DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 864

[Docket No. 94P–0341]

RIN 0910–ZA10

Medical Devices; Classification/ Reclassification of Immunohistochemistry Reagents and Kits

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule to classify/reclassify immunohistochemistry reagents and kits (IHC's) into three classes depending on intended use. FDA is classifying/reclassifying into class I (general controls) and exempt from premarket notification requirements IHC's used as adjunctive tests and presenting a low risk to public health. FDA is classifying/reclassifying into class II (special control) IHC's that detect or measure certain target analytes and that provide prognostic or predictive data that is not confirmed by routine histopathologic control specimens. The results of the class II IHC's are reported independently to the clinician, and the performance claims are widely accepted and supported by valid scientific evidence. FDA is classifying/reclassifying into class III (premarket approval) IHC's intended for any other use. The scope of products covered by this final rule includes both pre-1976 devices that have not been previously classified, as well as post-1976 devices that are statutorily classified into class III. The intent of this final rule is to regulate pre-1976 devices and post-1976 devices in a consistent fashion. Therefore, FDA is classifying or reclassifying these products as applicable.

EFFECTIVE DATE: This rule is effective August 17, 1998.

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SUPPLEMENTARY INFORMATION:

I. Background

Immunohistochemistry (IHC) is the diagnostic laboratory practice that combines immunologic techniques, using specially prepared antibody reagents, with the examination of intact cells and tissues under the microscope by a pathologist or other trained laboratory scientist. An IHC device is an in vitro diagnostic reagent or test kit that uses immunological methods to identify antigens in tissues or intact cells. An IHC reagent is the primary antibody of an IHC assay that is developed to specifically target, react to, or combine with, a particular cellular or tissue constituent, or antigen, using specific immunological characteristics of the antibody. IHC's may be used together with a secondary or reporter antibody, buffers, washing solutions, and controls. If an IHC primary antibody reagent is sold separately, there should be recommendations for what ancillary reagents and equipment should be used with the IHC reagent to achieve the performance characteristics claimed for the primary IHC reagent. If the IHC is marketed as a test kit, there should be performance data with the finished test kit.

II. Highlights of the Final Rule

In response to public comments, FDA has revised and clarified certain provisions of the final regulation. The revisions maintain the protection of the public health while reducing the regulatory burden on manufacturers by lowering the classification of a number of IHC's. The most significant changes from the proposed rule are as follows:

1. Under the final rule, most IHC's are being classified as class I devices, exempt from premarket notification. Class I includes all IHC's being used as adjuncts to conventional histopathologic diagnostic examination.

2. The definition of class II IHC's has been changed to include IHC's that are not directly confirmed by routine histopathologic control specimens and with claims that are widely accepted and supported by valid scientific evidence. Class II IHC's now include such products as estrogen and progesterone receptors (ER/PR's).

3. The definition of class III IHC's has been narrowed to include only those IHC's that do not meet the criteria for class I or II.

4. Accordingly, the rule lessens the regulatory burden for bringing IHC's to market because most IHC's are now classified/reclassified as class I or II. As post-1976 devices, most IHC's previously were class III devices under section 513(f)(1) of the Federal Food, Drug, and Cosmetic Act) (the act) (21 U.S.C. 360c(f)(1)).

In addition, the agency clarifies and reinforces the following points:

1. This final rule regulates only IHC's being used for diagnostic purposes. Neither the proposed rule nor the final rule would require submissions for reagents or test kits used for research purposes only. Nor does FDA require manufacturers of such research use only reagents or test kits to comply with general controls; and

2. IHC's used for diagnostic purposes have been and will continue to be subject to the current good manufacturing practices (CGMP's) under the act. The requirement to comply with CGMP's is a general control that all devices must meet (unless expressly exempt under section 513(d)(2)(A)) of the act without regard to their level of classification or whether they have been previously classified. (See H. Rept. 94–853 at 17 (1976).)

III. The Final Rule

A. General Approach

FDA believes that the final rule establishes reasonable requirements that can be implemented by the regulated industry without unnecessary burden. To ensure safety and effectiveness, all classes of IHC's will be subject to the following general controls: (1) Labeling requirements for in vitro devices (§ 809.10 (21 CFR 809.10)), (2) compliance with CGMP's, (3) registration and listing, (4) recordkeeping and medical device reporting (MDR), and (5) labeling for prescription use (§ 801.109 (21 CFR 801.109)). FDA has determined that these controls are necessary for a reasonable assurance of safety and effectiveness.

B. Class I Exempt From Premarket Notification

In the final rule, FDA has broadened the class I identification to include all adjunctive IHC's. This change places the majority of IHC's into class I. The final rule also modifies the language in the regulation to clarify that class I IHC's are used to classify tumors.

In response to comments submitted on the proposed rule, FDA reconsidered the regulation of class I IHC's and decided to exempt them from premarket notification (510(k)) requirements. In considering whether to exempt class I devices from premarket notification, FDA focuses on whether notification for the type of device is necessary for the protection of the public health. For the devices exempted from premarket notification by this rule, FDA has concluded that notification is unnecessary primarily for the following reasons:

1. The devices do not have a significant history of false or misleading performance claims or of risks

associated with inherent characteristics of the device, such as device design or materials. When making such determinations, FDA generally has considered the frequency, persistence, cause, or seriousness of such performance claims or risks, as well as other relevant factors.

FDA is unaware of IHC failure being reported in the MDR data base. IHC failures have been reported in the medical literature; the risks of such failure, however, are mitigated by widely accepted practices that are based on valid scientific evidence.

2. In general, FDA will exempt a device from premarket notification when the following factors apply: (a) Characteristics of the device necessary for its safe and effective performance are well established; (b) anticipated changes in the device that could affect safety and effectiveness will either be readily detectable by users by visual examination or other means, such as routine testing, before causing harm (e.g. testing of a clinical laboratory reagent with positive and negative controls), or not materially increase the risk of injury, incorrect diagnosis, or ineffective treatment; and (c) any changes in the device would not be likely to result in a change in the device's classification. FDA makes these determinations based on its knowledge of the device, including past experience and relevant reports or studies on device performance.

The characteristics of IHC's are well established. Although the method is not generally quantitative, the results generated using this technology are sufficiently accurate and precise to support subclassification of tumors (neoplasms), and detection and measurement of the presence or absence of clinically significant target analytes. There are sufficient quality assurance techniques in the use of IHC's to enhance the precision of the methodology and minimize the risks of misdiagnosis.

Because class I IHC's are identified as those that are used adjunctively to support conventional histopathological diagnosis and are controlled by readily available internal and external control materials, minor changes to the IHC would not materially increase the risk of injury, incorrect diagnosis, or ineffective treatment. Adjunctive test results are evaluated and incorporated into the diagnostic interpretation by the pathologist and are not usually reported directly to the clinician. Because laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) are required to run positive and negative quality control samples with all special stains, reagent failures are likely to be easily identified by pathologists. In addition, most slides will have normal along with abnormal tissue included as part of the tissue sample on the slide and this juxtaposition affords an additional opportunity to identify inappropriate or uncommon staining patterns.

Manufacturers are reminded that exemption from the requirement of premarket notification is not an exemption from CGMP's and the other applicable general controls.

Because IHC's have been classified in accordance with the risk associated with their intended use, a change in intended use or indications for use of an IHC would likely result in a reclassification. Such a change would not be considered minor and would probably require a submission to the agency. For a discussion of whether a change to a device would require a manufacturer to submit a 510(k), see the FDA's guidance entitled ''Deciding when to Submit a 510(k) for a Change to an Existing Device.''

