

Guidance for Industry

FDA Review of Vaccine Labeling Requirements for Warnings, Use Instructions, and Precautionary Information

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(4)(i). Submit comments on this guidance at anytime to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. You should identify all comments with the title of this guidance.

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at <http://www.fda.gov/cber/guidelines.htm>.

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. PURPOSE

This guidance document is meant to inform you, vaccine manufacturers, medical practitioners, and consumers, of the type of data that we, FDA, examine when determining the adequacy of vaccine labeling¹ by providing an overview of the vaccine labeling review process and describing our review of childhood vaccine labeling under section 314 of the National Childhood Vaccine Injury Act (NCVIA).² The processes described herein represent current FDA practices and do not represent any new interpretation of existing labeling statutes, regulations, or guidances.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. INTRODUCTION

FDA routinely assesses the warnings, use instructions, and precautionary information provided for licensed vaccines. Based on its surveillance of adverse event reporting and other data sources, we review the adequacy of vaccine labeling and, if necessary, communicate our findings to manufacturers. This guidance document provides FDA's current thinking about its surveillance and review of vaccine labeling.

The review of vaccine labeling completed by FDA pursuant to section 314 of the NCVIA provides a useful description of some of the methods we use to evaluate the adequacy of the warnings, use instructions, and precautionary information found in vaccine package inserts.

¹ The term "labeling," as defined in 21 U.S.C. § 321(m), means all labels and other written, printed, or graphic matter upon any article or any of its containers or wrappers, or accompanying such article and, therefore, includes any package inserts or information sheets that accompany vaccine products.

² Pub. L. No. 99-660, 100 Stat. 3755, *codified at* 42 U.S.C. § 300aa-1 *et seq.*

Section 314 of the NCVIA required FDA to review the warnings, use instructions, and precautionary information distributed with each vaccine listed in section 2114 of the Public Health Service Act (PHS Act)³ at the time of the NCVIA's passage. The statute also required FDA to determine whether such warnings, instructions, and information "adequately warn health care providers of the nature and extent of the dangers posed by such vaccines."⁴ If such information was found to be inadequate, section 314 of the NCVIA mandated that manufacturers be required to revise and reissue such warnings, use instructions and precautionary information as expeditiously as practical.

FDA continues to engage in an ongoing, case-by-case review of all vaccine labeling and routinely requires revision of labeling that is found to be inadequate to warn health care providers of the risks associated with the use of a particular vaccine.

III. FDA'S PROCESS FOR VACCINE LABELING REVIEW

The labeling requirements for biological products are found in several sections of the Federal Food, Drug, and Cosmetic Act (FDCA) and the PHS Act, including: Sections 201, 502, and 503 of the FDCA, and section 351 of the PHS Act. In addition to the statutory provisions, FDA's regulations on labeling requirements, including the content and format requirements for vaccine labeling, are found primarily in 21 CFR Parts 201 and 601.

Pursuant to 21 CFR 201.57(d), labeling must describe contraindications (situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit). The warning section of labeling, defined in section 201.57(e), requires, among other things, a description of serious adverse reactions, potential safety hazards, steps that should be taken in the occurrence of a serious adverse reaction and potential safety hazard, and limitations in use imposed by them.

A. Pre-Approval Review of Labeling

Under 21 CFR 601.2(a), manufacturers must submit proposed vaccine labeling to FDA as part of a biological license application (BLA). In addition, changes to existing vaccine labeling requires FDA review pursuant to 21 CFR 601.12(f). Most such changes require a BLA supplement (BLS) and transmittal Form FDA 2567. In its review, FDA determines whether the information presented in the labeling is scientifically accurate, conforms to regulatory requirements set out in 21 CFR 201.56 and 201.57, and includes requested revisions.

An important part of vaccine labeling is the package insert. FDA reviews the entire package insert to determine whether it is adequate. If we conclude that a proposed vaccine package insert does not contain adequate warnings, use instructions, and precautionary information, we communicate such findings to the manufacturer as soon as is practicable. When FDA concludes that a vaccine label's warnings, use instructions,

³ See 42 U.S.C. § 300aa-14.

⁴ See 42 U.S.C. § 300aa-1 note.

and precautionary information have been sufficiently revised to include current information regarding the nature and extent of the dangers posed by such vaccines, FDA formally approves the final draft labeling as described in 21 CFR 601.2 and 601.12(f).

