



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 660, 801, and 809

[Docket No. FDA-2013-N-0125]

RIN 0910-AG74

Use of Symbols in Labeling

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is issuing this final rule revising its medical device and certain biological product labeling regulations to explicitly allow for the optional inclusion of graphical representations of information, or symbols, in labeling (including labels) without adjacent explanatory text (referred to in this document as “stand-alone symbols”) if certain requirements are met. The final rule also specifies that the use of symbols, accompanied by adjacent explanatory text continues to be permitted. FDA is also revising its prescription device labeling regulations to allow the use of the symbol statement “Rx only” or “R only” in the labeling for prescription devices.

DATES: This rule is effective [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

FOR FURTHER INFORMATION CONTACT: For information concerning the final rule as it relates to devices regulated by the Center for Devices and Radiological Health (CDRH):

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For information concerning the final rule as it relates to devices regulated by the Center for Biologics Evaluation and Research: Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

SUPPLEMENTARY INFORMATION:

Executive Summary

Purpose of the Regulatory Action

The final rule explicitly permits the use of symbols in medical device labeling without adjacent explanatory text if certain requirements are met. The medical device industry has requested the ability to use stand-alone symbols on domestic device labeling, consistent with their current use on devices manufactured for European and other foreign markets. The final rule seeks to harmonize the U.S. device labeling requirements for symbols with international regulatory requirements, such as the Medical Device Directive 93/42/EEC of the European Union (EU) (the European Medical Device Directive) and global adoption of International Electrotechnical Commission (IEC) standard IEC 60417 and International Organization for Standardization (ISO) standard ISO 7000-DB that govern the use of device symbols in numerous foreign markets.

Summary of the Major Provisions of the Regulatory Action in Question

FDA has generally interpreted existing regulations not to allow the use of symbols in medical device labeling, except with adjacent English-language explanatory text and/or on in vitro diagnostic (IVD) devices intended for professional use. Under the final rule, symbols

established in a standard developed by a standards development organization (SDO) may be used in medical device labeling without adjacent explanatory text as long as: (1) The standard is recognized by FDA under its authority under section 514(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360d(c)) and the symbol is used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition, or alternatively, (2) if the symbol is not included in a standard recognized by FDA under section 514(c) or the symbol is in a standard recognized by FDA but is not used according to the specifications for use of the symbol set out in the FDA section 514(c) recognition, the device manufacturer otherwise determines that the symbol is likely to be read and understood by the ordinary individual under customary conditions of purchase and use in compliance with section 502(c) of the FD&C Act (21 U.S.C. 352(c)) and uses the symbol according to the specifications for use of the symbol set forth in the SDO-developed standard. In addition, in either case, the symbol must be explained in a paper or electronic symbols glossary that is included in the labeling for the medical device. Furthermore, the labeling on or within the package containing the device must bear a prominent and conspicuous statement identifying the location of the symbols glossary that is written in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used. As with text used in device labeling, the use of symbols must also comply with other applicable labeling requirements in the FD&C Act, such as section 502(a) and section 502(f), and relevant regulations such as 21 CFR part 801. In addition, the final rule allows the use of the symbol statement "Rx only" or "℞ only" for labeling of prescription devices.

Costs and Benefits

Benefits represent the reduction in costs associated with designing and redesigning the labeling for medical devices that are currently marketed in the United States and the EU. We estimate these annual cost savings to roughly range between \$7.9 million and \$25.5 million at a 3 percent discount rate, and \$7.7 million to \$25 million at a 7 percent discount rate. Costs represent the one-time administrative costs to redesign labeling to incorporate a new or changed symbol, to the one-time costs to create a symbols glossary that is included in the labeling for the device, and the recurring costs to revise these glossaries, as necessary. Annualized over a 20-year period, we estimate these costs to range from \$1.1 million to \$3.2 million. Annualized over a 20-year period, we estimate total annualized net to range from \$6.8 million to \$22.3 million at a 3 percent discount rate, and from \$6.6 million to \$21.7 million at a 7 percent discount rate.

The use of stand-alone symbols in device labeling is optional under the final rule. Those device manufacturers who now use labels without symbols, or who use symbols with adjacent explanatory text, may continue to do so. Therefore, medical device manufacturers would use stand-alone symbols as allowed by the final rule only if they expect a positive net benefit (estimated benefits minus estimated costs). Hence, the final rule is expected to provide a net benefit to manufacturers who opt to use the stand-alone symbols as allowed under this final rule.

Summary of Costs and Benefits of the Proposed Rule	Total Benefits Annualized Over 20 Years (in millions)	Total Costs Annualized Over 20 Years (in millions)	Total Net Benefits Annualized Over 10 Years (in millions)
Total	\$7.7 to \$25.5	\$1.1 to \$3.2	\$6.6 to \$22.3

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I. Background

FDA published a proposed rule to revise certain medical device and biological product labeling regulations by explicitly allowing labeling to contain certain stand-alone symbols. The proposed rule would allow stand-alone use of symbols in device labeling if the symbol is established as part of a standard developed by a nationally or internationally recognized standards organization, is part of a standard recognized by FDA for use in the labeling for medical devices, and is explained in a symbols glossary that contemporaneously accompanies the medical device (78 FR 23508, April 19, 2013). The preamble to the proposed rule describes

the background and the purpose of the rule as well as discusses that FDA recognition of the standard in which the symbol is contained would be under its authority in section 514(c) of the FD&C Act (21 U.S.C. 360d(c)). We refer readers to that preamble for information about the development of the proposed rule. The Agency requested public comments on the proposed rule, and the comment period closed on June 18, 2013.

As discussed further in section II.A, in this final rule FDA is making the following changes to the regulatory text of the final rule as compared to the proposed rule: (1) Deleting the term “standardized symbol” as that term was used in the proposed rule to refer only to symbols in FDA recognized standards and the scope of this final rule allows other alternatives; (2) providing that, in addition to symbols in a standard recognized by FDA under section 514(c) of the FD&C Act, the use of certain other SDO-established symbols is allowed; (3) clarifying that the symbols glossary must “be included in the labeling for the device,” in lieu of using the words “contemporaneously accompanies” the device, providing that such glossary can be in paper or electronic form, and that the labeling on or within the package containing the device must bear a prominent and conspicuous statement identifying the location of the symbols glossary; (4) adding a definition of what we mean by the term “standards development organization (SDO)” for purposes of this final rule; and (5) revising the definition of “symbols glossary” to mean a compiled listing of: (a) each SDO-established symbol used in the labeling for the device; (b) the title and the designation number of SDO-developed standard containing the symbol; (c) the title of the symbol and its reference number, if any, in the standard; and (d) the meaning or explanatory text for the symbol as provided in the FDA recognition, or if FDA has not recognized the standard or portion of the standard in which the symbol is located or the symbol is not used according to the specifications of the FDA section 514(c) recognition, the explanatory

text as provided in the standard. In addition, in this final rule, we renumbered 21 CFR 660.2(c), 660.28, 660.35, 660.45, and 660.55 to improve the readability of these sections. This final rule also contains conforming amendments to 21 CFR 660.20(a) and 660.50(a) that update references made in these sections to certain of the renumbered provisions. As stated previously, in the proposed rule, the Agency proposed to limit use of stand-alone symbols in device labeling only to those symbols that an SDO established in a standard that FDA recognized under its authority in section 514(c) of the FD&C Act. The reason for FDA's reliance on its recognition process in the proposed rule as a criterion for allowable stand-alone symbols was that the process offered FDA the opportunity to determine that the symbol was likely to be read and understood by the ordinary user under customary conditions of use as required by section 502(c) of the FD&C Act. In part, based on comments discussed in this document, which raised issues regarding some aspects of the section 514(c) recognition process, the Agency further considered the matter and concluded that its recognition process under section 514(c) of the FD&C Act is not the only way to ensure that the appropriate section 502(c) determination is made. FDA determined that, as an alternative to its section 514(c) recognition, manufacturers could themselves determine whether an SDO-established symbol is likely to be read and understood by the ordinary individual under customary conditions of purchase and use in compliance with section 502(c) of the FD&C Act. This would be consistent with what industry currently does when it uses text in labeling. We note, however, that FDA has the authority to make the definitive determination regarding compliance with the statute and can take enforcement action against violations, as warranted.

As provided in section 514(c)(1)(B) of the FD&C Act, a person can use a standard recognized by FDA to meet a statutory requirement and submit a declaration of conformity to FDA to certify that the device is in conformity with the standard. Section 514(c)(1)(B) of the

FD&C Act further provides that a person may elect to use data, or information, other than data required by a standard recognized by FDA to meet any requirement regarding devices under the FD&C Act. Apart from such compliance with the requirements of section 502(c) of the FD&C Act by conforming to a standard recognized for that purpose under section 514(c), the manufacturer must determine itself that the labeling also meets the other requirements of the FD&C Act, as it is the responsibility of all persons labeling devices to assure statutory and regulatory compliance. The final rule acknowledges the device manufacturer's responsibility to comply with the requirements of section 502(c) of the FD&C Act as well, by permitting the use of a stand-alone symbol in labeling that the manufacturer has determined meets such requirements. Accordingly, this final rule provides that a stand-alone symbol is allowed to be used in device labeling if: (1) The symbol is established in a standard developed by an SDO; and (2) the standard is recognized by FDA under its authority under section 514(c) of the FD&C Act and the symbol is used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition, or alternatively, if the symbol is not included in a standard recognized by FDA under section 514(c) or the symbol is in a standard recognized by FDA but is not used according to the specifications for use of the symbol set out in the FDA section 514(c) recognition, the device manufacturer otherwise determines that the symbol is likely to be read and understood by the ordinary individual under customary conditions of purchase and use in compliance with section 502(c) of the FD&C Act and uses the symbol according to the specifications for use of the symbol set forth in the SDO-developed standard. In addition, in either case, the symbol must be explained in a paper or electronic symbols glossary that is included in the labeling for the medical device. Furthermore, the labeling on or within the package containing the device must bear a prominent and conspicuous statement identifying the

location of the symbols glossary that is written in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used. The additional option to use stand-alone symbols established in SDO-developed standards that FDA has not recognized, as permitted in the final rule, will result in more timely availability of stand-alone symbols for use in device labeling, more convenience for industry, and conserves limited Agency resources.

See section III (Compliance and Enforcement) for our discussion to help manufacturers determine, if the symbol is not included in a standard or part of a standard that FDA has recognized under section 514(c) of the FD&C Act or if the symbol is used outside the specifications of the FDA section 514(c) recognition, whether the stand-alone use of the symbol in device labeling is likely to be read and understood by the ordinary individual under customary conditions of purchase and use in accordance with section 502(c) of the FD&C Act. In section III, we also clarify that the other provisions of section 502 of the FD&C Act also apply to the use of stand-alone symbols, such as section 502(a) of the FD&C Act if use of the symbol in its labeling causes the labeling to be false or misleading and section 502(f) of the FD&C Act if use of the symbol in device labeling results in inadequate directions for use of the device. For clarity, in this final rule, we have set out the definition of an “SDO.” For purposes of this rule, we define an SDO as an organization that is nationally or internationally recognized and that follows a process for standard development that is transparent (i.e., open to public scrutiny), where the participation is balanced, where an appeals process is included, where the standard is not in conflict with any statute, regulation, or policy under which FDA operates, and where the standard is national or international in scope (see 76 FR 23508 at 23511). (See also FDA answer to Question 18 (What organizations can develop consensus standards for FDA recognition?) in

the guidance document entitled “Frequently Asked Questions on Recognition of Consensus Standards; Guidance for Industry and FDA Staff” (September 2007), at. p. 7 (Ref. 1 and cited in the proposed rule (76 FR at 23508 at 23509)).

II. Comments on the Proposed Rule and FDA’s Responses

We received submissions from 16 commenters, representing a cross-section of individuals, professional and trade associations, and device manufacturers. Almost all comments supported the objectives of the rule in whole or in part. The great majority of comments either suggested changes to specific elements of the proposed rule or requested clarification of matters discussed in the proposed rule.

A. Options for Using Stand-Alone Symbols

(Comment 1) Two comments raised the challenges and impracticality of FDA authorization of symbols via section 514(c) recognition of the standard in which the symbol is established. One of these comments expressed concern that, under the section 514(c) process, FDA recognition of certain symbols for certain devices within the standards will present challenges to industry. For instance, “if FDA does not recognize the newest revisions of the standards, discrepancies could require going back to define symbols in text on labels.” Another commenter claimed that by limiting the recognition of symbols to certain devices, the Agency would be falling considerably short of harmonizing with other regulatory bodies, which is one major goal of this rulemaking. The comment went on to state that the European Medical Device Directive does not limit the use of recognized symbols to certain devices, i.e., does not limit which symbols can be used nor does it limit the devices for which a symbol can be used as long as the symbol is explained elsewhere in the device labeling. The comment opined that requiring

independent validation by FDA of the stand-alone symbols established in standards would be an unnecessary use of FDA resources.

