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Central Repository for Digital Pathology

WP5 - Regulatory framework for digital slides and AI-based methods

D5.02 Report on landscape of guidelines, standards and regulatory requirements relevant for digital pathology, non-clinical

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Abstract

As a preliminary step to establishing a regulatory dialogue about the use of digital pathology in the nonclinical area, a review of the current standards and Good Laboratory Practice (GLP) requirements for whole slide image and artifical intelligence use in nonclinical studies has been conducted. Particular attention was drawn to the use of digital slides as a surrogate for glass slides in nonclinical safety assessment within a GLP environment. An understanding of fundamental principles of GLP regulation, of their application to digitized images and their interpretation in the context of nonclinical studies, was provided. Critical elements such as differences between clinical and nonclinical pathology, GLP categorization of the different whole slide imaging system (WSI) components, specificities of peer reviews versus primary evaluations, technical requirements for WSI, GLP validation, standard operating procedures, archiving and storage were emphasized, and gaps were highlighted. Altogether this report is expected to set the scene for fruitful discussions with regulators in view of gaining acceptance of digital pathology in the GLP-regulated nonclinical space. Looking forward, digital pathology should be able to fit into a GLP environment barring proper validation. Based on the scarcity of published guidances for artificial intelligence in the nonclinical area, this topic is not covered in this document but will be in scope of subsequent regulatory interactions along the course of the consortium.

Methods

A review of Organization for Economic Cooperation and Development (OECD)- and Food and Drug Administration (FDA)-published documents pertaining to the field was performed. In addition, the input from opinion papers including those provided by professional societies was synthesized and incorporated to the document to identify alignments between industry partners and regulators, adress outstanding questions, and provide recommendations to mitigate those.

Results

The results consist of a comprehensive report provided as an annex that covers the following topics:

1. Digital pathology: differences between clinical and nonclinical pathology fields
2. GLP categorization of the different WSI components
    a. Specificity of peer reviews
    b. Specificities for primary slide evaluation
3. General (technical) requirements for WSI
4. WSI system GLP validation recommendations
5. Standard Operating Procedures for WSI users
6. Storage and archiving

Starting with some highlights of the major differences between clinical and nonclinical digital pathology, the principles of GLP regulation are reviewed and an attempt is made to fit digital pathology into this paradigm. An extrapolation of GLP validation principles for electronic systems is applied to digital pathology and the scope of accompanying standard operating procedure is described. Finally, some proposals regarding archiving are made based on current practice for specimens and the categorization of WSI proposed earlier on. Throughout this evaluation, open questions and gaps are brought forward, as these will represent the substrate to be discussed with regulatory authorities going forward.

Conclusion

Although GLP regulation has been in place for decades in nonclinical pathology, the recent technological evolution has allowed scientists to replace glass slides by digitized equivalents. As the profession is embracing this change, it relies on fundamental GLP principles to incorporate digital pathology in routine workflows. To aid in proper incorporation, a majority of requirements can be inferred from the extrapolation of existing guidances. In particular requirements for full systems/workflow validation, the need for a retention of digitized images and compliance with requirements for electronic records are well established. However, certain aspects such as storage duration, server access needs, or just GLP categorization of digital images still need to be discussed with regulatory authorities in order to achieve alignment in view of obtaining regulatory acceptance of digital pathology in the GLP-regulated nonclinical space .

This report successfully drew a picture of the regulatory landscape for nonclinical pathology and highlighted current knowledge and alignment gaps as a substrate for further engagement of regulatory authorities.

