From: Powell, Bradford C
To: Powell, Cynthia M.
Cc: Powell, Bradford C; Berg, Jonathan Sanford; Milko, Laura V.
Subject: Re: G150258/S003
Date: Wednesday, October 4, 2017 10:36:43 PM

I was in clinic all day today and was not able to look into what info Agilent may provide in terms of "validation".

Jonathan is having Alicia look into what samples we may have from NCGENES that might have been both run with v5 and v6 kits that we might be able to do a comparison on. This might take some time, though (and if I need to do it, I'm not sure that I could get to starting it until Friday afternoon after my AM clinic).

I think our easiest proposal would be to report the concordance of the calls with the identity SNPs (like we did for the original "device") for samples called with the v6 platform. We could probably use either NCGENES or NCNEXUS samples for that.

When they ask "Have you already implement this change?" do they mean have we started to analyze some samples with the new kits, or completed processing and reported results? I would think that since the "device" extends through secondary analysis (and potentially through reporting (I'm not sure where the "device" ends— I would say that the "device" would at least include the Sanger confirmation step), that intermediate steps may be studied/analyzed/validated without this being considered implemented yet. This might provide us with additional time to continue to work with them on how they would like us to validate this.

bp

> On Oct 4, 2017, at 4:20 PM, Powell, Cynthia M. <powellcm@med.unc.edu> wrote:
>
> Hi Bradford,
>
> Were you able to find out if Agilent did any validation on the new version and would share their data? Or if there is data we could give her from NC GENES? Or if we could rerun the 11 earlier samples?
>
> Thanks,
> Cindy
>
> ---
>
> **From:** Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
> **Sent:** Wednesday, October 04, 2017 3:27 PM
> **To:** Powell, Cynthia M. <powellcm@med.unc.edu>
> **Cc:** Berg, Jonathan Sanford <jonathan_berg@med.unc.edu>
> **Subject:** RE: G150258/S003

Hi Cindy,
Good afternoon. Do you have an update on our question?
Thanks,
Paula

From: Caposino, Paula
Sent: Tuesday, October 03, 2017 12:34 PM
To: 'Powell, Cynthia M.'
Cc: Berg, Jonathan Sanford
Subject: RE: G150258/S003

Hi Cindy,
Thanks for the quick response. I am not sure what you have available to validate the modified investigational device. If you do not have the 11 samples (or a representative subset) that you tested in April, we are happy to consider alternative approaches.
Thanks again,
Paula

From: Powell, Cynthia M. [mailto:powellcm@med.unc.edu]
Sent: Tuesday, October 03, 2017 12:23 PM
To: Caposino, Paula
Cc: Berg, Jonathan Sanford
Subject: RE: G150258/S003

Hello Paula,

Let me review this with Jonathan and our NHGRI project scientist and get back to you about this unanticipated situation. I do not know if we have samples left from the original 11 babies but will check on this. What would the alternative FDA requirement be if retesting the original samples is not possible? We have begun the last year of our research funding and this delay could severely impact being able to complete the study.

Cindy

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Tuesday, October 03, 2017 11:03 AM
To: Powell, Cynthia M. <powellcm@med.unc.edu>
Subject: RE: G150258/S003
Importance: High

Hi Cindy,
I have met with the review team and we have the following question/request?

Have you already implemented this change?

This type of change is actually outside the scope of a 5 day notice since it is a significant change to the investigational device and should be reviewed as an IDE supplement. In the future, you should submit these types of changes as IDE supplements.

Regarding the lack of validation, in order to approve this change, we are going to need some validation to understand if this device is reasonably accurate and similar to the different versions that have been previously approved. We also need to makes sure that there are no unanticipated changes because of the modifications. Dr. Berg indicated that it would be difficult to obtain the v5 library prep to perform this validation. One of the easier ways to validate this would be to retest the 11 samples you tested to support the previous version of the investigational device in G150258/S002 and compare the results using the new investigational device to the 2 previously approved versions. Let me know as soon as possible if this is something you think you would be able to do.

Again, I am happy to talk if you have any questions.

Thanks,
Paula

From: Powell, Cynthia M. [mailto:powellcm@med.unc.edu]
Sent: Friday, September 29, 2017 11:50 AM
To: Caposino, Paula
Cc: Berg, Jonathan Sanford
Subject: RE: G150258/S003

Hi Paula,

We only validated at the beginning of this research project to make sure we could get NGS results from using saliva samples from babies. This in no way validated the ability of NGS to pick up any specific sequence variants. Since we are Sanger sequencing and confirming all clinically significant results prior to returning them to participants we are not doing (nor do we have the funds from NIH to do) any additional validation. I am copying Dr. Jonathan Berg, co-PI on this project, so that he can help answer your questions about this and help clarify things.

