# DonnaLochner: FDA/CDRH/OSEL – Senior Scientific Advisor

Great comments Jay!  Regarding the type of MDDT (NAM or COA), I’ll just mention first of all that we have deviated from the draft guidance descriptions in this pilot program (and adjusted those descriptions for the final guidance that is currently circulating in-house).  For example, we accepted a computational model as a COA because it was modeling a clinical parameter used in patient selection for device clinical studies, even though a computational model is a non-clinical assessment method.

I think a case can be made for either NAM or COA.  I lean towards COA, because I would consider the pathology slide to be a clinical endpoint.  It’s my understanding that eeDAP aids in reader studies (by pointing the reader to the same area), with reader studies being a clinical outcome assessment.

I think Brandon should propose whichever he thinks makes the most sense.  The WG will let you know if we’ve decided to change to a different MDDT type. The MDDT type impacts which Office will lead the review, but doesn’t otherwise impact the Proposal/ submission requirements.

# Jay Vaishnav: OMPT/CDRH/OIR/DRH/DXRS

The eeDAP proposal looks really good.

Some comments:

1. During one of our initial meetings, Donna suggested that eeDAP could be a COA.   Donna has seen more MDDTs than I have, so please go with what she says.

However, going only by the draft guidance definition, my first thought was that eeDAP didn’t fit well into any of the tool categories (which is a shortcoming of the guidance), but that NAM seemed like the least stretch. The draft guidance says a NAM is a

…nonclinical test method…used in device development or evaluation that reflects device function or in vivo performance. A NAM…is developed to measure a parameter of interest or to substitute for another generally accepted test or measurement.  
  
eeDAP is a nonclinical tool that helps replace the usual method of a pathologist selecting high-powered fields randomly.

1. I didn’t understand what the highlighted regions were in Fig. 5.
2. eeDAP registers images.  When I’ve reviewed radiological software devices that have registration as a key feature, the typical test method is this:  The sponsor creates or identifies fiducial markers on the images, runs the registration, measures the distance between the fiducials, and confirms that it is less than some prespecified tolerance.

The study you propose is at a higher level, and looks at how similar a pathologists' performance is on WSI vs. glass slides, in the presence and absence of eeDAP.

On one hand, this method incorporates more of the pathologists’ workflow.  It’s also helpful in demonstrating the actual use of eeDAP.

On the other, the proposed study

1. seems to be more than you need to just demonstrate that the WSI and camera images are aligned.
2. doesn’t seem to actually directly validate the image registration.  
     
   (Comment from my husband:  Under conditions with high mitotic rates that are uniformly spread--which can happen for high-grade malignancies--one can imagine a scenario where pathologists consistently count similar numbers of mitotic figures even in different FOV.)
3. Nitpicky point, but you are registering the camera image with the WSI image.  If the pathologist is using the microscope eyepiece directly, the camera will have its own modulation transfer and whatnot, and the camera image will not be a perfect representation of what the pathologist sees. Pathologists do sometimes diagnose using the camera images, especially in teaching situations where many people need to look at one image.  Just a general point to consider in study design.
4. Consider dropping some of the description of how you originally used Aperio ImageScope, moved to BioFormats, etc.   I’m not sure how many FDA reviewers will really appreciate those details.  (I could be wrong; I haven’t interacted with that part of OIR much.  
     
   In reviewing regulatory submissions, I’ve found that it’s good for sponsors to leave out any  material that isn’t directly helpful to making their case.  You never know when somebody on the review team is going to latch onto something random and make a big fuss over it--and sometimes the random thing isn’t that germane to the actual regulatory decision, and might be something the team would not have ever paid attention to had the sponsor not mentioned it.

# Donna Lochner: FDA/CDRH/OSEL – Senior Scientific Advisor

I think you and Qi have done a very nice job on the Proposal.  It is easy to follow, and it’s really good the way you’ve followed the sections as outlined by FDA.  I don’t have the technical expertise in this area to make those specific comments, but a few things that I noticed:

* Section 3 Context of Use

I like the way you broke into the different sections to describe the elements of COU.  However, I think you need an overall statement (prior to 3.1) that is the COU statement (analogous to an IFU statement).  We have recently been telling people that the COU statement should specify:

* The type of tool (i.e., Clinical Outcome Assessment, Biomarker Test, or Nonclinical Assessment Model);
* The device or product area for which the MDDT will be qualified;
* The type of regulatory submission where the tool can be used; and
* How the tool will be used (e.g., any limits due to planned validation testing)

So for example, COU statement:

eeDAP is a Clinical Outcome Assessment used in reader studies for whole slide imaging premarket submissions (IDE, PMA (?)) to evaluate scanned images.

(This is my simplistic understanding, please adjust/ enrich the COU accordingly).

* Section 3.2 The stage of device development (e.g., early feasibility study, pivotal study, etc.)

This refers to when your MDDT is used during device development/ device review.  In other words, it refers to the tool being used during pivotal clinical studies/ reader studies (and feasibility? – are their feasibility studies in this area?) of WSI.  I think you need to rewrite this section.  If you want to retain the information you currently have in 3.2, it needs to be moved to a different/ renamed section.

* Section 8 – I like what you have there, and think you can also mention the WG and wiki approach you are taking.

I would add an affirmative statement such as “We hereby authorize FDA to make public sufficient information to support use of the qualified MDDT and for the general public to use and rely on data generated using the MDDT in gaining FDA clearance or approval of other devices.”  (This is a direct copy of the request in the guidance document).

* Section 9 – you should hyperlink to the articles or provide copies of them.  (I recently had a lead reviewer complain that the tool developer had not provided the referenced articles).
* Cover letter – be sure to include a signed cover letter.

Excellent Proposal – thank you!  
  
Donna

# WSI Working Group Member 1

Thank you very much for involving us to the project. The paper really is a good self-reflection of the system and points out what it is meant to take on and what it can’t do.

It could help WSI users to validate and evaluate the WSI systems.

As we discussed, we are very happy to participate and also support your proposal.

Our comments are:

Fields of view:  It was not clear in the document if pathologists are looking at exactly same FOV with WSI and with microscope.

( the areas captured by the camera is not exactly same area with microscope)

System requirement: It might be better to list system requirement to use the system.

Even we have the microscope and images, the resolution of monitor and etc which my effect on the interpretation.

If you would like to move forward to other areas,  we could suggest such as screening in cytology like thin preps where the cells are rather 2D and flat, might be amenable to this tasks since changes in magnification when screening are helpful but can be done without.  I believe automated cytology screening machines do that currently.  Another might be looking at peripheral smears for blasts, parasites.  Acid fast smears for tuberculosis.

As system: if you are interested in adding other scanners, robotic or non-robotic system method, we are very happy to work with your team.

Please let us know if you have any question or anything we can help.

Hope the proposal will be accepted.

# WSI Working Group Member 2

We have reviewed your eeDAP and we have following general remark:

eeDAP allows image registration between a live microscope image and a WSI image for a comparative study. It has the potential to be used for supporting evidence of scanner accuracy. Do companies in their development cycle have this in context of its use? We believe industry could use it in the validation cycle (studies) in the context of its use. When more is known on the study, Philips is open to discuss possibility to contribute in a planned study.

Let me know if you have questions.