(iii) *Limitations*. Administer as a single intramuscular injection. Do not slaughter swine within 24 days of treatment. Consult your veterinarian for assistance in the diagnosis, treatment, and control of parasitism.

PART 556—TOLERANCES FOR RESIDUES OF NEW ANIMAL DRUGS IN FOOD

3. The authority citation for 21 CFR part 556 continues to read as follows:

Authority: 21 U.S.C. 342, 360b, 371.

4. Section 556.225 is revised to read as follows:

§ 556.225 Doramectin.

A tolerance of 0.1 part per million (ppm) is established for parent doramectin (marker residue) in liver (target tissue) of cattle and 0.16 ppm in liver of swine.

Dated: October 22, 1997.

Stephen F. Sundlof,

Director, Center for Veterinary Medicine.

[FR Doc. 97–30562 Filed 11–20–97; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 558

New Animal Drugs for Use in Animal Feeds; Clopidol and Bacitracin Zinc With Roxarsone

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the animal drug regulations to reflect approval of an abbreviated new animal drug application (ANADA) filed by Alpharma Inc. The abbreviated NADA provides for using approved clopidol, bacitracin zinc, and roxarsone Type A medicated articles to make Type C medicated broiler chicken feeds used for prevention of coccidiosis, improved feed efficiency, improved pigmentation, and increased rate of weight gain.

EFFECTIVE DATE: November 21, 1997.

FOR FURTHER INFORMATION CONTACT: Jeffrey M. Gilbert, Center for Veterinary Medicine (HFV–128), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–594–1602.

SUPPLEMENTARY INFORMATION: Alpharma Inc., One Executive Dr., P.O. Box 1399, Fort Lee, NJ 07024, is sponsor of ANADA 200–207 that provides for combining approved clopidol, bacitracin zinc, and roxarsone Type A medicated articles to make Type C medicated feeds for broilers containing clopidol 113.5 grams per ton (g/t) and bacitracin zinc 4 to 25 g/t with roxarsone 45.4 g/t. The Type C medicated feed is used as an aid in the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *E. acervulina*, *E. brunetti*, *E. mivati*, and *E. maxima*, and for increased rate of weight gain, improved feed efficiency, and improved pigmentation.

Alpharma Inc.'s ANADA 200–207 is approved as a generic copy of Rhone-Poulenc, Inc.'s NADA 44–016. The ANADA is approved as of November 21, 1997 and 21 CFR 558.175 is amended to reflect the approval. The basis for approval is discussed in the freedom of information summary.

In accordance with the freedom of information provisions of 21 CFR part 20 and 514.11(e)(2)(ii), a summary of safety and effectiveness data and information submitted to support approval of this application may be seen in the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857, from 9 a.m. and 4 p.m., Monday through Friday.

The agency has determined under 21 CFR 25.33(a)(1) 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 558

Animal drugs, Animal feeds.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs and redelegated to the Center for Veterinary Medicine, 21 CFR part 558 is amended as follows:

PART 558—NEW ANIMAL DRUGS FOR USE IN ANIMAL FEEDS

1. The authority citation for 21 CFR part 558 continues to read as follows:

Authority: 21 U.S.C. 360b, 371.

§ 558.175 [Amended]

2. Section 558.175 *Clopidol* is amended in paragraph (d)(1)(iii)(*b*) by removing ''No. 000061'' and adding in its place ''Nos. 000061 and 046573.''

Dated: November 7, 1997.

Stephen F. Sundlof,

Director, Center for Veterinary Medicine.

[FR Doc. 97–30564 Filed 11–20–97; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 809 and 864

[Docket No. 96N–0082]

RIN 0910–ZA03

Medical Devices; Classification/Reclassification; Restricted Devices; Analyte Specific Reagents

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule to classify/reclassify analyte specific reagents (ASR's) presenting a low risk to public health into class I (general controls), and to exempt these class I devices from the premarket notification (510(k)) requirements. FDA is classifying/reclassifying ASR's used in certain blood banking tests as class II (special controls) because general controls are insufficient to provide a reasonable assurance of safety and effectiveness. Finally, ASR's presenting a high risk are being classified or retained in class III (premarket approval). FDA is also designating all ASR's as restricted devices under the Federal Food, Drug, and Cosmetic Act (the act), and establishing restrictions on their sale, distribution and use. The scope of products covered by this final rule 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 intent of this final rule is to regulate these pre- and post-1976 devices in a consistent fashion. This rulemaking does not affect requirements for reagents that are subject to licensure under the Public Health Service Act (the PHS Act). This rulemaking also does not affect reagents sold to nonclinical settings, including those reagents sold as components to manufacturers of cleared or approved in vitro diagnostic tests.

DATES: This rule is effective November 23, 1998.

FOR FURTHER INFORMATION CONTACT: Steven I. Gutman, Center for Devices and Radiological Health (HFZ–440), Food and Drug Administration, 2098 Gaither Rd., Rockville, MD 20850, 301–594–3084.

SUPPLEMENTARY INFORMATION:

I. Background

The the act (21 U.S.C. 201 *et seq.*), as amended by the Medical Device

Amendments of 1976 (Pub. L. 94–295) (the amendments) and the Safe Medical Devices Act of 1990 (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 degree of regulatory controls needed to protect the public health. The three categories of devices are as follows: Class I, general controls; class II, special controls; and class III, premarket approval.

Devices that were in commercial distribution before May 28, 1976 (the date of enactment of the amendments), are classified under section 360c of the act after FDA has: (1) Received a recommendation from a classification panel, an FDA advisory committee, (2) published the panel's recommendation 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 is substantially equivalent to a device classified under this scheme, is also classified into the same class as the device to which it is substantially equivalent.

A device that was not in commercial distribution prior to May 28, 1976, and that is not substantially equivalent to a preamendments device, is classified by statute into class III without any FDA rulemaking proceedings. FDA determines whether new devices are substantially equivalent to previously offered devices by means of the premarket notification procedure in section 510(k) of the act (21 U.S.C. 360(k)) and part 807 of the regulations (21 CFR part 807).

FDA held a meeting of its Immunology Devices Panel (the Panel) on January 22, 1996, to seek expert advice and public input on determining the regulatory controls to be placed on commercially marketed ASR's. ASR's are reagents composed of chemicals or antibodies that may be thought of as the ''active ingredients'' of tests that are used to identify one specific disease or condition. ASR's are purchased by manufacturers who use them as components of tests that have been cleared or approved by FDA and also by clinical laboratories that use the ASR's to develop in-house tests used exclusively by that laboratory. These in-house developed tests (sometimes referred to as ''home brew'' tests) include those that measure a wide variety of antibodies used in the diagnosis of infectious diseases, cancer, genetic, and various other conditions.

The Panel recommended that most ASR's be classified into class I because the Panel believed that general controls are sufficient to provide reasonable assurance of the safety and effectiveness of these ASR's. The Panel's recommendation for classification was based on the applicability of the general controls usually associated with class I products (e.g., registration, listing, current good manufacturing practice (CGMP), and medical device reporting), as well as the inclusion of restrictions on distribution, use and labeling. The Panel determined that the primary risks to health presented by ASR's sold to clinical laboratories are that they may be manufactured with variable quality, or be inappropriately labeled, or be used by persons without adequate qualifications. The Panel was also concerned that practitioners ordering the in-house tests made from ASR's may be unaware that the clinical performance characteristics of these tests have not been independently reviewed by FDA. In addition, the Panel identified a subset of ASR's whose use posed unique risks to public health because of the substantial clinical impact of the information generated using these devices.

After the Panel meeting, FDA published a proposed rule to regulate ASR's (61 FR 10484, March 14, 1996). FDA received 31 comments on the proposed rule from individuals, manufacturers, professional societies, and consumer and health associations. The majority of the comments support the regulations proposed by FDA. A summary of the comments and FDA's response to them is provided below:

II. The Final Rule

A. General Approach

The final rule classifies or reclassifies the majority of ASR's as class I medical devices. The final rule also exempts these class I devices from the premarket notification requirements of section 510(k) of the act. A small number of ASR's are being classified in class II or III because the agency has determined that additional requirements are necessary for their safe and effective use. Under the authority of section 520(e) of the act (21 U.S.C. 360j(e)), the final rule restricts the sale, distribution or use of all ASR's subject to the rule. FDA has determined that these restrictions are necessary to provide a reasonable assurance of the safety and effectiveness of ASR's, commensurate with their potentiality for harmful effect or the collateral measures necessary to their use. The final rule restricts ordering the use of in-house developed tests using ASR's to physicians or other health care practitioners authorized by applicable state law to access such tests. The final rule also restricts the sale of ASR's to those clinical laboratories regulated under Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high complexity testing. In order to clarify that the rule is intended to allow ASR's to be sold to State laboratories exempt from CLIA certification, the language of the regulation has been modified to refer to laboratories ''regulated'' under CLIA rather than ''certified'' under CLIA as had been proposed. In addition, to clarify that ASR's may be sold to Department of Veterans Affairs (Veterans Affairs) laboratories not covered by CLIA, the regulation has been modified to include Veterans Affairs laboratories regulated under comparable laws; currently that law is Pub. L. 102–139. The rule requires those laboratories covered by the regulation to provide a disclaimer with the results obtained through use of in-house developed tests incorporating these ASR's. The rulemaking does not affect reagents sold to nonclinical settings, including those sold as components to manufacturers of approved or cleared in vitro diagnostic tests. The rulemaking does not affect requirements for reagents that are subject to licensure under the PHS Act.

B. Class II or III ASR's

FDA has identified a small subset of ASR's that require class II special controls to provide a reasonable assurance of safety and effectiveness; these are ASR's used in blood banking tests classified as class II devices where the underlying tests have already been cleared for marketing under section 510(k) of the act.

Class II blood banking tests fall into two categories. One category consists of blood banking tests required by FDA that screen for diseases with a low potential for transmission. The second category consists of certain blood banking tests used electively by blood banks to screen for diseases that are likely to be transmitted to subsets of blood unit recipients known to be at greater risk of infection. An example of the second category is cytomegalovirus serological reagents, which are used in tests that aid in the diagnosis of diseases caused by cytomegaloviruses. An example of the first category is treponema pallidum nontreponemal test reagents, which are used in tests that aid in the diagnosis of syphilis.

Class II ASR's will be subject to special controls that consist of the following National Committee for

Clinical Laboratory Standards (NCCLS) documents: (1) ''Specifications for Immunological Testing for Infectious Disease; Approved Guideline'' (December 1994, NCCLS Document I/LA18–A) and (2) ''Assessment of the Clinical Accuracy of Laboratory Tests Using Receiver Operating Characteristic (ROC) Plots; Tentative Guideline'' (December 1993, NCCLS Document KGP10–T) and the following FDA guidance documents: (1) ''Review Criteria for Assessment of In Vitro Diagnostic Devices for Direct Detection of Mycobacterium spp.'' (July 6, 1993) and its ''Attachment 1'' (February 28, 1994); (2)'' Draft Review Criteria for Nucleic Acid Amplification-Based In Vitro Diagnostic Devices for Direct Detection of Infectious Microorganisms'' (June 14, 1993); and (3) the Center for Biological Evaluation and Research's ''Points to Consider in the Manufacture and Clinical Evaluation of In Vitro Tests to Detect Antibodies to the Human Immunodeficiency Virus, Type I'' (54 FR 48943, November 28, 1989). FDA believes these special controls are sufficient to ensure safe and effective use of these ASR's because these ASR's have previously been evaluated in tests classified as class II and cleared by FDA.

Persons interested in obtaining the documents previously referenced should refer to section IV in this document on ''Access to Special Controls.''

In addition to the small subset of ASR's discussed above that have been identified as class III, FDA also has identified another small subset of ASR's for which class III premarket approval is necessary to protect the public health. These class III ASR's are those whose use poses unique risks because of the substantial clinical and public health impact of the information generated by using these devices. This subset of ASR's are those incorporated in tests intended to diagnose those contagious diseases that are highly likely to be fatal and where accurate diagnosis offers an opportunity to mitigate the public health impact of the condition or those ASR's incorporated in class III tests intended to establish the safety of blood and blood products, including genetic tests intended to ensure the safety of the blood supply. Examples of class III ASR's include ASR's used in tests to diagnose human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) or tuberculosis.