B. Post-Approval Surveillance

FDA takes into account various sources of information during our surveillance and review of vaccine labeling requirements for warnings, use instructions, and precautionary information, including:

- The existing labeling requirements listed under 21 CFR 201.56 and 201.57;
- Epidemiological information contained in Morbidity and Mortality Weekly Reports (MMWR), published by the Centers for Disease Control and Prevention (CDC);⁵
- Reports in the medical literature; and
- Summaries from the Vaccine Adverse Event Reporting System (VAERS).

When new information on a vaccine's safety and efficacy becomes available after licensure, FDA reviews the data and determines whether package inserts and other labeling should be revised to include this new information. FDA notifies manufacturers if their package inserts do not reflect currently available information regarding the warnings, use instructions and precautionary information. In such a case, FDA also typically recommends that appropriate revision is necessary.

IV. FDA'S NCVIA VACCINE LABELING REVIEW

A. Legislative Background

Under section 314 of the NCVIA, FDA was required to determine whether the warnings, use instructions and precautionary information for certain enumerated childhood vaccines were adequate to warn health care providers of the nature and extent of the risks posed by such vaccines. The NCVIA limited this requirement to childhood vaccines listed in the Vaccine Injury Table (VIT) established in section 2114 of the PHS Act.⁶ If FDA determined that any such warnings, use instructions or precautionary information were inadequate, then manufacturers were required to revise and reissue such warnings, use instructions or precautionary information as expeditiously as practical.

On June 13, 1988, the Secretary delegated authority to implement section 314 of the NCVIA to the Assistant Secretary for Health (ASH).⁷ On September 16, 1988, the ASH delegated authority to implement section 314 of the NCVIA to the Commissioner of

⁵ See <http://www.cdc.gov/mmwr/>.

⁶ See 42 U.S.C. § 300aa-14.

⁷ 53 Fed. Reg. 22054 (June 13, 1988).

Food and Drugs.⁸ On April 1, 1993, FDA delegated to the Center for Biologics Evaluation and Research authority to implement section 314 of the NCVIA.⁹

B. FDA'S Process for Conducting the NCVIA Labeling Review

FDA conducted its review of vaccine labeling under section 314 of the NCVIA through a process that involved extensive opportunities for public comment on childhood vaccine labeling. By applying existing drug labeling regulations (e.g., 21 CFR 201.56 and 201.57), current labeling as supplied by the manufacturer, as well as a survey of medical practitioners, FDA created draft Summaries of Important Information (SII) for each applicable vaccine listed in section 2114's Vaccine Injury Table (VIT) and distributed them to the appropriate manufacturers on March 3, 1992.

On July 31, 1992, FDA announced the creation of a public docket and scheduled a public meeting to seek comments on manufacturers' and FDA's proposed revisions to the package inserts, which had been made available for public examination.¹⁰ At that time, FDA also made available the respective vaccines' most recently approved package inserts, manufacturers' proposed revised drafts of package inserts, as well as FDA's comments on the inserts. FDA established time frames for completion of its review and response to public comments.¹¹ Subsequently, FDA reviewed each manufacturers' proposed labeling changes, and, after considering the public record, approved labeling changes for the listed childhood vaccines, thus determining the revised labeling to be adequate to warn health care providers of the nature and extent of the risks posed by such vaccines.

Throughout its review process, FDA consulted the Advisory Commission on Childhood Vaccines (ACCV) to assess the warnings, use instructions and precautionary information issued for applicable childhood vaccines. The NCVIA mandated creation of the ACCV to provide expert advice to the Secretary about, among other things, the implementation of the statute. The ACCV also makes recommendations regarding changes to the VIT and surveys Federal, State and local information regarding childhood vaccine associated injuries.¹² FDA representatives attended ACCV meetings and briefed the ACCV on the labeling review.

1. Preparation of Summaries of Important Information

As discussed above, FDA prepared an SII for each vaccine listed in the VIT to serve as a guide to manufacturers when revising package inserts. Creation of the SIIs also facilitated harmonization of package inserts for similar vaccines produced by different manufacturers. In the SIIs, FDA recommended the location

⁸ 53 Fed. Reg. 36127 (September 16, 1988).

⁹ 58 Fed. Reg. 17105 (April 1, 1993).

¹⁰ 57 Fed. Reg. 33915 (July 31, 1992). As discussed below, this public meeting was held on September 18, 1992.

