sanofi

VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Citizen Petition Requesting FDA to Require Revisions to the Labeling of Seqirus' Fluad® and Fluad® Quadrivalent Influenza Vaccines (BL125510)

Dear Sir or Madam:

This petition for administrative action is submitted on behalf of the undersigned pursuant to U.S. Food and Drug Administration ("FDA") regulations at 21 C.F.R. § 10.30 and related provisions of the Federal Food, Drug, and Cosmetic Act ("FDCA") and the Public Health Service Act ("PHS Act") to request that the Commissioner of Food and Drugs immediately require revision of the labeling for the influenza vaccine products Fluad® and Fluad® Quadrivalent, both manufactured by Seqirus and approved under the same Biologics License Application ("BLA") (BL125510) via FDA's accelerated approval pathway. Fluad and Fluad Quadrivalent received accelerated approval, in 2015[1] and 2020,[2] respectively, for active immunization against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine for use in persons ≥ 65 years of age.[3]

As FDA has long recognized, truthful, non-misleading labeling is foundational to health care decision-making because it is the primary tool for educating health care professionals about the benefits and risks associated with a particular product. Such informed decision-making is necessary to ensure the protection of the public health, especially where it relates to the prevention or treatment of serious conditions such as influenza. To help ensure safe and effective use, FDA generally requires labeling not only to summarize the safety and effectiveness data supporting approval, but also to describe limitations of the existing evidence, particularly in the context of accelerated approval. As described further below, the absolute efficacy confirmatory study required by FDA as a condition of Fluad's accelerated approval failed to verify clinical benefit. This failure is nowhere referenced in the products' labeling. Prompt revision to the labeling for Fluad[4] and Fluad Quadrivalent is therefore necessary to comply with FDA labeling

[1] Marion F. Gruber, FDA, Accelerated Approval Letter: FLUAD (Nov. 24, 2015), http://wayback.archive-it.org/7993/20170722113927/https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM474523.pdf.
[2] Doran L. Fink, FDA, Supplemental Accelerated Approval Letter: FLUAD Quadrivalent (Feb. 21, 2020), https://www.fda.gov/media/135431/download.
[3] Seqirus Inc., FLUAD 2020-2021 Formula Label (Oct. 14, 2020), https://www.fda.gov/media/94583/download.
[4] Acknowledging that Seqirus is not expected to offer new batches of its trivalent Fluad formulation for commercialization in the United States, this formulation continues to hold accelerated approval from FDA for commercialization in the U.S., serves as the basis of the original BLA (BL125510) under which accelerated approval for Fluad Quadrivalent was granted through a supplemental BLA ("sBLA"), and continues to be listed on

regulations, to satisfy expectations as described in FDA guidance and demonstrated by labeling precedents, and to ensure that health care professionals, patients, payers, and others have accurate, meaningful, and up-to-date information to guide critical decisions related to immunization practices to protect the public health.

I. ACTION REQUESTED

Petitioner is requesting that FDA require Seqirus to amend the labeling for its influenza vaccine products Fluad and Fluad Quadrivalent in a manner consistent with FDA regulations, guidance documents, and precedents. In particular, petitioner requests that the labeling for these products, both of which received accelerated approval, contain a description of the limitations of existing evidence, including a description of results from an absolute efficacy confirmatory study that failed to meet its primary efficacy endpoints.

II. STATEMENT OF GROUNDS

a. Influenza is a serious condition for which informed decision-making is critical

Influenza is an acute respiratory illness, most often caused by transmission of influenza A or B viruses.[5] Influenza viruses typically circulate annually in the United States. While influenza in healthy individuals is generally characterized by fever, myalgias, cough and other respiratory symptoms, and malaise, most people recover without serious complications.[6] However, each year influenza is also associated with serious illnesses, hospitalizations, and deaths, particularly among older adults, very young children, pregnant women, and persons of all ages with chronic medical conditions.[7]

In the U.S., infection rates tend to be highest among vulnerable populations, with complications and hospitalizations being most common among persons age ≥ 65 years, children < 2 years, and persons with chronic conditions. While the impact of influenza is highly variable from year-to-year, the National Foundation for Infectious Diseases ("NFID") has assessed that influenza has been the cause of an average of 3,000-49,000 deaths annually,[8] with the U.S. Centers for Disease Control ("CDC") finding that approximately 51,000 deaths occurred due to influenza during the 2017-18 season, which was characterized by an unusually long duration of widespread high influenza activity in the United States compared with other recent seasons.[9]

Seqirus' website as a product available for commercialization and purchase in the U.S. As such, under FDA regulations and guidance the labeling for Fluad is still required to be updated, as outlined below.

[5] John J. Treanor, *Influenza Vaccination*, 375 New Eng. J. Med. 1261 (2016).

[6] *See, id.*; *see also* Lisa A. Grohskopf et al., *Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices, United States, 2021-22 Influenza Season*, 70 Morbidity & Mortality Weekly Rep. 1, 2 (2021).

[7] *See* Grohskopf et al., *supra* note 6.

[8] *See* NFID, *Influenza Vaccination Recommendations Across the Lifespan* (Nov. 11, 2020).

[9] *See* CDC, *Estimating Burden of Seasonal Flu in the United States 2017-2018*, https://www.cdc.gov/flu/about/burden/2017-2018.htm (last reviewed Sept. 30, 2021); *see also* Grohskopf et al., *supra* note 6; *but see* NFID, *supra* note 8 (placing the number of deaths attributable to influenza during the 2017-2018 season at approximately 80,000).

Additionally NFID estimates that 55,000-431,000 hospitalizations per year are attributable to influenza. During the 2019-20 season alone, the CDC estimates that influenza caused 38 million illnesses, 400,000 hospitalizations, and 22,000 deaths.[10]

Vaccinations provide important protection from influenza illness and its associated complications. During the six influenza seasons from 2010-11 through 2015-16, influenza vaccination prevented an estimated 1.6-6.7 million illnesses, 790,000-3.1 million outpatient medical visits, 39,000-87,000 hospitalizations, and 3,000-10,000 respiratory and circulatory deaths each season in the United States. During the unusually long 2017-18 season, vaccination prevented an estimated 7.1 million illnesses, 3.7 million medical visits, 109,000 hospitalizations, and 8,000 deaths, despite an overall estimated vaccine effectiveness rate of 38%.[11]

There are several influenza vaccines and vaccine types currently available in the U.S., each with distinct safety and efficacy data, and different patient populations for which they have been approved for use. As of the 2020-21 flu season, the U.S. marketplace for influenza vaccines included four egg-based inactivated influenza vaccines (quadrivalent) ("IIV4s"), one cell-based IIV4, one recombinant influenza vaccine (quadrivalent) ("RIV4"), one egg-based adjuvanted influenza vaccine that includes both trivalent ("aTIV") and quadrivalent ("aQIV") formulations, one egg-based high-dose inactivated influenza vaccine (quadrivalent) ("HDIIV4"), and one egg-based live attenuated influenza vaccine (quadrivalent) ("LAIV4").[12] The existing clinical data – particularly as it relates to data obtained through randomized, controlled clinical trials, which are considered the gold standard for effectiveness research[13] – for the various products indicates that they may not provide equal protection from influenza infection and its associated effects. As such, it is vitally important that health care providers, patients, and other stakeholders have access to accurate and up-to-date information about the effectiveness of available vaccines to inform health care decisions and protect the public health.