Under § 864.4020(b) (21 CFR 864.4020(b)), those analyte specific reagents that meet the class II or III ASR definition will be reviewed as a component of a test or kit. Because of the serious health risks associated with diseases diagnosed by tests utilizing class II or III ASR's, FDA believes that meaningful safety and effectiveness determinations require a review of the performance of the entire test or kit, including directions for use and expected analytical or clinical performance. Accordingly, FDA will undertake premarket review of the performance of the ASR and the test of which it is a component to determine the substantial equivalence or safety and effectiveness of class II and III ASR's. As a result, it is expected that most class II and III ASR's will not be marketed as independent components, separate from the test. Where manufacturers of the approved test or kit intend to market these class II and III ASR's independently, without the other components of the test, the restrictions issued under section 520(e) of the act will continue to apply. Cleared or approved class II or III ASR's that are marketed independently of kits may be sold only to in vitro diagnostic (IVD) manufacturers, laboratories qualified to do high complexity testing under CLIA, or nonclinical laboratories for research or other uses. These independently marketed ASR's must be labeled in accordance with § 809.10(e) (21 CFR 809.10(e)), which has been amended to include the following statement: ''Except as a component of the approved test (Name of approved test), analytical and performance characteristics are not established.''

Although manufacturers of Class II or III ASR's marketed as independent components are prohibited from making statements regarding the analytical or clinical performance of the ASR, they may identify the approved test or kit. Because the clinical laboratory is accountable for the use of the independently marketed ASR and its performance as a part of a test, the disclaimer required by § 809.30(e) (21 CFR 809.30(e) must be appended to the results of in-house developed tests using class II or III ASR's just as it is required with reports of results using class I ASR's. The same statement, of course, would not be applicable or required when test results are generated using the test that was cleared or approved in conjunction with review of the class II or III ASR.

C. General Controls

The final rule requires biological or chemical manufacturers and suppliers of ASR's to register with FDA and provide FDA with a list of the ASR's they supply to laboratories for use in developing in-house tests. The final rule also requires manufacturers and suppliers to conform to CGMP requirements (part 820 (21 CFR part 820)), as applicable. The final rule further requires manufacturers and suppliers to comply with medical device report (MDR) requirements (21 CFR part 803) and report to FDA adverse events that may have been due to the ASR's. FDA believes that these general controls address the risk to the public health presented by ASR's that may be manufactured with variable quality.

To reduce the burden on industry of complying with CGMP's, manufactures and suppliers have until November 23, 1998 to comply with part 820.

D. General Purpose Reagents

FDA has amended the definition of general purpose reagents to complement and be consistent with the ASR definition by adding language clarifying the distinction between ASR's and general purpose reagents.

E. Genetics Testing

FDA does not intend, at this time, to regulate ASR's used in genetic testing differently from other restricted class I medical devices that are exempt from premarket notification requirements. The ASR regulations are drafted to classify most ASR's used to develop in-house tests as class I devices because FDA believes this degree of regulatory control is commensurate with the need to bring consistency to the manufacture of these devices and to assure their safety and effectiveness when used by health and scientific personnel trained in laboratory practices.

FDA considered identifying a subset of ASR's that are used to develop tests intended for predictive genetic diagnosis as ASR's that pose unique risks to the public health because of the substantial clinical impact of the information generated using these devices. For the genetic tests currently in use, FDA is aware that both the genetic test and the ASR used in the genetic test are developed by the laboratory in-house. Because these ASR's are not being commercially marketed independently of the tests, they do not currently fall within the scope of this regulation. Nonetheless, FDA considered designating as class III devices those ASR's that would be marketed independently for use in tests intended for use in overtly healthy people to identify a genetic predisposition to a dementing disease, or to fatal or potentially fatal medical disorders (e.g., cancers or Alzheimer's disease), in situations where penetrance is poorly defined or variable and latency is 5 years or longer. However, after reviewing the comments and currently

available information, FDA has not yet identified criteria that would logically distinguish among genetic tests in order to determine which have the requisite impact to trigger more stringent controls. FDA has determined that the special issues related to genetic testing or predictive genetic testing do not warrant establishing a more stringent degree of regulatory control over ASR's used in these tests at this time. FDA believes that regulating most ASR's as restricted class I devices exempt from premarket notification establishes appropriate initial controls in the event more stringent requirements are later determined to be necessary for ASR's used in genetic tests.

FDA is aware of the public concern and desire that the regulation of products used in genetic testing be done in a thoughtful and prudent manner. As stated previously, FDA intends, with this regulation, to establish appropriate initial controls for ASR's use in genetic tests and to review agency policies relating to many aspects of regulation of genetic testing after FDA has had an opportunity to evaluate anticipated final recommendations from National Institute of Health's (NIH's) Task Force on Genetics Testing and other interested parties. After this review, FDA may propose additional regulation of genetic tests.

F. Definition of an ASR

Most comments found FDA's proposed definition for an ASR to be acceptable. However, FDA has decided to make minor changes to clarify the definition in response to some comments. FDA has amended § 864.4020(a) to clarify that the regulation only applies to reagents intended for use in a diagnostic application. FDA also has added the term ''ligand'' to the categories of materials that are within the definition of ASR because ligands bind the reagents to the analytes. Finally, FDA has amended the definition to clarify that binding between ASR's and their analytes may be through physical or chemical means.

G. Disclaimer

Under § 809.30, FDA is requiring that a disclaimer be appended by the laboratory to the test report informing the ordering practitioner of the test results obtained from the test in which the ASR was used. The statement will say, ''This test was developed and its performance characteristics determined by [Laboratory Name]. It has not been cleared or approved by the U.S. Food and Drug Administration.'' FDA believes the disclaimer clarifies the regulatory status of the test in which the ASR has been used, is consistent with other in vitro diagnostic labeling, and addresses the concern raised by the Panel that practitioners ordering the tests made from class I exempt ASR's or from class II or III ASR's marketed independently of an approved test may be unaware that the clinical performance characteristics of those tests have not been independently reviewed by FDA. The statement would not be applicable or required when test results are generated using the test that is cleared or approved in conjunction with review of the class II or III ASR. It will be FDA's responsibility to enforce the disclaimer requirement.

H. Sale Restrictions

The final rule does not regulate the sale of ASR's to nonclinical laboratories. FDA has amended § 809.30(a)(3) to clarify that ASR's may be sold for nonclinical uses or uses not directly related to patient care to academic and other research laboratories as well as to other nonclinical laboratories. It is not the intent of the ASR regulations to prevent the continued sale of ASR's to research institutions that are using these devices for nondiagnostic testing.

I. Labeling Changes and Ordering Restrictions

FDA has amended § 809.10(e)(9) to clarify that labeling for class I exempt ASR's must include the statement, ''Analyte Specific Reagent. Analytical and performance characteristics are not established.'' For class II and III ASR's, FDA has amended § 809.10(e)(9) to clarify that labeling must include the statement ''Analyte Specific Reagent. Except as a component of the approved/cleared test (Name of approved/cleared test), analytical and performance characteristics are not established.'' Such labeling is consistent with other IVD labeling and provides accurate information to users and purchasers of these products.

FDA has added § 809.10(f) to restrict ordering in-house developed tests using ASR's to physicians or other health care practitioners authorized by the law of the State in which the test is being offered. FDA believes that interpretation of results from in-house developed tests that use ASR's requires the expertise of a health care practitioner authorized by the State to provide a reasonable assurance of the safe and effective use of commercially marketed ASR's. Because the performance characteristics of the individual tests have not been cleared or approved by FDA, consumer use of such tests without the benefit of the experience of a health care professional would significantly undermine safe and effective use of these ASR's.

III. Response to Comments

A. Comments Received in Response to FDA's Solicitation of Opinions on Specific Issues

1. Genetic Testing

(Comment 1)

Several comments supported regulating ASR's used in genetic testing as class I exempt devices. Those comments asserted that:

(a) Use of genetic test results are better addressed through regulations pertaining to confidentiality of results, discrimination based on genetic information, and the qualifications of genetic counselors and physicians, and through standards and guidelines established by professional organizations rather than through more stringent device controls.

(b) CGMP requirements, labeling restrictions, as well as CLIA requirements for qualifying laboratories to perform high complexity testing adequately, address FDA concerns about the safety and effectiveness of ASR's used for such tests.

(c) More stringent classifications of ASR's used in genetic tests may hamper the availability of genetic testing, which would adversely affect the development and practice of genetic medicine by adding substantially to the time and expense associated with test development.

(d) Clinical laboratories have the responsibility and expertise to validate genetic tests, to establish standard operating procedures so that tests can be consistently replicated by technicians, and to generate in-house reference standards to test any new reagent lot for specificity.

(e) ASR's should not be singled out for more stringent classification because ASR's are only one component of the clinical assay; properties of the general reagents used in the assay, such as ionic strength, pH and concentration, as well as conditions and procedures at the test site, are also critical for determining analytical specificity.

(f) Genetic tests are not fundamentally different from other diagnostic technologies.

(g) The proposed ASR category would allow flexibility for medical decision making but a system that attempts to distinguish among different genetic categories of testing, such as diagnostic, carrier, population screening, or prenatal diagnosis, would be unwieldy.

(h) Many ASR's could be unintentionally overregulated if a higher

classification was established for this group of ASR's because a majority of ASR's could be used as ingredients in a genetic test, even if they were not sold for that use.

Other comments supported different treatment for ASR's used in genetic tests:

(a) One comment suggested that it was premature to regulate ASR's composed of human genetic products as class I until the molecular basis of human disease is better understood. Another comment suggested that ASR's should be regulated as class III medical devices if the practice of making in-house assays of genetic tests directly available to consumers becomes widespread or problematic.

(b) Two comments recommended that ASR's used in genetic screening tests for predictive purposes in apparently healthy persons should be regulated more strictly than class I, for example, by requiring premarket notification.

(c) One comment proposed that ASR's whose only labeled indications are in the area of genetic predisposition or in prognostic situations with long latency periods should be regulated as class II or III devices.

(d) Two comments proposed regulating ASR's used in genetic testing as class II devices. One comment proposed special controls for these ASR's and no exemption from notification. The second comment would allow the sale of ASR's to laboratories without regard to certification by CLIA.

(e) Because the clinical validity of ASR's may be difficult to establish, their sensitivity and predictive value may not be high, and the benefits they confer are not proven, one comment recommended that ASR's used in genetic screening tests for predictive purposes in apparently healthy persons should be available on an investigational basis only. Another comment said they should be available on an investigative basis until clinical validity is proven, and then they should be classified as class III devices. Two comments recommended that they should be regulated as class III devices.

In general, FDA agrees with those comments that support regulating ASR's used in genetic tests as class I exempt. (See the discussion in section II.E. of this document.) The regulations were issued to apply to ASR's as a category of device, and most ASR's can be used in a variety of in-house developed tests. At this time, FDA does not believe there is a scientific basis to distinguish between tests based on the use of DNA and tests based on the use of other proteins or substances, or between tests based on the use of DNA and tests based on the use of other molecular diagnostic technologies. However, FDA recognizes that there are special issues related to genetic testing or predictive genetic testing and that these issues may affect the degree of regulatory control needed to establish the safety and effectiveness of these tests or the ASR's used in their development. As stated previously, FDA intends to review its decision with respect to regulatory control of genetic testing after it has had an opportunity to evaluate final recommendations from NIH's Task Force on Genetics Testing and other interested parties.