C. Class II

In contrast to all adjunctive IHC's being placed into class I, the final rule clarifies that class II IHC's are IHC's that generate results that are not directly confirmed by routine histopathologic internal and external control specimens. Class II IHC's are intended to provide information that is ordinarily reported as independent diagnostic information to the clinician. For an IHC to be classified into class II, the claims associated with this information must be widely accepted and supported by valid scientific evidence. FDA believes that the manufacturer/sponsor can establish the acceptance of the intended use of the IHC and valid scientific evidence through sponsor-supported studies or scientific literature references, materials from professional educational seminars, and/or the citation of practice standards or guidelines, as described in the special control noted in the paragraph below. These IHC's must be developed and established by validation and correlation testing with well characterized clinical specimens that support the intended use of the IHC test system as an independent prognostic or predictive marker. FDA believes that providing valid scientific evidence of performance claims that are widely accepted and complying with the general controls should be sufficient to ensure the safe and effective use of these IHC's.

Class II IHC's are subject to a special control entitled ''FDA Guidance for Submission of Immunohistochemistry Applications to the FDA,'' FDA, Center for Devices and Radiologic Health, 1998. The updated guidance will assist sponsors in collecting and presenting data to FDA to establish that the claims associated with use of the device are widely accepted and that there is valid scientific evidence to support performance claims with clinical specimens. The special control is also intended to provide guidance to manufacturers about labeling for use of the device. This guidance has been issued as a Level 2 guidance consistent with the ''Good Guidance Practices'' (GGP's) FDA adopted for the development, issuance, and use of guidance documents (62 FR 8961, February 27, 1997). Persons interested in obtaining this document should refer to section VI of this document entitled ''Access to the Special Control.''

Several comments urged that IHC's for ER/PR's be classified as class II devices rather than as class III, as proposed. FDA concurs with this suggestion. By using well characterized clinical specimens and validating their IHC's against appropriate FDA approved chemical receptor assays, manufacturers can reliably characterize these products and support their clearance as class II devices. FDA believes that class II classification can now safely apply to IHC's for ER/PR's, including hormone receptors in breast cancer, because clinical reliance on such testing has been established in the medical literature and the information derived from such test results are well understood.

D. Class III

In response to comments on the proposed rule and changes to the class II classification, FDA has narrowed the scope of the class III identification. Under the final rule, IHC's that do not meet the criteria for class I or II will be classified into class III. Manufacturers of these IHC's must submit valid scientific evidence to support the new intended uses. An example of a class III IHC would be markers used to identify new, clinically significant target analytes in tissue specimens that cannot be confirmed by conventional histopathologic examination.

FDA has amended proposed § 864.1860(c) to indicate that postamendment class III IHC's cannot be commercially distributed unless the manufacturer has an approval under section 515 of the act (21 U.S.C. 360e).

IV. The Proposed Rule

In the **Federal Register** of June 14, 1996 (61 FR 30197), FDA published a

proposed rule to classify/reclassify IHC's. The proposed rule contained the reasons for the proposed classification/reclassification, summarized the Hematology and Pathology Device Panel's recommendation regarding the classification of IHC devices, identified the risks to health presented by the devices, included a summary of the data upon which the proposed classification/reclassification was based, and delineated the statutory authority under which FDA issues this rule. Written comments were due August 30, 1996.

The agency received 26 comments from individuals, manufacturers, professional societies, and the U.S. Small Business Administration. A summary of the written comments and FDA's response to them is provided in section V of this document.

V. Response to Comments

A. Classification

1. Two comments supported the classification of IHC reagents and test kits into classes based on intended use as a balanced and responsible level of regulation that would: (1) Not impinge on the continued availability of these materials; (2) not negatively impact the advance of new technology due to application of inappropriately stringent regulatory controls; (3) not be overly burdensome to FDA or industry; or (4) not be inconsistent with the needs and interests of the medical professions, clinical laboratories, FDA, and industry.

A third comment agreed with most of the proposed classification designations. A fourth comment stated that IHC's intended for adjunctive use were appropriately classified into class I. A fifth comment stated that most immunohistochemical antibody reagents should be regulated as class I because if they were ''over-regulated'' it would be difficult to bring the antibodies to market and the reagents were needed daily in the practice of surgical pathology.

A sixth comment suggested that the proper classification for many IHC reagents and test kits would be class I 510(k) exempt in vitro diagnostic (IVD) devices. The comment argued that premarket notification (510(k)) should not be necessary because: (1) 510(k) clearance will not impact significantly on the expertise of the pathologist nor on the quality or reproducibility of immunocytochemistry/immunohistochemistry, which was the central factor in the safe and effective use of immunocytochemistry/immunohistochemistry; (2) 510(k) clearance provided false reassurance to the inexperienced end user in making diagnoses based on possibly erroneous interpretations of data; and (3) of the negative implications of the cost of 510(k) clearance.

A seventh comment argued that the benefits do not outweigh the costs for class I devices to be required to submit a 510(k). The comment argued that manufacturers have no control over how accurately a pathologist interprets results and that the correct focus should be on CGMP standards and other key determinants of manufacturing consistency and compliance.

An eighth comment believed the majority of IHC's should be class I and exempt from premarket notification requirements. The comment argued that production of the antibody product was not the most critical and subjective step in this diagnostic technique and that FDA's resources were better spent in the area of ensuring reliable and consistent production through the controls of CGMP's, medical device reporting, registration, etc., to assure manufacturing consistency and compliance.

FDA has considered these comments and has concluded that premarket notification is unnecessary for the protection of the public health for class I IHC's, which are those used to produce diagnostic information that is confirmed readily by other tests or procedures. Section 513(d)(2)(A) of the act authorizes FDA to exempt class I IHC's from the requirement of premarket notification in section 510(k) of the act (21 U.S.C. 360(k)). This exemption permits manufacturers to introduce into commercial distribution those IHC's that fall within the class I classification without obtaining premarket clearance from FDA. 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 classifying these devices as class I and applying general controls will ensure that the majority of adjunctive IHC's are used safely and effectively without the need to require premarket notification. The Food and Drug Administration Modernization Act of 1997, which became effective on February 19, 1998, does not eliminate the need for this rule or require changes with respect to FDA's determinations about classification of these products. The rule establishes a classification scheme for all IHC's including many that were not previously classified as well as class III IHC's. The class I IHC's that are exempt from premarket notification under this rule do not fall into the category of those class I devices that continue to require premarket notification under the new legislation (section 510(l) of the act). Nor does the agency believe that the IHC's being classified into class II by this rule are appropriate for exemption from 510(k) submissions under new section 510(m) of the act.

2. One comment requested clarification concerning the scope of the proposed regulation as it pertains to ''ancillary reagents'' (including detection systems). The comment recommended that ancillary reagents, including secondary antibodies, buffers, and chromogens, should most appropriately be regulated as general purpose reagents under § 864.4010 (21 CFR 864.4010), and subject to § 864.1860 (21 CFR 864.1860) only when packaged with one or more primary antibodies as components of a complete test system.

FDA agrees in part with the comment. ''Ancillary reagents'' are subject to § 864.1860 when they are packaged with one or more primary antibodies as a complete test system. In addition, ancillary reagents are also subject to this regulation when they are sold with performance claims for their use as a general detection system in conjunction with primary antibodies that are sold separately. FDA agrees that secondary antibodies, buffers, and chromogens may be regulated as general purpose reagents under § 864.4010 when these reagents are sold without performance claims.