(Response 1) The changes in the final rule discussed previously will address many, if not most, of these commenters' concerns. The final rule gives the manufacturer the option of using a symbol contained in an FDA recognized standard or determining for itself that the SDO-established symbol is likely to be read and understood by the customary purchasers and users of the device. Under the final rule, if an FDA recognized standard is only for a subset of symbols or a subset of devices, the manufacturer could submit its declaration of conformity with that standard, and to address any symbols, devices, or users not included in the FDA recognition, could determine for itself that use of those symbols, on those devices, or for those users meets the requirements of section 502(c) of the FD&C Act. This would be consistent with what industry currently does when it uses text in labeling. We note, however, that FDA has the authority to make the definitive determination regarding compliance with the statute and can take enforcement action against violations, as warranted. Furthermore, manufacturers always have the option to request FDA recognition of certain standards if the manufacturer does not want to determine for itself the section 502(c) compliance of the use of the stand-alone symbol in device labeling. See Guidance for Industry and FDA Staff entitled "Frequently Asked Questions on Recognition of Consensus Standards" (Ref. 1). Because manufacturers are not limited to use of stand-alone symbols which are part of an FDA-recognized standard, the final rule should not present the challenges raised by the commenters.

When the symbol is not contained in an FDA-recognized standard, this final rule requires that all stand-alone symbols used in device labeling be established in a standard developed by an SDO, as is the case for FDA recognition of standards under section 514(c) of the FD&C Act.

Our definition of an SDO is intended to include the attributes that are required for voluntary consensus standards bodies, whose standards Federal Agencies are allowed to use for regulatory activities in lieu of a Government-developed standard. These attributes are openness, balance of interest, due process, an appeals process, and consensus (Refs. 2 and 3).

The symbols established in standards developed by SDOs, as defined in this final rule, will ordinarily have undergone the SDO's written procedures for approval or issuance and validation, and the final rule does not impose any additional requirements to revalidate that the symbol meets the requirements of section 502(c) of the FD&C Act if it is established in an FDA-recognized standard or has been appropriately validated by the SDO. See section II.D (FDA response to comments 10 and 11). As explained in the preamble to the proposed rule, FDA considers whether symbols have been validated through the standards development organization process when determining whether to recognize the symbols (see 76 FR 23508 at 23511). We also note that, contrary to the commenters' assertion regarding independent FDA validation of stand-alone symbols in a standard, FDA, as part of its section 514(c) recognition process, does not independently validate the symbols. For symbols in standards recognized by FDA under its authority in section 514(c) of the FD&C Act, FDA will have determined that the standard containing the symbol was developed by an SDO and that the SDO used its validation procedures in establishing the standard.

Under the final rule, a stand-alone symbol that is allowed to be used in device labeling is a symbol that: (1) is established in a standard developed by an SDO; and (2) is contained in a standard that FDA recognizes under section 514(c) of the FD&C Act and is used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition, or alternatively, if the symbol is not contained in a standard recognized by FDA under section

514(c) of the FD&C Act or the symbol is contained in a standard recognized by FDA but is not used according to the specifications for use of the symbol set out in the FDA section 514(c) recognition, is determined by the manufacturer to be likely to be read and understood by the ordinary individual under customary conditions of purchase and use in compliance with section 502(c) of the FD&C Act and is used according to the specifications for use of such symbol as set forth in such standard. In addition, in either case, the stand-alone symbol must be explained in a paper or electronic symbols glossary that is included in the labeling for the device. Furthermore, the labeling on or within the package containing the device must bear a prominent and conspicuous statement identifying the location of the symbols glossary that is written in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used. In device labeling, symbols that do not satisfy these criteria must be accompanied by adjacent explanatory text.

(Comment 2) Four comments requested that FDA authorize stand-alone use of all the symbols contained in ISO 15223-1:2012. One of these comments also encouraged the Agency to consider authorizing stand-alone use of the symbols in international standards ISO 7000, ISO 7010, and IEC 60417; another asked us to clarify that authorized stand-alone use will include the symbols in ANSI/AAMI ES60601-1:2005 and supersede IEC 60601-1. A separate comment recommended authorizing stand-alone use of the symbols in “ISO standard BS EN 980.”

(Response 2) As explained earlier in the Background section and section II.A (FDA response to Comment 1), this final rule provides additional flexibility by permitting the stand-alone use, in device labeling, of symbols that are part of a standard recognized by FDA under section 514(c) of the FD&C Act, as specified in the proposed rule, or, alternatively, a

manufacturer can use an SDO-established symbol not included in a standard recognized by FDA or a symbol in a standard recognized by FDA but not used in accordance with the specifications for use of the symbol set forth in FDA's section 514(c) recognition, if it otherwise determines that the symbol is likely to be read and understood by the ordinary individual under customary conditions of purchase and use in compliance with section 502(c) of the FD&C Act. Because FDA recognition of the underlying standard is not the only option for manufacturers, they are free to choose to select the additional option provided by the final rule with regard to using symbols established in the standards referenced in the comments. (See also section III regarding compliance and enforcement).

(Comment 3) Three comments stated that stand-alone symbols, once recognized through the section 514(c) process, should be allowed for all medical devices, rather than limited to use on any subset of devices. All three commenters believed that the Agency's actions in authorizing stand-alone symbols for IVD devices in the guidance document entitled "Use of Symbols on Labels and in Labeling of In Vitro Diagnostic Devices Intended for Professional Use" (November 2004) (the "IVD Symbols Guidance") at pp. 7-8 (Ref. 4), and in proposing for this rule that standardized symbols should be limited to a subset of devices, are confusing when limited use of stand-alone symbols is authorized based on device category and user groups.

(Response 3) FDA plans to continue to recognize symbols under its authority in section 514(c) of the FD&C Act for subsets of devices and/or subsets of users, as appropriate. Because the final rule does not limit the use of symbols to those in FDA-recognized standards, manufacturers have the option to use stand-alone symbols in the labeling for any medical device, as long as the symbol is established in a standard developed by an SDO and explained in a symbols glossary as provided in the standard and the manufacturer determines that the stand-

alone symbol on its particular device otherwise satisfies section 502(c) of the FD&C Act. Because the Agency is providing additional flexibility with regard to allowable stand-alone symbols, manufacturers are not limited as a result of FDA's recognition of a standard for only a subset of symbols, devices, or users. We note that use of stand-alone symbols beyond the specifications for use set out in FDA's recognition of the standard will require manufacturers to establish section 502(c) compliance for those symbols, devices, or users not included in FDA's recognition. If the manufacturer determines that the stand-alone symbol on its particular device otherwise satisfies section 502(c) of the FD&C Act, the manufacturer can use the stand-alone symbol in device labeling established in the standard only within the specifications for use of the symbol set out in the SDO-developed standard. Otherwise, a symbol used outside of the specifications for use set forth in the SDO-developed standard must be accompanied by adjacent explanatory text. See § 801.15(c)(1)(i)(C), as revised, in this final rule.

CDRH encourages stakeholders to recommend appropriate standards for FDA recognition under section 514(c) of the FD&C Act by following the instructions located at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Standards/ucm123739.htm>.

B. Matters Relating to the Extent to Which Symbols Can Be Used

1. Proprietary Symbols

(Comment 4) One of the comments stated that medical device manufacturers should be permitted to use proprietary symbols as long as the meaning of the proprietary symbol is described in documentation supplied with the device. The comment points out that the European Medical Device Directive allows the use of a symbol not developed as part of a standard as long as the symbol is defined in the labeling for the product.

(Response 4) We believe the commenter is referring to the provision in the EU's 1993 Medical Device Directive which states: "Any symbol or identification colours used must conform to the harmonized standards. In areas for which no standards exist, the symbols and colours must be described in the documentation supplied with the device." That is, the comment refers to a proprietary symbol that is not contained in a standard. Under the proposed rule and this final rule, for the use of a stand-alone symbol in device labeling to be allowed, the symbol must be established as part of a standard. In the preamble to the proposed rule, the Agency stated that it does not intend to recognize proprietary symbols (78 FR 23508 at 23511). This referred to proprietary symbols contained in a standard.

The Agency believes that proprietary symbols, whose use is subject to the symbol owner's exclusive rights and not freely available to the public, should be outside the SDO standards development process called for in the proposed rule and finalized in this rule. See the earlier discussion of SDO factors found in the National Technology Transfer and Advancement Act of 1995 (Ref. 2) and Circular A-119 (Ref. 3) to be considered when a Federal Agency uses standards developed outside the Government (Section I. (Background)).

Circular A-119 also provides that the Government use for regulatory purposes of a standard developed by non-Government body must include provisions requiring that owners of relevant intellectual property have agreed to make that intellectual property available on a non-discriminatory, royalty-free, or reasonable royalty basis to all interested parties (63 FR 8553 at 8554). The term "proprietary symbol," and the comment, begs the question of whether such symbol would be freely available to the public and whether the symbol's owner has retained its exclusive rights. Because this final rule is limited to symbols established in standards, it does not

allow proprietary symbols for use as stand-alone symbols. We note, however, that the rule allows use of a proprietary symbol accompanied by explanatory text adjacent to the symbol.

2. Pictograms

(Comment 5) Two comments asked us to clarify that product graphics or pictograms included in labeling, for example graphics showing the steps for using a device, are outside the scope of the proposed rule. One of the comments went further to assert that pictograms do not require accompanying English text to explain their meaning.

(Response 5) We agree that product graphics or pictograms included in labeling, for example graphics showing the steps for using a device, are outside this rulemaking. Symbols are not allowed for stand-alone use in this final rule unless they are established in a standard developed by an SDO and such graphics normally are not so established. Product graphics are typically unique to the individual product. They are not broadly applicable or used across a wide range of devices, and are unlikely to be established in an SDO-developed standard. Because the final rule is limited to symbols established in a standard, such product graphics are outside the scope of this final rule.

The Agency has interpreted its regulations generally to allow graphics, pictures, or symbols to meet the labeling requirements of this regulation except where it specifies particular labeling language (78 FR 23508 at 23509). Having said that, if a stand-alone graphical representation communicates required labeling information, such as directions for use required by § 801.5, the product graphic alone is unlikely to satisfy regulatory requirements, even when used under this final rule with accompanying adjacent English text, and further labeling may be needed in addition to what this final rule requires to explain the meaning of the symbol (see amended §§ 660.2(c), 660.28, 660.35, 660.45, 660.55, 801.15(c)(1) and 809.10).

3. Symbols Used on Non-Device Medical Products

(Comment 6) One comment argued that if a symbol is authorized for stand-alone use in device labeling, then that symbol should be authorized for all medical products, including for drugs or combination products. According to the comment, “a standard FDA recognizes” means a standard adopted “for all Centers” and for all FDA-regulated products, not just devices. While acknowledging the “procedural issues” associated with extending the scope of the final rule to non-device medical products, the commenter recommended flexibility “through enforcement discretion” until the regulations for drugs and non-device biological products can be updated to conform to the use of stand-alone symbols on medical devices.

(Response 6) The proposed rule would have authorized the stand-alone use of symbols explained in a symbols glossary included in the device labeling and contained in a standard recognized under section 514(c) of the FD&C Act, a provision applicable to medical devices only. The final rule also provides for the use in device labeling of stand-alone symbols if they are established in standards developed by an SDO, the manufacturer determines that the symbols are likely to be read and understood by the ordinary individual under customary conditions of use and purchase and the symbols are explained in a paper or electronic symbols glossary that is included in the labeling for the device. Because this rulemaking revises only the device and certain biological product labeling regulations, labeling for other FDA-regulated products is outside the scope of this rulemaking. Manufacturers considering the use of stand-alone symbols in labeling for other-FDA regulated products should contact the appropriate Center for the product regarding the permissibility of such use.

4. Combination Products

(Comment 7) One comment asked us to clarify how the rule applies to combination products, i.e., to medical products containing not only a device constituent but also a drug or biological product, for example, a drug/device combination.

(Response 7) Stand-alone symbols may be used in accordance with the final rule in the labeling applicable to a combination product as a whole if the primary mode of action (PMOA) for the product (see 21 CFR 3.2(k) and (m)) is that of a device. Stand-alone symbols may also be used in any separate labeling for the device constituent part of a combination product, regardless of the PMOA for the combination product (e.g., any separate labeling for the device constituent part of a convenience kit or other copackaged combination product, see § 3.2(e)(2)).

The appropriate use of stand-alone symbols in any other labeling associated with combination products is beyond the scope of this rulemaking. Manufacturers considering the use of stand-alone symbols in such other labeling for combination products should contact the lead Center for the product regarding the permissibility of the proposed use.

C. Labeling Information Not Required by or Under the Authority of the FD&C Act

(Comment 8) When adequate directions for use are known to the ordinary individual, some devices may be exempt from adequate directions for use (§ 801.116; see section 502(f)(1) of the FD&C Act). Some prescription devices are likewise not required to bear adequate directions for use if practitioners licensed by law to use the device are commonly aware of the directions, hazards, warnings, and other information necessary to use the device safely and for the purpose for which it is intended (§ 801.109(c)).

