MINI-SENTINEL CBER/PRISM SURVEILLANCE PROTOCOL

INFLUENZA VACCINES AND FEBRILE SEIZURES IN THE 2013-2014 AND 2014-2015 INFLUENZA SEASONS

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Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. Mini-Sentinel is one piece of the Sentinel Initiative, a multi-faceted effort by the FDA to develop a national electronic system that will complement existing methods of safety surveillance. Mini-Sentinel Collaborators include Data and Academic Partners that provide access to health care data and ongoing scientific, technical, methodological, and organizational expertise. The Mini-Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223200910006I.

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I. BACKGROUND

A. PUBLIC HEALTH SIGNIFICANCE AND STUDY MOTIVATION

During the 2010 Southern Hemisphere influenza season in Australia, an increased risk of febrile seizures was found in children 6 months to 4 years of age in the 24 hours following a trivalent inactivated influenza vaccine (TIV) manufactured by CSL Biotherapies (Fluvax ®, Fluvax Junior®)[1]. As a result, in the summer of 2010, the U.S. Advisory Committee on Immunization Practices (ACIP) recommended that Afluria® (an antigenically equivalent vaccine manufactured by CSL Biotherapies) should not be used in children ages 6 months to 8 years. However, the ACIP recommendations stated that Afluria could be used in children 5 to 8 years of age if they had medical conditions that increased the risk for influenza complications and no other licensed influenza vaccines were available. The FDA also updated the Warnings and Precautions sections of the Prescribing Information for Afluria to inform healthcare professionals that administration of a 2010 Southern Hemisphere TIV manufactured by CSL Biotherapies had been associated with an increased risk of fever and febrile seizure among young children, predominantly less than 5 years of age, in Australia[2,3]. Subsequently, the FDA approved use of Afluria was changed from 6 months and older to 5 years and older. The finding in Australia was the first associating influenza vaccination with increased risk of febrile seizures; several studies of influenza vaccines conducted in the U.S. in seasons prior to 2010-11 did not suggest an elevated risk of seizures following influenza vaccination.[4-7]

A study was conducted within Mini-Sentinel to examine the risk of febrile seizures following administration of 2010-11 TIV in children ages 6-59 months and to compare the risk of febrile seizures following same day vs. separate day administration of TIV and Prevnar 13 (PCV13) and/or DTaP.[8] Using a self-controlled risk interval (SCRI) design, Kawai and colleagues reported incidence rate ratios of 1.36 (95% CI 0.78, 2.39) for TIV, 1.02 (95% CI 0.53, 1.96) for DTaP, and 1.61 (95% CI 0.91, 2.82) for PCV13, after adjusting for concomitant vaccination, age, and calendar time. In addition, same day vaccination with TIV and PCV13 was not significantly associated with excess risk of febrile seizure when compared to separate day vaccination. The authors concluded that if there is an increased risk of febrile seizure following TIV or PCV13 vaccination, it is likely modest.

Yih and colleagues also evaluated the risk of seizures in children after influenza vaccination utilizing prospective sequential analysis within Mini-Sentinel during the 2013-14 surveillance season.[9] A statistical signal was identified at the 7th "look" in children 6-23 months who received inactivated (trivalent or quadrivalent) influenza vaccine (IIV) with concomitant PCV13, where the comparison group was IIV vaccinees from historical seasons prior to the widespread use of PCV13. The cumulative number of observed events in the risk interval (0-1 days) was 9 and the expected count was 3 (RR 3.1); by the last, 10th look, there were 12 cases observed, 4.5 expected, and a RR of 2.7. In contrast, the primary, SCRI analysis conducted within the study did not reveal any statistical signals, with 2 events in the risk interval and 5 events in the control interval (14-20 days) for a RR of 1.4. Additionally, no statistical signal was identified for seizures in children 6-23 months *without* concomitant PCV13 in either design. In the absence of PCV13, the RRs for seizures following TIV were 0.60 for the current vs. historical design and 0.37 for SCRI. Note that this study was designed to address the risk of seizures following IIV and so the association between PCV13 vaccination alone and seizures could not be assessed.

