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DEPARTMENT OF HEALTH AND HUMAN SERVICES
UNITED STATES PUBLIC HEATH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVAULATION AND RESEARCH
OFFICE OF VACCINES RESEARCH AND REVIEW
DIVISION OF VACCINES AND RELATED PRODUCTS APPLICATIONS

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Date: May 16, 2008 Time: ~5.00pm

To: Hatika Kohli

FAX Number: 416-667-2912 Phone Number: 416-667-2060

MESSAGE: Hatika,
as discussed on the phone
here are comments on the
PHC concept protocols
Any Qs. please call.

From: Theresa Finn

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Comments on proposed Pentacel Post-marketing Studies:

We have reviewed your post-marketing concept protocols and have the following comments for your consideration:

Surveillance for rates of Hib disease among persons aged 0-4 years of age receiving Pentacel or other Hib vaccines (M5A15). Concept protocol dated August 30, 2007:

1. We do not consider the planned Hib disease surveillance project as constituting or contributing to substantial evidence of the effectiveness of Pentacel, and thus, will not include results from this project in the Pentacel package insert to support any claims of effectiveness of Pentacel. Please acknowledge.

2. Please include, in the protocol, detailed methods for the sample surveys of brand specific vaccine use.

3. Sample size estimates are based on a projected 50% market share for Pentacel at the beginning of the project. Please provide a plan to extend the duration of the project should the Pentacel market share among Hib vaccines be less than projected.

Surveillance for rates of pertussis disease among persons 0-4 years receiving Pentacel or other pertussis vaccines (M5A16). Concept Protocol dated March 2, 2007:

1. We do not consider the planned pertussis surveillance studies as constituting or contributing to substantial evidence of the effectiveness of Pentacel, and thus, will not include results from these studies in the Pentacel package insert to support any claims of Pentacel effectiveness. Please acknowledge.

2. Because of limitations in study design and methods (e.g., non-random vaccine allocation; non-uniform case ascertainment) we do not concur with your proposal for non-inferiority hypothesis testing in the cohort surveillance study and the endemic case-control study. We do not view these studies as adequate to support comparative claims of effectiveness. Please acknowledge and amend the protocol accordingly.

3. For the cohort surveillance study, you plan to evaluate rates of pertussis among children <5 years of age who received 4 doses of Pentacel or 4 doses of another (single brand) pertussis vaccine. Because morbidity and mortality from pertussis is highest among children <12 months of age who are not old enough to have received a fourth dose of pertussis vaccine, we recommend that the primary analysis be conducted in children <5 years of age who have received 3 doses of Pentacel or other pertussis containing vaccine.

4. For the cohort study, you plan to determine vaccine specific coverage rates using the Wisconsin vaccine registry and "other suitable sources". Please specify the population covered by the Wisconsin Immunization Registry and describe the other sources of vaccination data that you will use.

6. Please provide details on how vaccination histories will be determined in the planned case-control studies.

7. The denominator for rates of disease will be calculated taking into account the market share of Pentacel among pertussis vaccines. Please explain how market share will be determined.

8. For each study and each analysis please provide the case definitions that will be used.

9. Sample size estimates are based on a projected 25-75% market share. Please include a plan to extend the studies should the Pentacel market share be less than 25%.

Post licensure safety surveillance study of routine use of Pentacel: Concept protocol dated March 5, 2007

1 We do not view non-randomized studies such as M5A11 as adequate to support comparative statements about products in the package insert. We do not concur with your plan to use rate ratios to compare adverse event rates between products in this study. It may be acceptable to include a description of the study methodology and observed rates of adverse events among children who received Pentacel in the Pentacel package insert. Please acknowledge.

2. The study endpoints are hospitalization, Emergency Department visits and several outcomes of interest. Deaths will also be identified. For each event please specify the post-vaccination period that will be used in the analyses.

3. Please revise your list of outcomes of interest to be relevant to the age group (children <5 years of age) who will receive Pentacel or control vaccines. Please specify the ICD-9 codes which will be used to identify the outcomes of interest.

4. In the protocol please provide a table of the expected incidence rate for each outcome of interest among children < 5 years. Given a sample size of 10,000 children administered Pentacel please include the probability of detecting at least one case of each outcome of interest.

5. Adverse events of interest will be detected using various computerized databases. Please describe the methods, if any, for verifying that identified events occurred post-vaccination (as opposed to exacerbation or recurrence of a pre-existing condition); for verifying diagnoses (as opposed to a suspected event that was

subsequently ruled out); and for further classifying certain events (e.g., seizures associated with fever vs. seizures not associated with fever).

6. For identification, description, investigation and interpretation of safety signals please refer to FDA's Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (http://www.fda.gov/Cder/guidance/6359OCC.htm)