Annex: Report on landscape of guidelines, standards, and regulatory requirements relevant for non-clinical digital pathology

bigpicture

Introduction

Digital Pathology (DP) is defined as "a blanket term that encompasses tools and systems to digitize entire (whole) pathology slides and associated metadata, their storage, review, analysis, and enabling infrastructure".[1] Although DP has been utilized nonclinically in the non-Good Laboratory Practice (GLP) area with many advantages (e.g., easier slide sorting and significant decreases in the need for slide shipment and pathologist traveling), hesitations to apply the DP system to the GLP environment remain, largely due to a lack of specific regulatory guidance in this field. Fortunately, several foundational documents and opinion papers have been published that allowed some initial validation efforts for digital peer-reviews and paved the way for the subsequent validation of GLP-compliant primary reads. In this report, we summarize the current regulatory status as well as opinions for non-clinical DP concerning minimal requirements for validating whole slide imaging (WSI) systems based on existing regulatory guidances and published literature. The report has been structured in major themes that should be considered by industry partners that are seeking to validate DP for GLP-compliant use. Of note, based on the scarcity of published guidances for artificial intelligence in the nonclinical area, this topic will not be covered in this report but will be in scope for subsequent interactions with regulatory authorities along the course of the consortium.

1. Digital pathology: differences between clinical and nonclinical pathology fields

Since the issuance of FDA guidance on the *Technical Performance Assessment of Digital Pathology Whole Slide Imaging Devices* in 2016,[2] several DP technologies and systems have been approved for clinical use. The evaluation process following scanner marketing clearance as a medical device comprised the validation of subsequent hardware, network and viewing monitors (i.e. both WSI system and associated workflow), and was substantiated by concordance studies[3,4]. This was made possible by a well-established FDA guidance[2] and some recommendations from the American College of Pathologists that enabled the validation of WSI for diagnostic purposes in pathology. Of note, because the assessment of accurate color reproduction is a key component for clinical WSI systems[2,5], it has been recommended to use a tissue calibrator slide for clinical qualification, although no formal endorsement or requirement of this approach by regulatory authorities has been published[6]. Compared with the widespread use of DP in the regulated clinical environment and in non-regulated environment (e.g. diagnostic veterinary laboratories), the nonclinical field has been lagging behind as very few attempts at utilizing DP technology in regulated (GLP) studies have been reported to date. Unlike a clear mandate for clinical DP, there is no expectation currently by regulatory authorities or published literature to use

scanners that have been thoroughly cleared as medical devices. Instead, the current expectation is to have each institution take a “fit for purpose” approach to qualify each instrument and validate the workflow and DP softwares. Without a standardized process, this approach could significantly limit the use of DP due to variations introduced by different instruments and practices. Some technical approaches may therefore be recommended for the qualification of scanners in the GLP-compliant nonclinical environment, taking into account the approaches used to demonstrate the performance of scanners in the context of their clearance as medical devices for clinical use.

As a non-binding and non-exclusive example, the Philips IntelliSite Pathology Solution 510K mentions detailed bench testing at the system level for “color reproducibility, spatial resolution, focusing test, whole slide tissue coverage, stitching error and turnaround time”. The level of granularity and technicality to address those should be clarified by the validation team.

Particular attention should be paid to critical parameters such as color, focus, resolution, completeness of tissue represented, precision, and reliability. As a means of unique slide identification and potentially metadata integration, and based on best practice for clinical WSI, bar-coding is recommended for nonclinical pathology[7].

2. GLP categorization of the different WSI components

As with any other information systems, the use of DP in a GLP environment will need to comply with general GLP principles as edicted by OECD and FDA[8,9] and thus a full set of SOPs will be required (detailed in Section 5).

There are basically two scenarios for the use of WSI within a GLP study:

(1) Use of DP in the context of informal consultations:

This common practice is considered equivalent to pathologists exchanging slides to seek informal advice, does not contribute to study report reconstruction, and thus does not require particular documentation. [10] In this context, the images captured only for illustrative purposes do not form the basis of the diagnosis and thus are not considered to be raw data[10].

(2) Use of digitized slides in a way that they become essential to the generation of raw data and thus reconstruction of the study report:

According to the definition and principles in FDA 1987 GLP Final Rule and FDA GLP regulation 21 CFR 58, 58.3, “Raw data” are defined as “any laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a nonclinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study.

OECD 2014 draft advisory document 16 (“The application of GLP principles to computerised systems”) provides a comparable definition of raw data but expands it to computerized systems, raw data being “all original laboratory records and documentation, including data directly entered into a computer

through an instrument interface, which are the results of original observations and activities in a study and which are necessary for the reconstruction and evaluation of the report of that study."