Several possibilities have been considered to explain the statistical signal identified in the Mini-Sentinel prospective sequential study for the 2013-14 season. Seizures in concomitant IIV and PCV13 vaccinees were analyzed separately from seizures in children who received IIV without PCV13. The signal arose from a comparison of observed seizure counts in concomitant IIV and PCV13 vaccinees with expected counts based on post-IIV seizure rates from before PCV13 vaccine was in general use. If the IIV vaccinees had been pooled (i.e., with no distinction with respect to concomitant PCV13 vaccination), there would have been no signal but rather 20 observed cases vs. 18.4 expected, for a RR of 1.1. Lacking data on the risk of seizures in PCV13 vaccinees not receiving IIV, the Post-Licensure Rapid Immunization Safety Monitoring Study (PRISM) prospective surveillance study was unable to determine whether the signal, if real, was due to the PCV13 vaccine entirely or to some interaction between 2013-14 IIV and PCV13.

The overall objective for the present study is to evaluate the statistical signal for seizures after concomitant IIV and PCV13 vaccination that was identified in current-versus-historical sequential analysis during 2013-14. We will use Mini-Sentinel electronic data from two surveillance seasons – 2013-14 and 2014-15, which had the same IIV vaccine formulation – and a SCRI study design to conduct this signal follow-up analysis. By using the SCRI design, we will minimize confounding, and our comparison will be of the risk in exposed vs. unexposed time from the same vaccinees rather than of the risk in exposed time of vaccinees in the seasons of interest vs. of different vaccinees in historical seasons. By using data from two seasons combined, we will increase power. This study will also provide insight into the role of PCV13 vaccination in generating the 2013-14 statistical signal by collecting information on the risk of febrile seizures among those who received only the PCV13 vaccine.

II. OBJECTIVES AND ACTIVITIES

The objective is to evaluate the statistical signal for seizures after concomitant IIV and PCV13 vaccination that was identified in current-versus-historical sequential analysis during 2013-14.

Primary activities:

1. To estimate the relative risk (RR) of febrile seizures following any IIV dose in the 2013-14 and 2014-15 seasons for children ages 6-23 months using a self-controlled risk interval design, adjusting for confounding by concomitant vaccination with PCV13, age, and seasonality.

2. To estimate the RR of febrile seizures following any PCV13 dose in the 2013-14 and 2014-15 seasons for children ages 6-23 months using a self-controlled risk interval design, adjusting for confounding by concomitant vaccination with IIV, age, and seasonality.

3. To explore whether the relative risk of febrile seizures after IIV is modified by concomitant vaccination with PCV13.

Secondary activities:

4. To explore the role of background rates in generating the 2013-14 statistical signal for concomitant IIV and PCV13, by assessing background rates in three prior influenza seasons (2010-11, 2011-12, and 2012-13, all of which occurred after the introduction of PCV13) and

comparing these with the comparator rates used in the 2013-14 PRISM sequential analysis pilot where only data from prior to July 2010 (before wide-scale use of PCV13) were used.

III. METHODS

A. STUDY POPULATION

The proposed Data Partners for participation in this activity are HealthCore, Aetna, Optum, and Humana. The population will consist of children 6-23 months of age who were members of any of the participating Data Partners for all of or a portion of the period of interest, July 1, 2013 to June 30, 2015. Within this population, children will be included in the study if they received a dose of IIV or PCV13 during the study period and at a minimum, were enrolled in medical coverage from 180 days prior to vaccination through 20 days after vaccination. We have elected to use the enrollment criterion of 180 days prior to vaccination to optimize the ability to identify history of seizure and patient comorbidities, while balancing the possibility of a large loss of case numbers with a stricter pre-vaccination enrollment criterion.

B. STUDY DESIGN

We propose to use the SCRI design to achieve the study objectives. As described in the PRISM 2010-11 study protocol by Kawai and colleagues, this design is well suited to study well-defined clinical events that have acute and transient effects. Because the self-controlled risk interval design compares risk in a risk vs. control interval within vaccinated individuals, it implicitly controls for bias due to time invariant confounders, such as race and socioeconomic status. Additionally, by only including vaccinated individuals, it avoids exposure misclassification resulting from individuals receiving influenza vaccines in non-traditional settings, which may not be captured in the current study's data sources (i.e., claims data). The potential disadvantage of this study design is that it does not implicitly adjust for time-varying confounders such as age or calendar time (i.e., seasonality), though the bias can be minimized by selecting risk and control intervals relatively close in time. An additional limitation is that the period of possibly elevated risk must be specified fairly accurately—the validity of the SCRI design depends on there being minimal excess risk due to vaccination in the control interval. We will allow a sufficient period of time (i.e., 12 days) to elapse between the risk and control intervals to allow for a wash out period.