Three comments suggested that manufacturers marketing devices that are exempt from adequate directions for use under § 801.116 or § 801.109(c) would needlessly be burdened under

this final rule to create a symbols glossary to explain symbols that they are using voluntarily to display information that is not required “by or under” the FD&C Act.

(Response 8) The final rule requires a symbols glossary when a stand-alone symbol is used to provide labeling information required by or under the authority of the FD&C Act. (§ 801.15(c)(1)). The commenters’ understanding of FDA authority “by or under” the FD&C Act is too narrowly focused on the regulations concerning adequate directions for use under section 502(f)(1).

A device that is exempt from section 502(f)(1) of the FD&C Act under § 801.116 or § 801.109(c) may still be required to include certain information in its labeling for other purposes in order to provide a reasonable assurance of the safety and effectiveness of the device. For example, a prescription device that is exempt from section 502(f)(1) of the FD&C Act must still include, under § 801.109(c), indications, effects, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions in its labeling.

Whether or not a medical device is exempt by regulation from section 502(f)(1) of the FD&C Act, the device is still subject to the other misbranding provisions of section 502. Consequently, we disagree that directions-for-use symbols voluntarily used on devices exempt from adequate directions for use under § 801.116 or § 801.109(c) should be categorically exempt from the symbols glossary requirement and the final rule.

(Comment 9) In discussing the symbols glossary requirement, the preamble to the proposed rule stated therefore, any stand-alone symbol on the labeling for a device that conveys directions for use would be subject to the symbols glossary requirements (78 FR 23508 at 23511). One commenter interpreted this statement as limiting the symbols glossary requirement

to symbols for directions-for-use information only. The commenter requested clarification that, under the final rule, use of a symbol that does not convey directions for use, such as “the manufacturing site symbol, lot symbol, etc.,” should therefore not trigger the symbols glossary requirement.

(Response 9) The preamble statement quoted in the comment refers to directions-for-use symbols as an example, and not by way of limitation; but we agree that clarification is appropriate.

FDA device labeling regulations specifically require information other than just directions for use, including the examples mentioned in the comment. For example, under § 801.1(a), the device label must identify the name and address of the manufacturer, packer, or distributor of the device. If an FDA-allowed stand-alone symbol is used, for example, in place of the wording “manufacturer:” or “manufacturing site:” followed by a name and address, the final rule requires that a symbols glossary must be included in the labeling for the device to explain the meaning of the symbol to the device’s user. There are many FDA regulations that require device labeling information; and the final rule, including the symbols glossary requirement, applies to any device using a stand-alone symbol to provide such information.

D. Validation of Stand-Alone Symbols Contained in Standards Not Recognized by FDA or Recognized for Only a Subset of Symbols, Devices, or Users

(Comment 10) One comment asked the Agency to ensure that each stand-alone symbol authorized under this rule can be relied upon and be used by device manufacturers, without separate validation by the manufacturer for its use on a specific device. Another comment asked us to clarify that FDA would not unnecessarily use its resources to revalidate symbols established in an SDO-developed standard.

(Response 10) The symbols established in standards developed by SDOs will ordinarily have undergone the SDO's written procedures for approval or issuance and validation (78 FR 23508 at 23511). In the validation process, studies can demonstrate end-user comprehension of the stand-alone symbol in the device labeling context; and validation data specifically applicable to medical devices may be submitted to the SDO for its review (78 FR 23508 at 23510, see for example AAMI/ANSI/ISO 15223-2:2010 (Part 2), Symbol Development, Selection and Validation).

The final rule does not impose any additional requirements on device manufacturers to revalidate that such symbols meet the requirements of section 502(c) of the FD&C Act if the symbol is established in an FDA-recognized standard or has been appropriately validated by the SDO. FDA does not intend to invite requests for it to validate or to revalidate a symbol allowed under the rule, i.e., a stand-alone symbol established in an SDO-developed standard and explained in the device labeling. However, we will consider information as appropriate, including post-market surveillance data indicating that a symbol used on a particular device is not understood by device users (section 502(c) of the FD&C Act), or that it causes the labeling to be false or misleading (section 502(a)), results in inadequate directions for use of the device (section 502(f)), or otherwise causes the device labeling to violate the misbranding provisions of section 502.

(Comment 11) One comment questioned why, if the validation process includes consumer testing, there was no analysis of this cost burden.

(Response 11) The final rule does not impose any new requirements for public participation in the standards development processes of SDOs or for the establishment of symbols in SDO-developed standards. The final rule does not affect the paperwork burden or

cost associated with the standards-development process establishing a symbol allowed by the final rule, and therefore, no cost estimate or economic analysis of the process is required.

The final rule establishes certain procedures and conditions for device manufacturers to use a symbol as a stand-alone symbol on medical device labeling, including specifically, that the symbol must be explained in a symbols glossary that is included in the labeling for the device. The proposed and final rules do analyze the paperwork burden and economic cost of these procedures and conditions, including the required symbols glossary.

The burden on persons seeking SDO development of standards establishing symbols, including the validation of those symbols in the standard, is a matter already considered under existing standards-development norms and is otherwise in the control of the relevant SDO. The final rule does not require the interested party to revalidate that the stand-alone symbol meets the requirements of section 502(c) of the FD&C Act if the symbol is established in an FDA-recognized standard or has been appropriately validated by the SDO. Any validation needed in order to comply with the requirements of section 502(c) of the FD&C Act is under the requirements of that statute, and is not being imposed by this final rule. Accordingly, there is no validation process required by the final rule, and no cost estimate or economic analysis is called for in the rule.

E. Symbols Glossary Requirement

(Comment 12) Four comments state that, in the case of stand-alone symbols established in an SDO-developed standard, a symbols glossary “contemporaneously accompanying” the device is unnecessary. Three of these comments specifically refer to the symbols contained in ISO 15223-1 and contend that the symbols glossary requirement does not harmonize with the European Medical Device Directive or with ISO 15233 because neither one requires an

accompanying symbols glossary. Alternatively, one comment suggested that the final rule should establish a sunset limitation for the symbols glossary requirement, so that, for example, the glossary rule would expire 2 years after the publication of the final rule.

(Response 12) FDA disagrees with the comments that its symbols glossary requirement is not necessary and does not harmonize with the European Medical Directive or with ISO 15233. The European Medical Device Directive states that “[i]n areas for which no standards exist, the symbols and colours must be described in the documentation supplied with the device.” The Directive does not otherwise preclude requiring documentation with such symbols. Many of the symbols contained in ISO 15223-1 explicitly restrict their use as follows: “In Europe, this symbol shall be explained in the information supplied by the manufacturer.” FDA is aware of many device manuals containing a symbols glossary that would comply with this final rule, and has in the past considered this a good practice. Furthermore, the IVD Symbols Guidance (Ref. 4) recommends that a glossary of terms accompany each IVD to define all the symbols used on that device’s label and/or labeling (at pp. 7-8). Following the effective date of this final rule, FDA intends to withdraw the IVD Symbols Guidance.

Concerning the comment recommending a sunset limitation on the symbols glossary requirement, the Agency disagrees. The symbols glossary is intended to allow users to become familiar with the meaning of the symbols and also acts as a reference for users to look up any definitions they may not recall. In these respects, the symbols glossary helps to satisfy, although it does not satisfy on its own, the requirements of section 502(c) of the FD&C Act by making it more likely that users under customary conditions of purchase and use have access to necessary reference materials to help them understand the symbols. Accordingly, we do not believe that a sunset limitation on the symbols glossary requirement is appropriate.

(Comment 13) Four comments requested FDA to clarify the meaning of the term “contemporaneously accompanies the device” in the symbols glossary requirement of the rule, in particular whether the term includes “all varieties of written or electronic materials that are connected to a manufacturer’s marketing and sale of a product, even when the materials are not physically with the medical device.” Two of these commenters believe that, in the case of prescription devices, the rule should permit electronic display of the symbols glossary under section 502(f) of the FD&C Act and that such electronic labeling should be treated as accompanying the device for purposes of the rule. One comment urged that a reference in the medical device labeling to an online FDA glossary should satisfy the glossary requirement. Another stated that electronic labeling is an accepted practice for IVDs in the EU.

(Response 13) In the proposed rule, one of the requirements for use of stand-alone symbols was that such symbols be explained in a symbols glossary that contemporaneously accompanies the device. FDA understands that the term “contemporaneously accompanies” in the proposed rule may have prompted confusion, and we are revising the codified language of the final rule to clarify that a stand-alone symbol must be explained in a paper or electronic symbols glossary that is “included in the labeling for the device.” We agree that flexibility is possible and appropriate to satisfy the symbols glossary requirement. The new wording permits flexibility in the form of the symbols glossary, as long as the glossary is included in the labeling for the device.

Furthermore, this final rule allows device manufacturers to provide the symbols glossary by electronic means. We have changed the codified to read “the symbol ... is explained in a paper or electronic symbols glossary that is included in the labeling for the device.” (See amended §§ 660.2(c), 660.28, 660.35, 660.45, 660.55, and 801.15(c)(1), and new § 809.10(g).)

That is, the symbols glossary can be provided by electronic means so long as the glossary is included in the labeling for the device. This change also takes into account the provisions of section 502(f) of the FD&C Act which provides that required labeling for certain prescription devices and certain IVD devices may be made available solely by electronic means. (See section 502(f) (“by electronic means”).

In the proposed rule, we inadvertently did not specify that the labeling of the device must direct the purchaser and user as to the location of the symbols glossary in the labeling for the device. Without directions as to the location of the symbols glossary in the labeling, the purpose of the symbols glossary would not be served. Therefore, this final rule provides that the symbol is explained in a paper or electronic symbols glossary that is included in the labeling for the device and the labeling on or within the package containing the device bears a prominent and conspicuous statement identifying the location of the symbols glossary. For example, the statement could read “The symbols glossary is provided [specify, e.g., in Section X of the package insert, as a separate insert within the package, on the side panel of the package, electronically at (insert URL address to symbols glossary on manufacturer’s Web site)].” The statement must be in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used.

In the proposed rule, the term “symbols glossary” was defined in the codified as “a compiled listing of each symbol used in the labeling of the device and of the meaning of or explanatory text for the symbol.” We are revising the codified language in the final rule to define “symbols glossary” as “compiled listing of: (1) Each SDO-established symbol used in the labeling for the medical device; (2) the title and designation number of the SDO-developed

standard containing the symbol; (3) the title of the symbol and its reference number, if any, in the standard; and (4) the meaning or explanatory text for the symbol as provided in the FDA recognition, or if FDA has not recognized the standard or portion of the standard in which the symbol is located or the symbol is not used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition, the explanatory text as provided in the standard (see amended §§ 660.2(c), 660.28, 660.35, 660.45, 660.55, and 801.15(c) and new § 809.10(g)). In finalizing the rule, we revised the "symbols glossary" definition to help accurately identify the SDO-developed standard containing the symbol and the symbol in the standard.

(Comment 14) One comment argued that a single copy of the glossary should satisfy the rule when the same devices are shipped together in a multipack. Another comment argued that replacement parts or disposable components servicing the device with stand-alone symbols in their labeling should be exempt from the glossary rule because the customer would already have received the glossary information with the original purchase of the device.

(Response 14) In both of these situations, the premise is that there is a stand-alone symbol that appears in the labeling for the individual device unit or the replacing component.

Typically, a replacement part for a medical device or disposable component is used later in time than the replaced component. The glossary delivered to the user with the original equipment might no longer be available to explain the meaning of the stand-alone symbol on the labeling for a replacement part. "Any component, part, or accessory" of a device, if its intended use is to service the device, is itself a device (section 201(h) of the FD&C Act (21 U.S.C. 321(h))). Under the final rule, the symbols glossary requirement therefore applies separately to replacement or disposable components when the labeling for the replacing component bears a stand-alone symbol because the symbols glossary must be included in the labeling for the device.

Additionally, the individual units of a multipack shipment, like replacement components, are likely to be used later such that the glossary delivered to the user of a multipack shipment might no longer be retained and available to explain the meaning of the stand-alone symbol on the labeling for the remaining individual units after the multipack is broken and the first unit or units are used. Under the final rule, the symbols glossary requirement therefore applies to the individual devices of a multipack shipment when the labeling for the individual units bears a stand-alone symbol because the symbols glossary must be included in the labeling for the device.

To reduce the burden of the glossary requirement for individual devices of a multipack shipment, manufacturers should consider the final rule's provision for use of an electronic symbols glossary. Such electronic glossary, however, must be included in the labeling for the device. In such situations, FDA requires that the labeling for the device must prominently and conspicuously include the URL address for a Web site that displays the symbols glossary on the manufacturer's Web site explaining the meaning of the stand-alone symbols used on that device's labeling.

F. Implementation of the Final Rule

(Comment 15) One comment asked FDA to clarify how much time manufacturers will have to convert existing symbols in labeling to stand-alone symbols.