Thanks,
Cindy

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Thursday, September 28, 2017 3:30 PM
To: Powell, Cynthia M. <powellcm@med.unc.edu>
Subject: RE: G150258/S003

Dear Cindy,
Thanks for the response.

As far as I understand, for the original investigational device (which included the XT Human All Exon v5 platform and the GenomeAnalysisToolKit for variant calls) you performed some validation i.e., DNA samples from 8 newborns that were interrogated for 8 SNPs showing that the investigational device was 100% concordant to Sanger. For the modification approved in the previous 5 day notice, G150258/S002 (which included the Agilent SureSelect XT2 Human All Exon v6 Enrichment Kit and the FreeBayes software package for variant calls) you looked at the overlap in variants between the original protocol and the modified protocol using 11 samples and you provided FDA with the following table to support the change:

	Variant counts			As % of total variants identified				
Sample #	XT alone	Both	XT2 alone	XT alone	Both	XT2 alone	overlap as % of XT	overlap as % of XT2
1	108	3265	79	3.13%	94.58%	2.29%	96.80%	97.64%
2	85	3110	109	2.57%	94.13%	3.30%	97.34%	96.61%
3	103	3089	106	3.12%	93.66%	3.21%	96.77%	96.68%
4	138	3190	159	3.96%	91.48%	4.56%	95.85%	95.25%
5	132	3222	85	3.84%	93.69%	2.47%	96.06%	97.43%
6	52	3192	63	1.57%	96.52%	1.91%	98.40%	98.06%
7	111	3176	96	3.28%	93.88%	2.84%	96.62%	97.07%
8	80	3312	83	2.30%	95.31%	2.39%	97.64%	97.56%
9	102	3171	132	3.00%	93.13%	3.88%	96.88%	96.00%
10	108	3242	84	3.15%	94.41%	2.45%	96.78%	97.47%
11	87	3170	91	2.60%	94.68%	2.72%	97.33%	97.21%
Average	100.5	3194.5	98.8	2.96%	94.13%	2.91%	96.95%	97.00%

We are trying to understand what validation/information you have performed/gathered to support the use of the new investigational device (which we understand now includes the Agilent SureSelect XT Human All Exon v6 platform and the FreeBayes software package for variant calls) which is different from the original device and the device modified in G150258/S002. As discussed during our review of your previous 5 day notice in G150258/S002, when we review a 5 day notice for an IDE change to an investigational device, one of the things that must look for is a description of the testing (clinical, preclinical, verification/validation activities or published literature) that was used to support the change. I am happy to discuss this further on the phone if you have questions.

Regards,

Paula

Paula Caposino, Ph.D.
Acting Branch Chief, Cardio-Renal Diagnostic Devices Branch
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics and Radiological Health

Center for Devices and Radiological Health
U.S. Food and Drug Administration
Tel: 301-796-6160
Paula.Caposino@fda.hhs.gov
<image001.png>

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:
https://www.research.net/s/cdrhcustomerservice?O=500&D=530&B=535&E=&S=E

THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by email or telephone.

From: Powell, Cynthia M. [mailto:powellcm@med.unc.edu]
Sent: Tuesday, September 26, 2017 12:16 PM
To: Caposino, Paula
Subject: RE: G150258/S003

Hi Paula,

Here are answers to your questions:

1. V6 is an incremental update of the exome library preparation kit that increases the number of regions covered and is optimized for better uniformity.
2. We did not do any validation testing specifically with V6 of the exome library preparation, in large part because there is no reason to think that FreeBayes variant calling will occur any differently using the newer exome library.

Please let us know if you need additional clarification.

Thank you,
Cindy

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Monday, September 25, 2017 3:56 PM
To: Powell, Cynthia M. <powellcm@med.unc.edu>
Subject: RE: G150258/S003

Dear Cindy,

Good afternoon. I am reviewing your new 5 day supplement for IDE G150258. I have a few questions before I can complete this review.

1. You are proposing to change the exome library preparation to use the Agilent SureSelect XT Human All Exon v6 platform. You indicate that at the time the IDE was originally approved, you used the XT Human All Exon v5 platform. Can you briefly describe what the differences are between v5 and v6?
2. Can you describe the validation testing that you performed to support the use of this library preparation platform (i.e., v6) with the FreeBayes software package?

Let me know if you would like to discuss these questions.

Thanks,
Paula

Paula Caposino, Ph.D.
Acting Branch Chief, Cardio-Renal Diagnostic Devices Branch
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration
Tel: 301-796-6160
Paula.Caposino@fda.hhs.gov
<image001.png>

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:
https://www.research.net/s/cdrhcustomerservice?O=500&D=530&B=535&E=&S=E
THIS MESSAGE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by email or telephone.