FDA believes that this final regulation will assure the quality of material being used to develop in-house genetics tests. When used as part of in-house developed tests, the ASR regulations restrict use of commercially marketed ASR's to tests that are ordered by an authorized practitioner and to those clinical laboratories regulated under CLIA as qualified to perform high complexity testing. Except when test results are generated using the test that was cleared or approved in conjunction with review of the class II or III ASR, FDA is also requiring that a disclaimer be appended to the test report stating that the clinical laboratory determined and developed the test performance characteristics and that the test that incorporated the ASR has not been cleared or approved by FDA. FDA believes these restrictions address many of the concerns raised by those comments supporting more stringent regulation of ASR's used in genetic testing. The issuance of these regulations does not preclude FDA from reevaluating in the future whether additional controls may be needed for genetics testing or for ASR's used in such tests. FDA will reevaluate whether additional controls may be needed to provide an appropriate level of consumer protection if further developments in this area result in significant uses of ASR's in genetic assays or other IVD tests offered over-the-counter (OTC).

(Comment 2)

One comment stated that issues raised by predictive testing which yields information about the potential future health status of the patient and his or her blood relatives have been addressed by policy statements from professional groups. This comment asserted that the most practical approach to oversight and regulation of genetic testing would build on the existing system of professional society standards, using a system that creates either incentives for compliance or disincentives for noncompliance. The comment also stated that reliance on voluntary professional standards would minimize costs to Government agencies and avoid burdening compliant manufacturers with unnecessary regulation. Another comment recommended that regulation of human genetic testing should be considered separately from decisions regarding the appropriate classification and regulatory controls applied to ASR's.

As stated previously, FDA recognizes that there are special issues related to genetic testing or predictive genetic testing. Implementation of a system based on professional standards for oversight of genetic testing is one option for addressing these issues. FDA does not believe the regulatory steps being taken in this final rule overly burden manufacturers or preclude other types of controls in the future, including systems based on the principles described in this comment.

2. Nucleic Acids

(Comment 3)

Several comments agreed with FDA's proposal to include human nucleic acids within the definition of ASR's. Those comments stated that: (a) It would be inconsistent to exclude human nucleic acids; (b) human nucleic acids are essential for good patient management where no FDA approved alternative test can substitute; (c) the scientific basis for nucleic acid hybridization and amplification techniques utilizing oligonucleotide ASR's have been known for many years so that adherence to CLIA regulations should be sufficient regulation; (d) because factors affecting test performance, reliability, and accuracy of test results are assay dependent and not disease dependent, all ASR's should be regulated similarly as class I devices exempt from premarket notification; (e) the ongoing refinement of reagents for diagnosis of susceptibility genes required by the practice of medicine is facilitated when ASR's are required only to meet a minimum number of regulatory requirements; (f) the availability of nucleic acid probes for use in the practice of medicine will be facilitated if these nucleic acids are regulated as class I devices exempt from the premarket notification requirement; and (g) like other ASR's, human nucleic acids can be used in disease staging.

Several comments supported the exclusion of the word ''nonhuman'' to modify nucleic acids in the ASR definition, stating that it would be virtually impossible to distinguish between a nucleic acid synthesized in the laboratory and a human nucleic acid, and that human nucleic acids are

not the only category of ASR capable of being used in genetic tests. One comment expressed concern that FDA has appeared to misunderstand the panel's intent, which was to exclude human nucleic acids because they are most often used to directly identify genetic material or gene products.

FDA agrees with the comments that support including human nucleic acids in the ASR definition. FDA appreciates the basis for the concern raised by the comment about the intent of the panel recommendation, but remains concerned about the broad nature of such an exclusion. Consequently, the definition of ASR's in the final rule includes human nucleic acids. As discussed earlier, at a future date, FDA may reevaluate whether additional controls over genetic tests are appropriate.

3. Analyte Specific Reagent

(Comment 4)

Several comments supported the use of the term ''analyte specific reagent'' and no comment suggested an alternative.

Accordingly, FDA has retained this term in the final regulation.

4. Disclaimer

(Comment 5)

Several comments agreed with the proposed disclaimer, noting that it clarifies the regulatory status of ASR's, it is consistent with the current practice of labeling research or investigational IVD's, and it provides an incentive for laboratories to have their assays approved or cleared.

Several comments supported having a disclaimer, but would like it to contain more information, including that the clinical performance of the test has not been established, that neither the laboratory test nor the procedures used to obtain the results have been reviewed by FDA, and that the ASR manufacturer is accountable for the ASR.

Other comments suggested that the disclaimer be deleted, or, at a minimum, amended to read that the laboratory assay used to report these results has been validated in accordance with the requirements of CLIA. One comment would amend the disclaimer to read as follows:

The reagents used in this test are regulated by the Food and Drug Administration (FDA) under the general controls of the Food, Drug, and Cosmetic Act (FDC Act). The regulations that implement the FDC Act require compliance with current good manufacturing practices (CGMP), accurate labeling and adverse event reporting, among others. The distribution of these reagents is limited to manufacturers of in vitro tests, laboratories qualified to perform high complexity testing and forensic and underwriter laboratories. This test was validated in accordance with the provisions of the Clinical Laboratory Improvement Amendments (CLIA'88). The program is managed by another federal agency, the Health Care Financing Administration (HCFA). (Laboratory Name) was certified/recertified by HCFA on (date) as a high complexity laboratory that is in compliance with CLIA regulations.

Three comments opposed requiring any disclaimer, claiming it has no impact on the final diagnosis and is an intrusion on the process of medical interpretation. One of these comments suggested that it would be more reasonable to require the laboratory director to provide interpretive reporting to the physician.

FDA has considered the comments and has determined to require the disclaimer discussed in the proposed rulemaking. FDA believes that the disclaimer is sufficiently clear to communicate that the test that used the ASR was developed, and its performance characteristics defined, by the laboratory without FDA review. FDA believes this statement clearly communicates to health care providers the regulatory status of the in-house test that has used the ASR. FDA believes this labeling requirement is necessary to address the concern raised by the Panel that physicians may not be aware that the results of the testing they order using ASR's are generated by tests that have not been independently reviewed by FDA. Rather than being an intrusion on medical interpretation, the required statement ensures that health care providers have additional information upon which to make independent judgments. This labeling requirement would not be applicable or required when test results are generated using the test that was cleared or approved in conjunction with review of the class II or III ASR. FDA does not believe a more detailed or lengthy statement is necessary.

B. General Comments

(Comment 6)

Several comments supported the regulation of ASR's as class I devices, exempt from premarket notification requirements in section 510(k) of the act. These comments stated that: (a) The CLIA regulations regarding in-house modification of materials or methods are adequate to protect the health and well-being of patients without increasing the regulatory burden on manufacturers and laboratories or overloading FDA's already encumbered review process by classifying ASR's in a more stringent category; (b) in-house modification of materials and methods falls within the scope of the practice of medicine, and a more stringent classification would hamper the ability to provide quality medical services and care to patients, such as diagnostic work performed by pathologists; (c) stringent regulation of in-house modified or developed materials and methods would constrain the development of new and better technologies and the improvement of existing IVD technologies; and (d) a substantial and appropriate measure of control is gained by the regulation announced in the proposed rule.

As recommended in these comments, FDA is finalizing the class I exempt classification as the classification for most ASR's.

(Comment 7)

One comment expressed concern that the proposed regulation would put companies that have made the investment to obtain clearance of 510(k)'s for class II antibodies at a competitive disadvantage if antibodies that are currently classified as class II are reclassified as class I devices exempt from premarket notification.

FDA disagrees with this comment. Manufacturers that have submitted or intend to submit antibodies for review as class II test systems would be allowed to market those devices with clear intended uses and indications for use, instructions for use, and appropriate definition of performance parameters. Manufacturers of class I exempt ASR's will be required to limit their labeling to a description of the identity and purity (including source and method of acquisition) of the ASR in addition to standard information already required for general purpose reagents (e.g., net weight; storage instructions). Sale of class I exempt ASR's is also restricted in accordance with other restrictions listed in 21 CFR 809.30(b), while manufacturers of class II test systems cleared by FDA would be allowed to market those devices without regard to the restrictions in 809.30.

(Comment 8)

One comment questioned whether classification of class III ASR's by the type of test for which it is to be used will create a quagmire of regulations, resulting in numerous exceptions to the class I status, confusion about how ASR's that can be used in multiple tests will be regulated, and the difficulty of distinguishing one fatal illness, such as HIV/AIDS, from another, such as herpes encephalitis.

FDA believes that through a narrow definition of the class II and III identification, the exceptions to the general ASR classification have been limited to a manageable number. Under the final rule, exceptions to the ASR class I exempt classification are analytes

used in developing a test intended for use in the: (a) Diagnosis of a contagious condition that is likely to result in a fatal outcome and where prompt accurate diagnosis offers the opportunity to mitigate the public health impact of the condition; (b) screening of a condition for which FDA has established a recommendation or requirement for the use of the test in safeguarding the blood supply or establishing the safe use of blood and blood products (e.g., hepatitis or tests for identifying blood groups); or (c) screening for blood banking when screening test has been classified as a class II device. Currently, FDA believes that ASR's used to test for evidence and monitoring for levels of HIV/AIDS and tuberculosis (TB) are examples that would fall within the class III exception, and reagents used in the diagnosis of diseases caused by cytomegaloviruses and treponema pallidum nontreponemal test reagents which aid in the diagnosis of syphilis fall within the class II exception.

Most blood banking tests fall into class III and some into class II. Class II blood banking tests fall into two categories. One category consists of blood banking tests required by FDA to screen for diseases with a low potential for transmission, e.g., syphilis. The second category consists of certain blood banking tests used electively by blood banks to screen for diseases that are likely to be transmitted to subsets of blood unit recipients known to be at greater risk of infection, e.g., cytomegalovirus. Because these blood banking tests have previously been classified into class II, FDA has determined that special controls are sufficient and that the submission of a premarket approval application (PMA) associated with a class III device is not necessary for the ASR used in the test.

(Comment 9)

One comment suggested that only those ASR's with the lowest risk factor for generating false results of little consequence should be classified as class I, and that the others should be classified as class II or III. The comment reasoned that the reliable, reproducible performance of a diagnostic test is dependent upon the entire integration of the test system. The comment also stated that while laboratories qualified to do high complexity testing have experience in utilizing and evaluating test systems developed by manufacturers, these laboratories do not have expertise in developing in vitro diagnostic tests. The comment noted that CLIA does not require the validation of diagnostic tests systems by rigorously controlled clinical trials to establish expected values and performance characteristics. Such trials are not required by CLIA but could be required by FDA if these tests were placed in class II or III.

FDA has considered this and related comments and appreciates the concerns raised about the development of in-house tests and the current marketing of test services based on tests that have not been reviewed independently for safety and effectiveness. FDA believes that clinical laboratories that develop such tests are acting as manufacturers of medical devices and are subject to FDA jurisdiction under the act. However, FDA recognizes that the use of in-house developed tests has contributed to enhanced standards of medical care in many circumstances and that significant regulatory changes in this area could have negative effects on the public health. For these reasons, FDA declines to accept the suggestion that all in-house developed tests be classified as class II or III medical devices. FDA views this final rule as a reasonable regulatory step at this time and an important contribution to assuring that the primary ingredients of most in-house developed tests are manufactured properly, used by trained professionals, and labeled accurately.

The focus of this rule is the classification and regulation of ASR's that move in commerce, not tests developed in-house by clinical laboratories or ASR's created in-house and used exclusively by that laboratory for testing services. The regulation restricts the sale of ASR's to a particular type of laboratory and FDA believes this restriction supports the safe and effective use of these ASR's. FDA believes that CLIA regulated laboratories qualified to perform high complexity testing have demonstrated expertise and ability to use ASR's in test procedures and analyses. In addition, the disclaimer being required by this rule will provide physicians with more complete information to better understand the basis of test development and to evaluate the information generated by the laboratory using the ASR.