---

[10] *See* NFID, *supra* note 9, at 5.
[11] *See* Grohskopf et al., *supra* note 6.
[12] *See* NFID, *supra* note 9, at 8.
[13] *E.g.*, Mili Duggal et al., *Eligibility Criteria and Clinical Trials: An FDA Perspective*, 109 Contemp. Clinical Trials 1 (2021), https://www.fda.gov/media/155043/download ("Marketing approval of new therapeutic products by United States (US) Food and Drug Administration (FDA) relies largely on randomized controlled trials (RCTs) which are considered the 'gold standard' to determine safety and efficacy."); Pallavi Mishra-Kalyani, U.S. Food & Drug Admin., *Statistical Considerations for External Controls in Pediatric Trials* 2 (2021), https://www.fda.gov/media/148543/download ("In general, randomized trials are preferred for providing evidence of drug efficacy . . . [r]andomized control trials (RCTs) are the gold standard for comparing treatments as the process of randomization removes confounding by known and unknown factors."); Suzanne White Junod, FDA, *FDA and Clinical Drug Trials: A Short History* 8, https://www.fda.gov/media/110437/download ("Although several kinds of randomized controlled methodologies can be useful to researchers and regulators, ultimately, it was the randomized, double-blinded, placebo controlled experiment which became the standard by which most other experimental methods were judged, and it has often subsequently been referred to as the 'gold' standard for clinical trial methodology."); *see* FDA, *Memorandum Explaining Basis for Declining Request for Emergency Use Authorization for Emergency Use of Hydroxycholoroquine Sulfate* 5 (2020), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/MemorandumDecliningRequestforHCQEUA_081020.pdf ("Randomized controlled trials are considered the gold standard for evaluating the effectiveness of a given intervention. Despite limitations, these trials represent the highest quality data . . . .").

sanofi

b. FDA's regulatory framework underscores the importance of labeling to inform safe and effective use of medical products

As described further below, FDA views product labeling as essential to guide health care decisions. Appropriate labeling is critical in any case, but especially in the context of accelerated approval, where clinical benefit has not yet been confirmed. Misrepresenting or failing to disclose available data relating to clinical benefit strips health care professionals and patients of the ability to make informed decisions about vaccinations and endangers the public health.

i. Regulatory landscape and FDA guidance

FDA may grant accelerated approval of products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments.[14] Accelerated approval may be granted upon "the basis of adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit."[15] As a condition of accelerated approval, confirmatory studies to confirm and verify efficacy or clinical benefit are generally required.[16] Such studies "must also be adequate and well-controlled," and "[t]he applicant shall carry out any such studies with due diligence."[17] FDA has made clear that clinical benefit is verified when confirmatory postmarketing clinical trials "show that the drug provides a clinically meaningful positive therapeutic effect, usually an effect on how a patient feels (*e.g.*, symptom relief), functions (*e.g.*, improved mobility), or survives."[18,19] Confirmatory studies are necessary because, while surrogate endpoints serve as markers of a reasonable expectation of clinical benefit, it is only through confirmatory studies that actual, objective clinical benefit can be assured. As such, FDA regulations further state that ordinarily the Agency will consider the conditions of accelerated approval subject to a postmarketing study satisfied when "FDA

[14] 21 U.S.C. § 356(c); 21 C.F.R. § 601.40 *et seq*.
[15] 21 C.F.R. § 601.41.
[16] The FDCA also provides limitations to the accelerated approval pathway, starting that:

> Approval of a product under this subsection may be subject to 1 or both of the following requirements:
> (A) That the sponsor conduct appropriate post-approval studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit.
> (B) That the sponsor submit copies of all promotional materials related to the product during the preapproval review period and, following approval and for such period thereafter as the Secretary determines to be appropriate, at least 30 days prior to dissemination of the materials.

21 U.S.C. § 356(c)(2).
[17] 21 C.F.R. § 601.41.
[18] FDA, *Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway: Guidance for Industry* 2 (2019), https://www.fda.gov/media/119755/download; *see* 21 C.F.R. § 601.46.
[19] In certain instances, as here, regulations and FDA guidances use the term "drug" generally to apply to drugs and biologics. For purposes of this petition, use of the term "drug" is intended to be inclusive of biological products, including Seqirus' influenza vaccine products, Fluad and Fluad Quadrivalent.

determines that the required . . . study verifies and describes . . . the product's clinical benefit and the [drug] product would be appropriate for approval under traditional procedures."[20]

Once a product has received approval, including through the accelerated approval pathway, the product labeling is essential to facilitate the safe and effective use of products.[21] Indeed, when issuing its labeling regulations, FDA expressly identified product labeling as "[t]he centerpiece of risk management for prescription drugs," because labeling is intended to:

> [R]eflect[] thorough FDA review of the pertinent scientific evidence and communicate[] to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively. FDA carefully controls the content of labeling for a prescription drug, because such labeling is FDA's principal tool for educating health care professionals about the risks and benefits of the approved product to help ensure safe and effective use.[22]

Furthermore, as medical literature grows at an inexhaustible rate, health care professionals rely on FDA regulatory oversight and product labeling to provide judicious, balanced, and independent evidence relating to the benefits and risks associated with marketed products. Not only does the product labeling serve as a trusted source of information for health care professionals, but it is also frequently relied upon by other stakeholders such as payers and professional societies. Additionally, labeling is critical to guide conversations between health care professionals and their patients,[23] and is the primary basis on which other product communications are based. Therefore, although FDA requires that advertising and promotional labeling be truthful and non-misleading,[24] among other requirements, it is particularly important that the product labeling be accurate, up-to-date, and complete. Inaccurate or misleading labeling may lead to misunderstanding among health care professionals and patients concerning the safety and efficacy of a given drug or biologic, and may impact health care decisions, prompting increased use of products for which efficacy has not been established and thereby harming public health. FDA regulations therefore expressly require that labeling "be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading."[25]

The labeling of prescription drugs and biologics, including vaccines and those products approved pursuant to accelerated approval, is governed by 21 C.F.R. §§ 201.56 and 201.57. FDA

---

[20] 21 C.F.R. § 601.46.
[21] *See* 21 C.F.R. § 201.56(a).
[22] Requirement on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3921, 3934 (Jan. 24, 2006).
[23] In the preamble to its issuance of labeling regulations, FDA stated that, "[o]n the basis of a series of national telephone surveys conducted by FDA to assess how patients receive information about their prescription medicines, the agency determined that the prescribing physician is the primary source of drug information for patients," and that "most consumers who receive product information, other than instructions for use on the sticker information, receive it orally from their physicians during an office visit." *Id.* at 3956.
[24] 21 C.F.R. § 202.1(e).
[25] 21 C.F.R. § 201.56(a)(2).

regulations require labeling to contain a summary of the essential scientific information, presented accurately, related to the drug or biologic.[26] As informed by regulations and FDA guidance, labeling is generally expected to contain sufficient information to inform the safe and effective use of the product, including by describing limitations of the available evidence, where applicable.[27] The uncertainties about clinical benefit and limitations of the usefulness of a given drug or biologic are required to be discussed in various places in the drug or biologic's labeling. Specifically, when the indication is approved based on a surrogate endpoint (*i.e.*, pursuant to the accelerated approval pathway), the "Indications and Usage" section must include "a succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits, with reference to the 'Clinical Studies' section for a discussion of the available evidence."[28] FDA has reaffirmed and clarified its commitment to requiring this level of disclosure in the "Indications and Usage" section numerous times, including through the issuance of a generally applicable labeling guidance titled *Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* ("Indications and Usage Guidance") and a guidance specific to drugs and biologics approved through the accelerated approval pathway titled *Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway* ("Accelerated Approval Labeling Guidance"). These guidances make clear that the "Indications and Usage" section should "[r]eflect the scientific evidence accurately" and should provide "a discussion of the available evidence."[29]

