jurisdictional questions, as well as on scientific matters where consultation will be helpful in resolving safety questions.

The agencies are also aware that, in some circumstances, evaluation of a particular substance introduced into a plant may require the expertise of both EPA and FDA. Both agencies agree that EPA will address under its regulatory jurisdiction the food safety issues associated with the pesticide, including marker genes used to confirm the presence of the pesticidal gene. 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 and should be addressed under the policy set forth elsewhere in this notice.

Based upon the agencies' current knowledge, examples of substances that fall under FDA's authority include: (1) Substances intended to alter the nutritional composition of the food (e.g., amino acids or carbohydrates); (2) substances intended to enhance the plant's resistance to chemical herbicides (e.g., bromoxynil, glyphosate, and sulfonylurea); and (3) substances intended to alter the flavor or the texture of the food.

Similarly, based upon the agencies' current knowledge of new plant varieties being developed using the new technologies of gene transfer, EPA is in the process of evaluating how or if it will exert its oversight for the following examples subject to its jurisdiction under FIFRA and therefore not under FDA's jurisdiction: (1) Substances that are intended to kill insects (e.g., *Bacillus thuringiensis* delta-endotoxin);

(2) Substances intended to protect plants from viral, fungal, or bacterial infection (e.g., cecropin); and (3) substances that are plant regulators and thus "pesticides" under FIFRA.

X. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

This action is intended to provide guidance to developers by describing the scientific considerations for the safe development of foods derived from new plant varieties.

XI. Comments

Interested persons may, on or before August 27, 1992, submit to the Dockets Management Branch (address above) written comments regarding this notice. 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 office above between 9 a.m. and 4 p.m., Monday through Friday.

XII. 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. Anonymous, "Biotechnologies and Food: Assuring the Safety of Foods Produced by Genetic Modification," International Food Biotechnology Council, Regulatory Toxicology and Pharmacology, Vol. 12, No. 3, Part 2 of 2 Parts, New York, December 1990.

2. Letter, Hopkins, D. D., R. J. Goldburg, and S. A. Hirsch to Dr. David Kessler, September 30, 1991, and enclosure, "A Mutable Feast: Assuring Food Safety in the Era of Genetic Engineering."

3. Letter, Richard D. Godown to James H. Maryanski, January 3, 1992; Letter, W. Douglas Crabb to Fred R. Shank, January 24, 1992.

4. Comments to Docket No. 90A–0416, Federal Register, May 1, 1991 (56 FR 20004).

5. Dale, E. C. and D. W. Ow, "Gene Transfer with Subsequent Removal of the Selection Gene from the Host Genome," Proceedings of the National Academy of Sciences USA, 88:10558–10562, 1991.

6. Anonymous, "Strategies for Assessing the Safety of Foods Produced by Biotechnology," World Health Organization, Geneva, 1991.

7. Pariza, M. W. and E. M. Foster, "Determining the Safety of Enzymes Used in Food Processing," Journal of Food Protection, 46:453–468, 1983.

Dated: April 2, 1992.

David A. Kessler,

Commissioner of Food and Drugs.

[FR Doc. 92–12660 Filed 5–26–92; 3:57 pm]

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