savings association, you must not take advantage of corporate opportunities belonging to the savings association.

(b) A corporate opportunity belongs to a savings association if:

(1) The opportunity is within the corporate powers of a savings association or a subsidiary of the savings association; and

(2) The opportunity is of present or potential practical advantage to the savings association, either directly or through its subsidiary.

PART 571—STATEMENTS OF POLICY

12. The authority citation for part 571 continues to read as follows:

Authority: 5 U.S.C. 552, 559; 12 U.S.C. 1462a, 1463, 1464.

§§ 571.4, 571.7, 571.9 [Removed]

13. Sections 571.4, 571.7 and 571.9 are removed.

Dated: May 29, 1996.

By the Office of Thrift Supervision.

Jonathan L. Fiechter,

Acting Director.

[FR Doc. 96–14000 Filed 6–13–96; 8:45 am]

BILLING CODE 6720–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 864

[Docket No. 94P–0341]

Medical Devices; Classification/ Reclassification of Immunohistochemistry Reagents and Kits

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to classify/reclassify immunohistochemistry reagents and kits (IHC's) (in-vitro diagnostic devices) into three classes depending on intended use. These actions are being taken under the Federal Food, Drug, and Cosmetic Act (the act), as amended by the Medical Device Amendments of 1976 (the 1976 amendments) and the Safe Medical Devices Act of 1990 (the SMDA). The intention of this proposal is to regulate these pre- and post-1976 devices in a consistent fashion. Therefore, FDA is proposing classification or reclassification of these products as applicable.

DATES: Submit written comments by August 30, 1996.

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

FOR FURTHER INFORMATION CONTACT: Max Robinowitz, Center for Devices and Radiological Health (HFZ–440), Food and Drug Administration, 2098 Gaither Rd., Rockville, MD, 20850–4011, 301–594–1293, ext. 136, or FAX 301–594–5941.

SUPPLEMENTARY INFORMATION:

I. Background

The act (21 U.S.C. 201 *et seq.*), as amended by the 1976 amendments (Pub. L. 94–295) and the SMDA (Pub. L. 101–629), established a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the act (21 U.S.C. 360c) established three categories (classes) of devices, depending on the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are: Class I (general controls), class II (special controls), and class III (premarket approval).

Under section 513 of the act (21 U.S.C. 360c), devices that were in commercial distribution before May 28, 1976, the enactment date of the 1976 amendments, are classified after FDA has: (1) Received a recommendation from a device classification panel (an FDA advisory committee); (2) published the panel's recommendations for comment, along with a proposed regulation classifying the device; and (3) published a final regulation classifying the device. A device that is first offered in commercial distribution after May 28, 1976, and which FDA determines to be substantially equivalent to a device classified under this scheme, is classified into the same class as the device to which it is substantially equivalent. The agency determines whether new devices are substantially equivalent to previously offered devices by means of premarket notification procedures in section 510(k) of the act (21 U.S.C. 360 (k)) and part 807 of the regulations (21 CFR 807). A device that was not in commercial distribution prior to May 28, 1976, and that has not been found by FDA to be substantially equivalent to a legally marketed device, is classified automatically by statute (section 513(f) of the act) into class III, without any FDA rulemaking proceeding.

The scope of products covered by this proposal includes both pre-1976 devices which have not been previously classified as well as post-1976 devices which are statutorily classified into class III. The intention of this proposal is to regulate these pre- and post-1976 devices in a consistent fashion. Therefore, FDA is proposing classification or reclassification of these products, as applicable.

Fluorescent-labeled immunohistochemistry in vitro diagnostic devices (IHC's) have been used for patient diagnosis since the early 1940's and enzyme-linked IHC's have been used since the early 1970's. IHC's, however, were not classified as a part of the 1979 FDA classification activities. In addition, new IHC's have been marketed for the first time since the passage of the 1976 amendments. When used in a standardized controlled manner, IHC's enhance the accuracy and scope of surgical pathology, provide objective data to histopathological examination, and contribute to improved patient care. IHC's can specifically and objectively demonstrate the presence and distribution of antigens that may be of use in narrowing differential diagnoses. IHC results are integrated by the user pathologist and interpreted together with other types of data used in pathological diagnostic decisionmaking (Refs. 1 through 4). Because pathologists, the principal users of IHC's, were concerned about the regulation of IHC's, the College of American Pathologists, the American Society of Clinical Pathologists, the Association of Pathology Chairs, the Biological Stain Commission, and the Association of Directors of Anatomic and Surgical Pathology requested a review of the classification of IHC reagents and submitted a Petition for Classification of IHC's as class II (special controls) medical devices during the summer of 1994. In response to this petition, FDA convened the Panel to consider classification/reclassification of these devices.