(Response 15) In the final rule, there is no required conversion to stand-alone symbols. The final rule does not mandate the use of stand-alone symbols. The use of stand-alone symbols is an alternative to labeling without symbols and to the currently-allowed use of symbols with adjacent explanatory text. Effective beginning on [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER] (see section VIII), the final rule expressly provides for the use of symbols accompanied by adjacent explanatory text in the device labeling

(amended §§ 660.2(c), 660.28, 660.35, 660.45, 660.55, and 801.15(c)(1) and new § 809.10(g)) and the use of stand-alone symbols that meet the requirements of the rule.

(Comment 16) One comment asked FDA to clarify whether manufacturers need to file a new 510(k) notification under 21 CFR part 807, subpart E or a Premarket Approval (PMA) supplement under 21 CFR part 814 when they replace symbols currently used with adjacent English text with stand-alone symbols and a symbols glossary in the device labeling.

(Response 16) In most cases, manufacturers who wish to update their device or product labeling only by substituting text with one or more stand-alone symbols allowed under the rule, or to remove explanatory text adjacent to such symbols (without making any changes to the meaning of the labeling), do not need to submit a new premarket submission prior to making that change. In some cases FDA may require, through regulation or order, through a special controls guideline, or on a case-by-case basis in reviewing premarket submissions, specific language in device labeling, or may require or prohibit use of symbols in a specific labeling context. For example, devices subject to a boxed-warning labeling requirement must strictly adhere to the exact language of the applicable regulation, and any use of symbols in the warning should be reviewed and specifically allowed by FDA in advance of such use.

For medical devices with an approved PMA, manufacturers may generally replace required information in existing labeling with equivalent stand-alone symbols that are allowed under the rule without the need to submit a PMA supplement. PMA holders that implement this type of change should notify the Agency of the change in the next annual report to the PMA, in accordance with § 814.84. As with 510(k)-cleared devices, however, in some cases FDA may require, through regulation or order, or on a case-by-case basis during premarket review, specific

language in device labeling, or may require or prohibit use of symbols in a specific labeling context.

Similarly, applicable biologics license holders that replace required information with stand-alone symbols that are allowed under the rule on the labeling for licensed products also regulated as devices should notify the Agency of the change in the next annual report to the manufacturer's Biologics License Application (BLA), in accordance with 21 CFR 601.12(f)(3)(i)(A); and the Agency will consider the change to be an editorial or similar minor change.

Manufacturers may substitute stand-alone symbols that are allowed under the rule for equivalent text on existing labels and labeling for medical devices that received premarket notification (510(k)) clearance without submitting a new 510(k) notification. For information on other labeling changes that might require submission of a new 510(k) notification, please see § 807.81(a)(3).

(Comment 17) Three comments urged FDA to maintain close cooperation and communication with industry in order to implement timely updates of the list of symbols permitted for stand-alone use through its standards-recognition process and to keep up with the revision of current international standards.

(Response 17) Under this final rule, any stand-alone symbol established in an SDO-developed standard and used in accordance with the specifications of the standard is allowed, regardless of whether or not FDA recognizes the standard or the part of the standard containing the symbol, under section 514(c) of the FD&C Act. Under the final rule, symbols established in a standard developed by an SDO may be used in medical device labeling without adjacent explanatory text as long as: (1) The standard is recognized by FDA under its authority under

section 514(c) of the FD&C Act and the symbol is used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition, or alternatively, (2) if the symbol is not included in a standard recognized by FDA under section 514(c) of the FD&C Act or the symbol is in a standard recognized by FDA but is not used according to the specifications for use of the symbol set out in the FDA section 514(c) recognition, the device manufacturer otherwise determines that the symbol is likely to be read and understood by the ordinary individual under customary conditions of purchase and use in compliance with section 502(c) of the FD&C Act and uses the symbol according to the specifications for use of the symbol set forth in the SDO-developed standard. In addition, in either case, the symbol must be explained in a paper or electronic symbols glossary that is included in the labeling for the device. Furthermore, the labeling on or within the package containing the device must bear a prominent and conspicuous statement identifying the location of the symbols glossary that is written in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used. Although FDA will continue to participate with SDOs in the standards development process and some of those standards may involve symbols in device labeling, the final rule will not require the close industry coordination and communication with FDA in order for firms to comply with the rule because of its additional flexibility.

(Comment 18) One comment recommended that when the Agency does not recognize all the symbols established in a standard for stand-alone use, it should clearly state why any rejected symbol is not included in order for interested parties to get "insights needed to validate the symbols."

(Response 18) Under the final rule, the fact that FDA does not recognize all the symbols established in a standard does not preclude a manufacturer from determining that the stand-alone use of the symbol is likely to be read and understood by the ordinary individual under customary conditions of use and purchase. Therefore, the Agency will not provide explanations of why it does not include certain symbols in a standard in its recognition under section 514(c) of the FD&C Act as requested by the commenter.

G. Symbol Statement “Rx Only” or “R Only”

(Comment 19) Two comments related to the provision of the rule authorizing use of the symbol statement “Rx Only.” One comment asked whether validation will be required in order to use “Rx Only” on a prescription device. The second comment asked whether FDA will be issuing guidance to support use of the symbol statement “Rx Only.”

(Response 19) This final rule does not require validation by the device manufacturer in order for it to use the symbol statement “Rx Only” on its prescription device. The symbol statement “Rx Only” has a separate statutory and regulatory history unrelated to the use of standards as allowed in this final rule.

As explained in the preamble to the proposed rule, section 126(a) of the FDA Modernization Act of 1997 (FDAMA) (Pub. L. 105-115), amending section 503(b)(4) of the FD&C Act (21 U.S.C. 353(b)(4)), allows use of this symbol statement on the labels of drug products in place of a full prescription use statement that indicates that the drug must be dispensed with a clinician’s prescription. FDAMA did not explicitly make the permitted use of “Rx Only” applicable to medical devices; however, the Agency published the guidance document entitled “Alternative to Certain Prescription Device Labeling Requirements,” January 2000 (the Rx Only Statement Guidance) (Ref. 5) stating that FDA would exercise enforcement discretion

for the use of “Rx Only” on prescription device labels. FDA’s reason for issuing that guidance document was a desire to minimize the burden of creating device labels and to make it flexible consistent with the statutorily permitted use of the “Rx Only” symbol statement for prescription drug products. In this rule, FDA is expressly allowing for use of “Rx Only” for the labels of prescription devices to give device manufacturers the option to use “Rx Only” in lieu of the longer statement currently in the regulations. FDA has included this change in this rulemaking given the changes involving symbols that the final rule is making to other sections of FDA’s labeling regulations.

Because the statutory authority for using the symbol statement “Rx Only” for drug products, and our purpose and intent in this final rule extending it to prescription devices, are clear and satisfy the misbranding requirements of section 502 of the FD&C Act pertaining to the symbol statement “Rx Only,” the Agency does not intend to issue a new guidance document regarding the use of “Rx Only.” We only restate in this document what we said in the preamble to the proposed rule about using the symbol statement “Rx Only.” It is important to note that the word “only” must immediately follow the symbol “Rx.” However, the symbol statement “Rx only” does not necessarily need to be bracketed in quotation marks, and the word “only” may appear in upper or lower case letters, for example, Rx only, Rx Only, or Rx ONLY. As in the case of labels for prescription drugs, the new label statement for prescription medical devices may be printed as either “Rx only” or “**R**x only.” (See 67 FR 4904, February 1, 2002.) The symbol statement “Rx only” in its entirety, or the **R** symbol in the symbol statement “Rx only,” may be printed in bold or in regular type.

III. Compliance and Enforcement

Under the final rule, manufacturers may use symbols in labeling in the following scenarios. First, manufacturers may continue to use symbols with adjacent explanatory text. See, e.g., § 801.15(c)(1)(i)(C) in this final rule.

Second, manufacturers may use a stand-alone symbol if the symbol is contained in a standard that FDA recognizes under its authority in section 514(c) of the FD&C Act for use on the labeling for medical devices (or on a subset of medical devices), is used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition, and is explained in a paper or electronic symbols glossary that is included in the labeling for the device and the labeling on or within the package containing the device bears a prominent and conspicuous statement identifying the location of the symbols glossary. See, e.g., § 801.15(c)(1)(i)(D) in this final rule. In this second scenario, FDA has, through the section 514(c) recognition process, made a determination that the symbol, is likely to be read and understood by the ordinary individual under customary conditions of purchase and use in compliance with section 502(c) of the FD&C Act. In this second scenario where a manufacturer wishes to use a stand-alone symbol that is in an SDO standard that has been recognized by FDA under section 514(c) to meet a requirement under the FD&C Act, such manufacturer would submit a declaration of conformity to FDA that certifies that the device is in conformity with the standard.

In a third scenario, the stand-alone symbol is not included in a standard that is recognized under FDA's section 514(c) authority or is in a standard that is recognized under FDA's section 514(c) authority but is not used according to the specifications for use of the symbol set forth in FDA's 514(c) recognition, manufacturers may use such symbol as a stand-alone symbol if the symbol has been established in a standard developed by an SDO, the manufacturer has made a

determination that the symbol in the labeling for a particular device is likely to be read and understood by the ordinary individual under customary conditions of purchase and use in compliance with section 502(c) of the FD&C Act, and such symbol is explained in a paper or electronic symbols glossary that is included in the labeling for the medical device, and the labeling on or within the package containing the device bears a prominent and conspicuous statement identifying the location of the symbols glossary. See, e.g., § 801.15(c)(1)(i)(E) in this final rule. In this third scenario where a manufacturer uses a symbol that has not been recognized by FDA under section 514(c) of the FD&C Act or uses a symbol from an FDA recognized standard but not in accordance with the specifications for use of the symbol set forth in FDA's section 514(c) recognition, the burden is on the manufacturer to determine that the symbol is likely to be read and understood by the ordinary individual under customary conditions of purchase and use such that the use of the symbol in labeling is in compliance with section 502(c) of the FD&C Act. See, e.g., § 801.15(c)(1)(i)(E)(3).

To clarify the requirements of the final rule, we include the following example:

Standard Z is a standard developed by an SDO. The scope of Standard Z is cardiac devices according to the specifications for use of the standard set forth by the SDO. FDA recognizes the standard for use of symbols in labeling for cardiac stents under its section 514(c) authority. As such, FDA's recognition is for a subset of the devices covered by Standard Z. Manufacturer A wishes to use stand-alone symbols (symbols without adjacent explanatory text) from Standard Z on cardiac stents. Manufacturer B wishes to use stand-alone symbols from Standard Z on cardiac pacemakers. Manufacturer C wishes to use stand-alone symbols from Standard Z on biliary stents, which are not cardiac devices.

Under the example, all the manufacturers could legally use the symbols from Standard Z with adjacent explanatory text. See e.g., § 801.15(c)(1)(i)(C). Manufacturer A can legally use stand-alone symbols from Standard Z in the labeling for cardiac stents, consistent with FDA's recognition of Standard Z for cardiac stents. See, e.g., § 801.15(c)(1)(i)(D). Manufacturer A must explain the stand-alone symbols in a paper or electronic symbols glossary that is included in the labeling for the device and the labeling on or within the package containing Manufacturer A's device must bear a prominent and conspicuous statement identifying the location of the symbols glossary. See, e.g., § 801.15(c)(1)(i)(D)(3). The symbol must be used according to the specifications of FDA's section 514(c) recognition, including the same meaning or explanatory text for the symbol in the symbols glossary as provided in FDA's recognition of Standard Z. See, e.g., § 801.15(c)(1)(i)(D)(2). As discussed again later, if FDA subsequently withdraws recognition of Standard Z because the stand-alone symbol is not likely to be read and understood by the ordinary individual under customary conditions of purchase and use, Manufacturer A must stop using the stand-alone symbol. If FDA withdraws its recognition of Standard Z for other reasons, the Manufacturer A may continue to use the stand-alone symbols from Standard Z, that FDA no longer recognizes, for cardiac stents (see, e.g. § 801.15(c)(1)(i)(E)(2)); but the use must be consistent with the specifications of Standard Z, including use of the explanatory text as provided in Standard Z (see, e.g., § 801.15(c)(1)(i)(E)(4)), and the burden is on Manufacturer A to determine that the symbol's use is likely to be read and understood by the ordinary individual under customary conditions of purchase and use (see, e.g. § 801.15(c)(1)(i)(E)(3)).

With regard to Manufacturer B, this manufacturer wishes to use a stand-alone symbol from Standard Z that would not be in accordance with the specifications for use of the symbol set forth in FDA's section 514(c) recognition. When FDA recognized Standard Z, the scope of

which is cardiac devices, it limited the specifications for use of the symbols to cardiac stents. Manufacturer B wishes to use the stand-alone symbol from Standard Z on cardiac pacemakers. Under the final rule, Manufacturer B may use stand-alone symbols outside the scope of FDA recognition (see, e.g., § 801.15(c)(1)(i)(E)(2)), but within the specifications for use of Standard Z (see, e.g., § 801.15(c)(1)(i)(E)(4)). In this scenario where Manufacturer B uses a symbol from Standard Z that has not been recognized under section 514(c) of the FD&C Act, the burden is on Manufacturer B to determine that the symbol's use on cardiac pacemakers, outside the scope of the FDA recognition, is likely to be read and understood by the ordinary individual under customary conditions of purchase and use. See, e.g., § 801.15(c)(1)(i)(E)(3). The same is true and same provisions apply if Manufacturer A uses a stand-alone symbol on cardiac stents that is not in accordance with the specifications for use of FDA's section 514(c) recognition. In these cases, Manufacturer B (and Manufacturer A, if its use of the stand-alone symbol is not in accordance with the specifications for use set forth in FDA's section 514(c) recognition) must use the stand-alone symbols of Standard Z consistent with the specifications for use of the symbol set forth in Standard Z, including use of the explanatory text as provided in Standard Z. See, e.g., § 801.15(c)(1)(i)(E)(4).

