Brief Summary of the Microbiology Devices Panel – March 8, 2019

Introduction:

The Microbiology Devices Panel of the Medical Devices Advisory Committee to the Food and Drug Administration met on March 8, 2019. The purpose of this meeting is to discuss new approaches to the development and evaluation of HR HPV devices that might allow for advances and innovation in this area and reduced burden.

Over the course of the last 16 years, data from basic scientific research as well as large scale epidemiological studies firmly established the value of testing for HR HPV genotypes in ruling out the likelihood of harboring a precursor to cervical cancer (i.e., precancer). This set the foundation for widening of cervical cancer screening intervals and, in some cases, recommendations for patient observation rather than immediate colposcopy. We believe the accumulated knowledge over the past 16 years, against the background of changing prevalence, could support innovation in the methods used in the development and evaluation of HR HPV devices.

Panel Deliberations/FDA Questions:

1. **Would the panel recommend one or a combination of the following three proposals to increase the number of women positive for CIN3+ and/or HR HPV in clinical studies:**

    A. **Supplementing from referral clinics**
    B. **Utilizing archived specimens**
    C. **Capping the vaccinated population**

The panel recommended supplementing enrollment from referral clinics as generally acceptable. For referral colposcopy clinics, considering the type of referral population and reason for patient referral would need to be considered. The panel cautioned that women seen at colposcopy clinics tend to have higher viral loads than women in general screening populations, and accordingly colposcopy clinics should not be the sole source CIN3+ specimens. The panel recommended having representation of women who are both well screened and under screened.

Panel members agreed that archived specimens are a valuable resource for HR HPV studies; however, concerns to be addressed included access to specimens, how the specimens were stored, nucleic acid stability (especially RNA), and specimen storage media. Archived specimens should be shown to be applicable to specimens in the intended use population for these devices. The historical test results should not be used to characterize archived specimens, and comparator testing should be performed

on each archived specimen with the device being studied. The need to insure quality of archived specimens may limit the use of this approach.

The panel believed that capping enrollment of vaccinated subjects in studies may be problematic due to difficulty in accurately identifying which patients were vaccinated and differences due to the particular vaccine administered and the number of doses received. The panel also expressed concern that devices may perform differently in vaccinated populations. The panel suggested other enrichment strategies, include reaching out to underserved women who may not have been previously screened as often as they should, as well as older women who may not have been eligible for the vaccine.

2. **Regarding the NILM/HR HPV double negative and ASC-US/HR HPV double negative populations in clinical studies supporting HPV device approval:**

   Do the benefits of colposcopy referral for the assessment of verification bias outweigh the risks associated with the procedure and potential overtreatment?

   Please discuss for each of the two populations separately.

Panelists agreed that the benefits of colposcopy referral for the assessment of verification bias did not outweigh the risks associated with the procedure and potential overtreatment for either population. While it was suggested that cytology assessment be included in clinical studies, the panel concurred that an ASC-US cytology result should not lead to colposcopy referral for women negative for HR HPV by multiple molecular tests due to the known high negative predictive value for FDA-approved tests.

3. **Regarding the indications for use (IFU), do the benefits outweigh the risks for:**

   A. **Consolidating the indications to encompass one general screening population**
   B. **Removing references to specific triage tests and clinical actions?**

   Please discuss any potential risk mitigation measures if a new IFU statement were to be used.

The majority of panelists recommended a more generic IFU statement for HR HPV devices that would encompass one general screening population. The panelists agreed that an IFU not tied to medical practice guidelines is preferable due to evolution of professional guidelines. Panelists also favored removing references to specific triage tests in labeling in order to keep up with the introduction of new triage technologies.

4. **Please discuss whether the following types of data evaluations are acceptable for the assessment of safety and effectiveness for new HR HPV devices:**

   A. **Adoption of a molecular composite comparator method**

   B. **Evaluation of relative performance against a clinical endpoint comparator**

   Please discuss the benefits and risks to these approaches, as well as minimum acceptable performance criteria.

4a) The panel expressed several concerns with utilizing a strictly molecular composite comparator approach, including necessity to ensure that a study sample set reflect the full spectrum of disease, and that a strictly molecular comparator assumes that current tests are "perfect" and may de-incentivize manufacturers from developing improved assays.

The panel agreed that the negative predictive value for current tests is extremely high, and accordingly that a molecular comparator was acceptable for determining a specimen to be a true negative in clinical studies for a new assay. For determining a specimen to be a true positive in clinical trials, histology would need to be included in the assessment. While the panel agreed that CIN3+ was the ideal histological endpoint for precancer, CIN2 should still be included in the evaluation of the test to determine if newer tests have a better ability to distinguish between transient vs. progressive CIN2 lesions.

The panel also emphasized the importance of characterizing specimens from patients with discordant results between multiple molecular comparator devices, either through histology or enhanced follow-up.

It was also mentioned that while a molecular composite comparator may be problematic for establishing performance characteristics of new devices, this may be an acceptable approach for evaluating modifications of approved devices.

Some panelists were concerned about the age groups that were included in the clinical study, particularly the 21-24 age group since these women are not to be tested for HR HPV according to national guidelines.

4b) was found to be acceptable.

5. **If the panel recommends assessing HR HPV device performance against a clinical endpoint comparator:**

    A. **Is utilizing a mixed histological/molecular comparator acceptable?**
    B. **If so, how should the combination of HPV result and histological diagnosis factor in when assigning "comparator positive" and "comparator negative" results?**

The panel generally agreed that a histological diagnosis should be adjudicated, and biomarkers that support a transforming HPV infection should be utilized. The panel suggested that the molecular component in the comparator could be tissue typing utilizing laser capture microdissection. This could be conducted on all lesions or may be limited to those with discrepant HPV results.

Open Public Speakers:

Dr. Jeffrey Andrews – BD Diagnostic Systems - Sparks, Maryland
Dr. Clementina Cocuzza, M.D., Ph.D. – Copan Flock Technologies, Brescia, Italy
Keivan Eitefagh – Cellsolutions- Greensboro, NC
Dr. Varuna Srinivasan, MBBS, MPH – National Center for Health Research-Washington, DC
Jeff Zinza – Hologic, Inc. – San Diego, CA

Guest Speakers:

Dr. Mark Schiffman, M.D., M.P.H. – National Cancer Institute, NIH, DHHS

Contact: Aden Sisay Asefa, MPH, Designated Federal Officer
(301) 796- 0400, adenasefa@fda.hhs.gov
Transcripts may be purchased from: (written requests only)
Free State Reporting, Inc. 1378
Cape St. Claire Road Annapolis, MD 21409
410-974-0947 or 800-231-8973 Ext. 103
410-974-0297 fax
Or
Food and Drug Administration
Freedom of Information Staff (FOI)
5600 Fishers Lane, HFI-35
Rockville, MD 20851
(301) 827-6500 (voice), (301) 443-1726