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Understanding FDA-Approved Labeling and CDC Recommendations for Use of Vaccines

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Abstract

Adherence to recommendations for the use of licensed vaccines ensures maximum individual and societal benefits from the national immunization program. The US Food and Drug Administration (FDA) licenses a vaccine once it determines that data submitted by the manufacturer reveal that the vaccine is safe and effective for its intended use. For each US-licensed vaccine, the FDA-approved prescribing information contains detailed information for health care providers to ensure safe and effective use. Centers for Disease Control and Prevention recommendations for the use of a licensed vaccine often are based on additional considerations, such as disease epidemiology, public acceptance, vaccine supply, and cost. Our objective in this article is to explain the reasons for the differences between FDA-approved prescribing information and Centers for Disease Control and Prevention recommendations for vaccine use.

Availability of safe and effective vaccines and adherence to national recommendations for immunization practices and vaccine use, including the recommended immunization schedules, are essential for the prevention and control of existing and emerging infectious diseases. The success of vaccines and public health vaccination programs in the United States is evidenced by the eradication of smallpox, the national elimination of polio, and historically low rates of measles, tetanus, diphtheria, rubella, and most other vaccine-preventable diseases.¹

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In the United States, the Center for Biologics Evaluations and Research (CBER) at the US Food and Drug Administration (FDA) regulates vaccines and ensures the safety and effectiveness of vaccines that are available to the public. The Centers for Disease Control and Prevention (CDC) makes recommendations for the use of FDA-licensed vaccines in the United States. Recommendations for vaccine use generally are consistent with FDA-approved prescribing information, which is commonly referred to as the “package insert.” However, differences between prescribing information and recommendations for vaccine use occur and may be a source of confusion for health care professionals. Our objective in this article is to explain how the roles of the FDA and CDC and the factors that are considered by the 2 agencies may lead to such differences.

REGULATION OF VACCINES AND CONTENT OF PRESCRIBING INFORMATION IN THE UNITED STATES

The CBER is responsible for the regulatory oversight of vaccine development and the licensure of new vaccines in the United States. The CBER regulates vaccines under authorities that are derived from federal laws by applying specific regulations that address manufacturing consistency, clinical investigations, standards for safety and effectiveness, licensing, and product labeling. The CBER evaluates manufacturing data as well as data from animal studies and human clinical studies that are submitted to the CBER by the manufacturer in a biologics license application. The CBER’s evaluation includes a review of clinical studies for adherence to ethical and scientific quality standards, an inspection of clinical study sites, statistical analyses of primary data from clinical studies, a review of assay validation information, a review of detailed manufacturing information, and an inspection of manufacturing facilities. To be licensed, a vaccine must be safe and effective for its intended use. In making this determination, the FDA assesses whether the vaccine’s benefits outweigh its risks. In some cases, the CBER seeks advice from the Vaccines and Related Biological Products Advisory Committee, a federal advisory committee that consists of experts external to the FDA.

In evaluating the safety of a vaccine, the CBER considers characteristics of both the population to receive vaccination as well as the disease(s) to be prevented. Although all vaccines are associated with some risk, the CBER considers a vaccine safe when it determines that the vaccine’s benefits outweigh the risks when the vaccine is used as intended.

All approved indications for vaccines must be supported by substantial evidence of effectiveness.² From a regulatory perspective, the most direct evidence of vaccine effectiveness is obtained from randomized controlled clinical trials in which the protective efficacy of the vaccine in preventing clinical disease is evaluated. Often, both clinical efficacy data and immunologic response data contribute to the evaluation of vaccine effectiveness. In general, regarding diseases for which there is a scientifically well-established immunologic marker that predicts protection and that can be measured reliably in a validated assay, immunologic response data provide sufficient evidence of effectiveness without the need for disease end point clinical efficacy trials. The FDA also may consider

data from certain observational studies to support vaccine effectiveness. In general, the CBER expects that the demonstration of effectiveness is based on adequate and well-controlled clinical studies. The CBER considers the following characteristics to determine if studies are adequate and well-controlled: prespecification of objectives and analysis methods; study designs that permit a valid comparison of a group that is receiving an investigational vaccine with a control group to provide a quantitative assessment of the vaccine's effect; methods of assigning participants to study groups to minimize bias and ensure comparability with regard to pertinent variables other than the vaccine (eg, randomization); measures to minimize bias on the part of the study participants, observers, and data analysts (eg, blinding); and an extent to which methods of the assessment of the vaccine's response are well-defined and reliable.³