Finally, Manufacturer C wishes to use stand-alone symbols in Standard Z for biliary stents. Under this final rule, this stand-alone use is not allowed. As provided in this final rule, the use of stand-alone symbols must be in accordance with the specifications for use of the symbol set forth in the SDO-developed standard. Standard Z, as developed by the SDO, specifies that it applies to cardiac devices. As such, the use of stand-alone symbols from Standard Z in biliary stents would not be in accordance with the specifications for use of the symbols set forth in Standard Z. See, e.g., § 801.15(c)(1)(i)(E)(4) in this final rule that requires

that a stand-alone symbol be used according to the specifications for use of the symbol set forth in the SDO-developed standard that FDA does not recognize. Accordingly, Manufacturer C's use of the symbols from Standard Z on biliary stents would require adjacent explanatory text. See, e.g., § 801.15(c)(1)(i)(C) in this final rule.

The final rule does not require the manufacturer to validate for a particular device, the stand-alone use of a symbol established in an SDO-developed standard, or part of a standard, that FDA has recognized under section 514(c) of the FD&C Act. In addition, the final rule does not require manufacturers to validate any stand-alone symbol. At the same time, this final rule does not preclude device manufacturers from undertaking any validation studies needed to assure that the use of the stand-alone symbol is likely to be read and understood by customary purchasers and users (section 502(c)) and complies with the other misbranding requirements of section 502 of the FD&C Act.

Manufacturers and importers should monitor complaints and adverse events that might be related to inadequate understanding of labeling, including misunderstanding about the meaning of stand-alone symbols used in the device labeling. Manufacturers must report adverse events as required by 21 CFR part 803. Reporting forms and instructions are available at <http://www.fda.gov/medwatch/safety.htm>. If, for example, postmarket surveillance data such as medical device reporting (MDR) suggests that the users of the device do not understand the meaning of a particular stand-alone symbol, and that such misunderstanding could lead to a safety issue, the Agency may take enforcement action against the device and device manufacturer.

If FDA withdraws recognition of a standard (e.g., Standard Z in the example) because the stand-alone symbol is not likely to be read and understood by the ordinary individual under

customary conditions of purchase and use, in that case, all manufacturers (both Manufacturers A and B) must stop using the stand-alone symbol upon withdrawal of recognition of the standard. FDA notes that it does not intend to take enforcement action under section 502(c) of the FD&C Act on the basis that the symbol is not likely to be read and understood by the ordinary individual under customary conditions of purchase and use that otherwise meets the requirements of this rule unless and until FDA issues either a notice of SDO-standard withdrawal applicable to the use or a symbol-specific Federal Register notice announcing FDA's determination that the symbol is not likely to be read and understood by the ordinary individual under customary conditions of purchase and use as required by section 502(c), and, as such, the future date on which FDA intends to take enforcement action against stand-alone use of such symbol.

In situations where FDA withdraws recognition of a standard, or portion thereof, for reasons other than that the stand-alone symbol is not likely to be read and understood as required by section 502(c) of the FD&C Act, manufacturers may continue to use symbols within that standard without adjacent text if the manufacturer determines that the symbol is likely to be read and understood by the ordinary individual under customary conditions of purchase and use in compliance with section 502(c). Therefore, in the example, if FDA withdraws its recognition of Standard Z for use of symbols in labeling for cardiac stents for a reason other than that the ordinary individual is not likely to read and understand the symbols under customary conditions of purchase and use in compliance with section 502(c) of the FD&C Act, Manufacturer A and Manufacturer B may continue to use their stand-alone symbols under § 801.15(c)(1)(i)(E) in this final rule. If FDA provided a meaning or explanatory text in its recognition of Standard Z, after the withdrawal Manufacturer A must use the symbols from Standard Z according to the specifications of Standard Z, including the same meaning or explanation in its symbols glossary

as provided in Standard Z for any remaining permitted use under the FDA withdrawal notice. See, e.g., § 801.15(c)(1)(i)(E)(4) and (iii)(B) in this final rule.

With regard to Manufacturer C, if it uses stand-alone symbols that are outside the scope of the SDO-developed standard, FDA intends to enforce compliance after the effective date of this final rule. See, e.g., § 801.15(c)(1)(ii) in this final rule.

IV. Legal Authority for the Final Rule

A device is misbranded under section 502(c) of the FD&C Act if any word, statement, or other information required by or under authority of this act to appear on the label or labeling is not in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use. Additionally, a device is misbranded under section 502(a) of the FD&C Act if its labeling is false or misleading in any particular. A device is also misbranded under section 502(f) of the FD&C Act unless its labeling bears adequate directions for use.

Under section 201(m) of the FD&C Act, the term “labeling” means all labels and other written, printed, or graphic matter: (1) Upon any article or any of its containers or wrappers or (2) accompanying such article. Under section 201(k) of the FD&C Act, the term “label” means a display of written, printed, or graphic matter upon the immediate container of any article; and a requirement made by or under authority of the FD&C Act that any word, statement, or other information appear on the label shall not be considered to be complied with unless such word, statement, or other information also appears on the outside container or wrapper, if any there be, of the retail package of such article, or is easily legible through the outside container or wrapper.

Section 514(c)(1)(A) of the FD&C Act authorizes FDA to recognize, by publication in the Federal Register, all or part of an appropriate standard established by a nationally or

internationally recognized standard development organization for which a person may submit a declaration of conformity in order to meet a premarket submission requirement or other requirement under the FD&C Act to which such standard is applicable. Section 514(c)(1)(B) of the FD&C Act further provides that a person may elect to use data, or information, other than data required by a standard recognized by FDA to meet any requirement regarding devices under the FD&C Act. Section 514(c)(2) of the FD&C Act allows FDA to withdraw recognition of a standard through publication of a notice in the Federal Register if FDA determines that the standard is no longer appropriate for meeting a device requirement under the FD&C Act.

Section 701(a) of the FD&C Act (21 U.S.C. 371(a)) gives FDA the authority to issue regulations for the efficient enforcement of the FD&C Act.

V. Economic Analysis of Impacts

We have examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us 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). We have developed a comprehensive Economic Analysis of Impacts that assesses the impacts of the final rule. We believe that the final rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this rule imposes no new

burdens, we certify that the final rule would not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before issuing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is \$146 million, using the most current (2015) Implicit Price Deflator for the Gross Domestic Product. This final rule would not result in an expenditure in any year that meets or exceeds this amount.

Summary

The final rule would provide medical device manufacturers with the option to use symbols established in SDO-developed standards for stand-alone use in labeling to communicate information to end users. Under the final rule, manufacturers would be allowed to substitute labels containing only written statements (text-only labels) or symbols with adjacent explanatory text with a label containing stand-alone symbols, provided that such symbols are established in a standard developed by a SDO as long as: (1) The standard is recognized by FDA under its authority under section 514(c) of the FD&C Act and the symbol is used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition, or alternatively, (2) if the symbol is not included in a standard recognized by FDA under section 514(c) of the FD&C Act or the symbol is in a standard recognized by FDA but is not used according to the specifications for use of the symbol set out in the FDA section 514(c) recognition, the device manufacturer otherwise determines that the symbol is likely to be read

and understood by the ordinary individual under customary conditions of purchase and use and uses the symbol according to the specifications for use of the symbol set forth in the SDO-developed standard. In addition, in either case, the symbol must be explained in a written or electronic symbols glossary that is included in the labeling for the medical device. Furthermore, the labeling on or within the package containing the device must bear a prominent and conspicuous statement identifying the location of the glossary that is written in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used. The use of such symbols must also comply with other applicable labeling requirements of the FD&C Act, such as section 502(a) and section 502(f). In addition, the final rule allows the use of the symbol statement “Rx Only” or “**R** only” for labeling of prescription devices.

Medical device manufacturers would only choose to use stand-alone symbols, as allowed by the final rule, if they expect a positive net benefit (estimated benefits minus estimated costs). Hence, the final rule is expected to provide a non-negative net benefit to each manufacturer that opts to use stand-alone symbols. Choosing to use stand-alone symbols under the final rule would potentially reduce the costs associated with designing and redesigning the labels on medical devices that are currently marketed in the United States and the EU. The estimated annual benefits range from \$7.9 million to \$25.5 million at a 3 percent discount rate, and \$7.7 million to \$25.0 million at a 7 percent discount rate. Those that opt to use stand-alone symbols under the rule would incur one-time administrative costs to redesign their labeling and create a symbols glossary that is included in the labeling for the device, and recurring costs to revise their glossaries, as necessary. Annualized over 20 years, we estimate total costs to range between \$1.1 million to \$3.2 million at a 3 percent discount rate, and from \$1.1 million to \$3.3 million at

a 7 percent discount rate. Annualized over 20 years, net benefits range from \$6.8 million to \$22.3 million at a 3 percent discount rate, and from \$6.6 million to \$21.7 million at a 7 percent discount rate. The costs and benefits accrue to the same entities, however, so any firm making the change to stand-alone symbols would, on net, reduce costs.

FDA also examined the economic implications of the final rule as required by the Regulatory Flexibility Act. If a rule will have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires Agencies to analyze regulatory options that would lessen the economic effect of the rule on small entities. We estimated the final rule's approximate impact on small entities using the percent costs per device distinguishable by Universal Product Code (UPC): The ratio between unit labeling costs and revenues among small entities. Our estimates indicate that the average percent costs per UPC ranges from 0.01 to 0.46 percent. Because companies can choose whether or not to use stand-alone symbols under the final rule, the Agency concludes that this final rule would not have a significant adverse impact on any small entities. Furthermore, our analysis suggests that companies could reap moderate cost-savings by using stand-alone symbols in device labeling. On average, companies that use stand-alone symbols under this final rule could expect to receive an average annual cost savings ranging from \$1,500 to \$4,500 per UPC. Because using stand-alone symbols is expected to lower the marginal cost of producing exports, medical device manufacturers, including small entities, may be able to increase their production either by starting to export products or by exporting more products.

The full analysis of economic impacts is available in the docket for this final rule (FDA-2013-N-0125) and at

<http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>
(Ref. 6).

VI. Paperwork Reduction Act of 1995

This final rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The title, description, and respondent description of the information collection provisions are provided in the following paragraphs with an estimate of the annual reporting and third-party disclosure burdens. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

Title: Medical Devices: Use of Symbols in Labeling--Glossary to Support the Use of Symbols in Labeling

Description: FDA is issuing a final rule revising medical device and certain biological product labeling regulations by explicitly allowing for the optional use in medical device labeling of stand-alone symbols established in an SDO-developed standard.

In particular, FDA will allow the use of stand-alone graphical representations of information, or symbols in the labeling for the medical devices, if the symbols are established in a standard developed by an SDO as long as: (1) The standard is recognized by FDA under its authority under section 514(c) of the FD&C Act and the symbol is used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition, or alternatively, (2) if the symbol is not included in a standard recognized by FDA under section 514(c) of the FD&C Act or the symbol is in a standard recognized by FDA but is not used according to the specifications for use of the symbol set out in the FDA section 514(c)

recognition, the device manufacturer otherwise determines that the symbol is likely to be read and understood by the ordinary individual under customary conditions of purchase and use and uses the symbol according to the specifications for use of the symbol set forth in the SDO-developed standard. In addition, in either case, the symbol must be explained in a written or electronic symbols glossary that is included in the labeling for the medical device. Furthermore, the labeling on or within the package containing the device must bear a prominent and conspicuous statement identifying the location of the glossary that is written in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used. The use of such symbols must also comply with other applicable labeling requirements of the FD&C Act, such as section 502(a) and section 502(f). The final rule also allows the use of the symbol statement “Rx Only” or “**R** only.”

Description of Respondents: The likely respondents for this collection of information are domestic and foreign device manufacturers who plan to use stand-alone symbols on the labels and/or labeling for their devices marketed in the United States.

