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1. Basic Information

Subject: **MDDT Incubator Phase Inquiry**

MDDT Type: **Nonclinical Assessment Model (NAM)**

MDDT Tracking Number: **MDDT031**

Submission Type: **MDDT proposal**

Division: **Division of Molecular Genetics and Pathology**

Branch: **Molecular Pathology and Cytology Branch**

Lead Reviewer: **Nick Anderson**

MDDT Name: **eeDAP, evaluation environment for digital and analog pathology**

2. Updated Context of Use:

eeDAP allows an investigator to design a study in which pathologists can evaluate pre-specified fields of view (FOVs) and features on a glass slide using a microscope. The FOVs and features are pre-specified by referring to a digital scan of the corresponding slide (a whole slide image: WSI) and identifying the (x,y) position of the center of the FOV or the feature.

3. Inquiry

We are writing this inquiry to get feedback on our updated Context of Use (COU) and the studies we have conducted to support the updated COU. As recommended in the letter accepting the eeDAP proposal into the incubator phase, we start by addressing the two issues enumerated by the FDA. Then we discuss the two studies taken to support the context of use, and some additional conditions for qualification.

As attachments to this inquiry, we are including a manuscript of one of the studies [Gong2018_Proc-SPIE_v10581p1058118], our original proposal, and the FDA letter accepting our proposal into the incubator phase. We did not rewrite the proposal deciding that it would be useful to first hear feedback on the updated COU and the studies conducted to date. Similarly, our tool development plan and timeline depend on the feedback. That said, we are optimistic that the updated COU and the studies conducted might allow us to immediately proceed to the MDDT qualification phase.

We are happy to receive your response to the questions in this inquiry (marked **Inquiry1Q1 - Inquiry1Q6**) and any other feedback to help us advance this MDDT proposal to the next step. Email is fine. Depending on the FDA response we will decide if we need a T-con or face-to-face meeting. We are also happy to provide more information and answer questions. As you know, Dr. Brandon Gallas, the lead on this

proposal, is an FDA employee working at the White Oak campus. He can visit for informal discussions or to answer any questions.

3.1 Issues in Acceptance letter

Issue 1, The deployment and use of the eeDAP system.

FDA:

CDRH recognizes three types of MDDT, distinguished primarily by how the tool measures relevant parameters. You propose the eeDAP as a Clinical Outcome Assessment tool, but based on your product description and the co-registration capabilities of eeDAP when evaluating specific fields of view (FOVs), it may fit better as a Nonclinical Assessment Model. We will work with you to refine the Context of Use Statement and determine the most appropriate tool type for eeDAP.

Response:

Not a problem. We shall refer to this MDDT as a Nonclinical Assessment Model (NAM).

Issue 2, The disadvantages of the eeDAP system.

FDA:

On page 9 of the submission, you describe the first of two major disadvantages as “when collecting data in digital mode, the image is displayed with Matlab. As such, eeDAP doesn’t evaluate the native image viewer’s human factors and workflow components.” There may be more than just the human factors and workflow components that are of concern. If the proposal is to have analytical and/or clinical studies conducted using eeDAP, it is not clear how the study data could be used to support the regulatory review of a whole slide imaging (WSI) device. FDA generally requires that analytical and/or clinical testing be conducted using the system (with the specified components) under review. As such, if eeDAP will serve as a surrogate for the WSI device submitted for review when conducting such studies, it will be necessary to submit technical performance documentation and testing for eeDAP.

Response:

We have updated the Context of Use (COU). The COU is now limited to the control of the microscope that allows collection of pathologist evaluations (the data) at pre-specified locations on a glass slide in microscope mode. Such data would be the reference data for data collected in a digital mode using WSIs, image viewing software, and a display.

Note that the COU does not make any claims about the presentation of WSI images or patches for collecting data in a digital mode. Instead, we recommend that data collected in a digital mode to support the regulatory review of a WSI scanner should be collected using the WSI scanner manufacturer’s viewing software. Such data collection should be feasible for any WSI viewing software.

Inquiry1Q1: Does the FDA believe that the updated COU (with revisions) can lead to a successful MDDT qualification? What kind of revisions does the FDA believe the COU needs?

Inquiry1Q2: Would the FDA recommend adding language to limit the COU so that users understand that eeDAP is not meant to be the interface for viewing WSIs or would the FDA like this to be addressed elsewhere in the future submission?

