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Dear Dr. Wharton and Members of the Advisory Committee on Immunization Practices (ACIP),

We write in follow-up to the letter that we submitted to the Federal Register in advance of the April 2025 meeting of the Advisory Committee on Immunization Practices (ACIP) regarding the dosing regimen for GARDASIL®9, which protects against certain HPV-related cancers and diseases.

As you know, Merck has publicly announced its intent to launch two large clinical trials to evaluate the potential for inclusion of a single dose regimen in the label for its nine-valent HPV vaccine. As is routinely done before starting major clinical trials, Merck sought feedback from FDA to ensure that the designs of its trials, if the results were positive, would be an acceptable basis for such a label change. This is to ensure efficient use of resources available for clinical development.

On April 15, 2025, Merck received written feedback from the Food and Drug Administration (FDA). excerpts of which are below. **The FDA comments make clear that even the studies proposed by Merck, which involve many more subjects and more extensive and more rigorous efficacy and durability data than the studies on single dose regimens currently available to ACIP, would not meet the criteria for efficacy required by FDA to balance the potential for risk of a drop in efficacy or durability.**

FDA Feedback: Substantial evidence is required to mitigate the risk that a single-dose regimen is less effective or less durable than the currently licensed regimen

> *"As mentioned in our previous communications dated 30 April 2024 and 07 June 2024, we continue to emphasize that since there is a risk that a single- dose regimen may be less effective, or less durable, than the currently licensed 2- or 3-dose regimens, licensure of a single-dose regimen will require substantial evidence of comparable effectiveness from an adequate and well-controlled study that directly compares the efficacy of the proposed single-dose regimen with the 3-dose regimen for all age groups for which use of the single-dose regimen is proposed."*

FDA Feedback: Specific evidence needed, not inferred

> *"… additional evidence needed to support a 1-dose regimen includes but is not limited to: (1) efficacy in both females and males, (2) assessment of endpoints other than cervical persistent infection, and (3) durability of protection."*

FDA Feedback: Large sample sizes are necessary to prove non-inferiority

> *"The noninferiority margins that you propose are too large and do not assure comparability of the single-dose regimen with the effectiveness of the 3-dose regimen of Gardasil 9… A significantly larger sample size than you propose may be required for study V503-100 to evaluate effectiveness of a single-dose regimen compared with 3-dose regimen of Gardasil 9 in females."*

FDA Feedback: Durability of protection must be demonstrated

> "*A study of nine years would generally be considered acceptable to assess durability of protection, once effectiveness of a 1-dose regimen of Gardasil 9 in comparison with a 3-dose regimen is established through adequate and well-controlled clinical trial.*"

Data currently available to ACIP falls far short of meeting these FDA evidentiary standards:

- Currently available studies use cervical persistent infection or immunogenicity endpoints rather than disease endpoints;
- There is an almost total lack of data in males;
- The number of subjects involved in the currently available studies falls far short of the 27,500 proposed by Merck for its studies, which were deemed inadequate by FDA to ensure tight non-inferiority margins;
- The arguments supporting long-term durability of protection after single dose are based primarily on antibody kinetics, observational studies, and relatively short-term (~5 year) follow up of randomized controlled trials, rather than a nine-year study as noted above.

We request that you share this feedback with members of the ACIP as well as members of the CDC HPV Work Group evaluating this topic. If desired, we would be happy to discuss this information further with you, the Work Group or ACIP.

Sincerely,

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