Memorandum

Date:	8/1/2022
Subject:	Critical Path Innovation Meeting Topic: Use of Digital Pathology in Good Laboratory Practice (GLP) Environment for Nonclinical Studies
Date of meeting:	6/15/2022
Requestor:	Innovative Medicine Initiative (IMI) BigPicture consortium (Consortium)

Note: Discussions at Critical Path Innovation Meetings are informal. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants.

FDA Representatives

Center for Drug Evaluation and Research (CDER)
CDER/Office of Center Director (OCD)
CDER/Office of Medical Policy (OMP)
CDER/Office of New Drugs (OND)
CDER/OND/Office of Drug Evaluation Sciences (ODES)
CDER/OND/ODES/Division of Biomedical Informatics, Research, and Biomarker Development (BIRBD)
CDER/OND/Office of Neuroscience (ON)/ Division of Pharm/Tox for Neuroscience (DPT-ON)
CDER/OND/Office of Oncologic Diseases (OOD)
CDER/Office of Translational Sciences (OTS)
CDER/OTS/Office of Study Integrity and Surveillance
CDER/OTS/OSIS/Division of New Drug Study Integrity (DNDSI)
Center for Devices and Radiological Health (CDRH)
CDRH/Office of Science and Engineering Laboratories (OSEL)
CDRH/OSEL/Division of Imaging, Diagnostics and Software Reliability (DIDSR)

IMI BigPicture Representatives

BIGPICTURE 3

BIGPICTURE Nonclinical Team Participants

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Quality Management

- **D. Jeffrey Beebie**, Pfizer Inc.; Director & Global GLP QA Team Lead, Regulatory Quality Assurance
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Information Technology

- **Ronald Menner**, Pfizer Digital Client Partner, Drug Safety R&D and Comparative Medicine
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1. BACKGROUND

Digital pathology (DP) is a blanket term that encompasses tools and systems to digitize entire (whole) pathology slides and associated metadata, their storage, review, analysis, and enabling infrastructure. Although DP has been utilized in the non-GLP area and is associated with numerous advantages such as streamlined slide sorting and reduced need for slide shipment and pathologist travel, a lack of regulatory guidance in the field has prevented application of the DP system to the GLP environment. Innovative Medicines Initiative (IMI) is an EU public-private partnership that funds health research and innovation. BIGPICTURE Central Repository for Digital Pathology is an ongoing project funded by IMI that aims to establish ethical and General Data Protection Regulation (GDPR)-compliant, quality-controlled whole slide imaging (WSI) platforms. The Consortium is requesting this CPIM to discuss use of digital pathology (DP) in the GLP environment for nonclinical studies and FDA's recently issued draft guidance on the use of WSI in non-clinical toxicology studies with the Agency.

2. DISCUSSION

Introductions and background information on the Consortium was provided. The Consortium posed a number of questions related to WSI systems for discussion.

Categorization of WSI components under GLP was discussed. Consortium noted that under existing GLP regulations whole slide images cannot be interpreted as raw data. They cannot be interpreted as specimens because specimens are defined as part of the test system. Consortium believes it should be possible to designate WSI as a faithful replica of the glass slides if they fulfill certain conditions, such as being generated by a validated system, fulfilling acceptable technical parameters, having all data from the original slide label and all tissues present, and being proven to be appropriate for evaluation. FDA inquired about why categorization is necessary. Consortium noted that until now, the regulations have been clear regarding how to deal with raw data and specimens in terms of documentation and archiving and that WSI falls in between these categories. It would be helpful to assign a category so that WSI can be mentioned in future regulations with clarity regarding how to deal with them.

FDA noted that it has concerns with categorization as a faithful replica because the WSI cannot be considered an exact copy of a glass slide as it is a 2-dimensional image and not a 3-dimensional image. Consortium responded that 2-D images will be enough to give rise to a diagnosis in the vast majority of cases assuming proper quality control to ensure that the images are in focus. In the rare instances where a 2-D image is not sufficient, a Z-Stack on the glass specimen may be useful. Consortium noted that capturing the Z-Stack in the whole slide is likely not technically feasible given the volumes being managed. A part of validation could include processes for pathologists to revert to glass slides when scientifically justified. Consortia believes that designation of WSI as a faithful replica is achievable right now, but more discussion and guidance are required on how validation can occur.