Nevertheless, FDA understands that the use of ASR's to develop in-house tests raise questions about the safety and effectiveness of the tests that incorporate these ASR's. FDA has determined that certain types of testing raise public health concerns that require more stringent regulation of the ASR's that are the main ingredients of those tests: testing for highly contagious and fatal diseases and testing that protects the safety of the blood supply require different and additional review. As proposed, FDA is now classifying the ASR's associated with such testing into class III. In addition, FDA is classifying into class II those ASR's that are used in blood banking tests which previously have been classified into class II. These class II and III devices will be reviewed in association with the test that is incorporating the ASR so that FDA can assure a level of safety and effectiveness that is commensurate with the intended use of the ASR. In addition, ASR's and tests using ASR's that meet the definition of a biologic remain subject to licensure under the PHS Act.

Finally, FDA notes that the comment misunderstood the requirements under CLIA with respect to tests in the waived category. Under CLIA, manufacturers are required to submit studies to demonstrate that the statutory criteria for waiver are met, and any waived test must either be approved/cleared by FDA for home use or be simple, easy to perform, and essentially error free. The Centers for Disease Control and Prevention (CDC) is responsible for implementing the categorization provision of CLIA, including waived States.

(Comment 10)

One comment expressed concern that FDA has not fully discussed regulating moderate risk products and suggested that the level of sophistication of diagnostic technology requires more than two categories.

Although the final rule establishes three classes of ASR's, FDA disagrees that most moderate risk ASR's require additional regulation. FDA believes that the classification of most ASR's as restricted class I devices in conjunction with existing CLIA regulations and professional organization's standards applicable to laboratories qualified to do high complexity testing is adequate for regulating ASR's used in both low and moderate risk in-house assays. In addition, FDA has identified a small subset of ASR's used in class II blood banking tests that require special controls to provide a reasonable assurance of safety and effectiveness and that will be regulated as class II devices. The regulation represents an incremental regulatory change and does not preclude future regulatory activity by FDA or other Federal or professional groups involved in oversight of laboratory activities from developing mechanisms to improve the quality of laboratory practice or test production.

(Comment 11)

Several comments objected to any FDA regulation of ASR's. One of these suggested that FDA should work with HCFA to amend HCFA's regulation of clinical laboratories if changes in current regulation of home brews are

necessary, claiming that FDA's regulation in this area would only increase the administrative costs of medical care. Another comment stated that: (a) There is an absence of safety or effectiveness concerns in ASR use; (b) regulating ASR's increases the burden on FDA's scarce resources and facilities; (c) CLIA regulation is sufficient; and (d) the proposed rule does not target the party best suited to address issues of analytical validity, which is the laboratory preparing the in-house test. Another comment expressed concern that the proposed rule encourages in-house production of ASR's. Another comment suggested providing guidances rather than regulating by rulemaking.

FDA disagrees with these comments. FDA intends that this final rule, developed with input from HCFA and CDC, complement existing regulations issued under CLIA. FDA's rule establishes a basic requirement that manufacturers of ASR's for use in clinical laboratories comply with appropriate CGMP's. CGMP procedures and controls are designed to ensure high quality devices. FDA believes that high quality ASR's are likely to lower costs of developing and maintaining test systems at individual laboratory sites and to decrease, rather than increase, total medical costs.

FDA regards regulating ASR's using general controls and exempting them from the premarket notification requirements as a minimal burden and an appropriate level of regulation for devices that pose less safety or effectiveness concerns than devices marketed as test systems or test kits. In keeping with this approach, this rule addresses quality and identity of the ASR's and does not address analytic validity of the devices. FDA does not expect this regulation to independently increase efforts by laboratories to develop ASR's in-house. FDA believes that the in-house development of ASR's is driven by research goals, and is not a practice that grows in response to regulatory efforts. Finally, while it may be necessary for FDA to develop guidances concerning ASR's in the future, FDA believes that establishing a classification for ASR's through rulemaking is the appropriate mechanism to ensure consistent regulation of these devices for their manufacturers and users.

(Comment 12)

One comment suggested that the Panel's recommendation would unfairly burden the manufacturer of the ASR and that the clinical laboratory was the best party to ensure that the appropriate restraints are placed on interpretation of a diagnostic test through a disclaimer provision.

FDA agrees in part with the comment. FDA intends to minimize the regulatory burden on ASR manufacturers by regulating most ASR's as class I devices exempt from premarket notification. The final rule requires that a disclaimer be appended to the test report by the laboratory that uses the ASR. That statement will inform the ordering practitioner that: ''This test was developed and its performance characteristics determined by (Laboratory Name). It has not been cleared or approved by the U.S. Food and Drug Administration.'' The statement would not be applicable or required when test results are generated using the test that was cleared or approved in conjunction with review of the class II or III ASR.

(Comment 13)

One comment expressed concern about regulating the ASR ingredient, rather than the final test product, claiming that most clinical laboratories will not establish the clinical performance of a diagnostic product via properly controlled and population representative clinical trials.

FDA understands the concern raised by this comment but disagrees that regulation of ASR's will not be useful and that regulation of all in-house developed tests is appropriate at this time. As discussed previously, FDA has concluded that its regulation of ASR's will contribute to consistency and quality in their manufacture and that the requirement that the laboratory using the ASR explain the regulatory status of the test in which it was used will increase the information available to physicians ordering these tests. Development of in-house laboratory tests is a complex process in which diagnostic performance may be assessed either through the medical practice associated with a given laboratory or scientific literature. Although the types of trials performed in support of these tests are likely to be variable, laboratories will be responsible for both the quality and interpretation of results generated from these tests.

(Comment 14)

One comment questioned whether FDA has the resources to require CGMP compliance from all ASR manufacturers and prevent the inappropriate use of ''research use only'' labeling.

FDA believes it does have resources to enforce the requirements established by this regulation. The regulation requires all ASR manufacturers to follow general controls and, as with other FDA regulations, it is primarily the responsibility of the manufacturer to comply with the regulations pertaining to ASR's. FDA intends to monitor the level of compliance through inspections and, where necessary, take enforcement actions. FDA also expects that the clinical laboratory and physician community will join manufacturers in encouraging compliance; laboratories purchasing these ASR's and physicians ordering tests using these ASR's will now expect them to be produced consistently in accordance with appropriate CGMP's.

(Comment 15)

One comment suggested regulating the ASR by the same classification as the final assay.

FDA disagrees with this comment. A single class I ASR may be potentially used in multiple different versions of a final assay, which are developed and run by individual clinical laboratories. Basing the regulation of every class I ASR on the final assay developed and run by individual clinical laboratories, therefore, would be problematic. FDA believes that existing mechanisms for laboratory oversight under the mandate of CLIA are sufficient in most cases to assure proper test control.

(Comment 16)

One comment requested information on how the proposed rule relates to the immunohistochemical (IHC) regulation and the definition of IHC's, the Compliance Policy Guide (CPG) for the Distribution of Research and Investigational Use Products, and other classification actions currently underway.

Depending on their labeling and intended use, devices for use as IHC stains could be marketed under a variety of options. When an IHC is developed as a kit or system for ''in vitro diagnostic use'' (with a proposed intended use, indications for use, instructions for use, and performance characteristics), it would be subject to review as a class I, II, or III device according to intended use as outlined in the proposed IHC regulation (61 FR 30197, June 14, 1996). When an IHC is developed and marketed as an ASR (intended for ASR use only, with no instructions for use, and no defined performance characteristics), it would be subject to general controls and restrictions established by this final regulation but would be exempt from premarket review. When an IHC is developed and used only for ''research use'' or ''investigational use,'' it would be subject to appropriate labeling only with no requirement for premarket review or compliance with the general controls or restrictions of this ASR regulation.

In August of 1992, FDA invited comment on a draft CPG entitled

''Commercialization of Unapproved In Vitro Diagnostic Devices Labeled for Research and Investigation,'' which was intended to clarify the regulation of devices ''for research use'' or ''for investigational use'' and to describe FDA's enforcement policy concerning research or investigational IVD's that are being illegally commercialized for diagnostic or prognostic purposes. Any final CPG issued on this subject will be consistent with the ASR regulations.

(Comment 17)

One comment recommended that FDA create a task force to assist FDA in further delineating and defining issues raised in the proposed rule.

FDA believes that the comments submitted in response to the proposed rule provide the assistance FDA sought in delineating and defining the issues raised in the proposed rule and believes that it is unnecessary to institute an additional procedure at this time to address these issues. Where products pose new or unusual risks, FDA may seek assistance in classifying the products.

C. Adverse Event Reporting

(Comment 18)

One comment objected to the requirement that the ASR supplier be required to report adverse events and asserted that it would add an unnecessary step to the reporting process because ASR suppliers depend on the clinical laboratory to inform them of the occurrence of an adverse event.

FDA disagrees with this comment. This requirement is consistent with the medical device reporting regulations in part 803, which require device user facilities and manufacturers to report deaths and serious injuries to which a device has or may have caused or contributed, and to establish and maintain an adverse event file. Under these regulations, the burden for reporting adverse events is shared by both health care providers and manufacturers. If a number of events become associated with a particular ASR, it is the manufacturer who is likely to be in the best position to investigate the cause of the adverse events and to take corrective action, if necessary.

D. ASR Definition in § 864.4020(a)

(Comment 19)

One comment expressed concern that the proposed definition of ASR's would adversely impact basic research, noting that it included every polyclonal or monoclonal antibody specific to a human antigen and every oligonucleotide primer used in polynerase chain reaction (PCR), reverse transcription or labeled for use in detecting hybridization, including those whose primary or entire use is in basic research.

FDA does not intend to have this regulation apply to basic research and has amended the definition of ASR § 864.4020(a) to clarify that the regulation applies only to reagents intended for use in a diagnostic application.

(Comment 20)

One comment would add the term ''ligand'' to the proposed ASR definition, stating it is the ligand which binds to the categories of materials that are proposed to be within the ASR definition. Two comments would add ''diagnostic'' to the definition to clarify that an ASR is only intended for diagnostic use. One comment suggested amending the ASR definition to read ''specific binding or chemical reaction,'' noting that binding between ASR's and analytes is often through physical means and that ASR's may also react chemically with analytes.

FDA agrees with the suggested clarifications and has modified the definition accordingly.

(Comment 21)

One comment stated that the chemical or biological source of a reagent should not preclude it from being identified as an ASR.

FDA agrees with this comment and believes that the definition of ASR's supports this concept.

E. Blood Supply

(Comment 22)

Two comments supported the regulations of ASR's used in tests intended to safeguard the blood supply as class III devices.

FDA agrees with these comments and will continue to classify ASR's used in tests intended to safeguard the blood supply as class III devices because of the serious health risks associated with their use in that setting. As discussed previously, ASR's used in tests that previously have been classified in class II, will be class II, rather than class III. ASR's and tests using ASR's that meet the definition of a biologic remain subject to licensure under the PHS Act.

(Comment 23)

One comment questioned whether it is consistent to apply class II or III and other regulatory requirements to manufacturers of ASR's used in blood banking tests and suggested it would be more appropriate to have the regulatory focus be on the developer of the in-house assay.

Although FDA has concluded that class I is an appropriate classification for most ASR's, FDA believes that regulation of the blood supply requires maximum assurance of safety, and that ASR's used in tests intended to safeguard the blood supply require a different and more stringent level of control. Accordingly, ASR's used for tests that are intended to assure the safety of the blood supply will be reviewed in association with the test that is going to incorporate that ASR. The concern of the comment is addressed, therefore, because the test will be reviewed in order to establish that the ASR can be used safely and effectively. FDA's Center for Biologic Evaluation and Research (CBER) will continue to take the lead in the review of such products and should be the point of contact for manufacturers of ASR's that are intended to be used in tests relating to the safety of the blood supply. These tests remain subject to licensure under the PHS Act.

(Comment 24)

One comment expressed concern that labeling test results using ASR's as not having been reviewed by FDA would restrict the use of valuable reagents used in immunohematology and suggested that the regulation of blood bank/immunohematology tests be specifically addressed by a panel of expert serologists.