As Figure 1 illustrates, exposed person time will be in the defined risk interval of 0-1 days post-vaccination[i] and unexposed person time will consist of person time in a control interval beyond the risk interval (days 14-20). In order to adjust for confounding by co-administration with 13-valent pneumococcal conjugate vaccine (PCV13) and/or diphtheria tetanus and pertussis (DTaP) containing

[i] A literature review performed by the Risk Interval Working Group of the Clinical Immunization Safety Assessment Network, an external collaboration between the CDC and six medical research centers, informed the choice of the 0-1 day risk interval for this protocol and for that used by Kawai et al and Yih et al in the preceding PRISM studies. See reference number 10. Rowhani-Rahbar A, Klein NP, Dekker CL, et al. Biologically plausible and evidence-based risk intervals in immunization safety research. Vaccine 2012;31:271-7.

vaccines, we will collect information on seizures in the similarly defined risk interval of 0-1 days post-vaccination and control interval of 14-20 days post-vaccination for these other vaccines, *regardless of co-administration with IIV.* We have elected to use this control interval for two main reasons: (a) a longer control interval produces more stable estimates of the background rate of febrile seizures, compared to a one or two day comparison interval, (b) this interval is identical to prior Vaccine Safety Datalink and PRISM studies and enables this study to directly add to the existing safety information, and (c) this interval avoids overlap with the known increased risk of febrile seizures in the 7-10 days following measles containing vaccines which may have been given on the same day. [11,12] The unequal lengths of time for the risk and control intervals will be accounted for in analysis.

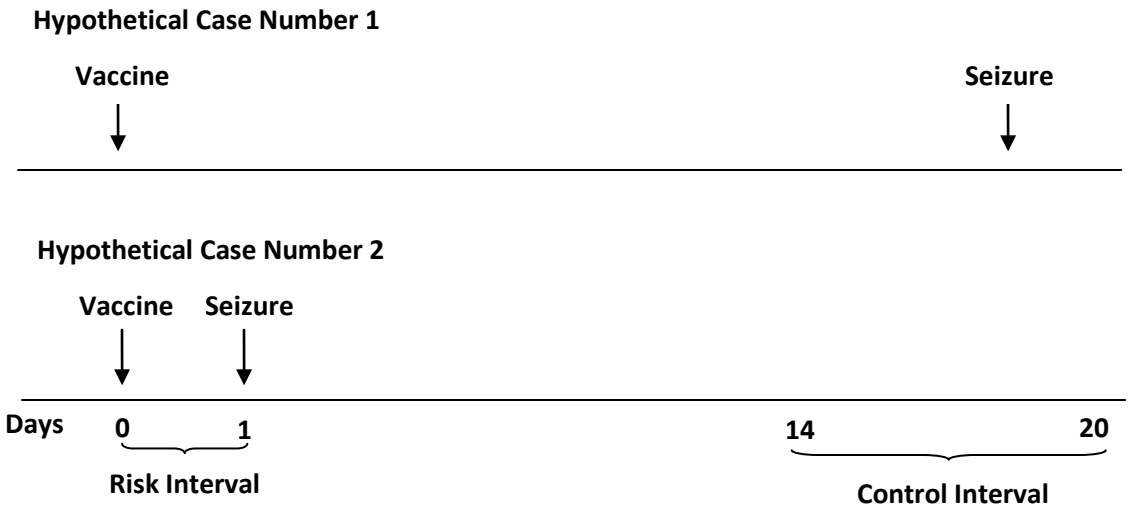

Figure 1: Self-controlled risk interval design to evaluate incidence rate ratios comparing rates in risk vs. control intervals. Two potential cases are shown below in relation to TIV administration. Only vaccinated cases are included in the study design.