For each FDA-licensed vaccine, the prescribing information addresses indications and usage; dosage and administration; contraindications; warnings and precautions; adverse reactions; any observed or predicted clinically significant interactions with drugs, including other vaccines; use in specific populations; clinical studies; storage and handling; and patient counseling information. Prescribing information for a vaccine is based on scientific data that are submitted by the manufacturer in a biologics license application and determined by the CBER to be satisfactory to support the approved indication(s), usage, dosing, and administration. The prescribing information is updated as needed to include the most current information about the vaccine that is available to and reviewed by the CBER. Although it is intended to provide adequate information for health care providers to ensure safe and effective vaccine use, the prescribing information also forms the basis for promotion and marketing by the manufacturer. The prescribing information does not necessarily address all aspects of vaccine use, such as recommendations that are specific to disease outbreaks, vaccine shortages, and all subpopulations with underlying medical conditions.

DEVELOPMENT OF CDC RECOMMENDATIONS FOR VACCINE USE

Once the FDA licenses a vaccine, recommendations for vaccine use in the United States are developed by the Advisory Committee on Immunization Practices (ACIP). The ACIP is an external federal advisory committee that provides advice to the director of the CDC on the use of vaccines in the civilian population.^{4,5} In addition, the ACIP has statutory authority for the Vaccines for Children program; the ACIP has sole responsibility and authority to determine the specific vaccines, number of doses, schedule, and contraindications for the Vaccines for Children program. The 15-member ACIP receives input from representatives of 31 liaison organizations as well as representatives from other federal agencies who participate as nonvoting members in the development of national vaccine recommendations for children, adolescents, and adults.⁶ ACIP members and representatives of liaison organizations participate in work groups that deal with specific vaccines. Work group members review relevant available scientific information, including data on vaccine safety and effectiveness from FDA-approved prescribing information and from pharmaceutical company presentations, as well as disease epidemiology, burden of disease, economic analyses, and implementation issues (Table 1). In public meetings of the ACIP, the work group summarizes this information and presents proposed policy options. The ACIP deliberates and votes on recommendations.⁵ The work group may review data from

postlicensure studies, when results become available, to inform potential revisions to recommendations.

The ACIP charter states that the committee should “provide advice and guidance to the director of the CDC regarding use of vaccines and related agents for effective control of vaccine-preventable diseases in the civilian population of the United States.”⁵ ACIP recommendations for the use of individual vaccines as well as the recommended childhood and adult immunization schedules become official when they are accepted by the CDC director and published in the CDC’s *Morbidity and Mortality Weekly Report*. Advice is provided for health care providers and public health officials regarding the use of licensed vaccines for different populations and circumstances. CDC recommendations are implemented by state immunization programs and may be used to develop school requirements for immunization. Recommendations for vaccine use are harmonized between the ACIP and liaison organizations, and, although rarely, recommendations from individual partner organizations may differ on the basis of variable interpretation of available data.

Since 2011, evidence-based recommendations from the CDC have been developed in part by the use of the Grading of Recommendations Assessment, Development, and Evaluation approach to assess the quality of evidence regarding the predicted benefit and potential harm, to provide transparency in the development of recommendations and to determine the strength of the recommendation.¹⁵⁻¹⁷ Additionally, in February 2018, the ACIP adopted an Evidence to Recommendations Framework to increase the transparency of the Grading of Recommendations Assessment, Development, and Evaluation process during the recommendation development phase (*Morbidity and Mortality Weekly Report* to be published). The CDC may consider a wider range of data on vaccine safety and effectiveness compared with data that are submitted to and considered by the CBER in making regulatory decisions.

Economic factors are not considered by the CBER in its risk/benefit assessment of a vaccine nor are they addressed in prescribing information. In contrast, when the ACIP considers recommendations for vaccine use, deliberations include economic considerations, specifically cost-benefit analyses, although there is no cost-benefit threshold that is required for inclusion in the immunization program. To help ensure data quality and consistency in the evaluation of economic data presented to the ACIP, the CDC has developed guidance for health economic studies presented to the ACIP.¹⁸ One frequently used measure to determine society’s willingness to pay for a vaccine is the quality-adjusted life-years saved ratio. ACIP committee members bring their individual values to how the cost-benefit analysis informs their vaccine recommendations.¹⁹

SELECTED EXAMPLES OF CONSIDERATIONS IMPORTANT TO DEVELOPMENT OF CDC RECOMMENDATIONS OTHER THAN FDA-APPROVED PRESCRIBING INFORMATION

In most instances, CDC recommendations for vaccine use are consistent with the relevant FDA-approved prescribing information. However, given the different roles of the FDA

and the CDC and the different considerations that impact regulatory decision-making and the development of recommendations, differences between FDA-approved prescribing information and CDC recommendations for vaccine use sometimes occur. Several examples of considerations that are important to the development of CDC recommendations are provided in Table 1. We discuss 2 additional examples in detail below (ie, the use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis, adsorbed [Tdap] in pregnant women and recommendations regarding the use of FluMist Quadrivalent [a live attenuated influenza vaccine] during the 2016–2017 and 2017–2018 influenza seasons).