FDA does not believe that the situation suggested by the comment is likely to occur. CBER has not licensed any biologic that is used in tests intended to safeguard the blood supply without reviewing and approving the test that will incorporate that biologic. This policy will not be affected by this final rule. Under this policy, an ASR should not be incorporated into a home brew test designed to protect the safety of the blood supply unless that test has been approved by FDA or is being investigated under an effective investigational new drug application. Because these ASR's would only be used in association with tests that have already been approved, the disclaimer would not be applicable or required when test results are generated using the test that was cleared or approved in conjunction with review of the class II or III ASR.

F. Certification

(Comment 25)

Several comments recommended that FDA not require ASR suppliers to certify that sales comply with the proposed sale restrictions, claiming that such certification would be a recordkeeping burden.

These comments appear to have misread the rule. There was no certification requirement in the

proposed ASR regulation and none has been included in the final rule. The ASR rule does not require ASR suppliers to certify that sales comply with the proposed sale restrictions.

G. CGMP's

(Comment 26)

Several comments objected to the application of CGMP's where ASR's are rare reagents made only once or so infrequently that CGMP's cannot be properly applied, or where ASR's are reagents made in an academic or research setting, or by very small companies. One comment suggested that acceptance specifications developed by individual laboratories for key ingredients and test performance criteria would determine an individual laboratory's standard for acceptability for manufacturing those ASR's.

In response to these comments, FDA notes that manufacturers are not required to follow CGMP's for reagents made and used within academic or research settings. For rare or infrequently made ASR's, FDA intends to apply only those provisions of the CGMP's as are appropriate to ensure the quality and purity of the ASR's being marketed for clinical applications. However, the size of a company that commercially markets ASR's will not exempt that manufacturer from compliance with appropriate CGMP's.

H. Economics

(Comment 27)

One comment stated that carefully controlled and documented performance of IVD tests will curb medical care costs by contributing to more specific diagnosis and more selective patient management. This comment suggested that FDA's regulation of ASR's is not stringent enough and that FDA should regulate in-house developed tests the same way FDA regulates other IVD's.

FDA believes that applying general controls to the majority of ASR's used to develop in-house tests is, in conjunction with CLIA certification of the laboratory, the appropriate degree of regulatory control. As discussed previously, FDA appreciates the concerns that have been raised about in-house developed tests that are not reviewed independently. If future developments in laboratory technologies or marketing of in-house developed tests indicate that additional regulation is necessary to provide an appropriate level of consumer protection, FDA may reevaluate whether additional controls over in-house developed tests are warranted.

(Comment 28)

Several comments expressed concern that the proposed regulations will increase the cost of diagnostic tests and/or decrease the availability of those reagents that are low use/low revenue products. The comments suggested that large companies will pass along the increased costs to consumers and that small companies will be unable to comply because the cost is prohibitively expensive. A comment also questioned what the regulatory impact would be on a clinical laboratory that both manufactures the ASR and uses the ASR in an in-house test.

FDA believes that the ASR regulations are a minimal regulatory burden and should improve the assurance of quality for purchasers of ASR's for use in test development without significantly increasing costs. In response to the concern that this regulation will eliminate the manufacture of low use ASR's, FDA notes that it has recently published regulations for humanitarian device exemption procedures (61 FR 33232, June 26, 1996) which could be applied to low use/low revenue products to prevent disruption of this important market. As explained previously, ASR's developed in-house and not marketed to other laboratories generally would not be subject to the ASR requirements established under the final rule. However, as noted previously, ASR's and tests incorporating ASR's that meet the definition of a biologic that are intended to protect the blood supply will remain subject to licensure under the PHS Act.

I. Sales Restriction to CLIA Regulated Laboratories That Perform High Complexity Testing

(Comment 29)

One comment objected to the restriction of sales of ASR's to CLIA laboratories that perform high complexity testing, stating that such laboratories may lack training and/or experience in such tests. The comment suggested that the sale of ASR's should be restricted to a laboratory's area of testing, rather than complexity of testing. Another comment stated that CLIA'88 does not provide assurance of safety and efficacy of tests because it does not require assessment of a test's clinical validity or utility. Several comments supported the proposed restriction of sales to laboratories qualified to perform high complexity testing under CLIA because CLIA established minimum standards for proficiency testing, quality assurance, quality control, and personnel.

FDA believes that restriction to a laboratory regulated under CLIA or comparable laws regulating Veterans Affairs laboratories as qualified to perform high complexity testing will ensure that these devices are handled in a setting that complies with the most stringent Federal regulatory standards for laboratory practice. FDA believes that these laboratory practice standards are a more appropriate regulatory distinction than areas of speciality, which may often overlap and are difficult to define.

FDA recognizes that CLIA does not require laboratories to assess the clinical validity of in-house developed tests. Nor do FDA's ASR regulations address the clinical validity of these tests. The purpose of restricting the sale of ASR's to laboratories qualified to perform high complexity testing under CLIA is to make certain that these devices are being handled by individuals whose training and experience are likely to assure the safe and effective use of the ASR's themselves. FDA currently believes that regulating the active ingredients of in-house developed tests should provide an appropriate level of regulation to protect the public health. However, the ASR regulations do not preclude FDA or other Federal agencies from taking other measures authorized by law to assure assessment of a test's clinical validity or utility if such measures are needed. As stated previously, at a future date, FDA may reevaluate whether additional controls over the in-house tests are warranted to provide an appropriate level of consumer protection.

(Comment 30)

One comment asked how ASR manufacturers can identify laboratories qualified to perform high complexity testing and whether ASR suppliers would be required to re-assess a laboratory's classification on an annual basis.

The ASR regulations require ASR manufacturers to label and market ASR's appropriately. FDA is allowing manufacturers and suppliers until November 23, 1998 to deplete their current stock of lables before requiring compliance with the labeling requirements. While the ASR regulations do not require ASR suppliers to certify sales to laboratories qualified to perform high complexity testing, such voluntary certification programs may be one way to ensure proper marketing of ASR's. Information concerning whether a particular laboratory is qualified to perform high complexity testing may be obtained by calling the State survey agency in the State where the laboratory is located.

(Comment 31)

Two comments stated that CLIA does not certify or regulate European clinical

laboratories. The comments suggested that, in foreign countries, ASR's be sold in accordance with the laws of that country.

FDA agrees and does not expect the ASR regulations to affect the marketing of ASR's to laboratories or suppliers in foreign countries.

J. Research

(Comment 32)

One comment asked whether ASR's could be sold to universities doing pure research, and if so, would such ASR's require a separate research use only (RUO) label.

ASR's can be sold to universities doing research and FDA has amended 809.30 to clarify this point. ASR's and products labeled ''for in vitro diagnostic use'' can be used for research purposes so an additional label would not be necessary in those circumstances. However, products that have not been manufactured in accordance with CGMP's and are labeled ''for research use only'' cannot be marketed under the ASR classification or used by laboratories to develop clinical diagnostics.

K. Contagious Fatal Diseases

(Comment 33)

Two comments supported the regulation of ASR's used in tests intended for use in the diagnosis of potentially fatal contagious diseases as class III devices. Several comments objected to classifying such ASR's as class III, stating that: (a) Stricter regulation will impair the ability of the clinical laboratories to respond rapidly to outbreaks of new or emerging infectious diseases, (b) the patient population is small, (c) the proposed regulation of other ASR's provides sufficient regulation, and (d) it will cause confusion in a variety of situations, for instance, where the disease typically is not fatal, but occasionally may cause fatalities, or where an ASR may be used for multiple purposes, ranging from screening procedures to monitoring treatment or progression of disease, or where an ASR is used for the diagnosis of both infectious and noninfectious diseases. One comment suggested that it would be more appropriate to require premarket notification for these ASR's or to regulate them as class II devices that require premarket notification and special controls, rather than classify these ASR's as class III.

FDA does not believe that regulating this limited category of ASR's as class III devices will confuse the industry or interfere with laboratory development of tests. ASR's will be identified as class III devices only when they are intended to be used either in tests that establish or safeguard the safety of the blood supply or in tests that diagnose contagious fatal diseases when prompt, accurate diagnosis can mitigate risks to the public health. Examples of the diseases that meet these requirements are HIV/AIDS and tuberculosis. The ASR's used in tests that diagnose such conditions pose unique risks because of the substantial clinical and public health impact of the information generated by these tests. The agency has concluded, therefore, that class III controls are appropriate.

The agency does not believe that the application of these controls will hamper the development of accurate tests to respond to new conditions. FDA has in place procedures to expedite review of products when a device offers a potential for clinically meaningful benefit as compared to the existing alternatives or when the new medical device promises to provide a significant advance over currently available modalities. FDA also has issued procedures for obtaining a humanitarian device exemption (HDE) to encourage the discovery and use of devices intended to benefit patients in the treatment or diagnosis of diseases or conditions that affect or are manifested in fewer than 4,000 individuals in the United States. Therefore the agency does not expect that this regulation will impair the ability of clinical laboratories to develop useful tests.

L. General Purpose Reagent in 21 CFR 864.4010

(Comment 34)

Several comments agreed with the proposed amendment of the definition of general purpose reagents, stating that it clarifies the distinction between general purpose reagents and ASR's.

FDA agrees with these comments.

(Comment 35)

One comment claimed that ASR's are analogous to general purpose reagents because both are building blocks utilized in the development of home brews and are sold to clinical laboratories with no analytical or performance claims. The comment believed, therefore, that all ASR's should be class I devices, exempt from premarket notification and CGMP's, except for record-keeping and complaint files. The comment suggested that a first logical step would be to require registration and listing for ASR's before deciding what other regulatory requirements are needed.

FDA disagrees with this comment and notes that registration and listing are required for ASR's that are sold to clinical laboratories under this regulation. FDA believes that ASR's are distinguishable from general purpose reagents because they are more complex and have an implied intended use as the active ingredient for in-house developed tests. FDA has concluded, therefore, that ASR's merit a more stringent level of regulation than that currently applied to general purpose reagents.

M. Labeling

(Comment 36)

One comment stated that the ASR supplier should only be responsible for statements made on the ASR labeling because the ASR manufacturers have no control over a clinical laboratory's acceptance criteria for reagents. Another comment stated that the proposed label only goes to the identity and purity of the ASR and does not provide any directions for use, which would be desirable if the goal is to provide some regulation of in-house assays.

The agency agrees that the ASR supplier can only be responsible for statements made in the ASR labeling. FDA disagrees that the ASR labeling should include additional information. FDA believes the labeling required by the final rule communicates data that are appropriate and useful to laboratories creating in-house tests and also will establish regulatory consistency for all manufacturers of ASR's who seek to market their products to laboratories. Directions for use are not included in these labels because the laboratory producing the test, not the manufacturer of the ingredients, is accountable for the use of the ingredient. As mentioned earlier, the focus of the rule is to provide regulation of the ASR's, not to oversee the development of in-house testing.

(Comment 37)

One comment stated that promotional materials need to be regulated consistently with approved labeling, so that the purchaser can assess differences in product characteristics between different suppliers.

FDA agrees with this comment and requires promotional materials to be consistent with appropriate labeling. In addition, under section 502(q) of the act (21 U.S.C. 352(q)), a restricted device is misbranded if its advertising is false and misleading in any particular. § 809.10(e) delineates which product characteristics ASR labeling must address.

(Comment 38)

One comment proposed that products that are intended for use in diagnostic assays should be labeled with that intended use but that all reagents should be freely available for basic research.

FDA agrees with this comment. Products labeled ''analyte specific reagent'' or ''for in vitro diagnostic use'' would not be precluded from use by research laboratories for research purposes. (See comment 32 of section III.J. of this document.)

(Comment 39)

One comment from a manufacturer doing business in the European community suggested labeling ASR's ''for research use'' and defining that use, as do the Europeans, to include any reagent product not intended for a specific, well-defined diagnostic application. The comment claimed that products labeled ''for in vitro diagnostic use'' are required to include instructions for use in Europe while the proposed ASR regulation does not allow instructions for use. The comment claimed that the conflicting labeling regulations would restrict the ability of small manufacturers to compete in the global market and suggested that FDA not require the products be labeled ''for in vitro diagnostic use.'' Another comment suggested that FDA should provide a ''safe harbor'' for ASR suppliers of the research community, and allow such ASR suppliers to label the products ''not intended for use in diagnostic tests.''