Peer review and GLP documentation requirements for use of WSI in nonclinical contexts was discussed. Informal consultations, mentoring, and other similar discussions are considered outside the scope of peer review and FDA would not expect any documents to be retained relating to these. With respect to contemporaneous and retrospective peer review, as noted in the current guidance, if the digital pathology image is read as opposed to the glass slide, the images and their documentation of peer review should be retained. Although peer review is outside the scope of the regulations, this represents the FDA's current thinking. Consortium questioned why contemporaneous peer review that is conducted before raw data is signed by the study pathologist and retrospective peer review should be treated in the same way.

Consortium noted that archiving of WSI should not be necessary if they do not contribute to the creation of raw data. FDA responded that the Agency is still going through the comments that have been submitted for the draft guidance and will have more information in the future.

Consortium had questions regarding annotating regions of interest during contemporaneous review of WSI in order to streamline the review process. If the content is not changed, does the image need to be archived and discarded similarly to peer review notes that are made on paper during traditional glass slide peer review? FDA responded that if the digital pathology images are used for the contemporaneous peer review, the Agency's current thinking is that the images would need to be retained. The peer review statement would be handled the same for contemporaneous peer review as retrospective peer review, and FDA would expect a peer review statement whether glass slides or digital images are read.

Consortium inquired about using record retention practices for specimens as a basis for WSI. Although whole slide images are not specimens or raw data and are not defined in the regulations, FDA does not have any concerns provided that the WSI images are archived and available in the event that reconstruction of the of study is necessary. Adherence to the guidance is recommended.

There was discussion regarding archiving requirements when converting WSI into different file formats that are viewable by different software but that do not correspond to a change in the content and meaning of the image that the pathologist views. FDA noted that this question is something that the Agency may not have considered and noted that it will discuss the issue internally. Question 7 of the draft guidance may relate to this issue. Consortium noted that in order to demonstrate fidelity of the original file format to the final format, concordance studies that demonstrate that pathologists will make the same interpretation across file formats without any change in outcomes may be necessary. FDA noted that an easier approach may involve using RGB values to conduct a pixel-by-pixel analysis that demonstrates that the images are identical. Consortium may be able to help create tools to perform these analyses, despite the fact that vendors may resist this type of equivalence. With respect to validation via the pixel pathway, FDA recommends characterizing the devices being used in terms of performance before using WSI in regulated studies. FDA is not prepared to define what a validation study would look like and would expect proposals on how this should be done.

Consortium asked if a copy of the image file needs to be retained after it is scanned during the WSI evaluation phase. FDA noted that a back-up is not necessary because the original is available. FDA also noted that there are pros and cons to creating a back-up in this situation and that this is something that can be proposed to the Agency for consideration.

With respect to archiving format, Consortium expressed a preference for DICOM because it is open-source and non-proprietary. Use of this format would require a migration to change the format of the file between evaluation and archiving. As discussed earlier, validation would be required to demonstrate that the pathologists will make the same call across file formats without any change in outcomes and or that the content of the images is not altered on a pixel-per-pixel basis. FDA did not object to use of the DICOM format.

Consortium inquired about physical inspection of the servers where archiving will take place. FDA did not directly address the issue of servers but noted that it does not inspect data differently depending upon the format, and the expectations are the same whether the image is digital or not. GLP compliance is required for electronic data.

Consortium had questions regarding consultation of electronic records versus retrieval of electronic records. It is often useful to compare WSI from a current study with observations made in previous studies. Consortium noted that these types of analyses can be streamlined if considered a consultation as opposed to a retrieval. FDA did not address this issue.

Barcoding of glass slides for specimens was discussed. Barcoding has the advantages of providing a unique identifier for each specimen and allowing metadata to be appended to each identifier. Consortium inquired whether it is necessary to combine the barcode with the human readable identification or whether the barcode alone is sufficient. FDA noted that there should not be an issue if Standard Operating Procedures are followed and are consistent with GLP requirements. FDA also noted that the question is related to testing facility procedures and is not specific to WSI.

3. NEXT STEPS AND ADDITIONAL RESOURCES

FDA has just begun the process of reviewing comments to the draft guidance. All comments to the draft guidance received during the official comment period will be discussed and addressed by FDA. Although FDA will not cross-link comments discussed during the CPIM to the official draft guidance comment review process, any comments made at the CPIM that overlap with comments received during the official comment period will be addressed by FDA. This summary will serve as documentation of comments made during the CPIM.