Thank you for your consideration.
Best regards,
Eric Suba

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Dear Dr. Suba,

Thank you for providing this information to the Food and Drug Administration (FDA). We appreciate the time and effort it took to communicate your concerns to FDA. Information obtained from individuals such as you is indispensable to us in protecting the public health. We take such reports seriously. The type and extent of any follow-up is dependent upon the nature of the problem, the possible impact on the public health, and the availability of our resources.

After careful review of this case, we found that the information we gathered together is not sufficient for us to pursue further compliance actions against QIAGEN since the claim that "HC2 significantly reduces deaths from cervical cancer compared to other method including Pap" is not found in their labeling, website or advertisements. FDA cannot regulate the data and claims published in a scientific journal.

If you have any questions regarding this letter, please contact me (Rose Xu) at 301-796-6187.

Rose Xu

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From: Eric.Suba@kp.org [mailto:Eric.Suba@kp.org]
Sent: Monday, March 25, 2013 05:12 PM
To: Saviola, James
Cc: Hawthorn, Anne T.; Foltz, Bridget A; Ross, Bruce; Carey, Carole C; Less, Joanne; Trautman, Kimberly A.; Richter, Kimber C.; OC-OIP-India; raustin@magee.edu <raustin@magee.edu>
Subject: Qiagen's misleading claims regarding India death-rate measurements

Hi Dr. Saviola

This is follow up to our previous conference call.

I would be grateful if the FDA would consider whether Qiagen's claims regarding India death-rate measurements (described below) constitute misleading advertising.

Please consider that, at 5pm on April 1 2009, the New England Journal of Medicine released its prepublication embargo on results from a large randomized trial of cervical screening in India.(attached as Sankar et al. NEJM; summarized below in Table 1) Simultaneously, Qiagen Corporation (which manufactures and markets the Hybrid Capture 2® HPV test used in the NEJM India study) issued a press release.(attached as Qiagen Press Release) Peer Schatz, Qiagen's CEO, was quoted in the press release as saying "This landmark study further validates the value of Qiagen's HPV test as the gold standard for cervical cancer screening."

Here is the crux of the matter: Because it is not possible for effects to result from causes that do not exist, claims of superior, "gold standard" Hybrid Capture 2® test performance based on death-rate measurements from the NEJM India study are false. The argument in support of Qiagen's claims being misleading is outlined in more detail below.

In the NEJM India study, process measurements (Table 1, Columns D and F) indicate Papanicolaou cytology was superior to Hybrid Capture 2®, while death-rate measurements (Table 1, Columns G and H) indicate Hybrid Capture 2® was superior to Pap cytology.

Because it is not possible for effects to result from causes that do not exist, it is not possible for the improved death-rates documented in Columns G and H to result from superior screening test performance that does not exist in Columns D and F. In fact, Pap cytology decisively outperformed Hybrid Capture 2® in India. Compared to Hybrid Capture 2®, Pap cytology demonstrated both superior sensitivity and superior specificity (detection rates for CIN2+ were used as surrogate measurements for sensitivity in this study, while screening test positivity rates are used as surrogate measurements for specificity).

The death-rate measurements in the NEJM study, unlike the process measurements, were flawed by statistical bias skewed in favor of Hybrid Capture 2®. I have cc'd Dr. Marshall Austin, who published a detailed analysis of the curious statistical bias at the heart of Qiagen's claims,(attached as Austin and Zhao) in case you would like to communicate directly with him.

I have been invited to publish an article about the India death-rate measurements the Indian Journal of
Medical Ethics and I will include your response to this request in that publication.

I will be happy to respond to any questions or comments you may have.

Sincerely yours,
Eric J. Suba M.D.

Qiagen’s claim that Hybrid Capture 2® "significantly reduces deaths from cervical cancer, compared to other methods including Pap" is scientifically specious, misleading advertising.

Cervical screening experiments in India, funded by the U.S. NCI and Bill & Melinda Gates Foundation, include cervical cancer death-rate measurements among large numbers of Indian women of lowest socioeconomic status who have not been offered any screening whatsoever. The U.S. Office for Human Research Protections (OHRP) has determined that NCI-funded death-rate measurements are unethical because participants were not given facts required to provide informed consent. OHRP does not have authority to investigate the Gates Foundation-funded death-rate measurements.