II. Panel Recommendation

The Hematology and Pathology Devices Panel (the Panel) met on October 21, 1994, and made the following recommendation regarding the classification of five Immunohistochemistry devices.

A. Identification

Immunohistochemistry test systems (IHC's) are in-vitro diagnostic devices that consist of polyclonal or monoclonal antibodies and ancillary reagents that are used to identify, by immunological techniques, antigens in specimens of tissues or intact cells in cytologic specimens. IHC's are primary antibody reagents that are labeled with instructions for use and performance

claims and packaged either prediluted or concentrated (neat), or as kits consisting of optimally-diluted primary antibody combined with detector systems. IHC's identify antigens in tissue or cell preparations using ligand-specific antibodies whose reactivity is detected and marked by secondary reagents that are recognized by pathologists using light or electron microscopes. Most IHC's are adjunctive to conventional histopathology and aid in the qualitative identification of antigens, thereby supplementing the conventional hematoxylin and eosin stains used in the diagnostic classification of normal and abnormal cells and tissues. Some IHC's may provide semi-quantitative or quantitative information about the antigen they identify in normal and abnormal cells and tissues.

B. Recommended Classification of the Hematology and Pathology Devices Panel

Class II (special controls). The Panel recommended that establishing special controls for IHC devices should be a high priority.

C. Summary of Reasons for Recommendation

The Panel recommended that IHC devices be classified into class II (special controls) because they perceived the need for special controls for IHC's that prescribe acceptable sensitivity, specificity, stability, accuracy and precision for these devices, and thereby minimize the possibility that these devices may generate inaccurate diagnostic information. Patients may be placed at unnecessary risk when reliance upon inaccurate diagnostic information results in initiating inappropriate therapies or withholding appropriate therapies.

The Panel stated that general controls for IHC's would not provide sufficient control over sensitivity, specificity, stability, accuracy and precision of IHC devices. The Panel stated that special controls are needed to provide reasonable assurance of the safety and effectiveness of IHC devices and that sufficient information is available to establish these special controls. The Panel recommended that manufacturers of IHC devices should follow the FDA's Guidance for Submission of Immunohistochemistry Applications and that this guidance should serve as a special control.

A major concern of the Panel was that manufacturers of IHC devices should be subject to current good manufacturing practice (CGMP) inspections in a timely manner to ensure safe, reliable, stable, and consistent IHC products.

D. Summary of Data Upon Which the Recommendation is Based

The Panel based its recommendation on the Panel members' personal knowledge of, and clinical experience with IHC devices, and presentations by Panel members, manufacturers, other interested parties, and FDA (Ref. 5).

E. Risks to Health

IHC in vitro diagnostic devices are intended for use as diagnostic tools. Risk to the patient may result from misdiagnosis and initiation of inappropriate therapies or withholding of appropriate therapies based on the results obtained with the IHC diagnostic device. The degree of risk depends on whether the product is used as an adjunct to conventional histopathological diagnostic techniques or provides information that is used independently of the usual diagnostic process. The highest risk products are those used as independent, stand-alone diagnostic tests that are the sole or major determinant for a medical decision and cannot be confirmed by conventional histopathologic techniques or other diagnostic tests or clinical procedures.

III. Proposed Classification/ Reclassification

Following the Hematology and Pathology Devices Panel meeting, the agency considered the Panel's recommendation. The agency agrees in part and disagrees in part with the Panel's recommendation. FDA believes that general class I controls are sufficient to ensure safety and effectiveness for those adjunctive IHC's that furnish information that may be incorporated into the pathologist's histopathology or cytopathology report but that is not reported directly to clinicians. These general controls include: (1) Existing labeling requirements (21 CFR 809.10) for in vitro devices, (2) compliance with good manufacturing practices, (3) registration, listing, and premarket notification (510(k)), (4) recordkeeping and medical device reporting (MDR), (5) restriction to prescription use (21 CFR 801.109.) Those IHC's that provide pathologists with adjunctive diagnostic information that may be incorporated into the pathologist's report, but that is not ordinarily reported to the clinician as an independent finding, are therefore proposed to be categorized as class I. These IHC's are used in adjunctive tests to subclassify malignant tumors, but the primary diagnosis of tumor (neoplasm) and malignancy is made by conventional histopathology using nonimmunological histochemical stains such as hematoxylin and eosin. Examples of these IHC's proposed for class I are differentiation markers, such as antikeratin antibodies.