¹¹ *Id.*

¹² *See* 42 U.S.C. § 300aa-19.

and content of specific package insert sections and subsections and in several instances, suggested precise wording.¹³

On March 3, 1992, FDA sent to the respective childhood vaccine manufacturers copies of the draft SIIs for each vaccine listed in the VIT. FDA notified manufacturers of the workshop planned for September 18, 1992, and requested them to submit to FDA suggested revisions of draft SIIs. FDA presented revised draft SIIs for public review prior to the workshop and accepted comments filed to Docket No. 91N-0494.¹⁴ The docket included the following: (1) package inserts most recently approved by FDA; (2) manufacturers' draft package inserts with FDA's comments, if revisions were still pending as of July 1992; or (3) the most recently approved package inserts and FDA's comments, if revised drafts had not been received by July 1992; and (4) copies of the SIIs.

As the basis for these draft SIIs, FDA used the labeling requirements listed under 21 CFR 201.56 and 201.57, the Advisory Committee on Immunization Practices' (ACIP) "Recommendations & Reports," and approved package inserts. FDA also referred to reports prepared by the Panel on the Review of Bacterial Vaccines and Toxoids¹⁵ and the Panel on the Review of Viral Vaccines and Rickettsia,¹⁶ epidemiological information from MMWR, literature references, and summaries from VAERS.

2. Public Participation

As noted previously, FDA took into account the views of several public panels during the review of childhood labeling. The Panel on the Review of Bacterial Vaccines and Toxoids and the Panel on the Review of Viral and Rickettsial Vaccines conducted separate reviews regarding the safety, efficacy, and labeling of bacterial vaccines, toxoids with standards of potency, antitoxins, and immune globulins; and viral and rickettsial vaccines, respectively. Each panel's review resulted in a proposed order that was published in the Federal Register. Both panels' reports recommended that information in the package insert be presented in a clear, unambiguous and accurate manner. The panels also reviewed FDA's requirements for package inserts and suggested the types of information that should be included. FDA considered the recommendations of both panels and incorporated many of them into the relevant SIIs.

¹³ Following is a list of the vaccines for which SIIs were prepared: (1) Diphtheria Toxoid Adsorbed; (2) Diphtheria and Tetanus Toxoids Adsorbed; (3) Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed; (4) Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed; (5) Measles and Mumps Virus Vaccine Live; (6) Measles and Rubella Virus Vaccine Live; (7) Measles, Mumps and Rubella Virus Vaccine Live; (8) Measles Virus Vaccine Live; (9) Mumps Virus Vaccine Live; (10) Pertussis Vaccine Adsorbed; (11) Poliovirus Vaccine Inactivated; (12) Poliovirus Vaccine Live Oral Trivalent; (13) Rubella and Mumps Virus Vaccine Live; (14) Rubella Virus Vaccine Live; (15) Tetanus and Diphtheria Toxoids Adsorbed (for Adult Use); (16) Tetanus Toxoid; (17) Tetanus Toxoid Adsorbed.

¹⁴ See 57 Fed. Reg. 33915 (Jul. 31, 1992).

¹⁵ See 50 Fed. Reg. 51002 (Dec. 13, 1985).

¹⁶ See 45 Fed. Reg. 25652 (Apr. 15, 1980).

At the September 1992 public workshop, FDA described its labeling review process and presented the reviews it had conducted for each childhood vaccine pursuant to section 314 of the NCVIA. Several groups presented comments, including: Government agencies such as the National Institutes of Health and the CDC; advisory bodies (including ACIP, ACCV, the American Academy of Pediatrics, and the National Vaccine Advisory Committee), and the Vaccine and Related Biological Products Advisory Committee; manufacturers; and interested members of the public. FDA considered these presentations and submissions made during the workshop, comments submitted to the Docket, as well as direct correspondence from manufacturers and other interested members of the public. FDA reviewed the revised labeling of the childhood vaccines enumerated in the VIT and determined that the labeling, as revised, contained adequate warnings.

V. CONCLUSION

As a result of the public process utilized to implement section 314 of the NCVIA, FDA determined that the warnings, use instructions, and precautionary information distributed with each vaccine set forth in section 2114 of the PHS Act adequately warned health care providers of the nature and extent of the dangers posed by such vaccines. FDA has reviewed the labeling of all vaccines originally listed in the VIT as well as those subsequently added to the table.

FDA's continuing review of warnings and precautions and use instructions sections of the label helps assure that labels in distribution are adequate to inform health care providers of the risks of vaccines. FDA continues to review vaccine labeling, taking into account timely information provided through, among other things, recommendations and reports of the ACIP, epidemiological information contained in the MMWR, reports in the medical literature; and summaries from VAERS.