3. Two comments requested clarification concerning whether devices in commercial distribution prior to May 28, 1976, must comply with the classification and requirements in the proposed rule, particularly the proposed labeling recommended in the March 28, 1995, guidance listed as Ref. 6 in the proposal (61 FR 30197 at 30199). The comment argued that the regulation of ''pre 1976 devices which have not been previously classified'' contradicts § 807.85(b)(1) (21 CFR 807.85(b)(1)), which exempts ''grandfathered'' products from 510(k) review.

These comments misunderstand the meaning of § 807.85(b)(1). Section 807.85(b)(1) establishes exemptions from premarket notification for private label distributors and repackagers who distribute devices that already are being legally marketed without making any changes to the device or its labeling beyond the addition of the private label name. The exemptions in § 807.85(b)(1) do not apply to device manufacturers and distributors generally.

It is true that the requirement to submit a premarket notification before introducing a device into the market

after May 28, 1976, does not apply to devices that were legally marketed prior to that date. However, as explained in 21 CFR 807.81(a)(3), a manufacturer of a device that was marketed prior to the 1976 amendments is required to file a 510(k) if the devices was significantly changed or modified in design, components, methods of manufacture, or intended use. A first time manufacturer of a device that the manufacturer believes to be the same or substantially equivalent to a device that is already marketed also must submit a 510(k) to establish that substantial equivalence, unless the product has been exempted from notification under 513(d)(2)(A).

As discussed previously, preamendment devices have been and will continue to be subject to general controls, such as CGMP's and the existing labeling requirements (§ 809.10) for in vitro devices. Although manufacturers of preamendment class II IHC's that are not required to submit 510(k)'s will have no need to utilize FDA's guidance being established as a special control, manufacturers of preamendment devices that are modified in a way that will require submission of a new 510(k) should consult the special control: ''FDA Guidance for Submission of Immunohistochemical Applications to the FDA'' when submitting premarket notifications for class II devices. Because this special control is a guidance, no manufacturer is bound to follow the details of the document (see response to comment 13 in section V of this document).

4. Three comments argued that additional regulation will do nothing to lower the risk of misinterpretation of results. The comment stated that IHC's have almost always been used as an adjunct to other diagnostic techniques and that the proposed regulations would not necessarily accomplish FDA's stated objectives of reducing risks to patients.

FDA's regulation of IHC assays is limited to oversight of the manufacturers of IHC reagents or test kits; the rule does not regulate the end users or their laboratories. FDA recognizes that safe and effective IHC's do not by themselves guarantee that an IHC in the end user's laboratory will be used accurately and reliably. FDA agrees that IHC assays are multistep IVD test systems that require the expert supervision of a qualified pathologist or laboratory scientist to ensure that all the preanalytic, analytic, and postanalytic steps are performed accurately and reliably.

FDA believes, however, that the building blocks of those assays should be safe, effective, and properly labeled for their intended use. The risks associated with use of an IHC include the likelihood of obtaining a false result, while the effectiveness of an IHC is dependent upon the likelihood of the IHC performing as claimed by the manufacturer. In accordance with § 809.10, the label must include, among other things, the intended use, indications for use, the instructions for use, and limitations. The manufacturer is required to support any performance claims for accuracy, precision, sensitivity, and specificity included on the label of the IHC device with valid scientific evidence. The labeling also should include statements that remind the end user of the variable nature of the specimens to be examined by the IHC, i.e., biologic variability of the tissues and patients, the need for procedures relating to preanalytic fixation, handling, processing, storage, and the variability and subjectivity in the interpretation of the IHC slides.

Contrary to the assertion of some comments, FDA believes that such regulation does reduce risks associated with use of IHC's. The requirements that labeled performance claims be supported by valid scientific evidence and that labeling include instructions for use, limitations, and information about variability significantly increases the likelihood that the end user will have a product that will be used safely and effectively in the laboratory.

In response to comments that implied that industry experts did not believe regulation of IHC's was necessary to reduce risks associated with their use, FDA notes that its classification/reclassification initiatives with respect to IHC's are based on input from public workshops, advisory panels to the FDA, and industry petitions for reclassification, as well as FDA experience with assessment of the safety and effectiveness of IHC devices.

FDA is aware that its regulation of IHC's is supported by other assurances of safe and effective performance of the assays. For example, there is widespread participation by end users in voluntary and mandatory training in IHC assays and proficiency testing in IHC assays by other government and professional organizations. End users may also use voluntary guidelines to ensure reliable and accurate performance of IHC assays within their laboratories, e.g., ''The National Committee for Clinical Laboratory Standards (NCCLS) Quality Assurance for Immunocytochemistry; Proposed Guideline, MM4–P,'' February, 1997. (The approved NCCLS guideline is expected within 2 years.) However, FDA believes such voluntary standards and practices cannot serve as a complete substitute for government regulation of these devices. The existence of such guidelines and widespread compliance with their recommendations has contributed to FDA's determination that most of these devices can be regulated at the least stringent level of control and be exempt from premarket notification.

5. One comment did not support placing IHC's in which test results were ''ordinarily reported as independent diagnostic information'' into class II because the manner in which IHC test results were reported was determined independent of the IHC supplier or FDA. The comment stated that because there may be significant laboratory-to-laboratory and within-laboratory variation in how results were reported, it would be difficult to consistently determine device classification on the basis of how results were reported.

FDA agrees that the IHC manufacturer is not responsible for how each end user laboratory scientist will report the results of an IHC assay. However, the manufacturer is responsible for recommendations and performance claims on the product's label (see § 809.10). Such indications and directions for use are important for the proper performance of the assay and as a reference for compliance with the CLIA requirements for the end user laboratory (42 CFR 493.1211). An individual laboratory that chooses to use the device differently or report results in a manner contrary to labeled recommendations is responsible for that decision and validation of that use.

FDA defines independent diagnostic information as information that: (1) Is the sole or a major determinant of a diagnosis; (2) is used by itself as the basis for a significant medical decision; or (3) may not be readily confirmed by other diagnostic tests or clinical procedures. FDA believes it is possible to identify IHC's for which test results ordinarily are reported as independent diagnostic information to the ordering clinician, and for which the claims associated with these data are widely accepted and supported by valid scientific evidence. Those IHC's that generate independent diagnostic information and where the claims are not widely accepted will be reviewed as class III devices and approved for marketing if there is valid scientific evidence to support those claims.

6. One comment stated that it was unclear why Ki-67 was class II, while hematoxylin and eosin (H & E) staining, which was the more critical assay, was class I. The comment added that class II reagents had no characteristics clearly

distinguishable from those proposed to be in class I.

The agency believes there are differences between H & E stains and IHC's. Despite the critical nature of the assay, biologic stains such as H & E have been placed in class I and exempted from 510(k) review because FDA determined that the stains were well understood, with commonly used controls that permit the user to readily detect deviations in staining properties. For these reasons, FDA concluded that general controls were sufficient and 510(k) submissions were not necessary to establish reasonable assurance of safe and effective use of H & E stains. IHC's, on the other hand, use monoclonal or polyclonal antibodies that may require specific testing or reagents to verify that the assay meets the manufacturer's specification for performance (see also comment 14 of section V of this document). Under the final rule, however, most IHC's will also be regulated as class I devices exempt from premarket notification.