The manufacturer (sponsor) of a class I IHC would be required to provide a premarket notification submission to FDA, including data documenting compliance with the labeling requirements in § 809.10 (21 CFR 809.10). Such manufacturers or sponsors may wish to follow the ''FDA Guidance for Submissions of Immunochemistry Applications to FDA'' (Guidance), for the purpose of documenting manufacturing. The FDA Guidance provides details about data that may be submitted to comply with § 809.10.

In considering whether to place any adjunctive IHC's into class I, FDA focused on whether this level of regulation is adequate for the protection of public health. FDA considers the total test performance for any in vitro diagnostic device to be dependent on the net results of preanalytic, analytic, and postanalytic factors. For example, variability in IHC results may be introduced at every step including collection and fixation of the specimen, automated processing, embedding, sectioning, staining of the final slide preparation, and the microscopic interpretation by the pathologist. FDA regulation and review are directed at ensuring that the manufacturer characterizes, manufacturers, and labels the IHC appropriately before it is marketed for professional use. Ongoing initiatives by professional organizations, manufacturers, and FDA are directed at ensuring that pre- and postanalytic, as well as analytic procedures, are properly performed. In the context of these initiatives, FDA believes that class I regulation will assure that these adjunctive IHC's are used safely and effectively.

IHC's that provide the pathologist with adjunctive diagnostic information that is ordinarily reported as independent diagnostic information to the ordering clinician are proposed to be classified in class II. Examples are IHC's for immunologic detection and semi-quantitative measurement of specific ligand markers of proliferation, such as Ki-67, or semi-quantitative determination of other analytes, such as hormone receptors, if they are reported for their prognostic implications. However, this classification does not apply to estrogen and progesterone receptors, which are in class III by previous regulation, and which provide

information that is the basis for significant medical decisions substantially independent of other pathological tests. FDA is proposing that class II IHC's be subject to general controls and to a special control: The FDA Guidance for submissions of Immunohistochemistry Applications to FDA (the guidance) (Ref. 6). The agency believes that the manufacturer/sponsor can establish reasonable assurance of the safety and effectiveness of a class II IHC by providing valid scientific evidence from sponsor-supported studies, as described in the guidance, or from the scientific literature. The guidance was drafted with input from the Biological Stain commission, the Joint Council of Immunohistochemistry Manufacturers, the College of American Pathologists, the American Society of Clinical Pathology, FDA, and comments from the public. The guidance also will provide information to aid the end-users of IHC's (pathologists and other laboratorians) with recommendations about appropriate positive and negative control tissue sections (or cytologic preparations) for each intended use of the IHC. The guidance will also describe the form and content for the package insert of IHC's and provide the sponsor with detailed recommendations about how to comply with § 809.10 (Ref. 6).

IHC's that generate information that is reported directly to the clinician to be used as the basis for significant medical decisions, and that either provide information substantially independent of other pathological (or cytopathological) aspects of the specimen or that have novel claims not supported by current widely accepted scientific pathophysiologic principles, would be categorized as class III. Examples of IHC's FDA proposes to put in class III are markers of clinically significant genetic mutations in tissues that are normal by conventional histopathology.

IV. 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. Taylor, C. R., and Cote, R. C., ''*Immunomicroscopy: A Diagnostic Tool for the Surgical Pathologist*,'' 2d ed., Philadelphia, W. B. Saunders, 1994.

2. True, L. D. (ed)., *Atlas of Diagnostic Immunohistopathology*, Philadelphia, Lippincott, 1990.

3. Nadji, M., and Morales, A. R., ''Immunoperoxidase Techniques: A Practical Approach to Tumor Diagnosis'' Chicago, American Society of Clinical Pathologists Press, 1986.

4. Taylor, C. R., ''Quality Assurance and Standardization in Immunohistochemistry,'' A Proposal for the Annual Meeting of the Biological Stain Commission, June 1991, *Biotechnic & Histochemistry*, 67:110–117, 1992.