Table 1.--Estimated Annual Reporting Burden¹

Activity	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
Glossary	3,000	1	3,000	1	3,000

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

Table 2.--Estimated Annual Third-Party Disclosure Burden¹

Activity	No. of Respondents	No. of Disclosures per Respondent	Total Annual Disclosures	Average Burden per Disclosure	Total Hours
Glossary	3,000	1	3,000	4	12,000

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

The estimated burden is based on the data in a similar collection for recommended glossary and educational outreach approved under OMB control number 0910-0553 (Use of Symbols on Labels and in Labeling of In Vitro Diagnostic Devices Intended for Professional

Use). As such, the PRA also covers the requirements of this final rule to submit the symbols glossary to FDA in otherwise required submissions during the premarket review process and to disclose it to third parties in otherwise required device labeling, which means adding to such submission or labeling a compiled listing of each SDO-established symbol used in the labeling for the device; the title and designation number of the SDO-developed standard containing the symbol; and the title of the symbol and its reference number, if any, in the standard; and the meaning or explanatory text for the symbol as provided in the FDA recognition or, if FDA has not recognized the standard or portion of the standard in which the symbol is located or the symbol is used not in accordance with the specifications for use of the symbol set out in the FDA section 514(c) recognition, the explanatory text as provided in the standard. We assume that the additional requirement of identifying in the symbols glossary the SDO-developed standard establishing the symbol and its reference number if any, not included in proposed rule, results in no significant additional cost burden.

The information collection provisions in this final rule have been submitted to OMB (control number 0910-0740) for review as required by section 3507(d) of the Paperwork Reduction Act of 1995.

Before the effective date of this final rule, FDA will publish a notice in the Federal Register announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. 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.

This final rule refers to previously approved collections of information found in FDA regulations. These collections of information are subject to review by OMB under the

Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in 21 CFR part 812 have been approved under OMB control number 0910-0078; the collections of information in 21 CFR part 807, subpart E have been approved under OMB control number 0910-0120; the collections of information in 21 CFR part 814, subparts A through E have been approved under OMB control number 0910-0231; the collections of information in 21 CFR part 801 and § 809.10 have been approved under OMB control number 0910-0485; and the collections of information in §§ 660.2, 660.28, 660.35, 660.45, and 660.55 have been approved under OMB control number 0910-0338.

VII. Analysis of Environmental Impact

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

VIII. Effective Date

This rule is effective on [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

IX. Federalism

We have analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

X. References

The following references are on display in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at <http://www.regulations.gov>. FDA has verified the Web site addresses, as of the date this document publishes in the Federal Register, but Web sites are subject to change over time.

1. Frequently Asked Questions on Recognition of Consensus Standards; Guidance for Industry and FDA Staff, September 2007, available at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm074973.htm>.
2. The National Technology Transfer and Advancement Act of 1995 (Pub. L. 104-113), section 12(d), 110 Stat. 783.
3. Office of Management and Budget, OMB Circular A-119 (63 FR 8546, February 19, 1998) (Final Revision).
4. Use of Symbols on Labels and in Labeling of In Vitro Diagnostic Devices Intended for Professional Use; Guidance for Industry and FDA Staff, FDA, November 2004, available at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085404.htm>.
5. Alternative to Certain Prescription Device Labeling Requirements; Guidance for Industry, FDA, January 2000, available at

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072747.htm>.

6. Use of Symbols in Medical Device Labeling: Final Regulatory Impact Analysis; Final Regulatory Flexibility Analysis; Unfunded Mandates Reform Act Analysis; available at

<http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/ucm350746.htm>.

List of Subjects

21 CFR Part 660

Biologics, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 801

Labeling, Medical devices, Reporting and recordkeeping requirements.

21 CFR Part 809

Labeling, Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321 et seq., as amended), the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 660, 801, and 809 are amended as follows:

PART 660--ADDITIONAL STANDARDS FOR DIAGNOSTIC SUBSTANCES FOR LABORATORY TESTS

1. The authority citation for part 660 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360, 360c, 360d, 360h, 360i, 371, 372; 42 U.S.C. 216, 262, 263, 263a, 264.

2. Amend § 660.2 by revising paragraph (c) to read as follows:

§ 660.2 General requirements.

* * * * *

(c) Labeling. (1) In addition to the items required by other applicable labeling provisions of this subchapter, the following shall also be included:

(i) Indication of the source of the product immediately following the proper name on both the final container and package label, e.g., human, guinea pig.

(ii) Name of the test method(s) recommended for the product on the package label and on the final container label when capable of bearing a full label (see § 610.60(a) of this chapter).

(iii) A warning on the package label and on the final container label if capable of bearing a full label (see § 610.60(a) of this chapter) indicating that the product and antigen if supplied, shall be handled as if capable of transmitting hepatitis.

(iv) If the product is dried, the final container label shall indicate “Reconstitution date: _____” and a statement indicating the period within which the product may be used after reconstitution.

(v) The package shall include a package enclosure providing:

(A) Adequate instructions for use;

(B) A description of all recommended test methods; and

(C) Warnings as to possible hazards, including hepatitis, in handling the product and any ancillary reagents and materials accompanying the product.

(2) The applicant may provide the labeling information referenced in paragraph (c)(1) of this section in the form of:

(i) A symbol accompanied by explanatory text adjacent to the symbol;

(ii) A symbol not accompanied by adjacent explanatory text that:

(A) Is contained in a standard that FDA recognizes under its authority in section 514(c) of the Federal Food, Drug, and Cosmetic Act;

(B) Is used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition; and

(C) Is explained in a paper or electronic symbols glossary that is included in the labeling for the device and the labeling on or within the package containing the device bears a prominent and conspicuous statement identifying the location of the symbols glossary that is written in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used; or

(iii) A symbol not accompanied by adjacent explanatory text that:

(A) Is established in a standard developed by a standards development organization (SDO);

(B) Is not contained in a standard that is recognized by FDA under its authority in section 514(c) of the Federal Food, Drug, and Cosmetic Act or is contained in a standard that is recognized by FDA but is not used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition;

(C) Is determined by the manufacturer to be likely to be read and understood by the ordinary individual under customary conditions of purchase and use in compliance with section 502(c) of the Federal Food, Drug, and Cosmetic Act;

(D) Is used according to the specifications for use of the symbol set forth in the SDO-developed standard; and

(E) Is explained in a paper or electronic symbols glossary that is included in the labeling for the device and the labeling on or within the package containing the device bears a prominent

and conspicuous statement identifying the location of the symbols glossary that is written in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used.

(3) The use of symbols to provide the labeling information referenced in paragraph (c)(1) of this section which do not meet the requirements of paragraph (c)(2) of this section renders a device misbranded under section 502(c) of the Federal Food, Drug, and Cosmetic Act.

(4) For purposes of paragraph (c)(2) of this section:

(i) An SDO is an organization that is nationally or internationally recognized and that follows a process for standard development that is transparent, (i.e., open to public scrutiny), where the participation is balanced, where an appeals process is included, where the standard is not in conflict with any statute, regulation, or policy under which FDA operates, and where the standard is national or international in scope.

(ii) The term “symbols glossary” means a compiled listing of:

(A) Each SDO-established symbol used in the labeling for the device;

(B) The title and designation number of the SDO-developed standard containing the symbol;

(C) The title of the symbol and its reference number, if any, in the standard; and

(D) The meaning or explanatory text for the symbol as provided in the FDA recognition or, if FDA has not recognized the standard or portion of the standard in which the symbol is located or the symbol is not used according to the specifications for use of the symbol set forth in FDA’s section 514(c) recognition, the explanatory text as provided in the standard.

* * * * *

3. Amend § 660.20 by revising paragraph (a) to read as follows:

§ 660.20 Blood Grouping Reagent.

(a) Proper name and definition. The proper name of this product shall be Blood Grouping Reagent and it shall consist of an antibody-containing fluid containing one or more of the blood grouping antibodies listed in § 660.28(a)(4).

* * * * *

4. Revise § 660.28 to read as follows:

§ 660.28 Labeling.

(a) In addition to the applicable labeling requirements of §§ 610.62 through 610.65 and § 809.10 of this chapter, and in lieu of the requirements in §§ 610.60 and 610.61 of this chapter, the following requirements shall be met:

(1) Final container label--(i) Color coding. The final container label of all Blood Grouping Reagents shall be completely white, except that all or a portion of the final container label of the following Blood Grouping Reagents may be color coded with the specified color which shall be a visual match to a specific color sample designated by the Director, Center for Biologics Evaluation and Research. Printing on all final container labels shall be in solid black. A logo or company name may be placed on the final container label; however, the logo or company name shall be located along the bottom or end of the label, outside the main panel.

Blood grouping reagent	Color of label paper
Anti-A.....	Blue.
Anti-B.....	Yellow.
Slide and rapid tube test blood grouping reagents only	
Anti-C.....	Pink.
Anti-D.....	Gray.
Anti-E.....	Brown.
Anti-CDE.....	Orange.
Anti- \bar{c}	Lavender.
Anti-e.....	Green.

(ii) Required information. The proper name “Blood Grouping Reagent” need not appear on the final container label provided the final container is distributed in a package and the package label bears the proper name. The final container label shall bear the following information:

(A) Name of the antibody or antibodies present as set forth in paragraph (a)(4) of this section.

(B) Name, address (including ZIP code), and license number of the manufacturer.

(C) Lot number, including subplot designations.

(D) Expiration date.

(E) Source of product if other than human plasma or serum.

(F) Test method(s) recommended.

(G) Recommended storage temperature in degrees Celsius.

(H) Volume of product if a liquid, or equivalent volume for a dried product if it is to be reconstituted.

(I) If a dried product, to remind users to record the reconstitution date on the label, the statement “RECONSTITUTION DATE _____. EXPIRES 1 YEAR AFTER RECONSTITUTION DATE.”

(iii) Lettering size. The type size for the specificity of the antibody designation on the labels of a final container with a capacity of less than 5 milliliters shall be not less than 12 point. The type size for the specificity of the antibody designations on the label of a container with a capacity of 5 milliliters or more shall be not less than 18 point.

(iv) Visual inspection. When the label has been affixed to the final container, a sufficient area of the container shall remain uncovered for its full length or no less than 5 millimeters of the

lower circumference to permit inspection of the contents. The label on a final product container for antibodies Anti-c, Anti-k, or Anti-s shall display a bar immediately over the specificity letter used in the name, i.e., Anti- \bar{c} , Anti- \bar{k} , or Anti- \bar{s} .

(2) Package label. The following information shall appear either on the package label or on the final container label if it is visible within the package.

- (i) Proper name of the product.
- (ii) Name of the antibody or antibodies present as set forth in paragraph (a)(4) of this section.
- (iii) Name, address (including ZIP Code), and license number of the manufacturer.
- (iv) Lot number, including subplot designations.
- (v) Expiration date.
- (vi) Preservative used and its concentration.
- (vii) Number of containers, if more than one.
- (viii) Volume or equivalent volume for dried products when reconstituted, and precautions for adequate mixing when reconstituting.
- (ix) Recommended storage temperature in degrees Celsius.
- (x) Source of the product if other than human serum or plasma.
- (xi) Reference to enclosed package insert.
- (xii) If a dried product, a statement indicating the period within which the product may be used after reconstitution.
- (xiii) The statement: "FOR IN VITRO DIAGNOSTIC USE."
- (xiv) The statement: "MEETS FDA POTENCY REQUIREMENTS."

(xv) If human blood was used in manufacturing the product, the statement: “CAUTION: ALL BLOOD PRODUCTS SHOULD BE TREATED AS POTENTIALLY INFECTIOUS. SOURCE MATERIAL FROM WHICH THIS PRODUCT WAS DERIVED WAS FOUND NEGATIVE WHEN TESTED IN ACCORDANCE WITH CURRENT FDA REQUIRED TESTS. NO KNOWN TEST METHODS CAN OFFER ASSURANCE THAT PRODUCTS DERIVED FROM HUMAN BLOOD WILL NOT TRANSMIT INFECTIOUS AGENTS.”

(xvi) A statement of an observable indication of an alteration of the product, e.g., turbidity, color change, precipitate, that may indicate possible deterioration of the product.

(3) Package insert. Each final container of Blood Grouping Reagent shall be accompanied by a package insert meeting the requirements of § 809.10. If two or more final containers requiring identical package inserts are placed in a single package, only one package insert per package is required.

(4) Names of antibodies.

Blood Group Designation for Container Label	
Anti-A	Anti-Jk ^b
Anti-A ₁	Anti-Js ^a
Anti-A, B	Anti-Js ^b
Anti-A and B	Anti-K
Anti-B	Anti- \bar{k}
Anti-C	Anti-Kp ^a
Anti-C ^w	Anti-Kp ^b
Anti- \bar{c}	Anti-Le ^a
Anti-CD	Anti-Le ^b
Anti-CDE	Anti-Lu ^a
Anti-Co ^b	Anti-Lu ^b
Anti-D	Anti-M
Anti-DE	Anti-M ^g
Anti-Di ^a	Anti-N
Anti-E	Anti-P ₁
Anti-e	Anti-S
Anti-Fy ^a	Anti- \bar{s}
Anti-Fy ^b	Anti-U

Anti-I	Anti-Wr ^a
Anti-Jk ^a	Anti-Xg ^a

(b) The applicant may provide the labeling information referenced in paragraph (a) of this section in the form of:

(1) A symbol accompanied by explanatory text adjacent to the symbol;

(2) A symbol not accompanied by adjacent explanatory text that:

(i) Is contained in a standard that FDA recognizes under its authority in section 514(c) of the Federal Food, Drug, and Cosmetic Act;

(ii) Is used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition; and

(iii) Is explained in a paper or electronic symbols glossary that is included in the labeling for the device and the labeling on or within the package containing the device bears a prominent and conspicuous statement identifying the location of the symbols glossary that is written in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used; or

(3) A symbol not accompanied by adjacent explanatory text that:

(i) Is established in a standard developed by a standards development organization (SDO);

(ii) Is not contained in a standard that is recognized by FDA under its authority in section 514(c) of the Federal Food, Drug, and Cosmetic Act or is contained in a standard that is recognized by FDA but is not used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition;

(iii) Is determined by the manufacturer to be likely to be read and understood by the ordinary individual under customary conditions of purchase and use in compliance with section 502(c) of the Federal Food, Drug, and Cosmetic Act;

(iv) Is used according to the specifications for use of the symbol set forth in the SDO-developed standard; and

(v) Is explained in a paper or electronic symbols glossary that is included in the labeling for the device and the labeling on or within the package containing the device bears a prominent and conspicuous statement identifying the location of the symbols glossary that is written in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used.