FDA has made changes to the final rule that further distinguish class I from class II IHC's. Class I IHC's are adjunctive IHC's. Class II IHC's generate results that ordinarily are independently reported to the clinician. However, the primary difference between a class I or II IHC depends on the manufacturer's claims in the proposed product labeling for an IHC reagent or test kit because it is these claims that establish the intended use of the IHC. An identical device can be subject to a range of regulatory controls—from the lowest to the highest levels of regulation—depending on the claims being made and on the issues of safety and effectiveness associated with those claims.

Ki-67, the example referenced in the comment, is the name of a monoclonal antibody clone that recognizes a nuclear antigen that is expressed only in proliferating cells. A Ki-67 IHC will yield a positive qualitative result in normal and abnormal proliferating cells. This result correlates with the presence of mitotic activity. A Ki-67 IHC would be classified into class I, exempt from premarket notification if: (a) The intended use of the assay result is to provide adjunctive information that indicates the presence or absence of cell proliferation in all or some of the cells within a tissue sample; (b) the IHC can be controlled by the user with readily available positive and negative tissues controls; (c) the result will be incorporated into the pathologist's differential diagnosis; and (d) the result will not be reported as independent information to the clinician.

A Ki-67 IHC would be classified into class II if: (a) The sponsor claims that the IHC results could be used as a stand-alone test to determine prognosis independent of other findings; (b) the user must use clinically well-characterized tissues to serve as positive and negative controls; or (c) the analytic result will be reported as independent information to the clinician. A Ki-67 IHC would be classified into class III if the sponsor claims that the IHC will be used in combination with a novel amplification method that would allow this IHC to be used as a stand-alone detection system for micrometastases in tissue, or some other new intended use.

The previous comment was in response to the proposed rule. As discussed previously, the final rule establishes that the majority of IHC's are adjunctive and will fall within class I, exempt from premarket notification. For those IHC's that are not adjunctive, the majority will be class II because they have claims that are widely accepted and supported by valid scientific evidence.

7. FDA received conflicting comments about the necessity of classifying certain types of IHC's in class III. Two comments stated that IHC's intended for stand-alone use in making clinically significant determinations, such as markers used for the detection of medically important genetic mutations in tissues that were normal by conventional histopathology, should be regulated as class III devices until more information regarding the safety and effectiveness of these tests became available. A third comment stated that, with the exception of a limited number of class III devices that define a site-specific therapeutic intervention and were used to provide circumstantial information in support of H & E based histopathological diagnosis, markers should be classified as class I exempt from premarket notification. A fourth comment added that the higher classifications were not relevant because currently there was no IHC for a prognostic/proliferation marker that was a reliable ''stand-alone'' indicator and whose use was generally accepted.

FDA agrees that the IHC's described in the first two comments should be regulated as class III devices and not be commercially marketed until a premarket approval application (PMA) establishes that there is valid scientific evidence to support safe and effective use of such products. The agency also agrees with the general point being made by the third comment and has classified the majority of IHC's into class I and exempted them from premarket notification requirements. With respect to the fourth comment, the agency does not agree that the identification of class III IHC's is not relevant. The fact that the comment is unaware of products currently on the market that fit the identification does not obviate the need for FDA to have regulations in place for review of such products when they become available.

B. Costs

8. One comment stated the FDA may also have underestimated the cost associated with the submission of 510(k) and PMA's and compliance inspections for many firms engaged in manufacturing IHC's for research purposes that will be required to register under the new rule.

This comment was made under the mistaken assumption that this rule applied to manufacturers of research products as well as to manufacturers of IHC's marketed for diagnostic use. As noted previously, this rule does not apply to manufacturers of research products and, therefore, imposes no new burden on them. FDA also believes that this comment was made under the mistaken assumption that this rule would create a new requirement for firms to comply with CGMP's. As discussed previously, the requirement to meet CGMP's is not the result of this rulemaking; manufacturers of IHC devices marketed for diagnostic use have always been required to comply with CGMP's under section 520(f) of the act (21 U.S.C. 360j(f). Finally, FDA reiterates that it has reconsidered its position since the proposed rule and has established a classification scheme that does not require 510(k)'s for the majority of these IHC devices, and that places most remaining IHC's in class II. Therefore, existing firms that are currently in compliance with CGMP's should not experience any increased costs because of this rule.

C. Definition of IHC

9. One comment supported the proposed definition for IHC reagents and test kits because the definition distinguished between IHC reagents and analyte specific reagents (ASR's) or flow cytometry reagents. The comment also supported the use of performance claims and directions for use with IHC's.

FDA agrees with this comment. The definition of IHC's and labeling requirements have been retained in the final rule.

10. One comment was concerned that the IHC definition was ''technology-specific'' and limited to only those devices that employ monoclonal or polyclonal antibodies. The comment

argued that the operating technology used by the device should be of secondary consideration, provided that the test was intended for adjunctive use along with other conventional histopathology techniques.

FDA disagrees with this comment. Although the operating technology of the device is of primary importance in identifying an IHC, the intended use of the device will establish its regulatory class. The final rule provides a broad and inclusive regulatory path for commercialization of new versions of currently available IHC devices or IHC devices that are intended to detect a new analyte in tissues or cells. This classification/reclassification is intended to decrease the burden on FDA and industry by obviating the need to individually classify IHC devices that detect previously identified or newly identified analytes.

D. Estrogen and Progesterone Receptors

11. Three comments recommended that ER/PR's be placed in class II instead of class III, as had been proposed. One comment argued that regulating hormone receptors as class III medical devices may limit the availability of an important testing modality, forcing patients to rely upon less accurate methodology for testing results. Two comments maintained that ER/PR's should not be class III because they were not used as stand-alone tests; the information they provided was substantially dependent on other pathological or cytopathological aspects of the specimen, and these tests did not have novel claims not supported by current widely accepted scientific pathophysiologic principles. A third comment recommended reclassifying ER/PR assays into class II because it was likely that there was a sufficient accumulated history of safe and effective use of the tests to support the reclassification and because FDA had published a guideline for premarket submissions of ER/PR assays that could be used as a special control.

FDA agrees with these comments and has modified the regulation accordingly. The first IHC tests for ER/PR's were in vitro steroid-binding chemical assays that used dextran-coated charcoal to separate bound from free fractions. These IHC tests were subject to class III premarket approval because there was no substantially equivalent legally marketed predicate device, a necessary requirement to qualify for premarket notification (510(k)). There were additional safety and effectiveness considerations raised by these devices, including the likelihood that ER/PR results would be used as stand-alone test results that would serve as the basis for choice of therapy and the inability to confirm these results by other IVD tests or clinical procedures. However, after evaluating the comments and reviewing the peer-reviewed literature regarding use of these IHC's, FDA believes that IHC's for estrogen, progesterone, or other hormone receptors now can be classified/reclassified into class II under the final regulation when their claims are widely accepted and there is valid scientific evidence to support those claims.

12. Two comments stated that there was confusion about which products were covered under the proposed rule and used estrogen receptor (ER) as an example. The comment suggested it was not appropriate to place all ER's in a single class because that class could not take into account differences between broad antigen recognition and clones reacting with certain epitopes or populations of ER, even though there was no clinical utility for some clones.