3.2 Studies to Support the COU

We have designed and executed two studies of the registration accuracy of eeDAP. Registration accuracy is the key characteristic pertaining to the COU. We define the registration accuracy to be the radial distance between the center of the microscope FOV and the object expected at the center of the microscope FOV. This distance is measured by a human (pathologist or researcher) using a ruler-type reticle in the microscope eyepiece. More details can be found in the attachment [Gong2018_Proc-SPIE_v10581p1058118]

The first registration accuracy study was designed and performed in the FDA digital pathology lab by the developers of eeDAP. We have included a conference proceedings paper describing the first registration study and results [Gong2018_Proc-SPIE_v10581p1058118]. Here is the abstract:

The purpose of this study is evaluating registration accuracy of evaluation environment of Digital and Analog Pathology (eeDAP). eeDAP was developed to help conduct studies in which pathologists view and evaluate the same fields of view (FOVs), cells, or features in a glass slide on a microscope and in a whole slide image (WSI) on a digital display by registering the two domains. Registration happens at the beginning of a study (global registration) and during a study (local registration). The global registration is interactive and defines the correspondence between the WSI and stage coordinates. The local registration ensures the pathologist evaluates the correct FOVs, cells, and features. All registrations are based on image-based normalized cross correlation. This study evaluates the registration accuracy achieved throughout a study. To measure the registration accuracy, we used an eyepiece ruler reticle to measure the shift distance between the center of the eyepiece and a target feature expected in the center. Two readers independently registered 60 FOVs from 6 glass slides, which covered different tissue types, stains, and magnifications. The results show that when the camera image is in focus, the registration was within 5 micrometers in more than 95% of the FOVs. The tissue type, stain, magnification, or reader did not appear to impact local registration accuracy. The registration error was mainly dependent on the microscope being in focus, the scan quality, and the FOV content (unique high-contrast structures are better than content that is homogeneous or low contrast).

The second registration accuracy study was designed and performed by collaborating pathologists with no experience using eeDAP. The goal was to determine if users that are not eeDAP experts can design and execute a registration accuracy study and get similar results. The collaborators were provided a tutorial and could troubleshoot issues with FDA scientists, but the work was done by the collaborating pathologists in their lab. Rather than exploring different tissue types and stains, two pathologists designed and conducted their study with 20 H&E stained glass slides (10 mouse brain + 10 human GIST tumor slides). While we intend to summarize the study in detail for the qualification submission the registration accuracy was within 5 micrometers in more than 95% of the FOVs.

Inquiry1Q3: Do the registration accuracy studies provide the kind of evidence that can support this MDDT?

Inquiry1Q4: What additional information about the studies would the FDA like to know?

3.3 Additional Conditions for Qualification

We would like to point out that some FOVs in the studies described above were purposefully selected to stress-test the registration process. Many FOVs had homogeneous, sparse, or low contrast content; such FOVs are challenging to register. We intend to provide instructions for choosing FOVs and examples for when registration is expected to succeed and when it may fail. With that said, there is no better training than actual doing.

The experience of designing and executing a registration accuracy study is, in some sense, training for designing and executing a task-based eeDAP study (a study of pathologists evaluating specimens). Furthermore, it seems appropriate and useful for users to run a registration accuracy study for the FOVs they intend to evaluate during a task-based eeDAP study. This would confirm that the task-based eeDAP study could successfully register all the FOVs, not just 95% of FOVs. Any FOVs that fail to be registered could be replaced, left out, or addressed by some other means.

Inquiry1Q5: We plan to recommend that every task-based eeDAP study be preceded by a registration accuracy study using the task-based eeDAP study slides and FOVs. Would the FDA prefer to require such a registration accuracy study for any task-based study submitted to the agency as a condition under which the MDDT is qualified?

3.4 Next Steps

Inquiry1Q6: Are the changes to the COU and the evidence summarized here adequate to advance us to the pre-qualification phase or the qualification phase?

4. References

- Gong2018_Proc-SPIE_v10581p1058118
 - Gong, Q.; Berman, B. P.; Gavrielides, M. A. & Gallas, B. D. (2018), Registration accuracy between Whole Slide Images and Glass Slides in eeDAP workflow, *in* Metin Gurcan & John Tomaszewski, ed., 'Medical Imaging 2018: Digital Pathology', pp. 1058118.

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