The FDA-approved prescribing information for each of the US-licensed Tdap vaccines, Adacel and Boostrix, conveys that the vaccine is indicated for active booster immunization against tetanus, diphtheria, and pertussis. Both vaccines currently are approved for use in an age range that includes women of childbearing age. Neither vaccine is contraindicated for use in pregnant women. However, neither vaccine is approved by the FDA for use in pregnant women to prevent pertussis in young infants.

In an effort to optimize the prevention of pertussis in infants who are too young to have completed the primary vaccine series but who experience the highest morbidity and mortality from pertussis, the CDC recommends Tdap administration to pregnant women during every pregnancy.²⁰ This immunization strategy is based on an expectation of protection of the infant through passive immunization via transplacental transfer of vaccine-induced maternal antibodies against pertussis.

In developing this recommendation, the CDC considered published peer-reviewed literature, unpublished data, expert opinion, epidemiological data on pertussis, and a decision analysis model to assess the cost-effectiveness of vaccinating pregnant women.²⁰ The information reviewed by the ACIP included data revealing higher concentrations of antibodies to pertussis antigens in newborn infants whose mothers received Tdap during pregnancy compared with infants of mothers who were not vaccinated.²¹ Subsequent to the recommendation, the CDC assessed published safety data that suggested no increased risk of adverse birth outcomes from the vaccination of pregnant women.²² The information that was considered by the CDC would not necessarily meet FDA standards for demonstrating safety and effectiveness to support a specific indication for the use of Tdap vaccines in pregnant women to prevent pertussis in infants.²³ It should be noted that the absence of an FDA-approved indication in the prescribing information for a vaccine may be because of a lack of sufficient data submitted to the FDA for review rather than the availability of data revealing that its use in a particular setting is ineffective or unsafe.

Another example pertains to FluMist Quadrivalent, an FDA-licensed live attenuated influenza vaccine that is administered intranasally. For the 2016–2017 and 2017–2018 influenza seasons, the CDC recommended against the use of FluMist Quadrivalent.²⁴ This recommendation was based on postlicensure data from test-negative, case-control observational studies in the United States that revealed limited vaccine effectiveness from 2013 to 2016 (3 influenza seasons), including low effectiveness compared with inactivated vaccines, particularly with respect to the H1N1 subtype.^{24,25} The FDA determined that the benefit of FluMist Quadrivalent continued to outweigh potential risks. The FDA's

determination was based on a review of information on the consistency of manufacturing, prelicensure clinical data, and effectiveness data, including data from observational studies that were conducted in the United States, Finland, and the United Kingdom during the 2015–2016 influenza seasons.²⁶ The FDA also considered potential limitations of observational studies in the effectiveness of the influenza vaccine and the variability of the influenza vaccine composition and effectiveness across influenza seasons.²⁶ This example reveals that in the setting of multiple vaccines that have the same indication, the CDC may recommend 1 vaccine over another to provide the greatest public health impact from vaccination. This example also reveals that recommendations from the CDC for vaccine use may be restricted relative to FDA-approved prescribing information.

The considerations that impact regulatory decision-making and the development of recommendations for vaccine use sometimes result in differences between FDA-approved prescribing information and CDC practice recommendations. A better understanding of these considerations should aid health care providers in making decisions about the use of vaccines. FDA regulatory activities and CDC recommendations for the use of vaccines together contribute to optimizing individual and public health benefits of vaccination.

ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
CBER	Center for Biologics Evaluations and Research
CDC	Centers for Disease Control and Prevention
FDA	Food and Drug Administration
Tdap	tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis, adsorbed

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Considerations Other Than FDA-Approved Prescribing Information Important to Development of CDC Vaccine Recommendations

TABLE 1

Considerations	Examples Relevant to Specific Vaccines	
	Relevant Information in FDA-Approved Prescribing Information	Summary of Relevant CDC Recommendations
Characteristics of a disease outbreak	The prescribing information for MMR does not address the use of a third dose in the context of a mumps outbreak nor does it include data on the safety and effectiveness of a third dose of MMR.	A third MMR dose is recommended for people who are identified as at an increased risk for mumps during an outbreak. Considerations included epidemiological data on mumps outbreaks that consisted of a high proportion of cases in people who previously received 2 MMR doses as well as published safety and effectiveness data on a third dose of MMR in a mumps outbreak. ⁷
Potential public health impact	The prescribing information for each of the 2 US-licensed meningococcal group B vaccines conveys that the vaccine is approved for use in people 10–25 y of age.	The CDC recommends vaccination with the meningococcal group B vaccine for people 10 y of age who are at an increased risk of disease because of host or environmental factors. Vaccination is not recommended for the general population because of the expected low public health impact due to low overall disease incidence. The CDC recommends that non-high-risk adolescents and young adults 16–23 y of age may be vaccinated on the basis of individual clinical decision-making; the preferred age for vaccination is 16–18 y of age on the basis of the disease epidemiology (peak during late adolescence) and limited data on the duration of protection. ⁸
Health economic considerations	The prescribing information for varicella virus vaccine includes an approved schedule of 2 sequential doses for children 12 mo–12 y of age as well as data from clinical studies in which the safety and effectiveness of 2 doses were evaluated. The prescribing information does not address health economic considerations for 1 vs 2 doses.	The CDC's recommendation for a second dose of varicella vaccine in children 12 mo–12 y of age is based in part on the societal benefit of reducing school and work absences. ⁹
Simplified vaccination schedule	As conveyed in the prescribing information, the FDA-approved schedules for the 2 licensed rotavirus vaccines contain some differences in ages that are recommended for vaccine administration, reflecting the schedules that were evaluated in clinical trials.	CDC recommendations harmonize the age that is recommended for completion of the rotavirus vaccination series. ¹⁰
Interchangeability of vaccines from different manufacturers	The prescribing information for DTaP and DTaP-containing combination vaccines states that insufficient data are available on the safety and effectiveness of interchanging DTaP vaccines from different manufacturers for successive doses of the DTaP vaccination series.	The CDC recommends that, when feasible, the same manufacturer's DTaP vaccines should be used for each dose in the series. However, vaccination should not be deferred because the type of DTaP vaccine that was previously administered is unavailable or unknown. ¹¹
Revaccination of nonresponders	The prescribing information for hepatitis B vaccines does not specifically address the vaccination of health care providers who are nonresponders.	The CDC recommends that health care providers who have been vaccinated and are at an increased risk of exposure to hepatitis B virus receive postvaccination serologic testing 2–3 mo after completing the series to determine if they have a protective level of antibodies. The CDC recommends revaccination of nonresponders on the basis of published data revealing that some nonresponders may respond to revaccination. ¹²
Use in subpopulations for which there are no safety and effectiveness data in the prescribing information	The prescribing information for PCV13 does not specifically address use in people with a cerebrospinal fluid leak or cochlear implant.	The CDC recommends the use of PCV13 in children 6–18 y of age with a cerebrospinal fluid leak or cochlear implant who have not been previously vaccinated. ¹³
Vaccine acceptance by the public	As determined by the FDA, all US-licensed vaccines are safe and effective for their intended use, and preferences for 1 vaccine over another are not stated in the prescribing information.	The CDC generally recommends a preferred use of licensed combination vaccines over separately administered vaccines. ⁹
Vaccine supply	The prescribing information for vaccines does not provide information on the prioritization of doses in the event of vaccine shortages.	During a period of a Hib vaccine shortage, the CDC recommended a deferral of the booster dose for all children except children who were at an increased risk for invasive disease due to Hib. ¹⁴

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CDC recommendations for a particular vaccine may include multiple considerations listed in the table. The FDA-approved prescribing information for US-licensed vaccines is available at: <https://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm093833.htm> (US Food and Drug Administration. Vaccines Licensed for Use in the United States. Accessed 07.12.2018). CDC recommendations for vaccines are available at: www.cdc.gov/vaccines/acip/ (Centers for Disease Control and Prevention. Advisory Committee on Immunization Practices. Accessed July 12, 2018). DTaP, diphtheria-tetanus toxoids and acellular pertussis vaccine absorbed; Hib, Haemophilus influenzae type b; MMR, measles, mumps, and rubella virus vaccine; PCV13, pneumococcal 13-valent conjugate vaccine (diphtheria CRM197 protein).