FDA is interested in working with international groups to harmonize labeling whenever such changes are practical and possible. FDA has modified § 809.10(e)(9) to require the label to read ''analyte specific reagent'' and has amended the definition of ASR to clarify that ASR's are intended for use in a diagnostic application. FDA believes these changes will address the potential problems raised by the comments.

N. Section 809.10(e)

(Comment 40)

One comment recommended that § 809.10(e) be clarified to indicate that labeling of ASR's may also include information concerning expiration date, chemical/molecular composition, nucleic acid sequence, binding affinity, cross-reactivities, and interference with substances of known clinical significance.

FDA agrees with this comment and has modified § 809.10(e) accordingly.

O. Section 809.10(e)(9)

(Comment 41)

Two comments would add to § 809.10(e)(9) the following: ''For analyte specific reagent use only,'' claiming it is consistent with the investigational and research use labeling for IVD's and that it clarifies the ASR's regulatory status.

FDA generally agrees with these comments and has amended the labeling regulation to reflect that the products are for use as analyte specific reagents. Because these ASR's can also be used for research purposes, the regulation requires the label to read ''Analyte Specific Reagent,'' rather than ''For analyte specific reagent use only.''

(Comment 42)

One comment would add to § 809.10(e) the following for reagents not intended for diagnostic use: ''For laboratory research use only. CAUTION: Not for diagnostic use. The safety and efficacy of this product in diagnostic or other clinical uses has not been established.''

FDA declines to amend the ASR labeling regulation to include this language. FDA believes it would be confusing to have a requirement not applicable to ASR's but applicable to ''research use'' reagents in this section. The ASR regulations are intended to complement and be consistent with existing regulations. Regulations governing the labeling of research use only products are codified at § 809.10(c).

P. Section 809.30(b)

(Comment 43)

One comment recommended adding the following to § 809.30(b)(3): ''educational, academic and other research laboratories and nonclinical laboratories,'' stating it would minimize confusion and avoid the need for double-labeling of ASR's sold for diagnostic and research use. Another comment suggested that FDA add university and Government laboratories that are performing basic research to § 809.30(b)(3).

FDA has amended the regulation to include laboratories performing research as an example of organizations that use the reagents to make tests for purposes other than providing diagnostic information to patients and practitioners. As discussed previously, double labeling of ASR's sold for both diagnostic and research use will not be necessary.

(Comment 44)

One comment recommended directing the restrictions of § 809.30 to the users of ASR's rather than the sellers of ASR's by amending § 809.30(b) to delete, ''sold to,'' and to add, ''used in diagnostic applications by.''

FDA believes the concerns expressed by this comment have been addressed. Changes made in the final regulation clarify that the requirements only apply to ASR's used in diagnostic applications. Section 520(e) of the act provides that FDA may restrict the sale of a device to provide a reasonable assurance of safety and effectiveness of the device. FDA believes that the sale restrictions are necessary to provide reasonable assurance of the safe and effective use of ASR's; sale is restricted to those laboratories that have the expertise and qualifications to use ASR's to develop in-house tests, and to assess the performance of the ASR's. As recommended by the comment, the use of the ASR by the laboratory is also being restricted because such use must be associated with a disclaimer when the ASR is incorporated by the laboratory into a test that has not been independently reviewed by FDA.

Q. Section 809.30(d)

(Comment 45)

One comment suggested more fully defining ''identity and purity'' with regard to ASR's to include source and method of acquisition.

FDA agrees with this comment and modified identity and purity in § 809.30 to include source and method of acquisition.

R. Prescription

(Comment 46)

One comment objected to any distinction between assays that use ARS's and other laboratory tests with respect to who can order or receive results. The comment stated that: (a) CLIA requires that laboratories follow state laws regulating health care providers and access to health care testing and that FDA should not preempt such state requirements; (b) the implication that assays developed using ASR's are inherently less reliable or harder to interpret than comparable laboratory tests is unwarranted; and (c) such a restriction is the regulation of the provision of laboratory services, which is not within FDA's jurisdiction.

Other comments that opposed a prescription use requirement, stated that: (a) The ASR manufacturer does not play a significant role in determining the claims or uses of ASR's; (b) there are no clear reasons for the requirement; (c) most States already prohibit laboratories from reporting results directly to patients; (d) it is unneeded because state regulation makes all IVD tests that are not specifically cleared or approved for consumer self testing de facto prescription-use devices; (e) tests that contain ASR's as ingredients are likely only to be available from laboratories qualified to perform high complexity testing under CLIA and will not ordinarily be available for consumer self testing; and (f) professionals other than physicians should also be allowed to request tests, e.g., genetic counselors

accredited by the appropriate professional society.

One comment supported the idea that the use of tests containing ASR's should require a physician's order because the performance characteristics of such tests are not as well documented as OTC tests that have been reviewed by FDA.

In the proposed rule, FDA solicited comment on whether tests developed by the laboratories using ASR's should be made available only on order of a physician. FDA has reviewed the comments and has decided that tests developed by laboratories using ASR's should be available only on the order of a physician or other persons authorized by applicable state law to order such tests. FDA disagrees with comments that have suggested that results from in-house assays developed using ASR's are no different from other IVD test results and that OTC access to the use of ASR's in these settings does not raise issues of their safety and effectiveness. Traditionally, IVD test results are evaluated in the context of a patient's history, physical examination and other sources of diagnostic information. In many cases, those tests are approved or cleared by FDA and their performance criteria have been established. Despite that review, and as several comments indicate, a professional intermediary is ordinarily necessary to assure that the test is ordered appropriately and results are interpreted effectively. By contrast, results of IVD tests using ASR's may be particularly difficult for lay persons to interpret correctly without the guidance of a physician because the performance characteristics of the individual tests often have not been cleared or approved by FDA.

State laws vary concerning access to in-house developed testing but FDA has found none that establish an affirmative right for consumers to access such testing without the order of a health care professional. Therefore, although FDA's regulations would preempt different or additional State laws as they might apply to in-house developed testing, there appear to be no conflicts between the final rule and current state requirements. If particular situations subsequently arise that raise questions of preemption, FDA notes that states may request an advisory opinion from FDA or apply for exemptions from the Federal regulations under section 510(k) of the act.

Nor does FDA agree that this restriction is an unauthorized intrusion into the provision of laboratory services. FDA's focus is on safe and effective use of ASR's and FDA's determination that use should only be on the order of a qualified health professional is consistent with its authority to regulate medical devices. FDA believes that meaningful interpretation of results based on use of ASR's requires the expertise of a health care practitioner licensed by the State to provide a reasonable assurance of the safe and effective use of these devices. FDA is concerned that OTC access to results based on the use of ASR's would require FDA to establish more stringent regulatory controls in order to protect the public health. However, rather than restricting the ordering of tests using ASR's to physicians only, FDA is broadening that category to include all health care practitioners licensed by the State to order such tests.

IV. Access to Special Controls

The two NCCLS documents entitled ''Specifications for Immunological Testing for Infectious Disease: Approved Guideline'' NCCLS Document I/LA18–A, December 1994 and ''Assessment of the Clinical Accuracy of Laboratory Tests Using Receiver Operating Characteristic (ROC) Plots: Tentative Guideline'' and NCCLS Document KGP10–T, December 1993, may be obtained by writing the National Committee for Clinical Laboratory Standards (NCCLS) at 940 West Valley Rd., suite 1400, Wayne, PA 19087 or calling NCCLS at 610–688–0100 or faxing your request to NCCLS at 610–688–0700.

To receive the document entitled ''Review Criteria for Assessment of In Vitro Diagnostic Devices for Direct Detection of Infectious Microorganisms spp,'' FDA, July 6, 1993, and its Attachment 1, February 28, 1994, via fax machine, call the CDRH Facts-On-Demand system at 800–899–0381 or 301–827–0111 from a touch-tone telephone. At the first voice prompt press 1 to access Division of Small Manufacturers Assistance (DSMA) Facts, at second voice prompt press 2, and then enter the document No. 862 followed by the pound sign (#). Then follow the remaining voice prompts to complete your request.

To receive the document from the Center for Biologics Evaluation and Research, FDA, entitled ''Points to Consider in the Manufacture and Clinical Evaluation of In Vitro Tests to Detect Antibodies to the Human Immunodeficiency Virus, Type I 1989'' (54 FR 48943, November 28, 1989) via fax machine, call the CDRH Facts-On-Demand system at 800–899–0381 or 301–827–0111 from a touch-tone telephone. At the first voice prompt press 1 to access DSMA Facts, at second voice prompt press 2, and then enter the document number 662 followed by the pound sign (#). Then follow the remaining voice prompts to complete your request.

The Center for Devices and Radiological Health (CDRH), FDA, 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 Web. The CDRH home page is updated on a regular basis and includes: The ''Draft Review Criteria for Nucleic Acid Amplification-Based In Vitro Diagnostic Devices for Direct Detection of Infectious Microorganisms,'' FDA, July 6, 1993, document; 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. The document entitled ''Draft Criteria for Nucleic Acid Amplification-Based In Vitro Diagnostic Devices for Direct Detection of Infectious Microorganisms,'' FDA, July 6, 1993, is available at: ''http://www.fda.gov/cdrh/ode/odecl861.html''.

A text-only version of the CDRH Web site is also available from a computer or VT–100 compatible terminal by dialing 800–22–0185 (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.

V. Analysis of Impacts

FDA has examined the impact of the final rule under Executive Order 12866, the Unfunded Mandates Reform Act (Pub. L. 104–4), and the Regulatory Flexibility Act (5 U.S.C. 601–612). 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). FDA believes that this final rule is consistent with the regulatory philosophy and

principles identified in the Executive Order. In addition, the final rule is not a significant regulatory action as defined by the Executive Order.

Title II of the Unfunded Mandates Reform Act requires that agencies prepare a written statement and economic analysis for any rule that may result in an annual expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million (adjusted annually for inflation). The expenditures required by this rule will be far below this amount.

The Regulatory Flexibility Act requires agencies to prepare a Regulatory Flexibility Analysis for each rule unless the agency certifies that the rule would not have a significant economic impact on a substantial number of small entities. As explained below, the agency estimates that this final rule may impose significant costs on some small businesses. However, because FDA cannot adequately certify the extent of this impact, it has prepared a Regulatory Flexibility Analysis as part of its economic assessment.

A. Purpose and Objective of the Rule

As described previously in this document, FDA is taking this action to classify/reclassify analyte specific reagents (ASR's) presenting a low risk to public health into class I (general controls), and to exempt those class I ASR's from premarket notification. FDA is also restricting the sale, distribution, and use of all ASR's. FDA is regulating these reagents to ensure that ASR's are manufactured with appropriate quality controls, are labeled appropriately, and are used by persons with adequate qualifications to protect the public health and safety. The rule also classifies a small subset of ASR's into class II or III. Class II ASR's are those used in blood banking tests that have previously been classified as class II devices. Class III ASR's are those used in tests intended for use in the diagnosis of a contagious condition that is highly likely to result in a fatal outcome and where prompt, accurate diagnosis offers the opportunity to mitigate the public health impact of the condition, or for those used in tests intended for use in the diagnosis of a condition for which FDA has recommended or required testing in order to safeguard the blood supply or establish the safe use of blood and biological products.

B. Type and Number of Entities Affected

This rule will predominantly affect manufacturers and suppliers of ASR's that are for sale to clinical laboratories and, to a lesser extent, the clinical laboratories that develop and perform in-house tests using ASR's. Because ASR manufacturers and suppliers have not previously been required to register with the agency, FDA is uncertain of the number of entities that will be affected by this rule. The agency estimates that there are approximately 300 companies, of which most, if not all, are classified as small entities. (The Small Business Administration defines an entity in this industry as small if it employs less than 500 people.) HCFA estimates that there are approximately 57,000 certified or accredited clinical laboratories, most of which are small, that could potentially be required to add the statement delineated in the regulation to their test results. FDA does not know how many of these laboratories currently develop and perform in-house testing using ASR's.