5. Transcripts of the Hematology and Pathology Devices Panel meeting, October 21, 1994.

6. FDA Guidance for Submission of Immunohistochemistry Applications to the FDA, FDA Center for Devices and Radiologic Health, 1995, available through the Division of Small Manufacturers' Assistance (DSMA), 1–800–638–2041.

7. Taylor, C. R., et al., Report of the Immunohistochemistry Steering Committee of the Biological Stain Commission, ''Proposed Format: Package Insert for Immunohisto Chemistry Products,'' *Biotechnic & Histochemistry*, 67:328–338, 1992.

V. Environmental Impact

The agency has determined under 21 CFR 25.24(e)(2) 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.

VI. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96–354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the proposed rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the agency believes only a small number of firms will be affected by this rule when finalized, the agency certifies that the proposed rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

VII. Request for Comment

Interested persons may, on August 30, 1996 submit to the Dockets 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 864

Blood, Medical devices, Packaging and containers.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 864 be amended as follows:

PART 864—HEMATOLOGY AND PATHOLOGY DEVICES

1. The authority citation for 21 CFR part 864 continues to read as follows:

Authority: Secs. 501, 510, 513, 515, 520, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351, 360, 360c, 360e, 360j, 371).

2. Section 864.1860 is added to subpart B to read as follows:

§ 864.1860 Immunohistochemistry reagents and kits.

(a) *Identification*. Immunohistochemistry test systems (IHC's) are in-vitro diagnostic devices consisting of polyclonal or monoclonal antibodies labeled with directions for use and performance claims, which may be packaged with ancillary reagents in kits. Their intended use is to identify, by immunological techniques, antigens in tissues or cytologic specimens. Similar devices intended for use with flow cytometry devices are not IHC's.

(b) *Classification of immunohistochemistry devices*. (1) Class I for IHC's that provide the pathologist with adjunctive diagnostic information that may be incorporated into the pathologist's report, but that is not ordinarily reported to the clinician as an independent finding. These IHC's are used after the primary diagnosis of tumor (neoplasm) and malignancy is made by conventional histopathology using nonimmunologic histochemical stains such as hematoxylin and eosin. Examples of class I IHC are differentiation markers, such as keratin, which are used in adjunctive tests to subclassify malignant tumors.

(2) Class II for IHC's that provide the pathologist with adjunctive diagnostic information that is ordinarily reported

as independent diagnostic information to the ordering clinician. Examples are IHC's for immunologic detection and semi-quantitative measurement of specific ligand markers of proliferation, such as Ki-67, or semi-quantitative determination of other analytes, such as hormone receptors, if they are reported for their prognostic implications. However, this classification does not apply to estrogen and progesterone receptors that are classified as class III devices.

(3) Class III for IHC's that generate information that is reported directly to the clinician to be used as the basis for significant medical decisions, and that either provide information substantially independent of other pathological (or cytopathological) aspects of the specimen or that have novel claims not supported by current widely accepted scientific pathophysiologic principles. Examples are markers used to identify clinically significant genetic mutations in tissues that are normal by conventional histopathologic examination.

(c) *Date PMA or notice of completion of a PDP is required.* No effective date has been established for the requirement for premarket approval for the devices described in paragraph(b)(3) of this section. See § 864.3 for effective dates of requirement for premarket approval.

Dated: May 31, 1996.

D.B. Burlington,

Director, Center for Devices and Radiological Health.

[FR Doc. 96–15140 Filed 6–13–96; 8:45 am]

BILLING CODE 4160–01–F

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 180

[PP 5E4573/P662; FRL–5375–1]

RIN 2070–AC18

Fenarimol; Pesticide Tolerance For Residues in or on Filberts

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: EPA proposes to establish a tolerance for residues of the fungicide fenarimol in or on the raw agricultural commodity filberts. The proposed regulation to establish a maximum permissible level for residues of the fungicide was requested in a petition submitted by the Interregional Research Project No. 4 (IR-4).

DATES: Comments, identified by the docket number [PP 5E4573/P662], must be received on or before July 15, 1996.

ADDRESSES: By mail, submit written comments to: Public Response and Program Resources Branch, Field Operations Division (7506C), Office of Pesticide Programs, Environmental Protection Agency, 401 M St., SW., Washington, DC 20460. In person, bring comments to: Rm. 1132, CM #2, 1921 Jefferson Davis Highway, Arlington, VA 22202.