1) Statistical bias has caused false interpretations of these death-rate measurements.
   a) Papanicolaou cytology demonstrated a higher detection rate (a surrogate measurement of screening-test sensitivity) than Hybrid Capture 2®. (Table 1, Column F)
   b) Papanicolaou cytology demonstrated a lower screening test-positive rate (a surrogate measurement of screening-test specificity) than Hybrid Capture 2®. (Table 1, Column D)

Nevertheless:

   c) Cervical cancer death rates among women screened with Hybrid Capture 2® were reported to be half those of women screened with Papanicolaou cytology. (Table 1, Column H)

However:

   d) It is not possible for effects to result from causes that do not exist.
      i) It is therefore not possible for improvements in cervical cancer death rates (Table 1, Column H) to result from improvements in screening test performance that do not exist (Table 1, Columns D and F).
         (1) Extraordinary improvements in cervical cancer death rates, apparently caused by screening women with Hybrid Capture 2®, (Table 1, Column H) were in fact caused by statistical bias. (Austin and Zhao, attachment 3)
   e) Cervical cancer death rates among women screened with Papanicolaou cytology were reported to demonstrate no statistically significant differences from cervical cancer death rates among unscreened women. (Table 1, Column G)
      i) This is a scientifically absurd result that contradicts over 50 years of global clinical experience.
         (1) Cervical screening is one of the few preventive interventions to have received an "A" recommendation from the United States Preventive Services Task Force in the absence of randomized trials confirming effectiveness. According to the Task Force, Papanicolaou screening reduces cervical cancer rates by 60%-90% within three years of its introduction to previously-unscreened communities; these reductions of suffering and death are "consistent and equally dramatic across populations." Smoking cessation also received an "A" recommendation from the Task Force in the absence of randomized trials confirming effectiveness.
         (2) Claims that Papanicolaou screening does not cause cervical cancer prevention (Table 1, Columns G and H) are as absurd as claims that no-smoking does not cause lung cancer prevention.
         (3) The apparent lack of any improvement in cervical cancer death rates among women screened
with Papanicolaou cytology, compared to women who were not screened at all, was in fact also caused statistical bias. (Austin and Zhao, attachment 3)

2) A false appearance of scientific meaning from these death-rate measurements has been used to publicize misleading claims about a proprietary cervical screening test that is unaffordable to the Indian population among whom it was studied.

a) Apparent improvements in cervical cancer death rates among women screened with Hybrid Capture 2® (Table 1, Columns G and H) have been irrationally attributed to non-existent advantages in Hybrid Capture 2® test performance (Table 1, Columns D and F) and have served as the basis for a well-organized global marketing campaign promoting sales of Hybrid Capture 2®.

### Table 1. Summary of results from Osmanabad, India cervical screening study published in April 2, 2009 issue of New England Journal of Medicine (Sankar et al. NEJM, attachment 1)

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening test used</td>
<td>#Women eligible for screening</td>
<td>#Women screened (% of eligible)</td>
<td>#Positive screening tests (% of women screened)</td>
<td>#Colposcopies among screen-positive women (% of screen-positive women)</td>
<td>#Screen-positive women with CIN2+ on biopsy (% of women screened)</td>
<td>Cervical cancer deaths per 100,000 person-years</td>
<td>Reduction in cervical cancer mortality (compared to no-screening)</td>
</tr>
<tr>
<td>Hybrid Capture 2®</td>
<td>34,126</td>
<td>27,192 (79.7%)</td>
<td>2812 (10.3%)</td>
<td>2505 (89.1%)</td>
<td>318 (1.17%)</td>
<td>12.7</td>
<td>50%</td>
</tr>
<tr>
<td>Papanicolaou cytology</td>
<td>32,058</td>
<td>25,549 (79.7%)</td>
<td>1787 (7.0%)</td>
<td>1570 (87.9%)</td>
<td>345 (1.35%)</td>
<td>21.5</td>
<td>No significant reduction</td>
</tr>
<tr>
<td>None (control group)</td>
<td>31,488</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>25.8</td>
<td>--</td>
</tr>
</tbody>
</table>

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Hi Dr. Suba,

As a follow up to our call earlier today, Bruce Ross is the FDA Office of International Programs person in India. Bruce.Ross@fda.hhs.gov Bruce could hopefully coordinate as appropriate with the Indian government and within OIP regarding oversight of clinical studies by Ethics Committee in India.

I imagine that similar to an Institutional Review Board here in the U.S., an Ethics Committee in India would have reviewed the ACCP and Gates Foundation studies on cervical cancer screening.

Here are a couple of hits from a quick search for “Ethics Committees in India” that may be of interest.

Registration of Ethics Committee to approve clinical trials made mandatory now, February 24, 2013 http://www.thehindu.com/news/cities/Delhi/registration-of-ethics-committee-to-approve-clinical-trials-made-mandatory-now/article4449026.ece


I will ask my colleagues in the Office of Good Clinical Practice if they might have a contact person for you at PRIMR, the Public Responsibility in Medicine and Research, for you to contact regarding questions about oversight of studies funded by non-profit foundations.

Thanks for taking the time to talk with us.

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