When clinical benefit is uncertain, FDA has stated that it may be appropriate to provide in the "Indications and Usage" section "additional context about the approval . . . by identifying the clinical outcome(s) that are expected (based on the effect demonstrated on the surrogate or intermediate clinical endpoint) but not yet established." As an example of the type of language that would be expected in such an instance, FDA's guidance offers: "This indication is approved under accelerated approval based on a reduction in alkaline phosphatase *[see Clinical Studies (14.1)]*. An improvement in survival or disease-related symptoms have not been established."[30]

While the "Indications and Usage" section of a drug or biologic subject to accelerated approval is intended to refer succinctly to the evidence and its limitations, the "Clinical Studies" section of the labeling – herein referred to as "Section 14" – provides a more detailed summary

[26] *See id.* § 201.56(a).
[27] *Id.* § 201.56(a)(1) (stating that "labeling must contain a summary of the essential scientific information needed for the safe and effective use of the drug").
[28] *Id.* § 201.57(c)(2)(i)(B).
[29] In theIndications and Usage Guidance, FDA expresses the general principle that to comply with the general labeling requirements in 21 C.F.R. §§ 201.56 and 201.57, the Indications and Usage section must "[r]eflect the scientific evidence accurately." FDA, *Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products – Content and Format: Guidance for Industry* 2 (2018), https://www.fda.gov/media/114443/download. FDA also reaffirmed this principle specifically in the context of labeling for accelerated approval products in a subsequent guidance document, stating that the Indications and Usage section for accelerated approval products should state the surrogate endpoint "and the limitations of that endpoint [as well as] a cross-reference to the CLINICAL STUDIES section for a discussion of the available evidence." FDA, *Accelerated Approval Labeling Guidance*, *supra* note 18, at 4.
[30] FDA, *Accelerated Approval Labeling Guidance*, *supra* note 18, at 4

to "facilitate an understanding of how to use the drug or biologic safely and effectively."[31] As the range of studies that might "facilitate an understanding of how to use the drug safely and effectively" could be expansive, FDA issued a guidance document specific to the requirements for Section 14 ("Section 14 Guidance") that elaborates on how this regulatory standard ought to be interpreted. Specifically, FDA has explained that Section 14 should provide "concise, accurate summaries of information from studies *concerning* a drug's effectiveness (and sometimes safety) that practitioners consider important to clinical decision making."[32] The universe of studies to be discussed are not simply those *supporting* or *validating* efficacy or safety, but instead are all those *concerning* efficacy or safety that might impact a clinician's decision as to whether or not to recommend the product for a particular patient. Indeed, the Section 14 Guidance indicates that, in addition to clinical studies that provide primary support for effectiveness, Section 14 should "usually" describe results of clinical studies that provide "other important information about a drug's effectiveness," including "[s]tudies that suggest lack of effectiveness in a clinical situation or lack of effect on a particular endpoint where the drug might have been expected to work."[33]

On the whole, the FDCA, its implementing regulations, and FDA guidance indicate that the limitations of the available evidence to confirm efficacy or clinical benefit for products approved pursuant to the accelerated approval pathway should be meaningfully and accurately described in the product's labeling. Such limitations should be both referenced in the "Indications and Usage" section and described in further detail in Section 14, with the aim of ensuring that the essential scientific evidence is presented to allow health care providers and patients to fully understand the safety and efficacy of the product.

ii. Inclusion of confirmatory study results in labeling for other accelerated approval vaccines

In addition to FDA's regulations and guidance documents, a review of the labeling history for other vaccine products that received accelerated approval indicates that it is appropriate practice to include a discussion of confirmatory trials in Section 14 of the product labeling. Historically, manufacturers of vaccine products receiving accelerated approval –

---

[31] 21 C.F.R. § 201.57(c)(15).

[32] FDA, *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format: Guidance for Industry* 2 (2006), https://www.fda.gov/media/72140/download (emphasis added). This is not to say that all data obtained in the course of study of a drug or biologic should be listed; to the contrary, 21 C.F.R. § 201.57(c)(15) goes on to state that, "[f]or biological products, any clinical study that is discussed that relates to an indication for or use of the biological product must constitute or contribute to substantial evidence . . . ." With regard to determining what types of studies inform substantial evidence of safe and effective use, FDA clarifies in its Section 14 Guidance that "[g]enerally, [Section 14] should include information from the adequate and well-controlled studies that demonstrate the effectiveness of the drug for its approved indication." It then goes on to identify categories of studies that should not be included, including, "[a]dditional studies that reach the same conclusion [as the clinical studies that provide primary support for effectiveness," "[c]linical studies with results that imply effectiveness for an unapproved indication, use, or dosing regimen," "[a]ctive control clinical studies that imply comparative effectiveness or safety claims not supported by substantial evidence," and "[s]tudies that are not adequate and well-controlled within the meaning of 21 CFR 314.126." FDA, *Section 14 Guidance*, *supra*, at 2-3.

[33] FDA, *Section 14 Guidance*, *supra* note 32, at 2.

including influenza vaccine products – have updated the product labeling to include a description of confirmatory trials both in instances where such confirmatory trials were successful at validating or confirming efficacy or clinical benefit, and where such confirmatory trials were unsuccessful.

FDA's Accelerated Approval Labeling Guidance explicitly addresses the expectation that labeling be updated to reflect the results of successful confirmatory trials. Specifically, the guidance makes clear that:

> Following successful verification and description of clinical benefit in the postmarketing studies, the information in the INDICATIONS AND USAGE section should be revised. The indication generally should reflect the population and condition for which there is substantial evidence of effectiveness, including any new or remaining limitations of use. The statements concerning limitations of usefulness and continued approval should be removed or revised, as appropriate. In addition, other sections of labeling (e.g., ADVERSE REACTIONS and CLINICAL STUDIES) should be revised, as appropriate, to reflect the new data (e.g., the CLINICAL STUDIES section generally should be revised to include a description of the clinical studies that verified clinical benefit).[34]

It is unsurprising, then, that a review of the approval history and labeling for various vaccines receiving accelerated approval, including both influenza and non-influenza vaccines, demonstrates that successful confirmatory trials are typically reflected in labeling following the trials' completion.[35]

---

[34] FDA, *Accelerated Approval Labeling Guidance*, *supra* note 18, at 5.

[35] For example, the accelerated approval for GlaxoSmithKline's Fluarix influenza vaccine was granted subject to the completion of two confirmatory studies: (1) a comparative safety and immunogenicity study of Fluarix against a comparator influenza vaccine, and (2) a placebo-controlled clinical endpoint efficacy study of Fluarix in subjects 18-64 years of age. Norman W. Baylor, FDA, Accelerated Approval Letter: Fluarix (Aug. 31, 2005), http://wayback.archive-it.org/7993/20170723030311/https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm113113.htm. Ultimately, both confirmatory studies were found to verify and describe the clinical benefit, and supplemental approval was granted to include data from such studies in the labeling for the product. Wellington Sun, FDA, Accelerated Approval Supplement: Fluarix (Oct. 2, 2009), http://wayback.archive-it.org/7993/20170723030254/https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm191884.htm. A review of the labeling for Fluarix has found that both confirmatory trials – NCT00197288 and NCT00363870, respectively – are reflected in Section 14 of the Fluarix label. GlaxoSmithKline, FLUARIX 2015-2016 Formula Label 13-16, https://www.fda.gov/media/84804/download.
Non-influenza vaccines, including Wyeth Pharmaceuticals' Prevnar 13, follow this same pattern. Wyeth Pharmaceuticals received accelerated approval for an additional indication for Prevnar 13 – which had already been approved for active immunization for the prevention of invasive disease caused by Streptococcus pneumonia serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 2F, and for the prevention of otitis media caused by serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F in children 6 weeks through 5 years of age – on December 30, 2011. The additional indication was for the prevention of pneumonia and invasive disease caused by *S. pneumonia* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F in persons 50 years of age or older. Wellington Sun, FDA, Accelerated Approval Letter: Prevnar 13 (Dec. 30, 2011), http://wayback.archive-it.org/7993/20170723031317/https:/www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm285434.htm. As such, following its accelerated approval, the labeling for Prevnar 13 made clear the limitations of the