FDA disagrees with these comments and believes they are based on a misunderstanding of the proposed rule. FDA does not intend to require premarket submissions for reagents or tests kits that are for ''research use only.'' The regulation requires premarket submissions only for ER/PR reagents or test kits that are intended to be marketed ''for in vitro diagnostic use'' to obtain clinical information. If an IHC reagent or test kit marketed for clinical use includes antibodies, FDA requires the IHC manufacturer to identify the clones of those monoclonal antibodies used in the IHC reagent or test kit that support that intended use.

E. Guidance Document

13. One comment argued that a guidance document cannot be a special control because using a draft guidance document as a special control is an inappropriate use of guidance documents, and that it seemed to contradict the interim policy announced by FDA concerning guidances to use a guidance as if it were a rule.

FDA disagrees that a guidance document cannot be a special control. ''Guidelines (including guidelines for the submission of clinical data in premarket notification submission * * *)'' are expressly listed in section 513(a)(1)(B) of the act as an example of special controls. In addition, FDA guidance documents are specifically listed as potential special controls in the legislative history of the Safe Medical Devices Act of 1990 (H. Committee Rept. 101–808, October 5, 1990, p. 28).

Moreover, consistent with FDA's policy on GGP's, the agency published for public comment a ''draft'' of this FDA guidance document in advance of it being used as a special control (62 FR 8961, February 27, 1997). The guidance entitled ''FDA Guidance for Submission of Immunohistochemical Applications to the FDA'' was developed by FDA in conjunction with professional organizations, manufacturers of immunohistochemical products, and the advisory committees of FDA. The draft has been revised in response to public comments, and the guidance is available to the public as delineated in section VI of this document.

FDA is using this guidance in conformance with its policy concerning guidances. The guidance is intended to provide information about acceptable ways to facilitate the gathering of data to ensure reasonable safety and effectiveness of those IHC devices whose safety and effectiveness cannot be ensured by general controls alone. Although the guidance represents FDA's best thinking about ways to efficiently and effectively gather and submit data to support the marketing of these devices, neither the manufacturer nor the agency is bound by the details of that guidance. As stated in the guidance document, manufacturers are free to use alternative methods that achieve the same underlying standard of safety and effectiveness.

F. Impact of Proposed Rule

14. One comment stated the author's belief that IHC's were utilized under the guidance of board certified pathologists a significant percentage of the time and had a performance record equal to or greater than stains used since the turn of the century. This comment maintained that undue restrictions on the use of the reagents would impact on the availability of existing and future antibodies to the detriment of patient care.

FDA agrees in part with this comment. FDA is treating IHC's used to provide adjunctive information the same as H & E stains by classifying these products into class I and exempting them from the requirement to submit 510(k)'s. Histopathologic and cytologic diagnostic tests that use either conventional stains such as hematoxylin and eosin or IHC methodologies are part of a multistep process that requires the direct supervision of a qualified pathologist or other laboratory scientist to ensure safe and effective results. However, FDA does not consider IHC's to be equivalent to conventional biologic stains and has not exempted IHC's from CGMP requirements although it did exempt the stains from CGMP's. FDA considers IHC's to be

more complex to develop, manufacture, and standardize. FDA exempted conventional biologic stains from premarket notification and compliance with CGMP's because these stains have well-established chemical and physical specifications and quality assurance. In addition, there are voluntary organizations such as the Biologic Stain Commission that test and certify the specifications of biologic stains. The final rule ensures that all commercialized IHC reagents and test kits for in vitro diagnosis are manufactured under general controls including CGMP, thereby enhancing reliability and consistency for end users of these products.

G. Panel Meeting

15. One comment stated that the October 21, 1994, meeting of the Hematology and Pathology Devices Panel (the Panel) was procedurally flawed. The comment referenced a complaint filed by a Washington, DC, law firm that FDA inaccurately described the regulations to the Panel members, and that this alleged misinformation was the basis for their recommendations. The comment recommended that it be stated in the administrative record that the advisory Panel meeting was procedurally flawed, that the Panel recommendations should not be used to support the decisions made by FDA about the classification of these products, or that the Panel meeting should be invalidated and reconvened for further consideration of the issue.

This comment refers to a complaint about a FDA employee's public comment that CGMP inspections for class I IVD device manufacturers are so relatively low on the priority list for the agency actions that there is a strong likelihood that these manufacturers will not get timely CGMP inspections. The comment argues that this statement exerted undue influence on the Panel. Because requiring compliance with CGMP's was a high priority for pathologists and other laboratory scientists, the comment asserts that the Panel recommended that IHC's should be class II medical devices in large part to ensure timely CGMP inspections.

FDA does not agree with this comments' characterization of the Panel meeting. While FDA agrees the Panel was concerned that IHC's be subject to CGMP's, FDA believes the availability and need for a special control is the basis for the Panel's recommendation that most IHC's be classified as class II. However, as discussed previously, FDA has reconsidered this recommendation of the Panel and amended the proposed rule to place most IHC's in class I and exempt from premarket notification. FDA does not believe that class II regulation is required for all IHC reagents and test kits for the reasons discussed in section III.B of this document. Unless specifically exempted, all manufacturers of FDA regulated medical devices must comply with general controls, which include CGMP's, regardless of whether or not the device is in class I, II, or III, or exempt from premarket notification. While FDA acknowledges that its limited resources do not allow inspections to be as frequent as it might wish, the agency's experience shows that competitors and dissatisfied customers will provide the agency with information about circumstances that require more immediate followup.

H. Practice of Medicine

16. One comment argued that whether a reagent was used to make ''significant medical decisions'' was an inappropriate criterion for classification. The comment argued that classifications did not rely on the intent of the manufacturer, but on the physician's usage, which the comment argued was the practice of medicine and beyond the responsibility of a manufacturer. The comment stated that the basis for device classification in this rule was medical practice (e.g. ''significant medical decisions,'' ''markers of clinically significant genetic mutations,'' and ''adjunctive diagnostic information that was ordinarily reported as independent diagnostic information to the ordering clinician'') that was inconsistent with the current requirements of law for determining classification and an attempt to regulate the practice of medicine.

FDA does not regulate medical practice. FDA regulates the manufacturers of IVD tests to ensure reasonable safety and effectiveness of these products for the claimed intended use and indications for use. The rule focuses on the use to which the information being generated by the IHC will be put because it is the IHC's intended use that determines the level of safety and effectiveness that must be assured. An IHC manufacturer must document the safety and effectiveness of these intended uses and indications for use with valid scientific evidence. If a laboratorian or clinician uses an IHC test for purposes not recommended by the IHC manufacturer, these would be off-label uses that become the responsibility of the laboratory scientist or clinician to establish and validate.

The level of risk to a patient associated with use of an IVD must account for the consequences of inaccurate results. The level of risk rises with the seriousness of consequences from a false result, the likelihood of the false result occurring, and the number of persons likely to be exposed to the risk of a false result. All of these risks are weighed against the benefit of the assay if it is performed accurately for its intended use and the risk from not having the results from the IHC assay. When evaluation of risks and benefits requires FDA to seek information about the use to which test results are to be put, such data collection is not an intrusion into the practice of medicine but the necessary review of information that is essential to establish whether the product can be marketed as labeled by the manufacturer with reasonable assurance of safety and effectiveness.