C. EXPOSURE

Of the inactivated influenza vaccines available for use in children during the seasons under study, Fluzone Quadrivalent® (approved June 7, 2013) and Fluzone® were the only FDA-approved IIV for children 6 to 23 months of age, the population of interest.

Any dose of age-appropriate Fluzone® or a 'generic' code for influenza vaccination will be counted as an exposure; based on the 2010-11 PRISM study, we expect that the majority of the non-specific IIV doses are Fluzone®. IIV will be identified using claims data from the Data Partners. CPT (Current Procedural Terminology), Healthcare Common Procedure Coding System (HCPCS), National Drug Code (NDC), and International Classification of Diseases, 9th Edition (ICD9) procedure codes (Table 1) will be used to identify IIV in claims data. NDC codes are not listed due to the large number of codes (>190), but can be obtained directly from protocol authors via email (Noelle_Cocoros@HPHC.org). We will exclude those vaccinations that are not approved for the age (since we are using electronic data only and will not use chart information to confirm a vaccine was incorrectly coded). Immunization registry data will not be

included in this study; it was used in the previous PRISM studies but yielded very little data in the age group of interest while requiring substantial additional resources.

Table 1: Vaccine codes to identify potential administration of IIVs. NDC codes will also be used to identify potential administration of IIV products.

Description	Code	Code Type
Influenza virus vaccine, inactivated, subunit, adjuvanted, for intramuscular use	90653	CPT
Influenza virus vaccine, split virus, preservative free, for children 6-35 months of age, for intramuscular use	90655	CPT
Influenza virus vaccine, split virus, for children 6-35 months of age, for intramuscular use	90657	CPT
Influenza virus vaccine, quadrivalent, split virus, preservative free, when administered to children 6-35 months of age, for intramuscular use	90685	CPT
Influenza virus vaccine, quadrivalent, split virus, when administered to children 6-35 months of age, for intramuscular use	90687	CPT
Administration of influenza virus vaccine	G0008	HCPCS

D. CASE DEFINITION

Identifying potential febrile seizure cases (ICD9 data)

Potential cases of febrile seizure will be identified in the electronic data using two case definitions, both based on ICD9 diagnosis codes:

- Narrow case definition (primary): 780.31 (febrile seizures) or 780.32 (complex febrile seizures) in the inpatient or emergency department (ED) setting. In the 2010-11 PRISM study, this case definition had a positive predictive value of 91% and accounted for >90% of the chart-confirmed febrile seizure cases. Only codes that are the first in a 42-day period (occurring in *any* setting) will be included to avoid including follow-up visits for seizure episodes.
- Broad case definition (secondary): 780.3 (convulsions), 780.31 (febrile seizures), 780.32 (complex febrile seizures), or 780.39 (other) in the inpatient or emergency department (ED) setting. This was the case definition used in the 2013-14 PRISM study which generated a statistical signal; it had a PPV of ~70% in 2010-11 study. Only codes that are the first in a 42-day period (occurring in *any* setting) will be included to avoid including follow-up visits for seizure episodes.

E. POTENTIAL CONFOUNDERS AND EFFECT MODIFIERS

Because the study design is self-controlled, the analysis will be inherently adjusted for measured and unmeasured confounders that do not vary over relatively short periods of time, such as gender, race/ethnicity, and chronic disorders. However, because concomitant vaccinations may act as confounders and/or effect modifiers, we will collect information on these factors and adjust for/examine their effects in multivariate regression.

In the primary analysis, we will adjust for age in weeks and calendar time in weeks, using background rates from vaccinated and unvaccinated children within the four participating Data Partners and methods comparable to those in the PRISM 2010-11 study. A secondary analysis will be conducted without adjustments for age or calendar time.

Information on seizures following vaccines commonly administered concomitantly with IIV – PCV13 and DtaP-containing vaccines specifically – will be collected using the same outcome definition described and will be examined as potential confounders or effect modifiers. The analysis on concomitant vaccines will focus on PCV13. Adjustment for concomitant vaccination with DTaP-containing vaccines will be included in a secondary model since inclusion of the covariate may negatively impact power due to anticipated low case numbers.

PCV13 will be identified in claims data using CPT, HCPCS, and NDC (Table 2).

Table 2: Codes used to identify potential administration of Prevnar 13. NDC codes corresponding to the vaccines in this table will also be used to identify potential administration of Prevnar 13.