Conversely, FDA has not specifically addressed the way in which failed confirmatory trials are expected to be disclosed in product labeling, beyond reiterating the general expectation that Section 14 include a description of the available evidence[36] and noting that failure of a confirmatory study to verify and describe the predicted clinical effect may serve as a basis for withdrawal of an accelerated approval.[37] However, a review of precedent, including the labeling history for GlaxoSmithKline's influenza vaccine FluLaval – the only influenza vaccine besides Fluad that was approved through the accelerated approval pathway for which the confirmatory study required as a condition of approval was unsuccessful in meeting its primary endpoints – indicates that it is also appropriate practice to include in the labeling reference to and discussion of confirmatory trials that failed to meet their primary endpoints.

FluLaval received accelerated approval on October 5, 2006.[38] As a condition of accelerated approval, FDA required that the applicant – at the time, ID Biomedical Corporation – undertake two postmarketing studies.[39] These studies, identified as IDB 707-108[40] and IDB 707-106,[41] were a comparative safety and immunogenicity study of FluLaval against an approved competitor, and a placebo-controlled efficacy study, respectively. Ultimately, IDB 707-106 failed to meet the success criteria for demonstration of clinical efficacy that were pre-defined in the study protocol, leading FDA to find that adequate effectiveness had not been demonstrated

---

accelerated approval for this particular indication, including a caveat that applied only to the ≥ 50 years of age indication that read: "[t]his indication is based on immune responses elicited by Prevnar 13. There have been no controlled trials in adults demonstrating a decrease in pneumococcal pneumonia or invasive disease after vaccination with Prevnar 13." Wyeth Pharmaceuticals, Prevnar 13 2010 Formula, https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=163343 (last accessed Jan. 4, 2022). As part of the accelerated approval for this indication, FDA required completion of a confirmatory efficacy study known as CAPiTA (NCT00744263). *See* Sun, Accelerated Approval Letter: Prevnar 13, *supra*. Following the successful completion of the CAPiTA study, FDA approved Wyeth's application to update its package insert to include data from the confirmatory efficacy study. Wellington Sun, FDA, Accelerated Approval Supplement Letter: Prevnar 13, http://wayback.archive-it.org/7993/20170723031241/https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM448058.pdf (last accessed Jan. 4, 2022). The labeling for Prevnar continues to reflect the results of the confirmatory CAPiTA study. *See* GlaxoSmithKline, Prevnar 13 Label 28, https://www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Package-Insert------Prevnar-13.pdf.

[36] FDA, *Accelerated Approval Labeling Guidance*, *supra* note 18, at 4.

[37] *Id.* at 5.

[38] Mary A. Malarkey & Norman W. Baylor, FDA, Accelerated Approval Letter: FluLaval (Oct. 5, 2006), http://wayback.archive-it.org/7993/20170723030452/https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm112909.htm.

[39] *Id.*

[40] ID BioMedical Corp., *Study Comparing Immune Response to, and Safety of, Fluviral and Fluzone Influenza Vaccines in Persons 50 y.o. and Over (NCT00232947)*, NIH (2006), https://clinicaltrials.gov/ct2/show/NCT00232947?id=NCT00232947&draw=2&rank=1.

[41] ID BioMedical Corp., *Study of the Protective Effect of an Injectable Influenza Vaccine Against Influenza Illness in Adults Under 50 y.o. (NCT00216242)*, NIH (2007), https://clinicaltrials.gov/ct2/show/NCT00216242?id=NCT00216242&draw=2&rank=1.

and that the accelerated approval requirement to verify clinical benefit was not fulfilled.[42] FDA subsequently required that ID Biomedical Corporation undertake an additional comparator-controlled efficacy confirmatory study.[43]

In its communications regarding the failure of IDB 707-106 to meet its primary efficacy endpoints, FDA stated that, "because the results of the clinical endpoint study did not demonstrate adequate effectiveness of FluLaval, the accelerated approval requirement to verify clinical benefit was not fulfilled. *Therefore, the prescribing information was updated to include results from the efficacy and immunogenicity studies*."[44] FDA went on to note that the revisions "primarily involved Section 6.0 Adverse Reactions and Section 14.0 Clinical Studies, which were revised to include the results of both trials."[45]

Following completion of the subsequently required confirmatory trial, the labeling for FluLaval was amended again to include reference to *all* of the required confirmatory trials. Specifically, Section 14 of the current FluLaval labeling includes a discussion of the design and results of each of the three confirmatory trials. Whereas the discussion for IDB 707-108, which successfully met each of its endpoints, notes that "[n]on-inferiority of FLULAVAL to the comparator vaccine was established for all 6 co-primary endpoints,"[46] the discussion of the failed efficacy confirmatory study states that, "[o]f note, the 1.2% attack rate in the placebo group for culture-confirmed, antigenically match strains was lower than expected, contributing to a wide confidence interval for the estimate of vaccine efficacy"[47] and includes a note that the "[l]ower limit of the one-sided 97.5% CI for vaccine efficacy against influenza due to antigenically matched strains was less than the pre-defined success criterion of ≥35%."[48] Clearly, then, precedent indicates that unsuccessful or failed efficacy studies are relevant and appropriately included in the labeling for an accelerated approval product.

c. Clinical benefit of Seqirus' Fluad and Fluad Quadrivalent have not been verified in confirmatory studies

Fluad is an adjuvanted seasonal aTIV vaccine that received accelerated approval for active immunization against disease caused by influenza subtypes A and type B in persons 65 years of age and older on November 24, 2015.[49] Fluad Quadrivalent is a quadrivalent

---

[42] Sara Gagneten, FDA, *Summary Basis for Regulatory Action: FluLaval* (June 9, 2011), http://wayback.archive-it.org/7993/20170723030436/https:/www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm259581.htm.
[43] Wellington Sun, FDA, Accelerated Approval Supplement Letter: FluLaval (June 9, 2011), http://wayback.archive-it.org/7993/20170723030439/https:/www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm258964.htm.
[44] Gagneten, *supra* note 42 (emphasis added).
[45] *Id.*
[46] GlaxoSmithKline, FLULAVAL 20XX-20XX Formula Label 20 (2016), http://wayback.archive-it.org/7993/20171101183143/https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM112904.pdf.
[47] *Id.* at 18.
[48] *Id.* at 19
[49] Gruber, *supra* note 1.

formulation of the vaccine that received accelerated approval for the same indication through a supplement to the Fluad BLA on February 21, 2020.[50] Fluad Quadrivalent's accelerated approval is subject to completion a confirmatory trial, the anticipated completion date for which is March 31, 2024.[51]

i. Initial accelerated approval of Seqirus' Fluad vaccine

The BLA for Fluad® included immunogenicity and safety data from a Phase 3 clinical trial conducted in adults ≥ 65 years of age,[52] and accelerated approval was based on such immunogenicity data serving as the relevant surrogate endpoint.[53] As a condition of accelerated approval, FDA required that a confirmatory trial be undertaken to assess the efficacy of the vaccine. Specifically, the Agency required a postmarketing trial "to assess the efficacy of Fluad aQIV . . . as compared to an active control, Tdap . . . in adults 65 years of age and older,"[54] herein referred to as "Efficacy Trial V118_18." As such, the original labeling for Fluad stated in its "Indications and Usage" section that, "Approval is based on the immune response elicited by FLUAD. Data demonstrating a decrease in influenza disease after vaccination with FLUAD are not available *[see Clinical Studies (14)]*."[55]