C. Description of Economic Impact

The economic impact of this rule on individual manufacturers and suppliers will vary greatly. For the majority of firms that have other products already regulated by FDA, the added costs will be minimal because these firms are already required to register and list. If there are any firms without extensive experience producing FDA regulated products and without a comprehensive quality control program that produce many ASR's and that also derive a high percentage of income generated from sale of ASR's for clinical use, those firms will face greater costs.

1. Impact on Manufacturers and Suppliers

Because manufacturers of ASR's were not previously required to register and list with the agency, FDA does not know the precise number of firms and profile of the industry. The agency believes it probable, however, that the majority of ASR manufacturers also produce other medical devices already regulated by FDA and thus, can adapt their existing procedures and controls to these new requirements at a significantly lower cost than firms without such experience.

This rule requires manufacturers and suppliers of ASR's for sale to clinical laboratories to: (1) Register and list their ASR products with the agency, (2) conform to applicable medical device current good manufacturing practice requirements (21 CFR part 820), (3) comply with MDR reporting requirements (21 CFR part 803), (4) relabel products in accordance with this rule, and (5) restrict the sale of ASR's for clinical use to clinical laboratories that are CLIA certified as qualified to perform high complexity testing. The economic impact of these requirements on individual manufacturers will vary with a number of factors including: (1) Whether the firm currently produces other FDA regulated products and, therefore, has experience with FDA regulations, (2) the nature and number of ASR's produced, (3) the size of the firm, and (4) the adequacy of the firm's existing quality control procedures.

a. Registration and listing. The majority of manufacturers and suppliers of ASR's will incur a small cost to register and list their products with the agency. For manufacturers familiar with this requirement, the average time estimated to comply with the registration and listing requirement is 0.8 hour per year. For those manufacturers that do not currently produce any FDA regulated products, the initial registration and listing may require up to 2 hours of time (a combination of management and clerical time). If half of the estimated 300 manufacturers and suppliers have previous FDA experience, the estimated number of hours to comply with this requirement in the first year will be a maximum of 420 hours for a total industry cost of $9,555. In recurring years, registration and listing will require a total of 240 hours for an industry cost of $5,460 per year.

b. CGMP and MDR compliance. The actual costs of instituting CGMP and MDR procedures will vary greatly and, among other things, depend on the number and nature of the products produced, the size of the firm, and the nature of its current quality control system. FDA believes that the majority of firms have many of the necessary quality control procedures in place. However, for the smaller percentage of firms that do not currently have CGMP and MDR procedures in place, the cost of compliance with these two rules can be significant.

To comply with the CGMP regulation, manufactures will need to write and implement standard operating procedures for their operation, perform appropriate validation, train their employees, and develop, implement, and maintain procedures for reporting deaths and serious injuries related to their products. There will be additional documentation costs on an annual, recurring basis, and some firms may have to hire an additional person to perform the quality assurance function. Firms without FDA experience and those with limited regulatory staff may hire an industry consultant to help them come into compliance with this rule.

FDA believes that the majority of firms have experience producing FDA-related products. However, for the smaller number of firms that have little

or no experience producing FDA-regulated products, that have limited quality control procedures, and that could require the help of a consultant to assist with CGMP compliance, the one-time costs range from $50,000 to $200,000 depending on the number of products produced and the size of the firm. In addition, firms that must hire a quality assurance manager may incur costs of $40,000 to $50,000 per year in additional salary and documentation costs. Alternatively, firms that produce other medical devices under the CGMP regulations would incur much smaller costs because they would expand their current procedures to include ASR production. FDA cannot estimate the total economic impact of these two requirements because the agency does not know how many of the firms that produce ASR's also produce other regulated medical devices. The agency believes, however, that the majority of the manufacturers affected by this rule also produce other medical devices and/or have many of the necessary quality control procedures in place. These firms will incur costs significantly lower than the $50,000 to $200,000 estimated above.

c. Class II and III ASR's. A small subset of ASR's are classified as Class II or III devices. In addition to the general controls, these products will also be subject to special controls. To market these ASR's, manufacturers or suppliers must have an approved 510(k) for a class II device or a PMA for a class III device. Because FDA will review the performance of these ASR's with the test for which it is a component, the agency believes that these ASR's will not be marketed as independent components. Manufacturers of these ASR's are either currently marketing them to kit manufacturers or are themselves manufacturing the kits or tests that already have approved 510(k)'s or PMA's for marketing. Thus, no costs were estimated for this requirement.

d. Labeling. FDA is allowing manufacturers and suppliers up to 1 year to deplete current labeling stock before requiring compliance with the labeling requirements. All ASR manufacturers or suppliers must review their labeling, including promotional materials, to ascertain compliance with the new labeling requirements. The agency believes that, except for those ASR's sold to in vitro diagnostic manufacturers, almost all ASR's will require relabeling. The economic impact of this requirement is the one-time cost of redesigning and reviewing the new labeling. The agency estimates that the cost to redesign the label is $89.50 (1 hour to redesign the label, 3 hours of middle management review) and the cost to redesign promotional materials is $115.50 (1 hour to redesign materials and 4 hours to review). Because manufacturers have not been required to list their products with the agency, FDA does not know how many ASR products are sold to clinical laboratories. Industry experts estimate that between 5,000 and 10,000 ASR's are marketed. Assuming there are 7,500 ASR products, the total cost to redesign both labels and promotional materials is $1.5 million ($671,250 for labels, $866,250 for promotional materials) or $205 per product. The impact on an individual firm will depend on the number of products produced.

e. Restriction of sales. This rule restricts the sale of ASR's for clinical use to laboratories certified to perform high complexity testing under CLIA. HCFA estimates that there are approximately 57,000 accredited and certified laboratories in the United States. Because of the large number of laboratories, the agency believes this restriction will have no economic impact on the industry. FDA received no comments to the proposed rule that suggested otherwise.

2. Impact on Clinical Laboratories

Clinical laboratories that develop in-house tests using ASR's will be required to inform the person ordering the tests that these tests were not cleared or approved by FDA. In addition, ordering of such tests is limited to physicians and other persons authorized by applicable State law. FDA believes the economic impact of these two requirements on clinical laboratories will be minimal. As discussed earlier in this preamble in section III.A.4 of this document, the disclaimer is not inconsistent with existing CLIA requirements. In addition, both state laws and current industry practice limit the access of testing to trained professionals. Moreover, no comments were received with regard to either of these requirements suggesting that they would increase the economic burden on clinical laboratories. Since FDA has not mandated the specific means by which clinical laboratories must comply with the disclosure statement requirement, laboratories that produce computer generated reports may choose to reprogram to add the statement, to order preprinted report forms, or to order a stamp. FDA estimates a one-time cost of about $80 per establishment. However, because FDA does not know how many clinical laboratories develop and use in-house tests using ASR's, the agency cannot estimate the total industry impact of this requirement.

D. Analysis of Alternatives

The agency considered a number of alternatives in developing the proposal and this final rule. The rejected alternatives would have created a greater economic burden on industry without an appreciable increase in public health or safety. The agency considered: (1) Enforcing its statutory authority and regulating all postamendment ASR's as class III devices subject to the premarket approval procedures, (2) classifying a greater number of ASR's as class II or III devices, and (3) requiring premarket notification for all class I ASR's. These alternatives, which were discussed in the preambles to the proposed and final rules, were rejected because the agency determined that for the majority of ASR's (the class I products) general controls would be sufficient to ensure that ASR's are of consistent quality and have appropriate labeling. As a result, the agency believes that the current rule is the least burdensome alternative that meets the agency's public health goal.

E. Response to Comments Concerning Small Business

The major concern of small business with regard to the economic impact of this rule is the cost of complying with the CGMP regulation. One comment suggested that the CGMP regulation should not be applied to small companies. Another suggested that small companies would be at a competitive disadvantage to large firms, suggesting that large firms could pass through any increase in compliance costs, while small firms would be unable to afford the initial costs of developing CGMP's.

As a rule, the nature of a firm's existing quality system will be the major determinant of the cost of compliance with the CGMP regulation. The more comprehensive a firm's quality system and the more closely it resembles the CGMP, the easier it will be for a firm to adapt its current practice. The agency recognizes that for some firms with limited quality control systems and no experience manufacturing FDA regulated products, the cost of developing CGMP's can be significant. These costs would vary directly, although not proportionally, with the size of the firm. Smaller firms tend to have fewer products and, thus, need to develop fewer procedures and controls. They also have fewer employees to train. Larger firms are more likely than very small firms to currently manufacture other medical devices already subject to CGMP's. Such firms would have proportionately lower

compliance costs. FDA recognizes that some of the firms that sell only a small percentage of their products to the clinical laboratory market may choose not to comply with the CGMP regulation and sell their products only to manufacturers of IVD tests or kits, or to research laboratories. The agency believes, however, that this will have no significant effect on the supply of ASR's to clinical laboratories.

To reduce the burden on industry, FDA has delayed the effective date for required CGMP compliance to 1 year after the date of publication of this final rule and allowed the industry time to deplete current stock of labeling. In addition, the agency has taken steps specifically to assist small businesses with compliance through the Division of Small Manufacturers Assistance (DSMA). DSMA provides guidance documents through the FDA's World Wide Web site (http://www.fda.gov) and fax-on-demand system (800–899–0381 or 301–827–0111), as well as participating in agency and industry sponsored workshops, conferences, and meetings to inform and assist businesses with compliance issues. In particular ''The Medical Device Quality Systems Manual: A Small Entity Compliance Guide,'' available on the web site, provides examples of procedures and forms that can be adopted and modified by manufacturers to reduce their cost of compliance.

F. Summary

Because the firms that would be affected by this regulation are not currently required to register or list their ASR products, FDA cannot make a precise estimate of the total cost of this rule. The greatest cost, however, would be to facilities that are not currently subject to any CGMP's. FDA does not know how many firms would fall into this category, but even if all of the affected facilities needed to implement such requirements for the first time, the cost of the rule would be far below the $100 million threshold that determines an economically significant regulation under Executive Order 12866 or the Unfunded Mandate Reform Act. For some individual firms, the economic impact of this rule will be significant, but because the agency lacks an accurate profile of the industry, it can not determine if a substantial number of firms will be significantly affected.

VI. Environmental Impact

FDA has determined under 21 CFR 25.34(b) that this action is of the 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.

VII. The Paperwork Reduction Act of 1995

A. Comments on the Paperwork Reduction Act Statement

One comment stated that the estimate in the proposed rule of additional recordkeeping requirements was not accurate because the estimate did not account for the burden resulting from registration, listing, medical device reporting or application of the CGMP's. The comment also stated that FDA should not establish a certification program to demonstrate compliance with proposed restrictions.

FDA agrees that the estimate did not contain the burden for registration, listing, medical device reporting, or application of CGMP's. The registration, listing, medical device reporting collections of information have already been approved by OMB (OMB control number 0910—0059). On October 7, 1996, FDA published the CGMP final rule (61 FR 52602) and provided a 60-day comment period to submit written comments to FDA on the information collection provisions of the rule as required under the Paperwork Reduction Act of 1995. A notice soliciting comments for an additional 30 days on these provisions is under development. These burdens were not included in the chart because any CGMP, medical device reporting, registration and listing requirements have already been estimated separately.

Neither the proposed nor the final rule contain a certification requirement. Questions concerning certification are addressed in section III.F. of this document.

B. Information Collection Provisions in the Final Rule

This final rule contains information collection provisions that are subject to review by OMB under the Paperwork Reduction Act of 1995 (44 U.S. 3501–3520). OMB did not approve FDA's information collection submitted to OMB with the proposed rule. The title, description and respondent description of the information collection requirements are shown below with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, gathering and maintaining the data needed, and completing and reviewing the collection of information.

Title: Labeling Requirements for Analyte Specific Reagents—Labeling for Laboratories.