I. Prescription

17. One comment stated that it was inappropriate to include § 801.109, which provides that antibodies be provided only upon authorization by a physician, as a general control applying to IHC's. The comment argued that it would put severe restrictions on a researcher wishing to purchase the reagents and was a complete change from the way IHC's were currently ordered. The comment maintained that many of the requirements of § 801.109 were inappropriate for IHC's, such as frequency or duration of administration and side effects, and that generating and tracking this information would be burdensome to the manufacturers and result in added cost to the customer. The comment added that this requirement appeared to impose a ''drug model'' on device manufacturers. The comment recommended that the proper general control was 21 CFR 801.119. A related comment questioned whether a physician prescription was necessary for the research use of FDA-approved and marketed IHC reagents and stated that such a requirement had a high potential to hinder legitimate biomedical research efforts. Five other comments stated that a key concern was that IHC reagents be purchased only on the order of a physician, even if the reagents were being used for research use.

FDA disagrees with these comments. As stated previously, the rule does not apply to IHC's used for research and FDA does not require any premarket submissions from manufacturers of products labeled and intended ''for research use only.'' FDA does not restrict the purchase of reagents or test kits used for research, and FDA does not require a physician's prescription if

these products are not to be used for diagnosis or management of patients.

Section 801.109 applies only to IVD devices intended for clinical use in the diagnosis and management of patients. These devices are required to be in the possession of practitioners licensed by law to use or order such devices. Physicians are not the only practitioners allowed to use or order IVD tests. Other practitioners include dentists, veterinarians, nurses, or others licensed by applicable State law to use or order the use of the device.

J. Research Use

18. Several comments were concerned that the proposed rule would limit basic research by requiring IHC's used only in research to be subject to the requirements of this regulation. Another comment requested clarification about FDA's position with respect to antibodies intended for use as immunohistochemical research reagents and whether such antibodies could be marketed as ASR's. The comment also questioned whether low or moderate complexity clinical laboratories would be able to use these products if the products were marketed as ASR's.

As discussed previously, FDA does not require premarket submissions from manufacturers or users of in vitro reagents or test kits that are labeled ''for research use only.'' FDA introduced the ASR regulations to allow manufacturers to simplify the commercialization of new ASR's for diagnostic use before these reagents have established performance characteristics. IHC reagents may be marketed as ASR's as long as they comply with the ASR regulations(§ 809.10, 21 CFR 809.30, and 864.4020). The product must be manufactured under general controls, which include CGMP's. The product cannot be sold with any performance claims, intended use, indications for use or instructions for use. It is the responsibility of the end user to validate the intended use, indications for use, and performance characteristics of the ASR. It is because of the high level of proficiency required of the end user that the ASR regulations restrict the use of ASR's to high complexity laboratories.

K. Reimbursement Status

19. One comment asked FDA to discuss with the Health Care Financing Administration (HCFA) and announce the Medicare reimbursement status of: (1) IHC reagents in the interim period while manufacturers prepared and FDA cleared 510(k) submissions, and (2) IHC reagents that have been designated as ASR's.

Manufacturers who have questions about HCFA reimbursement should address their questions directly to HCFA. FDA's regulatory decisions are based on providing assurance of safety and effectiveness of these devices and are made independent of HCFA's reimbursement decisions. HCFA does consider FDA's clearance and approval of IVD devices as part of HCFA's decision to approve reimbursement. HCFA's decision to reimburse for IVD devices is a cost-benefit decision about whether the device is reasonable and necessary to establish a diagnosis or for patient management.

L. Small Entities

20. One comment from a trade association requested that FDA re-examine its assertion that ''the proposed rule will not have significant impact on a large number of small entities.'' The comment stated it was aware that FDA made no formal study in arriving at its conclusion and has not placed any data in the docket to support the decision. The comment stated that most of the suppliers of antibodies to the research community are small businesses that would be severely affected by a requirement to manufacture small quantities of a large number of products under CGMP regulations. The comment argued that its membership estimates the cost of an antibody submission at between $10,000 and $40,000 per antibody when the manufacturer follows the draft guidance document and that the sales volume of most of these products could not justify this expense.

Another comment stated that FDA had offered no analysis or study to support its conclusion that there would be no significant economic impact on a substantial number of small entities. The comment stated that, in order for an agency to certify that a rule would not have a significant economic impact on a substantial number of small entities, an agency must first demonstrate that it had made a reasonable preliminary assessment of what constituted a small entity in the affected industry, the number of small entities likely to be affected, and the impact of the regulation on those businesses. The comment argued that FDA had an affirmative obligation to explain why reasonable alternatives were rejected and to demonstrate that there had been outreach to the affected industry.

These comments were made under the mistaken assumption that this rule applied to manufacturers of research IHC products. Manufacturers of preamendment IHC medical devices for diagnostic use already are required to comply with general controls applicable to all manufacturers of devices, and this rule does not add any new obligation with respect to that requirement. All postamendment IHC devices require premarket approval or an order finding substantial equivalence unless exempted by statute or regulation. The effect of this rule is to establish that the majority of these postamendment devices will now be in class I and exempt from any premarket submissions. Although these devices will continue to be subject to general controls, the rule will impose no new burdens for most of these devices. In fact, the rule will reduce the economic burden for many of these manufacturers because they will no longer be required to submit PMA or 510(k) applications for most of their products.

FDA has prepared an analysis of impact for this rule in section VII of this document and alternatives to the final rule are discussed there. In response to the comment on agency outreach to the affected industry, FDA notes that it convened a public meeting of the Hematology and Pathology Devices Panel in October 1994 and received written comments from interested parties before, during, and after the meeting.

FDA believes this final regulation will not have a significant adverse impact on small businesses that currently are in the business of manufacturing IHC's. FDA believes the regulation ensures the public that IHC reagents and test kits are reasonably safe and effective for their intended use. At the same time, FDA does not intend or expect the regulation to impede the timely development of safe and effective medical devices. The level of regulation is designed to be in proportion to the need for regulatory oversight based on claims and promotion that a manufacturer makes for its products and the risks the products pose. A product that is to be sold and used as a ''for research use only'' reagent or test kit does not fall within the scope of the rule and the manufacturer of these devices currently does not have to comply with CGMP's. However, an IHC manufacturer that wants to promote reagents for diagnosis or management of patients is required to comply with the final rule and provide valid scientific evidence to support its claims for the intended use of the device, indications for use, and performance characteristics, unless exempted by the rule.

The agency notes that the final rule exempts most IHC's from premarket submission requirements because the majority of IHC's are adjunctive and will be classified as class I, exempt from

premarket notification. Even when premarket submissions are required, for the most part premarket notification (510(k)) is required, rather than premarket approval. Most of the remaining IHC's will be classified as class II devices because they provide independent information and have claims that are widely accepted and supported by valid scientific evidence. Moreover, FDA is providing guidance for those IHC's requiring 510(k)'s. The guidance entitled ''FDA Guidance for Submission of Immunohistochemical Applications to the FDA'' serves as a special control to assist sponsors in collecting and presenting these data to FDA for clearance of their class II devices. The guidance may also serve as a resource for manufacturers of class I IHC's who do not have to submit 510(k)'s but will nevertheless want to properly develop and validate their products prior to marketing. PMA's are only needed for those IHC's that do not meet the class I and II criteria.

The regulation does require manufacturers of class II and class III IHC's to submit valid scientific evidence to support the intended use of these products. In many cases, much of the necessary data may be available in the peer reviewed/refereed scientific literature. In those cases where published data are available, the burden on the manufacturer is minimal, and the guidance being established as a special control can provide small and large firms with information to help identify and submit such data. However, published data may not be available for other IHC reagents or test kits that the manufacturer wishes to modify or for new intended uses or indications for use of these IHC devices. In those cases, manufacturers will have to gather new testing data to support the claims.