Description	Code	Code Type
Pneumococcal conjugate vaccine, 13 valent, for intramuscular use	90670	CPT
Pneumococcal conjugate vaccine, polyvalent, for children under five years, for intramuscular use	90669	CPT
Administration of pneumococcal vaccine	G0009	HCPCS
Patient documented to have received pneumococcal vaccination	G8115	HCPCS
Pneumococcal vaccine administered or previously received	G8864	HCPCS
Pneumococcal screening performed and documentation of vaccination received prior to discharge	G9279	HCPCS

DTaP will be defined as DTaP alone or administered in any combination vaccine and will be identified in claims data using CPT codes (Table 3).

Table 3: Vaccine codes to identify potential administration of DTaP containing vaccines. NDC codes corresponding to the vaccines in this table will also be used to identify potential administration of DTaP containing vaccines.

Description	Code	Code Type
Diphtheria, tetanus toxoids, and acellular pertussis vaccine, haemophilus influenza Type B, and poliovirus vaccine, inactivated (DTaP - Hib - IPV), for intramuscular use	90698	CPT
Diphtheria, tetanus toxoids, and acellular pertussis vaccine (DTaP), for use in individuals younger than 7 years, for intramuscular use	90700	CPT
Diphtheria, tetanus toxoids, and acellular pertussis vaccine and Haemophilus influenza B vaccine (DTaP-Hib), for intramuscular use	90721	CPT
Diphtheria, tetanus toxoids, acellular pertussis vaccine, Hepatitis B, and poliovirus vaccine, inactivated (DTaP-HepB-IPV), for intramuscular use	90723	CPT
Diphtheria, tetanus toxoids, acellular pertussis vaccine, haemophilus influenza Type B, and poliovirus vaccine, inactivated (DTaP-Hib-IPV), for intramuscular use	V06.8	ICD9 Diagnosis

F. ANALYSIS PLAN

We will estimate incidence rate ratios using conditional Poisson regression, where the outcome is the occurrence of febrile seizure and the main exposure of interest is interval type with respect to receipt of a IIV (i.e., risk or control interval). We will examine this association after adjustment for concomitant vaccination with PCV13 as well as DTaP-containing vaccines. To adjust for confounding by co-administration of PCV13 and DtaP-containing vaccines, we will include main effect terms in the model. Due to concerns with small sample size, adjustment for concomitant vaccination with DtaP-containing vaccines will be considered secondary as the additional adjustment will increase the degrees of freedom and therefore impact power.

The primary analysis will be adjusted for confounding by age and seasonality, while an alternative analysis will be unadjusted for age and seasonality. Specifically, in the primary analysis, we will adjust for age and seasonality using ICD9-coded data on the background rate of seizures in the unvaccinated person-time of the Mini-Sentinel cohort. Preparatory work will include assessing which influenza season(s) to use for background rates. The rates will be incorporated into the conditional Poisson model described above via the offset term to incorporate a child's different baseline risk of seizures by age and calendar time across the child's follow-up.

To obtain offset terms that incorporate these differences in underlying rates of seizures by age in weeks and calendar time, using the background rates of febrile seizures (narrow case definition) in the cohort, we will conduct Poisson regression modeling of the background incidence rate with age in months and calendar week in the influenza seasons as covariates. The regression equation might look like the following:

$$\lambda \text{ (age, calendar weeks)} = \lambda_0 + \beta_1 * \text{age} + \beta_2 * \text{age}^2 + \beta_3 * \text{calendar week} + \beta_4 * \text{ calendar week}^2$$

Additional polynomials or splines could be considered during the art of model building. Categorical variables may be considered instead of continuous variables. Interaction terms may be considered if, for instance, the risk of seizures by calendar week varies by age. The model for the background rate of seizures will be fit and finalized prior to its application to age and seasonality adjustments in the primary analysis.

We will examine whether co-administration of PCV13 modifies the rate ratios by fitting an additional model for the potential effect modifier. For example, to examine the role of effect modification of, first, IIV and febrile seizures by concomitant PCV13, and second, PCV13 and febrile seizures by concomitant IIV, we will build a model with main effect terms for IIV and PCV13, and a two-way interaction term of IIV with PCV13. If the interaction term is not statistically significant, we will interpret the results as indicating there is no increased risk of febrile seizures beyond the risk from the independent vaccines. See Table 4 for a shell of the results we will generate for the primary analysis.