The manufacturer of Fluad at the time of its accelerated approval had communicated with FDA's Center for Biologics Evaluation and Research ("CBER") about the design of the confirmatory trial as early as 2010,[56] and these communications indicate that CBER had considered the design of an acceptable confirmatory study in some detail.[57] Subsequent to those discussions, and considering input from CBER's Vaccines and Related Biological Products Advisory Committee ("VRBPAC"), FDA decided that it was appropriate for the confirmatory study to evaluate the efficacy of the aQIV formulation of the vaccine, rather than the aTIV

[50] Fink, *supra* note 2.
[51] *Id.*
[52] FDA, Clinical Review: FLUAD 5 (2015), http://wayback.archive-it.org/7993/20170723125607/https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM478096.pdf.
[53] FLUAD 2015-2016 Formula Label, https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=195648.
[54] Gruber, *supra* note 1, at 2-3.
[55] FLUAD 2015-2016 Formula Label, *supra* note 53.
[56] FDA, Clinical Review, *supra* note 52, at 9.
[57] *Id.* at 58.

formulation, despite the fact that the accelerated approval had been granted for the aTIV formulation.[58,59]

ii. Failure of Fluad's confirmatory study, Efficacy Trial V118_18

The confirmatory study, Efficacy Trial V118_18 (National Clinical Trial Number: NCT02587221),[60] was a Phase 3, randomized, observer blind, controlled, multicenter clinical study, the primary efficacy endpoint of which was to demonstrate absolute vaccine efficacy of Fluad Quadrivalent versus a non-influenza comparator when administered as a single dose to prevent first occurrence RT-PCR confirmed influenza, due to any strain of influenza regardless of antigenic match to the strains selected for the seasonal vaccine, in subjects ≥ 65 years of age.[61] The study was completed on July 23, 2018.[62] Ultimately, the absolute vaccine efficacy was estimated to be 19.80%, which did not meet the pre-specified criterion of lower limit ≥ 40%.[63] The company explained this failure to meet its primary endpoint by stating that most influenza cases were caused by A/H3N2 strains and were antigenically unmatched to the vaccine strain.[64] The study also included a secondary immunogenicity endpoint that it was successful in satisfying.[65] Despite its failure to meet its primary efficacy endpoint, and as described further in Section II.d., *infra*, Efficacy Trial V118_18 was not ever and is not currently mentioned in the labeling for Fluad.[66]

iii. Subsequent accelerated approval of Fluad® Quadrivalent

Despite the failure of Efficacy Trial V118_18 to satisfy its primary endpoint and successfully demonstrate vaccine efficacy for the aQIV formulation of Fluad, Seqirus then sought accelerated approval for this aQIV formulation, Fluad Quadrivalent, through a BLA supplement. In support of its application, Seqirus undertook another clinical trial (National

---

[58] In support of this trial design, the previous manufacturer explained to VRBPAC that "[a]djuvanted TIV and adjuvanted QIV are actually the same vaccine, produced the same rate [sic]. The only difference is an additional B strain which is added. We know they contain the same dose of MF59, and we also know from the literature and from our own research that addition of an additional B strain will not have an impact on the response for the other three antigens or on the safety profile." FDA, 139th Meeting of the Vaccine and Related Biological Products Advisory Committee (VRBPAC Meeting Transcript) 121-22 (Sept. 15, 2015), http://wayback.archive-it.org/7993/20170405194055/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM466047.pdf.

[59] *Id*. at 142.

[60] Seqirus, *Clinical Study to Evaluate the Efficacy, Safety and Immunogenicity of an MF59-Adjuvanted Quadrivalent Influenza Vaccine Compared to Non-influenza Vaccine Comparator in Adults ≥ 65 Years of Age (NCT02587221)*, NIH (2020), https://clinicaltrials.gov/ct2/show/study/NCT02587221?id=NCT02587221&draw=2&rank=1.

[61] FDA, Clinical Review Memorandum: FLUAD QUADRIVALENT 10 (Feb. 21, 2020), https://www.fda.gov/media/135686/download.

[62] *See* Seqirus, *supra* note 60.

[63] FDA, Statistical Review: FLUAD QUADRIVALENT 5 (Feb. 21, 2020), https://www.fda.gov/media/135687/download.

[64] *Id.*

[65] *Id.*

[66] FLUAD 2020-2021 Formula Label, *supra* note 3.

Clinical Trial Number: NCT03314662),[67] herein referred to as "Immunogenicity Trial V118_20," to evaluate safety and immunogenicity of Fluad Quadrivalent as compared to the licensed aTIV formulation of the vaccine, Fluad, as well as with an additional aTIV vaccine containing the alternate B strain, in adults ≥ 65 years of age.[68] The co-primary endpoints of Immunogenicity Trial V118_20 were (1) to demonstrate that vaccination with Fluad Quadrivalent elicits an immune response that is not inferior to that of either comparator aTIV vaccine; and (2) to assess the immunogenicity of Fluad Quadrivalent based on CBER recommendations.[69,70] Initially, Seqirus submitted only Immunogenicity Trial V118_20 in support of its supplemental BLA ("sBLA") to obtain accelerated approval of Fluad Quadrivalent.[71]

Ultimately, Immunogenicity Trial V118_20 met the primary endpoint requiring non-inferior immunogenicity as compared to the aTIV formulations, but failed to meet the co-primary endpoint of immunogenicity criteria needed to support accelerated approval based on relevant

[67] Seqirus, *Phase 3 Safety and Immunogenicity Study of aQIV in Elderly Patients (NCT03314662)*, NIH (2020), https://clinicaltrials.gov/ct2/show/record/NCT03314662?id=NCT03314662&draw=2&rank=1.
[68] FDA, Statistical Review, *supra* note 63, at 7.
[69] *Id.* at 23.
[70] FDA has issued a guidance document that provides insight into the clinical data required to support the licensure of seasonal inactivated flu vaccines through both the traditional and accelerated approval pathways. According to the guidance, "the immune response elicited following receipt of the vaccine may serve as a surrogate endpoint that is likely to predict clinical benefit." The guidance then goes on to provide possible approaches for establishing effectiveness based on immune responses for purposes of obtaining accelerated approval, recommending two specific study designs that are sufficient: (1) a non-inferiority immunogenicity trial of hemagglutination inhibition ("HI") antibody responses to the new vaccine as compared to a U.S. licensed seasonal inactivated influenza vaccine (except for those granted accelerated approval whose clinical benefit awaits confirmation) that should assess the co-primary endpoints for HI antibodies to each viral strain contained in the vaccine: (i) geometric mean titer ("GMT"), and (ii) seroconversion rates; and (2) a placebo-controlled immunogenicity trial in which HI antibody responses to the new vaccine are assessed where the study is adequately powered to assess the co-primary endpoints for HI antibodies to each viral strain contained in the vaccine: (i) seroconversion rates, and (ii) percentage of subjects achieving an HI antibody titer ≥ 1:40. The guidance then also provides further recommendations for the criteria related to the named endpoints. With regard to the non-inferiority immunogenicity study endpoints, the guidance recommends that (1) the upper bound of the two-sided 95% confidence interval ("CI") on the ratio of the GMTs ($GMT_{U.S.\ licensed\ vaccine}/GMT_{new\ vaccine}$) should not exceed 1.5, and any proposal for use of a different GMT ratio should be based upon the characteristics of the assay that will be used to assess antibody responses; and (2) the upper bound of the two-sided 95% CI on the difference between the seroconversion rates ($seroconversion_{U.S.\ licensed\ vaccine} - seroconversion_{new\ vaccine}$) should not exceed 10 percentage points. With regard to the placebo-controlled immunogenicity trial, the guidance pulls from guidelines in the Committee for Medicinal Products for Human Use of the European Medicines Agency and provides recommendations based on age group, stating that: (1) for adults < 65 years of age and for the pediatric population (i) the lower bound of the two-sided 95% CI for the percent of subjects achieving seroconversion for HI antibody should meet or exceed 40%, and (ii) the lower bound of the two-sided 95% CI for the percent of subjects achieving an HI antibody titer ≥ 1:40 should meet or exceed 70%; and (2) for adults ≥ 65 years of age (i) the lower bound of the two-sided 95% CI for the percent of subjects achieving seroconversion for HI antibody should meet or exceed 30%, and (ii) the lower bound of the two-sided 95% CI for the percent of subjects achieving an HI antibody titer ≥ 1:40 should meet or exceed 60%. FDA, *Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines* (2007), https://www.fda.gov/media/73706/download.
[71] FDA, Clinical Review Memorandum, *supra* note 62, at 5.