There also may be IHC reagents or test kits that do not have the potential volume of sales to justify any manufacturer's business decision to comply with FDA's requirements for data to support the reasonable assurance of safety and effectiveness for particular labeled claims and uses. In those cases, the manufacturer may commercialize the IHC products with lesser performance claims or as an ASR and transfer the responsibility for validation of the finished assay to the user. In addition, manufacturers of low use/low revenue products may choose to commercialize the IHC under the humanitarian device exemption procedures (21 CFR part 800, subpart H). Each IHC manufacturer, whether a large or small firm, will be able to control the impact of the final rule on its business by carefully evaluating the claims and uses it intends to promote for particular products.

The minimal level of IHC IVD device regulation will be the ASR regulation. Class I ASR's are exempt from premarket notification, but must be manufactured in compliance with general controls to be legally marketed as IVD reagents for diagnosis and management of patients. Because ASR's do not require data to support an intended use, indications for use, or performance characteristics; ASR product labeling cannot include any claims for intended use, indications for use, or performance characteristics. The sale of ASR's is restricted to high complexity laboratories that are able to take the responsibility for establishing and validating the reagent for an intended use, indications for use, and performance characteristics of the finished assay (62 FR 62243, November 21, 1997).

21. One comment requested that new hearings be held and that representatives of all small companies who will be affected by the regulation be given an opportunity to speak and be heard not only by FDA but also by congressional representatives.

The Administrative Procedures Act gives agencies discretion over whether to hold oral hearings in connection with informal rulemakings (5 U.S.C. 553(c)). FDA believes that providing an opportunity for written comment on the proposed rule has provided sufficient opportunity for small entities to comment on this rulemaking. Moreover, FDA has already held a public hearing soliciting comment on the classification of immunohistochemical devices. That hearing, which was convened on October 21, 1994, was open to all interested parties, including small business entities and their representatives. Input from regulated industry played an important part in shaping FDA's proposal for regulating IHC's. Moreover, FDA has made extensive changes to the final rule based on the agency's evaluation of the written comments. FDA believes that it would be an unnecessary use of scarce agency resources to hold a hearing for this rulemaking. Furthermore, FDA has no authority to require congressional attendance or participation at the agency's hearings.

VI. Access to the Special Control

To receive the special control entitled ''FDA Guidance for Submission of Immunohistochemistry Applications to the FDA,'' FDA, Center for Devices and Radiologic Health, 1998, via fax machine, call the CDRH Facts-On-Demand system at 800–399–0381 or 301–827–0111 from a touch-tone telephone. At the first voice prompt, press 1 to access the Division of Small Manufacturers Assistance (DSMA) Facts. At the second voice prompt, press 2, and then enter the document No. 364 followed by the pound sign (#). Then follow the remaining voice prompts to complete your request.

CDRH maintains an entry on the World Wide Web (www) for easy access to information, including text, graphics, and files that may be downloaded to a PC with access to the www. The CDRH home page is updated on a regular basis and includes the guidance cited previously, as well as other guidance documents; device safety alerts; **Federal Register** reprints; information on premarket submissions (including lists of approved applications and manufacturers' addresses); small manufacturers' assistance; and information on video conferencing and electronic submissions, mammography matters, and other device-oriented information. The CDRH home page may be accessed at http://www.fda.gov/cdrh.

A text-only version of the CDRH Web site is also available from a computer or VT–100 compatible terminal by dialing 800–222–0185 (terminal settings are 8/1/N). Once the modem answers, press ENTER several times and then select menu choice 1: FDA BULLETIN BOARD SERVICE. From there follow instructions for logging in, and at the BBS TOPICS PAGE, arrow down to the FDA home page (do not select the first CDRH entry). Then select MEDICAL DEVICES AND RADIOLOGICAL HEALTH. From there select CENTER FOR DEVICES AND RADIOLOGICAL HEALTH for general information, or arrow down for specific topics.

VII. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612) (as amended by subtitle D of the Small Business Regulatory Enforcement Fairness Act of 1966 (Pub. L. 104–121), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4)). 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 final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule has been determined to be a

significant regulatory action as defined by the Executive Order and so is subject to review under the Executive Order.

A. Description of Impact

The intended purpose of this final rule is to regulate pre- and postamendment IHC devices in a consistent manner. Presently, preamendment IHC's are unclassified, while most postamendment IHC's are statutorily classified into class III. Both pre- and postamendment devices are currently subject to general controls, and postamendment devices require FDA approval before marketing. This rule will categorize IHC devices based on their potential risk to public health into one of the three device classes. The great majority of IHC's will be categorized as class I devices and will be exempt from premarket notification. The IHC's that fall into class II will require premarket clearance and be subject to a special control, in addition to general controls. Currently, there are no IHC devices on the market that will fall into class III.

The economic impact of this rule on manufacturers of IHC's will be negligible. Currently, manufacturers of all IHC devices are required to follow general controls. Under this rule, most preamendment IHC devices marketed with their original (pre-1976) claims will be categorized as class I devices and consequently exempt from premarket notification requirements. Therefore, there will be no change in the regulatory requirements that manufacturers of these devices must follow. The manufacturers of postamendment devices may realize an economic savings as a result of this rule. Manufacturers of the postamendment devices, which are currently statutorily classified into class III, would have been required to submit 510(k)'s or PMA's to be legally marketed. The final rule classifies most IHC's in class I and exempts them from premarket notification, eliminating the requirement for manufacturers to make premarket submissions for these devices. Most postamendment devices that will require submissions have been classified into class II and will not require a PMA approval. One comment suggested that the cost to submit a 510(k) ranged from $10,000 to $40,000 per antibody (see comment 21 of this document). The cost of preparing a PMA would be much higher. In addition, the special control established by this rule for class II IHC's is a guidance document intended to help manufacturers prepare 510(k)'s efficiently and effectively.

FDA can not reliably estimate the total number of manufacturers of IHC's affected by this rule. Currently, there are fewer than 25 firms listed with the agency as manufacturers of 510(k) or PMA IHC devices. Most, if not all, of these firms are small, based on the Small Business Administration's definition of a small medical device entity (fewer than 500 employees).

B. Response to Comments by Small Business

Some small businesses and the Small Business Administration commented that the proposed rule would impose a severe economic burden on IHC manufacturers, driving some companies out of business. These comments misunderstood the scope of the proposed rule by assuming that it would apply to IHC's used for research. In fact, there will be no new regulatory costs for research firms. As discussed previously, FDA has classified the majority of IHC devices as class I, exempt from premarket notification. The final rule also narrowed the identification of class III devices so that many devices that would have been class III under the proposal will be class II under the final rule and not require a PMA.

There were also comments from small businesses that stated the rule, as proposed, would have a negative effect on new product introduction. With the changes made to the proposal, the agency believes that the final rule will have no negative effect on new product introduction and will introduce consistency in the regulation of IHC's. Currently, postamendment IHC's require PMA's or 510(k)'s. With this rule, most new products will be classified as class I exempt from premarket notification.

C. Summary

In the proposed rule, FDA considered requiring 510(k)'s or PMA's for all IHC's. In response to comments, the agency reconsidered its position and determined that the necessary safeguards to public health could be achieved with general controls alone for the majority of currently marketed IHC's. Because this rule classifies these postamendment devices into class I, exempt from premarket notification, or into class II, the cost of the rule will be far below the $100 million threshold that determines an economically significant regulation under Executive Order 12866 and the Unfunded Mandates Reform Act. Because the rule will safeguard the public health and impose almost no new burden on industry, the agency certifies that the rule will not have a significant impact on a substantial number of small entities.