(c) The use of symbols in device labeling to provide the labeling information referenced in paragraph (a) of this section which do not meet the requirements in paragraph (b) of this section renders a device misbranded under section 502(c) of the Federal Food, Drug, and Cosmetic Act.

(d) For purposes of paragraph (b) of this section:

(1) An SDO is an organization that is nationally or internationally recognized and that follows a process for standard development that is transparent, (i.e., open to public scrutiny), where the participation is balanced, where an appeals process is included, where the standard is not in conflict with any statute, regulation, or policy under which FDA operates, and where the standard is national or international in scope.

(2) The term “symbols glossary” means a compiled listing of:

(i) Each SDO-established symbol used in the labeling for the device;

- (ii) The title and designation number of the SDO-developed standard containing the symbol;
- (iii) The title of the symbol and its reference number, if any, in the standard; and
- (iv) The meaning or explanatory text for the symbol as provided in the FDA recognition or, if FDA has not recognized the standard or portion of the standard in which the symbol is located or the symbol is not used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition, the explanatory text as provided in the standard.

5. Revise § 660.35 to read as follows:

§ 660.35 Labeling.

(a) In addition to the items required by § 809.10 of this chapter and other applicable labeling provisions of this chapter, the following information shall be included in the labeling:

(1)(i) A logo or company name may be placed on the final container label, however, the logo or company name shall be located along the bottom or end of the label, outside of the main panel.

(ii) If washing the cells is required by the manufacturer, the container label shall include appropriate instructions; if the cells should not be washed before use, e.g., if washing will adversely affect the product, the package insert shall explain.

(2) The container label of Group O cells shall state:

“FOR USE IN DETECTION OF UNEXPECTED ANTIBODIES” or “FOR USE IN IDENTIFICATION OF UNEXPECTED ANTIBODIES” or “NOT FOR USE IN DETECTION OR IDENTIFICATION OF UNEXPECTED ANTIBODIES”.

(3) Except as provided in this section, the container and package labels shall state the percentage of red blood cells in the suspension either as a discrete figure with a variance of more

than $[\pm]$ 1 percentage unit or as a range the extremes of which differ by no more than 2 percentage units. If the stated red blood cell concentration is less than 2 percent, the variance shall be no more than $[\pm]$ 0.5 percentage unit.

(4) The words “pooled cells” shall appear on the container and package labels of products prepared from pooled cells. The package label or package insert shall state that pooled cells are not recommended for pre-transfusion tests, done in lieu of a major crossmatch, to detect unexpected antibodies in patients’ samples.

(5) The package insert of a pooled product intended for detection of unexpected antibodies shall identify the number of donors contributing to the pool. Products designed exclusively for ABO Serum Grouping and umbilical cord cells need not identify the number of donors in the pool.

(6) When the product is a multicontainer product, e.g., a cell panel, the container label and package label shall be assigned the same identifying lot number, and shall also bear a number or symbol to distinguish one container from another. Such number or symbol shall also appear on the antigenic constitution matrix.

(7) The package label or package insert shall state the blood group antigens that have been tested for and found present or absent on the cells of each donor, or refer to such information in an accompanying antigenic constitution matrix. Cells for ABO Serum Grouping are exempt from this requirement. The package insert or antigen constitution matrix shall list each of the antigens tested with only one source of antibody.

(8) The package label or package insert shall bear the cautionary statement: “The reactivity of the product may decrease during the dating period.”

(9) The package insert of a product intended for the detection or identification of unexpected antibodies shall note that the rate at which antigen reactivity (e.g., agglutinability) is lost is partially dependent upon individual donor characteristics that are neither controlled nor predicted by the manufacturer.

(10) The package insert shall provide adequate directions for use.

(11) The package insert shall bear the statement:

“CAUTION: ALL BLOOD PRODUCTS SHOULD BE TREATED AS POTENTIALLY INFECTIOUS. SOURCE MATERIAL FROM WHICH THIS PRODUCT WAS DERIVED WAS FOUND NEGATIVE WHEN TESTED IN ACCORDANCE WITH CURRENT FDA REQUIRED TESTS. NO KNOWN TEST METHODS CAN OFFER ASSURANCE THAT PRODUCTS DERIVED FROM HUMAN BLOOD WILL NOT TRANSMIT INFECTIOUS AGENTS.”

(12) The package insert or the antigenic constitution matrix for each lot of product shall specify the date of manufacture or the length of the dating period.

(13) Manufacturers shall identify with a permanent donor code in the product labeling each donor of peripheral blood used for detection or identification of unexpected antibodies.

(b) The applicant may provide the labeling information referenced in paragraph (a) of this section in the form of:

(1) A symbol accompanied by explanatory text adjacent to the symbol;

(2) A symbol not accompanied by adjacent explanatory text that:

(i) Is contained in a standard that FDA recognizes under its authority in section 514(c) of the Federal Food, Drug, and Cosmetic Act;

(ii) Is used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition; and

(iii) Is explained in a paper or electronic symbols glossary that is included in the labeling for the device and the labeling on or within the package containing the device bears a prominent and conspicuous statement identifying the location of the symbols glossary that is written in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used; or

(3) A symbol not accompanied by adjacent explanatory text that:

(i) Is established in a standard developed by a standards development organization (SDO);

(ii) Is not contained in a standard that is recognized by FDA under its authority in section 514(c) of the Federal Food, Drug, and Cosmetic Act or is contained in a standard that is recognized by FDA but is not used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition;

(iii) Is determined by the manufacturer to be likely to be read and understood by the ordinary individual under customary conditions of purchase and use in compliance with section 502(c) of the Federal Food, Drug, and Cosmetic Act;

(iv) Is used according to the specifications for use of the symbol set forth in the SDO-developed standard; and

(v) Is explained in a paper or electronic symbols glossary that is included in the labeling for the device and the labeling on or within the package containing the device bears a prominent and conspicuous statement identifying the location of the symbols glossary that is written in

English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used.

(c) The use of symbols in device labeling to provide the labeling information referenced in paragraph (a) of this section which do not meet the requirements of paragraph (b) of this section renders a device misbranded under section 502(c) of the Federal Food, Drug, and Cosmetic Act.

(d) For purposes of paragraph (b) of this section:

(1) An SDO is an organization that is nationally or internationally recognized and that follows a process for standard development that is transparent, (i.e., open to public scrutiny), where the participation is balanced, where an appeals process is included, where the standard is not in conflict with any statute, regulation, or policy under which FDA operates, and where the standard is national or international in scope.

(2) The term “symbols glossary” means a compiled listing of:

- (i) Each SDO-established symbol used in the labeling for the device;
- (ii) The title and designation number of the SDO-developed standard containing the symbol;
- (iii) The title of the symbol and its reference number, if any, in the standard; and
- (iv) The meaning or explanatory text for the symbol as provided in the FDA recognition or, if FDA has not recognized the standard or portion of the standard in which the symbol is located or the symbol is not used according to the specifications for use of the symbol set forth in FDA’s section 514(c) recognition, the explanatory text as provided in the standard.

6. Revise § 660.45 to read as follows:

§ 660.45 Labeling.

(a) In addition to the requirements of §§ 610.60, 610.61, and 809.10 of this chapter, the labeling shall bear the following:

(1) The “d and y” antigen subtype and the source of the product to follow immediately the proper name on both the final container label and the package label. If the product is intended to identify antibodies to the “r and w” antigen subtype, the antigen subtype designation shall include the “r and w” antigen subtype.

(2) The name of the test method(s) recommended for use of the product on the package label and on the final container label, when capable of bearing a full label (see § 610.60(a) of this chapter).

(3) A warning on the package label and on the final container label stating that the product is capable of transmitting hepatitis and should be handled accordingly.

(4) The package shall include a package insert providing:

- (i) Detailed instructions for use,
- (ii) An adequate description of all recommended test methods, and
- (iii) Warnings as to possible hazards, including hepatitis transmitted in handling the product and any ancillary reagents and materials accompanying the product.

(b) The applicant may provide the labeling information referenced in paragraph (a) of this section in the form of:

- (1) A symbol accompanied by explanatory text adjacent to the symbol;
- (2) A symbol not accompanied by adjacent explanatory text that:
 - (i) Is contained in a standard that FDA recognizes under its authority in section 514(c) of the Federal Food, Drug, and Cosmetic Act;

(ii) Is used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition; and

(iii) Is explained in a paper or electronic symbols glossary that is included in the labeling for the device and the labeling on or within the package containing the device bears a prominent and conspicuous statement identifying the location of the symbols glossary that is written in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used; or

(3) A symbol not accompanied by adjacent explanatory text that:

(i) Is established in a standard developed by a standards development organization (SDO);

(ii) Is not contained in a standard that is recognized by FDA under its authority in section 514(c) of the Federal Food, Drug, and Cosmetic Act or is contained in a standard that is recognized by FDA but is not used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition;

(iii) Is determined by the manufacturer to be likely to be read and understood by the ordinary individual under customary conditions of purchase and use in compliance with section 502(c) of the Federal Food, Drug, and Cosmetic Act;

(iv) Is used according to the specifications for use of the symbol set forth in the SDO-developed standard; and

(v) Is explained in a paper or electronic symbols glossary that is included in the labeling for the device and the labeling on or within the package containing the device bears a prominent and conspicuous statement identifying the location of the symbols glossary that is written in

English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used.

(c) The use of symbols in device labeling to provide the labeling information referenced in paragraph (a) of this section which do not meet the requirements of paragraph (b) of this section renders a device misbranded under section 502(c) of the Federal Food, Drug, and Cosmetic Act.

(d) For purposes of paragraph (b) of this section:

(1) An SDO is an organization that is nationally or internationally recognized and that follows a process for standard development that is transparent, (i.e., open to public scrutiny), where the participation is balanced, where an appeals process is included, where the standard is not in conflict with any statute, regulation, or policy under which FDA operates, and where the standard is national or international in scope.

(2) The term “symbols glossary” means a compiled listing of:

- (i) Each SDO-established symbol used in the labeling for the device;
- (ii) The title and designation number of the SDO-developed standard containing the symbol;
- (iii) The title of the symbol and its reference number, if any, in the standard; and
- (iv) The meaning or explanatory text for the symbol as provided in the FDA recognition or, if FDA has not recognized the standard or portion of the standard in which the symbol is located or the symbol is not used according to the specifications for use of the symbol set forth in FDA’s section 514(c) recognition, the explanatory text as provided in the standard.

7. Amend § 660.50 by revising paragraph (a) to read as follows:

§ 660.50 Anti-Human Globulin.

(a) Proper name and definition. The proper name of this product shall be Anti-Human Globulin which shall consist of one or more antiglobulin antibodies identified in § 660.55(a)(4).

* * * * *

8. Revise § 660.55 to read as follows:

§ 660.55 Labeling.

(a) In addition to the applicable labeling requirements of §§ 610.62 through 610.65 and § 809.10 of this chapter, and in lieu of the requirements in §§ 610.60 and 610.61 of this chapter, the following requirements shall be met:

(1) Final container label--(i) Color coding. The main panel of the final container label of all Anti-IgG, -C3d (polyspecific) reagents shall be white or colorless and printing shall be solid dark contrasting lettering. The main panel of the final container label of all other Anti-Human Globulin reagents shall be black with solid white lettering. A logo or company name may be placed on the final container label; however, the logo or company name shall be located along the bottom or end of the label, outside of the main panel.

(ii) Required information. The proper name “Anti-Human Globulin” need not appear on the final container label provided the final container is distributed in a package and the package label bears the proper name. The final container label shall bear the following information:

(A) Name of the antibody or antibodies present as set forth in paragraph (a)(4) of this section. Anti-Human Globulin may contain one or more antibodies to either immunoglobulins or complement components but the name of each significant antibody must appear on the final container label (e.g., anti-C3b, -C3d, -C4d). The final container labels of polyspecific Anti-Human Globulin are not required to identify antibody specificities other than anti-IgG and anti-

C3d but the reactivity of the Anti-Human Globulin shall be accurately described in the package insert.