CBER guidance.[72] These immunogenicity results from Immunogenicity Trial V118_20 differed significantly from the immunogenicity results in Efficacy Trial V118_18,[73] which also studied the aQIV formulation and which FDA had previously seen, as well as those seen in a previous study of the Fluad aTIV formulation.[74] In response to FDA's concerns about this variance in immunogenicity data, Seqirus undertook a post-hoc exploratory study aimed at remedying what Seqirus believed had caused the divergent results, but the results of such post-hoc study still failed to meet the pre-specified immunogenicity criterion.[75]

Given the overall uncertainty regarding the interpretability of the immunogenicity analyses seen in Immunogenicity Trial V118_20, FDA concluded that the immunogenicity data from this study would not be sufficient to support the accelerated approval of Fluad Quadrivalent, though the safety results could still be considered, as they were not impacted by the variability in assay protocols. As a result, Seqirus submitted the data from Efficacy Trial V118_18 to supplement its sBLA. Despite the failure of Efficacy Trial V118_18 to achieve its primary endpoint and demonstrate efficacy of Fluad Quadrivalent and the mixed immunogenicity data emerging from the variance in the immunogenicity results from Efficacy Trial V118_18 and Immunogenicity Trial V118_20, FDA decided that the immunogenicity and safety data from V118_18 would serve as the primary evidence to support accelerated approval of Fluad Quadrivalent, and that Immunogenicity Trial V118_20 would be used only to provide additional supportive safety data.[76] Fluad Quadrivalent received accelerated approval based on these data on February 21, 2020; this accelerated approval included as a required condition the completion of another confirmatory trial with a projected completion date of March 31, 2024.[77]

d. Labeling for Seqirus' Fluad and Fluad Quadrivalent vaccines is inconsistent with FDA regulations, guidance, and precedents because it does not describe the failed confirmatory studies

Neither the labeling for Fluad, nor the labeling for Fluad Quadrivalent, refers to the failed absolute efficacy confirmatory study, Efficacy Trial V118_18, despite the fact that FDA labeling regulations and guidance repeatedly underscore the importance of labeling that informs the safe

[72] *See, id.*; *see also* FDA, Statistical Review, *supra* note 63, at 5.
[73] Efficacy Trial V118_18 also included a secondary endpoint to assess immunogenicity of Fluad Quadrivalent for all influenza strains. The study ultimately met the CBER immunogenicity criteria as described in the "Clinical Data Needed to Support Licensure of Seasonal Inactivated Vaccines" guidance.
[74] FDA, Clinical Review Memorandum, *supra* note 62, at 5.
[75] Seqirus hypothesized that the variance in results might be due to the difference in assay methods used in Efficacy Trial V118_18 and Immunogenicity Trial V118_20. Seqirus conducted a post-hoc exploratory study to assess this hypothesis by re-testing randomly selected samples of Fluad Quadrivalent from each of the Efficacy Trial V118_18 and Immunogenicity Trial V118_20 studies using the Efficacy Trial V118_18 assay protocol. While this post-hoc study indicated that the two assay methods may have been one of the contributing factors for variance in immune response observed between the studies, the percentages of subjects achieving seroconversion were still low for both B strains and did not meet CBER criteria for accelerated approval. *See* FDA, Statistical Review, *supra* note 63, at 5-6. *See also* FDA, Clinical Review Memorandum, *supra* note 62, at 5-6.
[76] FDA, Clinical Review Memorandum, *supra* note 62, at 5.
[77] Fink, *supra* note 2.

and effective use of the product, including by describing limitations of the available evidence.[78] Additionally, regulations require that labeling "must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading."[79] As described below, the omission of information about the failure of Efficacy Trial V118_18 to achieve its efficacy endpoints and thereby display clinical benefit renders the current labeling for Fluad and Fluad Quadrivalent outdated and misleading. False or misleading labeling limits the ability of health care professionals and patients to make informed decisions about vaccination practices, potentially jeopardizing both the health of individual patients and the public health. As such, the labeling for both Fluad and Fluad Quadrivalent must be updated in accordance with FDA regulations and guidance.

i. Fluad labeling

At the time of its original approval in 2015, the labeling for Fluad included a statement in the "Indications and Usage" section that read:

> Approval is based on the immune response elicited by FLUAD. Data demonstrating a decrease in influenza disease after vaccination with FLUAD are not available *[see Clinical Studies (14)]*.[80]

However, the labeling for Fluad has since been updated, with the updates first reflected in the labeling for the Fluad 2020-21 formulation.[81] The current "Indications and Usage" section of the labeling for Fluad no longer includes the explicit statement described above regarding the lack of efficacy data and instead includes a statement that reads:

> This indication is approved under accelerated approval based on the immune response elicited by FLUAD. (1) Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. (14)[82]

The new language does not clearly describe the limitations of the available clinical evidence, and this update is particularly notable when read in conjunction with FDA's Accelerated Approval Labeling Guidance. In its guidance, FDA expressly states that it may be appropriate to include additional context about limitations of existing evidence "by identifying the clinical outcome(s) that are expected . . . but not yet established."[83] The example language provided by FDA, which reads, "An improvement in [clinical benefit] have not been established," provides a level of clarity more akin to Seqirus' 2017 labeling than its current labeling. As such, and recalling that the "Indications and Usage" section is expected to present the limitations of usefulness of the drug or biologic and any uncertainty about anticipated clinical benefits, the updated labeling

[78] In the context of Fluad and Fluad Quadrivalent, proper labeling is especially important because, among other things, Seqirus does not generally disclose the failed efficacy trial in its advertising and promotional materials.
[79] 21 C.F.R. § 201.56(a)(2).
[80] FLUAD 2015-2016 Formula Label, *supra* note 53.
[81] FLUAD 2020-2021 Formula Label, *supra* note 3, at 1.
[82] *Id*.
[83] FDA, *Accelerated Approval Labeling Guidance*, *supra* note 18, at 4.

should have fully and clearly presented the limitations of the existing data by retaining the express statement that absolute efficacy has not yet been established.

Further, while the current labeling does note that accelerated approval is contingent on completion of a confirmatory trial, it fails to disclose that the confirmatory trial that was specifically required as a condition of accelerated approval has been completed but failed to verify the expected clinical benefit. Similarly, Section 14 refers only to the single immunogenicity study that served as the basis for Fluad's initial accelerated approval.[84] Neither section, then, discloses the results of the failed confirmatory trial, the primary focus of which was to obtain evidence regarding efficacy, and the "Indications and Usage" section, in fact, implies that the required confirmatory trial has not been completed.