Table 4. SHELL TABLE – Risk of febrile seizure following IIV and/or PCV13 vaccines

Exposure	Cases in risk interval (0-1 day)	Cases in control interval (14-20 days)	Unadjusted RR (95% CI)	IRR, adjusted for age, calendar time (95%CI)	IRR, adjusted for age, calendar time, DtaP, and PCV13 or IIV (95% CI)
IIV					
PCV13					

We will also assess the possibility of effect modification of rate ratios by season.

For the fourth activity – exploring the role of background rates of febrile seizures (narrow and broad definitions) in generating the 2013-14 statistical signal – we will collect febrile seizure data for children aged 6-23 months for the seasons under study as well as three prior influenza seasons (2010-11, 2011-12, and 2012-13). Rates will be calculated and compared for exposed time (risk windows for IIV and PCV13 alone and concomitantly) and unexposed time in the five seasons. They will also be compared with background rates used for current vs. historical sequential analysis during 2013-14, when background rates of seizures in the 0-1 days after IIV were purposely restricted to seasons prior to July 2010 in order to avoid seasons where an increased risk of post-IIV seizures had been observed.

IV. POWER CALCULATIONS

We performed power calculations for a range of incidence rate ratios for febrile seizures and IIV, adjusted for PCV13, for both seasons combined, using the narrow case definition. For the power calculations we estimated the number of febrile seizure cases among children ages 6-23 months for the participating Data Partners in July 2013 through June 2015 based on results of the 2010-11 PRISM study and the 2013-14 PRISM sequential surveillance study. (The assumed incidence rate ratio for PCV13 for the power calculations in Table 5 was 3.0, though the power results are similar for different values of the incidence rate ratio for PCV13.)

Table 5: Power calculations for febrile seizures and IIV, adjusted for PCV13

Estimated number of cases	Power by incidence rate ratio for IIV			
	1.5	2.0	2.5	3.0
330	68	99	100	100

V. DATA SET CREATION

We will use the Mini-Sentinel Common Data Model (MSCDM) to access data from the Mini-Sentinel Distributed Database (MSDD), which allows Data Partners to maintain control over patient-level data. Data Partners extract and output data info eight files of standard format. The files relevant for the present study are: Enrollment, Demographic, Encounter, Procedure, Diagnosis, and Dispensing.

The Workgroup will provide Data Partners with programs to be run on the patient-level files. The programs will produce aggregate data on vaccinations and seizures and fever events organized in strata defined by variables such as week of vaccination, type of vaccine, dose number, age, Data Partner, and sex, with counts of patients, vaccine doses, and seizure and fever events in each stratum. Data Partners will return the aggregate data for analysis at the Mini-Sentinel Operations Center, using Mini-Sentinel's secure file transport methods.

VI. INSTITUTIONAL REVIEW BOARD APPROVAL AND OTHER AUTHORIZATIONS

Per the privacy section on the Mini-Sentinel policies and procedures manual.[13]

4.1 Mini-Sentinel Activities Are Public Health Practice, Not Research

The HHS Office of Human Research Protections (OHRP) determined that the regulations administered by OHRP (45 CFR Part 46, "Common Rule") do not apply to the activities that are included in the FDA's Sentinel Initiative. FDA stated that this assessment also applies to Mini-Sentinel, as it is part of the Sentinel Initiative.

Additionally, FDA determined that Mini-Sentinel activities are public health activities in support of FDA's public health mission. It is therefore not necessary for the Collaborating Institutions to obtain approval from their respective Institutional Review Boards (IRBs) or Privacy Boards, or to obtain waivers of authorization under HIPAA, to participate in Mini-Sentinel activities (45 CFR §164.512(b)).

The HIPAA Privacy Rule permits covered entities the use and disclosure of protected health information (PHI) to public health authorities without patient authorization. Public health authorities include the FDA. The Operations Center and Collaborating Institutions are also public health authorities for purposes of the Mini-Sentinel pilot, because they are acting under contract with and under the authority of the FDA.

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