(B) Name, address, and license number of the manufacturer.

(C) Lot number, including any subplot designations.

(D) Expiration date.

(E) Source of the product.

(F) Recommended storage temperature in degrees Celsius.

(G) Volume of product.

(H) Appropriate cautionary statement if the Anti-Human Globulin is not polyspecific.

For example, “DOES NOT CONTAIN ANTIBODIES TO IMMUNOGLOBULINS” or “DOES NOT CONTAIN ANTIBODIES TO COMPLEMENT COMPONENTS.”

(I) If the final container is not enclosed in a package, all items required for a package label shall appear on the container label.

(iii) Lettering size. The type size for the designation of the specific antibody on the label of a final container shall be not less than 12 point, unless otherwise approved by the Director, Center for Biologics Evaluation and Research. The prefix anti- and other parts of the name such as polyspecific may appear in smaller type.

(iv) Visual inspection. When the label has been affixed to the final container, a sufficient area of the container shall remain uncovered for its full length or for no less than 5 millimeters of the lower circumference to permit inspection of the contents.

(2) Package label. The following items shall appear either on the package label or on the final container label if see-through packaging is used:

(i) Proper name of the product, and the name of the antibody or antibodies as listed in paragraph (a)(4) of this section.

(ii) Name, address (including ZIP code), and license number of the manufacturer.

(iii) Lot number, including any subplot designations.

(iv) Expiration date.

(v) Preservative(s) used and its concentration.

(vi) Number of containers, if more than one.

(vii) Recommended storage temperature in degrees Celsius.

(viii) Source of the product.

(ix) Reference to enclosed package insert.

(x) The statement: "For In Vitro Diagnostic Use."

(xi) The statement: "Meets FDA Potency Requirements."

(xii) A statement of an observable indication of an alteration of the product, e.g., turbidity, color change, precipitate, that may indicate possible deterioration of the product.

(xiii) Appropriate cautions.

(3) Package insert. Each final container of Anti-Human Globulin shall be accompanied by a package insert meeting the requirements of § 809.10 of this chapter. If two or more final containers requiring identical package inserts are placed in a single package, only one package insert per package is required.

(4) Names of antibodies. Anti-Human Globulin preparations may contain one or more of the antibody specificities listed in this paragraph as described in paragraph (a)(1)(ii)(A) of this section.

Antibody designation on container label	Definition
(1) Anti-IgG, -C3d; Polyspecific...	Contains anti-IgG and anti-C3d

	(may contain other anticomplement and anti-immunoglobulin antibodies).
(2) Anti-IgG.....	Contains anti-IgG with no anti-complement activity (not necessarily gamma chain specific).
(3) Anti-IgG; heavy chains.....	Contains only antibodies reactive against human gamma chains.
(4) Anti-C3b.....	Contains only C3b antibodies with no anti-immunoglobulin activity. <u>Note:</u> The antibody produced in response to immunization is usually directed against the antigenic determinant which is located in the C3c subunit; some persons have called this antibody “anti-C3c.” In product labeling, this antibody should be designated anti-C3b.
(5) Anti-C3d.....	Contains only C3d antibodies with no anti-immunoglobulin activity.
(6) Anti-C4b.....	Contains only C4b antibodies with no anti-immunoglobulin activity.
(7) Anti-C4d.....	Contains only C4d antibodies with no anti-immunoglobulin activity.

(b) The applicant may provide the labeling information referenced in this section in the form of:

(1) A symbol accompanied by explanatory text adjacent to the symbol;

(2) A symbol not accompanied by adjacent explanatory text that:

(i) Is contained in a standard that FDA recognizes under its authority in section 514(c) of the Federal Food, Drug, and Cosmetic Act;

(ii) Is used according to the specifications for use of the symbol set forth in FDA’s section 514(c) recognition; and

(iii) Is explained in a paper or electronic symbols glossary that is included in the labeling for the device and the labeling on or within the package containing the device bears a prominent

and conspicuous statement identifying the location of the symbols glossary that is written in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used; or

(3) A symbol not accompanied by adjacent explanatory text that:

(i) Is established in a standard developed by a standards development organization (SDO);

(ii) Is not contained in a standard that is recognized by FDA under its authority in section 514(c) or is contained in a standard that is recognized by FDA but is not used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition;

(iii) Is determined by the manufacturer to be likely to be read and understood by the ordinary individual under customary conditions of purchase and use in compliance with section 502(c) of the Federal Food, Drug, and Cosmetic Act;

(iv) Is used according to the specifications for use of the symbol set forth in the SDO-developed standard; and

(v) Is explained in a paper or electronic symbols glossary that is included in the labeling for the device and the labeling on or within the package containing the device bears a prominent and conspicuous statement identifying the location of the symbols glossary that is written in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used.

(c) The use of symbols in device labeling to provide the labeling information referenced in paragraph (a) of this section which do not meet the requirements of paragraph (b) of this section renders a device misbranded under section 502(c) of the Federal Food, Drug, and Cosmetic Act.

(d) For purposes of paragraph (b) of this section:

(1) An SDO is an organization that is nationally or internationally recognized and that follows a process for standard development that is transparent, (i.e., open to public scrutiny), where the participation is balanced, where an appeals process is included, where the standard is not in conflict with any statute, regulation, or policy under which FDA operates, and where the standard is national or international in scope.

(2) The term “symbols glossary” means a compiled listing of:

- (i) Each SDO-established symbol used in the labeling for the device;
- (ii) The title and designation number of the SDO-developed standard containing the symbol;
- (iii) The title of the symbol and its reference number, if any, in the standard; and
- (iv) The meaning or explanatory text for the symbol as provided in the FDA recognition or, if FDA has not recognized the standard or portion of the standard in which the symbol is located or the symbol is not used according to the specifications for use of the symbol set forth in FDA’s section 514(c) recognition, the explanatory text as provided in the standard.

PART 801--LABELING

9. The authority citation for part 801 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 360d, 360i, 360j, 371, 374.

10. Amend § 801.15 by revising the section heading and paragraph (c)(1) to read as follows:

§ 801.15 Medical devices; prominence of required label statements; use of symbols in labeling.

* * * * *

(c)(1)(i) All words, statements, and other information required by or under authority of the act to appear on the label or labeling for a device shall appear thereon in one or more of the following formats:

(A) The English language;

(B) In the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be substituted for English;

(C) A symbol accompanied by adjacent explanatory English text, or text in the predominant language of the Territory, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English;

(D) A symbol not accompanied by adjacent explanatory text that:

(1) Is contained in a standard that FDA recognizes under its authority in section 514(c) of the act;

(2) Is used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition; and

(3) Is explained in a paper or electronic symbols glossary that is included in the labeling for the device and the labeling on or within the package containing the device bears a prominent and conspicuous statement identifying the location of the symbols glossary that is written in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used;

(E) A symbol not accompanied by adjacent explanatory text that:

(1) Is established in a standard developed by a standards development organization (SDO);

(2) Is not contained in a standard that is recognized by FDA under its authority in section 514(c) of the act or is contained in a standard that is recognized by FDA but is not used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition;

(3) Is determined by the manufacturer to be likely to be read and understood by the ordinary individual under customary conditions of purchase and use in compliance with section 502(c) of the act;

(4) Is used according to the specifications for use of the symbol set forth in the SDO-developed standard; and

(5) Is explained in a paper or electronic symbols glossary that is included in the labeling for the device and the labeling on or within the package containing the device bears a prominent and conspicuous statement identifying the location of the symbols glossary that is written in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used;

(F) The symbol statement "Rx only" or "R only" may be used as provided under § 801.109(b)(1).

(ii) The use of symbols in device labeling which do not meet the requirements of paragraph (c)(1)(i) of this section renders a device misbranded under section 502(c) of the act.

(iii) For purposes of paragraph (c)(1)(i) of this section:

(A) An SDO is an organization that is nationally or internationally recognized and that follows a process for standard development that is transparent, (i.e., open to public scrutiny), where the participation is balanced, where an appeals process is included, where the standard is

not in conflict with any statute, regulation, or policy under which FDA operates, and where the standard is national or international in scope.

(B) The term “symbols glossary” means a compiled listing of:

(1) Each SDO-established symbol used in the labeling for the device;

(2) The title and designation number of the SDO-developed standard containing the symbol;

(3) The title of the symbol and its reference number, if any, in the standard; and

(4) The meaning or explanatory text for the symbol as provided in the FDA recognition or, if FDA has not recognized the standard or portion of the standard in which the symbol is located or the symbol is not used according to the specifications for use of the symbol set forth in FDA’s section 514(c) recognition, the explanatory text as provided in the standard.

* * * * *

11. Amend § 801.109 by revising paragraph (b)(1) to read as follows:

§ 801.109 Prescription devices.

* * * * *

(b) * * *

(1) The symbol statement “Rx only” or “**R** only” or the statement “Caution: Federal law restricts this device to sale by or on the order of a _____”, the blank to be filled with the word “physician”, “dentist”, “veterinarian”, or with the descriptive designation of any other practitioner licensed by the law of the State in which the practitioner practices to use or order the use of the device; and

* * * * *

PART 809--IN VITRO DIAGNOSTIC PRODUCTS FOR HUMAN USE

12. The authority citation for part 809 continues to read as follows:

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

13. In § 809.10:

- a. Add a last sentence to paragraph (a)(4),
- b. Add a last sentence to paragraph (b)(5)(ii), and
- c. Add paragraph (g).

The additions read as follows:

§ 809.10 Labeling for in vitro diagnostic products.

(a) * * *

(4) * * * The limiting statement appropriate to the intended use of a prescription in vitro diagnostic product shall bear the symbol statement “Rx only” or “**R** only” or the statement “Caution: Federal law restricts this device to sale by or on the order of a _____”, the blank to be filled with the word “physician”, “dentist”, “veterinarian”, or with the descriptive designation of any other practitioner licensed by the law of the State in which the practitioner practices to use or order the use of the device.

* * * * *

(b) * * *

(5) * * *

(ii) * * * The limiting statement appropriate to the intended use of a prescription in vitro diagnostic product shall bear the symbol statement “Rx only” or “**R** only” or the statement “Caution: Federal law restricts this device to sale by or on the order of a _____”, the

blank to be filled with the word “physician”, “dentist”, “veterinarian”, or with the descriptive designation of any other practitioner licensed by the law of the State in which the practitioner practices to use or order the use of the device.

* * * * *

(g)(1) The applicant may provide the labeling information referenced in this section in the form of:

(i) A symbol accompanied by explanatory text adjacent to the symbol;

(ii) A symbol not accompanied by adjacent explanatory text that:

(A) Is contained in a standard that FDA recognizes under its authority in section 514(c) of the act;

(B) Is used according to the specifications for use of the symbol set forth in FDA’s section 514(c) recognition; and

(C) Is explained in a paper or electronic symbols glossary that is included in the labeling for the device and the labeling on or within the package containing the device bears a prominent and conspicuous statement identifying the location of the symbols glossary that is written in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used;

(iii) A symbol not accompanied by adjacent explanatory text that:

(A) Is established in a standard developed by a standards development organization (SDO);

(B) Is not contained in a standard that is recognized by FDA under its authority in section 514(c) of the act or is contained in a standard that is recognized by FDA but is not used

according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition;

(C) Is determined by the manufacturer to be likely to be read and understood by the ordinary individual under customary conditions of purchase and use in compliance with section 502(c) of the act;

(D) Is used according to the specifications for use of the symbol set forth in the SDO-developed standard; and

(E) Is explained in a paper or electronic symbols glossary that is included in the labeling for the device and the labeling on or within the package containing the device bears a prominent and conspicuous statement identifying the location of the symbols glossary that is written in English or, in the case of articles distributed solely in Puerto Rico or in a Territory where the predominant language is one other than English, the predominant language may be used; or

(iv) The symbol statement "Rx only" or "℞ only" used as provided under paragraphs (a)(4) and (b)(5)(ii) of this section.

(2) The use of symbols in device labeling which do not meet the requirements of paragraph (g)(1) of this section renders a device misbranded under section 502(c) of the act.

(3) For purposes of paragraph (g)(1) of this section:

(i) An SDO is an organization that is nationally or internationally recognized and that follows a process for standard development that is transparent, (i.e., open to public scrutiny), where the participation is balanced, where an appeals process is included, where the standard is not in conflict with any statute, regulation, or policy under which FDA operates, and where the standard is national or international in scope.

(ii) The term "symbols glossary" means a compiled listing of:

- (A) Each SDO-established symbol used in the labeling for the device;
- (B) The title and designation number of the SDO-developed standard containing the symbol;
- (C) The title of the symbol and its reference number, if any, in the standard; and
- (D) The meaning or explanatory text for the symbol as provided in the FDA recognition or, if FDA has not recognized the standard or portion of the standard in which the symbol is located or the symbol is not used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition, the explanatory text as provided in the standard.

Dated: June 8, 2016.

Leslie Kux,

Associate Commissioner for Policy.

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