As discussed above, FDA has made clear that the "Indications and Usage" section is expected to "[r]eflect the scientific evidence accurately,"[85] and that Section 14 is required to include a discussion of all studies that provide important information concerning a drug or biologic's effectiveness, including but not limited to those that "suggest lack of effectiveness in a clinical situation or lack of effect on a particular endpoint where the drug might have been expected to work."[86] Such requirements ensure that health care professionals and patients have access to relevant information about a drug's safety and effectiveness, and can therefore make informed health care decisions to protect the public health. Undoubtedly, an adequate and well-controlled clinical trial required as a condition of accelerated approval that fails to meet pre-determined endpoints regarding efficacy would fall within this category. Recognizing that the failure of Efficacy Trial V118_18 to meet its efficacy endpoints has been attributed, at least in part, to the fact that most influenza strains in the trial were antigenically mismatched to the vaccine,[87] such mismatch does not negate the regulatory requirement that essential efficacy information be disclosed in the product's labeling. Regardless of this potential explanation, Efficacy Trial V118_18 remains the only randomized, well-controlled study of absolute efficacy of the vaccine. Therefore, FDA regulations and guidance require that such efficacy data be disclosed in Fluad's labeling.[88] Additionally, the implication in Fluad's current labeling that the confirmatory study may have not yet been completed exacerbates the potential for the labeling to mislead health care professionals, patients, payers, and may put recipients of the vaccine at the same risk of contracting influenza and related complications as those who receive a virtual placebo (*i.e.*, Tdap as the active comparator in the confirmatory study).

Further, the omission of information regarding the results of the failed confirmatory trial is inconsistent with FDA's precedent in the case of FluLaval, the only other influenza vaccine

[84] *Id.* at 10.
[85] FDA, *Indications and Usage Guidance*, *supra* note 29, at 2.
[86] FDA, *Section 14 Guidance*, *supra* note 32, at 2.
[87] FDA, Statistical Review, *supra* note 63.
[88] Should FDA view the influenza strain mismatch as sufficiently relevant to facilitate a complete and accurate understanding of the efficacy results of Efficacy Trial V118_18, an appropriate approach under FDA regulations and guidance may be to include a statement explaining the mismatch in any discussion of such results; omitting discussion of the results in their entirety in Fluad's labeling, however, runs afoul of FDA regulations and guidance requiring an accurate reflection of available scientific evidence.

that was approved through the accelerated approval pathway for which the confirmatory study required as a condition of approval was unsuccessful in meeting its primary endpoints. In the case of FluLaval, which was required to undertake additional confirmatory studies following the failure of its first confirmatory study to meet its primary endpoints, the product labeling was updated to include not only the subsequent successful confirmatory studies but also the initial unsuccessful confirmatory study, so as to accurately and completely portray the limitations of the existing effectiveness data.[89] In addition to being inconsistent with FDA regulations and guidance, failing to require that the labeling for Fluad be similarly updated to reflect and disclose the failure of its required confirmatory study to meet its primary efficacy endpoints is arbitrary in light of FDA's directly applicable labeling precedent. Given the serious nature of influenza as a medical condition, ensuring that health care professionals and patients fully understand the limitations of the efficacy data regarding the available vaccine options is vital to the protection of the public health.

ii. Fluad Quadrivalent labeling

The current labeling for Fluad Quadrivalent is similarly deficient from a regulatory perspective and has the potential to confuse stakeholders who rely on labeling to inform health care decisions. Similar to the labeling for Fluad, the "Indications and Usage" section of the labeling for Fluad Quadrivalent includes a statement that reads:

> This indication is approved under accelerated approval based on the immune response elicited by FLUAD QUADRIVALENT (1). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.[90]

As previously discussed, FDA has made clear that it may be appropriate to include additional context regarding the clinical benefit that may be expected but has not yet been established. To minimize confusion regarding the data that currently exist, the labeling for Fluad Quadrivalent, like the labeling for Fluad, should include explicit reference to the fact that a decrease in influenza disease has not yet been established.

Further, Fluad Quadrivalent's accelerated approval relied primarily on the secondary immunogenicity results of Efficacy Trial V118_18, which failed to achieve its primary efficacy endpoint. Notably, the labeling for Fluad Quadrivalent contains certain results of Efficacy Trial V118_18; Section 14 of the labeling for Fluad Quadrivalent states that, "Immunogenicity of FLUAD QUADRIVALENT was evaluated in Study 1 (NCT02587221) [Efficacy Trial V118_18], a randomized, observer-blind, non-influenza comparator-controlled multicenter efficacy study" and goes on to present the successful immunogenicity data.[91] The labeling does not, however, disclose or make any mention of the existence of efficacy data resulting from

[89] FLULAVAL 20XX-20XX Formula Label 20 (2016), *supra* note 46, at 20.
[90] Seqirus Inc., FLUAD QUADRIVALENT 2021-2022 Formula Label 1 (2021), https://www.fda.gov/media/135432/download.
[91] *Id*. at 10.

Efficacy Trial V118_18, nor does it identify that the immunogenicity endpoints were secondary endpoints of the study and that the primary endpoints were focused on efficacy of Fluad Quadrivalent.[92] Even assuming that the failure of Efficacy Trial V118_18 to meet its primary efficacy endpoints may have been attributable in part to a mismatch in influenza strains,[93] there is no clear or discernible reason for the labeling to omit any discussion whatsoever of the efficacy results—particularly where immunogenicity results from the failed Efficacy Trial V118_18 were deemed sufficiently important to describe in detail in Section 14.[94] Such selective disclosure of the results of Efficacy Trial V118_18 not only presents an incomplete picture of the actual outcomes of the study, but it creates an inaccurate and misleading presentation of the existing efficacy data for Fluad Quadrivalent. This type of misleading and inaccurate data disclosure has the potential to meaningfully impact vaccination decisions that could adversely affect the public health, as clinical data has provided no indication that Fluad and Fluad Quadrivalent lead to a decrease in influenza – a serious condition with significant health effects.

Efficacy Trial V118_18 constitutes essential scientific information to inform the safe and effective use of Fluad Quadrivalent not only because it suggests a potential lack of effectiveness in a clinical situation or lack of effect on a particular endpoint where the drug might have been expected to work, but because it remains the *only* efficacy data for Fluad Quadrivalent obtained from randomized, controlled trials, which are considered the gold standard for efficacy research.[95] Acknowledging that Fluad Quadrivalent's accelerated approval is conditioned upon the completion of an additional efficacy confirmatory trial, FDA regulations explicitly state that labeling "must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading,"[96] a requirement that by its language is triggered upon the emergence of meaningful additional data. Under FDA regulations and guidance, the results of the ongoing confirmatory trial will undoubtedly also constitute essential scientific information required to be included in the labeling upon its completion in 2024.