VIII. 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. Baddoura, F. K. , C. Cohen, E. R. Unger, P. B. DeRose, and M. Chenggis, ''Image Analysis for Quantitation of Estrogen Receptor in Formalin-fixed Paraffin-embedded Sections of Breast Carcinoma,'' *Modern Pathology*, January 1991, 4(1):91–95.

2. Esteban, J. M., P. L. Kandalaft, P. Mehta, T. L. Odom-Maryon, S. Bacus, and H. Battifora, ''Improvement of the Quantification of Estrogen and Progesterone Receptors in Paraffin-embedded Tumors by Image Analysis,'' *American Journal of Clinical Pathology*, January 1993, 99(1):32–38.

3. Esteban, J. M., C. Ahn, P. Mehta, and H. Battifora, ''Biologic Significance of Quantitative Estrogen Receptor Immunohistochemical Assay by Image Analysis in Breast Cancer,'' *American Journal of Clinical Pathology*, August 1994, 102(2):158–162.

4. Esteban, J. M., C. Ahn, H. Battifora, and B. Felder, ''Predictive Value of Estrogen Receptors Evaluated by Quantitative Immunohistochemical Analysis in Breast Cancer,'' *American Journal of Clinical Pathology*, October 1994, 102 (4 Supplement 1), S9–S12.

5. Molino, A., R. Micciolo, M. Turazza, F. Bonetti, Q. Piubello, A. Corgnati, L. Sperotto, G. Martignoni, A. Bonetti, R. Nortilli, et al., ''Estrogen Receptors in 699 Primary Breast Cancers: A Compatison of Immunohistochemical and Biochemical Methods,'' *Breast Cancer Research Treatment*, June 1995, 34(3):221–228.

IX. 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.

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, 21 CFR part 864 is amended as follows:

PART 864—HEMATOLOGY AND PATHOLOGY DEVICES

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

Authority: 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 considered IHC's.

(b) *Classification of immunohistochemistry devices*—(1) Class I (general controls). Except as described in paragraphs (b)(2) and (b)(3) of this section, these devices are exempt from the premarket notification requirements in part 807, subpart E of this chapter. This exemption applies to 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) has been made by conventional histopathology using nonimmunologic histochemical stains, such as hematoxylin and eosin. Examples of class I IHC's are differentiation markers that are used as adjunctive tests to subclassify tumors, such as keratin.

(2) Class II (special control, guidance document: ''FDA Guidance for Submission of Immunohistochemistry Applications to the FDA,'' Center for Devices and Radiologic Health, 1998). These IHC's are intended for the detection and/or measurement of certain target analytes in order to provide prognostic or predictive data that are not directly confirmed by routine histopathologic internal and external control specimens. These IHC's provide the pathologist with information that is ordinarily reported as independent diagnostic information to the ordering clinician, and the claims associated with these data are widely accepted and supported by valid scientific evidence. Examples of class II IHC's are those intended for semiquantitative measurement of an analyte, such as hormone receptors in breast cancer.

(3) Class III (premarket approval). IHC's intended for any use not described in paragraphs (b)(1) or (b)(2) of this section.

(c) *Date of PMA or notice of completion of a PDP is required.* As of May 28, 1976, an approval under section 515 of the Federal Food, Drug, and Cosmetic Act is required for any device described in paragraph (b)(3) of this section before this device may be commercially distributed. See § 864.3.

Dated: February 6, 1998.

D.B. Burlington,

Director, Center for Devices and Radiological Health.

[FR Doc. 98–14605 Filed 6–2–98; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF TRANSPORTATION

Coast Guard

33 CFR Part 100

[CGD 05–98–035]

RIN 2115–AE46

Special Local Regulations for Marine Events; The Great Chesapeake Bay Swim Event, Chesapeake Bay, MD

AGENCY: Coast Guard, DOT.

ACTION: Notice of implementation.

SUMMARY: This notice implements 33 CFR 100.507 for the Great Chesapeake Bay Swim Event to be held on June 14, 1998. These special local regulations are needed to provide for the safety of participants and spectators on the navigable waters during this event. The effect will be to restrict general navigation in the regulated area for the safety of participants in the swim and their attending personnel.

EFFECTIVE DATE: 33 CFR 100.507 is effective from 10 a.m. until 4 p.m., on June 14, 1998.

FOR FURTHER INFORMATION CONTACT: LT J. Driscoll, Marine Events Coordinator, Commander, Coast Guard Activities Baltimore, 2401 Hawkins Point Rd., Baltimore, MD 21226–1797, (410) 576–2676.

SUPPLEMENTARY INFORMATION: The March of Dimes will sponsor the Great Chesapeake Bay Swim Event on Chesapeake Bay in the vicinity of the William P. Lane Jr. Memorial Twin Bridges. Approximately 600 swimmers will start from Sandy Point State Park and swim between the William P. Lane Jr. Memorial Twin Bridges to the Eastern Shore. A large fleet of support vessels will be accompanying the swimmers. Therefore, to ensure the safety of the participants and support vessels, 33 CFR 100.507 will be in effect for the duration of the event. Under provisions of 33 CFR 100.507, no vessels may enter the regulated area without permission of the Coast Guard patrol commander. Vessel traffic will be permitted to transit the regulated area as the swim progresses. As a result, maritime traffic should not be significantly disrupted.

Dated: May 20, 1998.

Roger T. Rufe, Jr.

Vice Admiral, U.S. Coast Guard Commander, Fifth Coast Guard District.

[FR Doc. 98–14705 Filed 6–2–98; 8:45 am]

BILLING CODE 4910–15–M

DEPARTMENT OF TRANSPORTATION

Coast Guard

33 CFR Part 100

[CGD01–98–057]

RIN 2115–AE46

Special Local Regulation: Fireworks Displays Within the First Coast Guard District

AGENCY: Coast Guard, DOT.

ACTION: Notice of Implementation.

SUMMARY: This document provides notice of the dates and times of the special local regulations contained in 33 CFR 100.114, Fireworks Displays Within the First Coast Guard District. All vessels will be restricted from entering the area of navigable water within a 500-yard radius of the fireworks launch platform for each event listed in the table below. Implementation of these regulations is necessary to control vessel traffic within the regulated area to ensure the safety of spectators.

EFFECTIVE DATE: The regulations in 33 CFR 100.114 are effective from one hour before the scheduled start of the event until thirty minutes after the last firework is exploded for each event listed in the table below. The events are listed chronologically by month with their corresponding number listed in the special local regulations, 33 CFR 100.114.

ADDRESSES: Comments should be mailed to Commander (osr), First Coast Guard District, Captain John Foster Williams Federal Building, 408 Atlantic Ave., Boston, MA 02110–3350, or may be hand delivered to Room 734 at the same address, between 8 a.m. and 4 p.m., Monday through Friday, except federal holidays. Comments will become part of this docket and will be available for inspection or copying at the above address.

FOR FURTHER INFORMATION CONTACT: Lieutenant Commander Mark A. Cawthorn, Office of Search and Rescue Branch, First Coast Guard District at (617) 223–8460.

SUPPLEMENTARY INFORMATION: This notice implements the special local