Description: The final rule amends the labeling requirements for certain in vitro diagnostic products to require that manufacturers of analyte specific reagents provide certain information concerning the reagents to laboratories that will use the reagents to develop tests for clinical use. The final regulation will also require that advertising and promotional material for analyte specific reagents include information about the identity and purity of the reagents and not make any claims about analytic or clinical performance. The purpose of the regulation is to assure that laboratories developing tests using these reagents have sufficient information about their identity and purity.

Description of Respondents: Businesses and other for profit organizations.

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
809.10(e)	300	1	300	25	7,500
809.30(d)	300	1	300	25	7,500
Total				50	15,000

The proposed rule provided a 30-day comment period. As discussed previously, the revised burden hour estimates in the final rule are based partially on comments received. FDA has submitted the information collection provisions of the final rule to OMB for review. Prior to the effective date of this final rule, FDA will publish a notice in the **Federal Register** of OMB's decision to approve, modify, or disapprove the information collection

provisions. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

List of Subjects

21 CFR Part 809

Labeling, Medical devices.

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 parts 809 and 864 are amended as follows:

PART 809—IN VITRO DIAGNOSTIC PRODUCTS FOR HUMAN USE

1. The authority citation for 21 CFR part 809 continues to read as follows:

Authority: 21 U.S.C. 331, 351, 352, 355, 357, 360b, 360c, 360d, 360h, 360i, 360j, 371, 372, 374, 381.

2. Section 809.10 is amended in paragraph (a) by adding at the end of the first sentence ''or as provided in paragraph (e) of this section'' and by adding new paragraph (e) to read as follows:

§ 809.10 Labeling for in vitro diagnostic products.

* * * * *

(e)(1) The labeling for analyte specific reagents (e.g., monoclonal antibodies, deoxyribonucleic acid (DNA) probes, viral antigens, ligands) shall bear the following information:

(i) The proprietary name and established name (common or usual name), if any, of the reagent;

(ii) A declaration of the established name (common or usual name), if any;

(iii) The quantity, proportion, or concentration of the reagent ingredient; and for a reagent derived from biological material, the source and where applicable, a measure of its activity. The quantity, proportion, concentration, or activity shall be stated in the system generally used and recognized by the intended user, e.g., metric, international units, etc.;

(iv) A statement of the purity and quality of the reagent, including a quantitative declaration of any impurities present and method of analysis or characterization. The requirement for this information may be met by a statement of conformity with a generally recognized and generally available standard that contains the same information, e.g., those established by the American Chemical Society, U.S. Pharmacopeia, National Formulary, and National Research Council. The labeling may also include information concerning chemical/molecular composition, nucleic acid sequence, binding affinity, cross-reactivities, and interaction with substances of known clinical significance;

(v) A statement of warnings or precautions for users as established in the regulations contained in 16 CFR part 1500 and any other warnings appropriate to the hazard presented by the product;

(vi) The date of manufacture and appropriate storage instructions adequate to protect the stability of the product. When applicable, these instructions shall include such information as conditions of temperature, light, humidity, date of expiration, and other pertinent factors. The basis for such instructions shall be determined by reliable, meaningful, and specific test methods, such as those described in § 211.166 of this chapter;

(vii) A declaration of the net quantity of contents, expressed in terms of weight or volume, numerical count, or any combination of these or other terms that accurately reflect the contents of the package. The use of metric designations is encouraged, wherever appropriate;

(viii) The name and place of business of manufacturer, packer, or distributor;

(ix) A lot or control number, identified as such, from which it is possible to determine the complete manufacturing history of the product;

(x) For class I exempt ASR's, the statement: ''Analyte Specific Reagent. Analytical and performance characteristics are not established''; and

(xi) For class II and III ASR's, the statement: ''Analyte Specific Reagent. Except as a component of the approved/cleared test (Name of approved/cleared test), analytical and performance characteristics of this ASR are not established.''

(2) In the case of immediate containers too small or otherwise unable to accommodate a label with sufficient space to bear all such information, and which are packaged within an outer container from which they are removed for use, the information required by paragraphs (e)(1) through (e)(6) of this section may appear in the outer container labeling only.

3. New § 809.30 is added to subpart C to read as follows:

§ 809.30 Restrictions on the sale, distribution and use of analyte specific reagents.

(a) Analyte specific reagents (ASR's) (§ 864.4020 of this chapter) are restricted devices under section 520(e) of the Federal Food, Drugs, and Cosmetic Act (the act) subject to the restrictions set forth in this section.

(b) ASR's may only be sold to:

(1) In vitro diagnostic manufacturers;

(2) Clinical laboratories regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), as qualified to perform high complexity testing under 42 CFR part 493 or clinical laboratories regulated under VHA Directive 1106 (available from Department of Veterans Affairs, Veterans Health Administration, Washington, DC 20420); and

(3) Organizations that use the reagents to make tests for purposes other than providing diagnostic information to patients and practitioners, e.g., forensic, academic, research, and other nonclinical laboratories.

(c) ASR's must be labeled in accordance with § 809.10(e).

(d) Advertising and promotional materials for ASR's:

(1) Shall include the identity and purity (including source and method of acquisition) of the analyte specific reagent and the identity of the analyte;

(2) Shall include the statement for class I exempt ASR's: ''Analyte Specific Reagent. Analytical and performance characteristics are not established'';

(3) Shall include the statement for class II or III ASR's: ''Analyte Specific Reagent. Except as a component of the approved/cleared test (name of approved/cleared test), analytical and performance characteristics are not established''; and

(4) Shall not make any statement regarding analytical or clinical performance.

(e) The laboratory that develops an in-house test using the ASR shall inform the ordering person of the test result by appending to the test report the statement: ''This test was developed and its performance characteristics determined by (Laboratory Name). It has not been cleared or approved by the U.S. Food and Drug Administration.'' This statement would not be applicable or required when test results are generated using the test that was cleared or approved in conjunction with review of the class II or III ASR.

(f) Ordering in-house tests that are developed using analyte specific reagents is limited under section 520(e) of the act to physicians and other persons authorized by applicable State law to order such tests.

(g) The restrictions in paragraphs (c) through (f) of this section do not apply when reagents that otherwise meet the analyte specific reagent definition are sold to:

(1) In vitro diagnostic manufacturers; or

(2) Organizations that use the reagents to make tests for purposes other than providing diagnostic information to patients and practitioners, e.g., forensic, academic, research, and other nonclinical laboratories.

PART 864—HEMATOLOGY AND PATHOLOGY DEVICES

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

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

5. Section 864.4010 is amended by revising paragraph (a) to read as follows:

§ 864.4010 General purpose reagent.

(a) A general purpose reagent is a chemical reagent that has general laboratory application, that is used to collect, prepare, and examine specimens from the human body for diagnostic purposes, and that is not labeled or otherwise intended for a specific diagnostic application. It may be either an individual substance, or multiple substances reformulated, which, when combined with or used in conjunction with an appropriate analyte specific reagent (ASR) and other general purpose reagents, is part of a diagnostic test procedure or system constituting a finished in vitro diagnostic (IVD) test. General purpose reagents are appropriate for combining with one or more than one ASR in producing such systems and include labware or disposable constituents of tests; but they do not include laboratory machinery, automated or powered systems. General purpose reagents include cytological preservatives, decalcifying reagents, fixative and adhesives, tissue processing reagents, isotonic solutions and pH buffers. Reagents used in tests for more than one individual chemical substance or ligand are general purpose reagents (e.g., *Thermus aquaticus* (TAQ) polymerase, substrates for enzyme immunoassay (EIA)).

* * * * *

6. New § 864.4020 is added to subpart E to read as follows:

§ 864.4020 Analyte specific reagents.

(a) *Identification.* Analyte specific reagents (ASR's) are antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acid sequences, and similar reagents which, through specific binding or chemical reaction with substances in a specimen, are intended for use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens. ASR's that otherwise fall within this definition are not within the scope of subpart E of this part when they are sold to:

(1) In vitro diagnostic manufacturers; or

(2) Organizations that use the reagents to make tests for purposes other than providing diagnostic information to patients and practitioners, e.g., forensic, academic, research, and other nonclinical laboratories.

(b) *Classification.* (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.

(2) Class II (special controls/guidance documents), when the analyte is used in blood banking tests that have been classified as class II devices (e.g., certain cytomegalovirus serological and treponema pallidum nontreponemal test reagents). Guidance Documents:

1. ''Specifications for Immunological Testing for Infectious Disease; Approved Guideline,'' NCCLS Document I/LA18–A, December 1994.

2. ''Assessment of the Clinical Accuracy of Laboratory Tests Using Receiver Operating Characteristic (ROC) Plots; Tentative Guideline,'' NCCLS Document KGP10–T, December 1993.

3. ''Review Criteria for Assessment of In Vitro Diagnostic Devices for Direct Detection of Mycobacterium spp,'' FDA, July 6, 1993, and its ''Attachment 1,'' February 28, 1994.

4. ''Draft Review Criteria for Nucleic Acid Amplification-Based In Vitro Diagnostic Devices for Direct Detection of Infectious Microorganisms,'' FDA, July 6, 1993.

5. The Center for Biologics Evaluation and Research, FDA, ''Points to Consider in the Manufacture and Clinical Evaluation of In Vitro Tests to Detect Antibodies to the Human Immunodeficiency Virus, Type I'' (54 FR 48943, November 28, 1989).

(3) Class III (premarket approval), when:

(i) The analyte is intended as a component in a test intended for use in the diagnosis of a contagious condition that is highly likely to result in a fatal outcome and prompt, accurate diagnosis offers the opportunity to mitigate the public health impact of the condition (e.g., human immunodeficiency virus (HIV/AIDS)or tuberculosis (TB)); or

(ii) The analyte is intended as a component in a test intended for use in donor screening for conditions for which FDA has recommended or required testing in order to safeguard the blood supply or establish the safe use of blood and blood products (e.g., tests for hepatitis or tests for identifying blood groups).

(c) *Date of 510(k), or date of PMA or notice of completion of a product development protocol is required.* (1) Preamendments ASR's; No effective date has been established for the requirement for premarket approval for the device described in paragraph (b)(3) of this section. See § 864.3.

(2) For postamendments ASR's; November 23, 1998.

(d) *Restrictions.* Restrictions on the sale, distribution and use of ASR's are set forth in § 809.30 of this chapter.

Dated: November 13, 1997.

William B. Schultz,

Deputy Commissioner for Policy.

[FR Doc. 97–30334 Filed 11–20–97; 8:45 am]

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DEPARTMENT OF TRANSPORTATION

Federal Highway Administration

23 CFR Part 657

RIN 2125–AE20

Truck Size and Weight; Office of Management and Budget Control Number and Expiration Date

AGENCY: Federal Highway Administration (FHWA), DOT.

ACTION: Final rule; technical amendment.

SUMMARY: This document adopts a technical amendment to the regulations at 23 CFR part 657 to provide the Office of Management and Budget (OMB) control number for the Federal Highway Administration's (FHWA) collection of information from the States about their size and weight enforcement programs and explains the significance of referencing that number in 23 CFR part 657.

EFFECTIVE DATE: November 21, 1997.

FOR FURTHER INFORMATION CONTACT: Mr. Tom Klimek, Office of Motor Carrier Information Analysis, (202) 366–2212, or Mr. Charles Medalen, Office of the Chief Counsel, (202) 366–1354, Federal Highway Administration, 400 Seventh Street, SW., Washington, D.C. 20590. Office hours are from 7:45 a.m. to 4:15 p.m., e.s.t., Monday through Friday, except Federal holidays.

SUPPLEMENTARY INFORMATION: Federal law requires each State to certify to the Secretary of Transportation before January 1 of each year that it is enforcing: (1) Federal law regarding (i) vehicle weight on the Interstate System and (ii) vehicle size on the former Federal-aid primary, secondary and urban systems; and (2) State size and weight laws on the former Federal-aid primary, secondary and urban systems [23 U.S.C. 141(a)].