[92] FLUAD QUADRIVALENT 2021-2022 Formula Label, *supra* note 90.
[93] FDA, Statistical Review, *supra* note 63.
[94] When viewing Seqirus' labeling and promotional practices for Fluad and Fluad Quadrivalent in the aggregate, it becomes all the more important that the efficacy limitations evidenced in Efficacy Trial V118_18 be disclosed, even if such limitations include qualifying language explaining that the failure may be attributable in part to influenza strain mismatch. In Seqirus' promotional materials for its adjuvanted vaccine products, Seqirus expressly advertises, among other things, that adjuvanted vaccines like Fluad and Fluad Quadrivalent "[b]roaden[] the immune response by creating more diverse, cross-reactive antibodies. *This may be important if there is a mismatch between the influenza virus strains in the vaccine and the circulating influenza strains*." Seqirus, *Adjuvanted Influenza Vaccine Technology*, https://www.flu360.com/adjuvant-technology (emphasis added). That the failure of Efficacy Trial V118_18 to demonstrate efficacy of Fluad Quadrivalent has been attributed in part to influenza strain mismatch, and that Seqirus has subsequently asserted in promotional materials that immunogenicity results of its adjuvanted vaccine products indicate potential benefit in the instance of mismatch without disclosing such failure in either its promotional materials or labeling is highly misleading. Including a discussion of the efficacy results of Efficacy Trial V118_18 in the labeling for Fluad and Fluad Quadrivalent would not only be consistent with FDA regulations and guidance, but would also afford health care providers and patients the opportunity to fully understand and assess the available evidence regarding efficacy, particularly in instances where there is a influenza strain mismatch.
[95] *See* Duggal et al., *supra* note 13.
[96] 21 C.F.R. § 201.56(a)(2).

In addition to compliance with FDA regulations and guidance, updating the labeling for Fluad Quadrivalent would also be consistent with the directly applicable labeling precedent for FluLaval, described in detail in Section II.b.ii. The labeling for FluLaval, the only other influenza vaccine product approved via the accelerated approval process for which the initial required efficacy confirmatory study failed to meet its primary endpoints, includes discussion of both the initial failed efficacy confirmatory study, as well as all subsequent confirmatory studies that were completed. This approach, which accurately summarizes the universe of meaningful efficacy data including that which "suggest[s] lack of effectiveness in a clinical situation or lack of effect on a particular endpoint where the drug might have been expected to work,"[97] adheres to FDA regulations and guidance and should therefore serve as a model for the labeling of Fluad and Fluad Quadrivalent.

In contrast, by omitting any mention of the failed primary efficacy endpoint from Efficacy Trial V118_18, despite the fact that Efficacy Trial V118_18 was first and foremost an absolute efficacy study of the Fluad Quadrivalent product, the labeling for Fluad Quadrivalent runs afoul of FDA regulations and guidance and raises significant public health concerns. As has been made clear, the "Indications and Usage" section is expected to "[r]eflect the scientific evidence accurately,"[98] and Section 14 is required to include a discussion of all studies that provide important information concerning a drug or biologic's effectiveness, including but not limited to those that "suggest lack of effectiveness in a clinical situation or lack of effect on a particular endpoint where the drug might have been expected to work."[99] That Efficacy Trial V118_18 resulted in unfavorable efficacy data regarding the clinical benefit of Fluad Quadrivalent does not mean that such data ought not to be included in the product's labeling. In fact, that the only randomized, well-controlled trial studying the efficacy of Fluad Quadrivalent may suggest a lack of efficacy makes it all the more important that this potential limitation be made clear in the labeling; failing to disclose the results of this trial in the labeling for Fluad Quadrivalent is plainly an omission of essential scientific information related to the product's efficacy required by FDA regulations.[100] Given that labeling is expected to accurately represent the essential scientific information available in order to enable health care providers and patients to make informed and thoughtful decisions about health care and vaccinations, these omissions are particularly troubling, as they could lead to detrimental effects on the public health.

e. Conclusion

As described above, the current labeling for Seqirus' Fluad and Fluad Quadrivalent vaccines is inconsistent with FDA labeling regulations, guidance, and precedents because it does not sufficiently disclose the limitations of the usefulness of the product or accurately reflect the available scientific evidence. Specifically, the labeling for each of the two products neglects to disclose the failure of Efficacy Trial V118_18 to meet its primary absolute efficacy endpoint; this study provides invaluable information about the efficacy of these products that would

[97] FDA, *Section 14 Guidance*, *supra* note 32, at 2.
[98] FDA, *Indications and Usage Guidance*, *supra* note 29, at 2.
[99] FDA, *Section 14 Guidance*, *supra* note 32, at 2.
[100] *See* 21 C.F.R. § 201.56(a).

"facilitate an understanding of how to use the drug[s] safely and effectively," which is at the heart of FDA's regulation of drug and biologic labeling requirements. Such disclosures are crucial to protect the public health. FDA has made clear the importance of labeling, identifying it as the "centerpiece of risk management" for prescription drugs and biological products, intended to provide a fair summary of efficacy and safety information so as to effectively educate health care professionals and patients and facilitate the protection of the public health.

Accordingly, FDA should require that the labeling for both Fluad and Fluad Quadrivalent be updated and amended to include a description of the limitations of existing evidence including the results of Efficacy Trial V118_18. Specifically, the undersigned requests that the "Indications and Usage" sections for both Fluad and Fluad Quadrivalent be updated to read:

> This indication is approved under accelerated approval based on the immune response elicited by FLUAD [QUADRIVALENT]. (1) Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. A decrease in influenza disease following vaccination with FLUAD [QUADRIVALENT] has not been established, and clinical data supporting absolute efficacy are not available *[see Clinical Studies (14)]*.

Additionally, Section 14 of the labeling for both Fluad and Fluad Quadrivalent should be updated to include a discussion of Efficacy Trial V118_18. Such a discussion should include, at minimum, a description of the study design, including identifying the critical endpoints, and a detailed summary of the study findings, including both the efficacy and immunogenicity results.[101]

Influenza is a serious disease against which vaccinations have the potential to provide meaningful protection. In order for health care professionals and patients to be able to make informed and thoughtful vaccination decisions, however, they must be given access to the essential scientific information about the efficacy and safety of products. Failing to provide necessary information in a product's label poses a threat not only to the health of individual patients, but also to the public health at large.

III. ENVIRONMENTAL IMPACT STATEMENT

We claim categorical exclusion under 21 C.F.R. § 25.31(a) from the environmental assessment. An assessment is not required because the requested action would not increase the use of the active moiety that is the subject of this petition.

IV. ECONOMIC IMPACT

Will be submitted upon request.

[101] FDA, *Section 14 Guidance*, *supra* note 32, at 2.

V. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

Sarah Lieber

Electronically signed by: Sarah Lieber
Reason: Certification
Date: Mar 1, 2022 09:14 EST

Sarah Lieber
Head of North America, Global Labelling and Advertising & Promotion
Global Regulatory Affairs

Active_114054348_26_FLUAD Citizen Petition Draft - Lieber 1March2022.DOCX

Final Audit Report 2022-03-01

Created:	2022-03-01
By:	Stephen Yakely (Stephen.Yakely@sanofi.com)
Status:	Signed
Transaction ID:	CBJCHBCAABAAzF_WJfTAzVcPtGkB30al7AHkIiO9eLXO

"Active_114054348_26_FLUAD Citizen Petition Draft - Lieber 1 March2022.DOCX" History

Document created by Stephen Yakely (Stephen.Yakely@sanofi.com)
2022-03-01 - 1:49:59 PM GMT- IP address: 165.225.220.96

Document emailed to Sarah Lieber (Sarah.Lieber@sanofi.com) for signature
2022-03-01 - 1:51:42 PM GMT

Email viewed by Sarah Lieber (Sarah.Lieber@sanofi.com)
2022-03-01 - 2:08:02 PM GMT- IP address: 193.47.56.115

Sarah Lieber (Sarah.Lieber@sanofi.com) verified identity with Adobe Sign authentication
2022-03-01 - 2:14:31 PM GMT

Document e-signed by Sarah Lieber (Sarah.Lieber@sanofi.com)
Signature Date: 2022-03-01 - 2:14:31 PM GMT - Time Source: server- IP address: 136.226.1.102

Agreement completed.
2022-03-01 - 2:14:31 PM GMT