Comments and data may also be submitted to OPP by sending electronic mail (e-mail) to: opp-docket@epamail.epa.gov. Electronic comments must be submitted as an ASCII file avoiding the use of special characters and any form of encryption. Comments and data will also be accepted on disks in WordPerfect 5.1 file format or ASCII file format. All comments and data in electronic form must be identified by the docket number [PP 5E4573/P662]. Electronic comments on this proposed rule may be filed online at many Federal Depository Libraries. Additional information on electronic submissions can be found in the ''SUPPLEMENTARY INFORMATION'' section of this document.

Information submitted as a comment concerning this document may be claimed confidential by marking any part or all of that information as ''Confidential Business Information'' (CBI). CBI should not be submitted through e-mail. Information marked as CBI will not be disclosed except in accordance with procedures set forth in 40 CFR part 2. A copy of the comment that does not contain CBI must be submitted for inclusion in the public record. Information not marked confidential may be disclosed publicly by EPA without prior notice. All written comments will be available for public inspection in Rm. 1132 at the Virginia address given above, from 8 a .m. to 4:30 p.m., Monday through Friday, excluding legal holidays.

FOR FURTHER INFORMATION CONTACT: By mail: Hoyt L. Jamerson, Registration Division (7505W), Office of Pesticide Programs, Environmental Protection Agency, 401 M St. SW., Washington, DC 20460. Office location and telephone number: Sixth Floor, Crystal Station #1, 2800 Jefferson Davis Highway, Arlington, VA 22202, (703) 308–8783; e-mail: jamerson.hoyt@epamail.epa.gov.

SUPPLEMENTARY INFORMATION: The Interregional Research Project No. 4 (IR-4), New Jersey Agricultural Experiment Station, P.O. Box 231, Rutgers University, New Brunswick, NJ 08903, has submitted pesticide petition (PP) 5E4573 to EPA on behalf of the Oregon Filbert Commission.

This petition requests that the Administrator, pursuant to section 408(e) of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a(e), amend 40 CFR 180.421 by establishing a tolerance for residues of the fungicide fenarimol [alpha-(2-chlorophenyl)-alpha-(4-chlorophenyl)-5-pyrimidine methanol] in or on the raw agricultural commodity filberts at 0.02 parts per million (ppm).

The scientific data submitted in the petition and other relevant material have been evaluated. The toxicological data considered in support of the proposed tolerance include:

1. A 1–year feeding study with dogs fed diets containing 0, 1.25, 12.5, or 125 milligrams/kilogram (mg/kg)/day. The no-observed-effects level (NOEL) for this study is established at 12.5 mg/kg/day. The high dose level (125 mg/kg/day) caused increased serum alkaline phosphatase, increased liver weights, an increase in *p*-nitroanisole *o*-demethylase activity, and mild hepatic bile stasis.

2. A 2–year chronic feeding/carcinogenicity study in rats fed diets containing concentrations of 0, 50, 130, or 350 ppm (equivalent to 0, 2.5, 6.5, or 17.5 mg/kg/day) with a systemic NOEL of 130 ppm (equivalent to 6.5 mg/kg/day). An increase in fatty liver changes was observed in rats fed diets containing 350 ppm. There were no carcinogenic effects observed under the conditions of the study.

3. A second 2–year chronic feeding/carcinogenicity study in rats fed diets containing 0, 12.5, 25, or 50 ppm (equivalent to 0, 0.63, 1.25, or 2.5 mg/kg/day) with no systemic or carcinogenic effects observed under the conditions of the study.

4. A 2–year carcinogenicity study in mice fed diets containing concentrations of 0, 50, 170, or 600 ppm (equivalent to 0, 7, 24.3, or 85.7 mg/kg/day) with a NOEL for systemic effects at 170 ppm. An increase in fatty liver changes was observed in mice at the 600 ppm dose level. There were no carcinogenic efects observed under the conditions of the study.

5. A developmental toxicity study with rabbits given oral doses of 0, 5, 10, or 35 mg/kg/day with no developmental toxicity observed under the conditions of the study.

6. A developmental toxicity study with rats given oral doses of 0, 5, 13, or 35 mg/kg/day demonstrated hydronephrosis at 35 mg/kg/day. The NOEL for developmental toxicity in this study is established at 13 mg/kg/day.