"Raw data" may include "photographs, microfilm or microfiche copies, computer printouts, magnetic media, including dictated observations, and recorded data from automated instruments while "specimens" (such as wet tissues and glass slides) are defined as parts of the test system" that have to be authenticated at the time of generation and later have to be archived"[10].

In the event that exact transcripts of raw data have been prepared (e.g., tapes which have been transcribed verbatim, dated, and verified accurate by signature), the exact copy or exact transcript may be substituted for the original source as raw data.

There is a general agreement between industry and regulatory authorities that the signed pathology report corresponds to the pathology raw data according to the definition and principles in GLP[10]. If reconstruction of the report requires re-evaluation of specimens, an amended report is needed and also considered raw data[8].

Consequently, whole slide images (used in a way such as they become essential to the generation of raw data and thus reconstruction of the study report) are neither raw data (e.g., signed pathology report) nor specimens (part of the test system), and there has been a gap understanding what the regulatory category of digitized slides should be. Several proposals have been made, ranging from "true specimens", "exact copies of the glass slides" to "raw data source", but no consensus has been achieved to date[11]. However, there is an agreement on the fact that digital images should represent a faithful reproduction of glass slides, providing an equivalent experience to that of a light microscope for a pathologist.

The notion of faithful reproduction (faithful replica) of a glass slide implies that acceptable technical parameters (color, resolution, focus) are met, that human readable data from original slide label are present, and that ability to see all tissues present on the original slide is preserved. Equipment for digitization should be adequately maintained, and computerized systems that manage, store, transfer or migrate images should be validated. If all the above features are adequately maintained, as supported by a robust validation package, digitized slide integrity can be maintained.

Although there is a recognized specificity for pathology raw data (the signed report is raw data), the regulatory intent may be interpreted in a way that an exact copy of an original study deliverable (i.e. microscopic slide) which is assessed, reported or needed for reconstruction needs to be controlled under GLP regulation. This faithful replica scenario implies retention of the glass and the scanned image. A clarification about expectations might be needed from regulatory authorities since the glass slides may fade with long-term archiving, while the digital images will remain unchanged overtime.

It should be discussed with regulatory authorities, whether digitized slides used in a way such as these become essential to the generation of raw data (i.e., for primary study read or retrospective peer

review), and thus the reconstruction of the study report, should have a specific status for which the terminology remains to be decided, and that is neither raw data nor specimens. Since whole slide images correspond to the material from which the pathology diagnoses are derived, we propose these should be archived for a duration that also remains to be determined. Finally, based on their digital nature, digitized slides used under GLP need to comply with Electronic records / Electronic signatures requirements[12].

a. Specificity of peer reviews

Two types of peer reviews are commonly distinguished: contemporaneous versus retrospective[13]. It has been assumed that for contemporaneous GLP digital peer reviews (executed prior to the generation of the signed pathology report) the peer review working notes and digital images do not need to be retained or archived as long as the primary read had been performed on glass slides. [5,14-16] The reasoning behind this assumption is that the raw data (signed pathology report) has not been generated yet, and the contemporaneous peer review contributes to the dynamic process of diagnosis establishment. In addition, in case of discrepancies of opinions between the primary and the peer review pathologists, it is assumed that such discrepancies should be resolved on glass slides.

To date, no GLP inspection of studies claiming a GLP-compliant digital peer review has confirmed these assumptions.

As per OECD GLP good practice frequently asked questions (FAQ),"if the study pathologist uses digitized slides for the initial read OR the peer review pathologist uses them for the retrospective peer review, they should be retained in the archive for as long as the other study materials as they were used to generate raw data. Digitized slides should be archived in an electronic format that ensures their integrity over time and allows their review if required for regulatory purpose".[17] In case the retrospective peer review does not lead to a modification of the raw data, it may be considered that the WSI does not need to be archived.

In the case of a retrospective GLP digital peer review, understanding that the raw data has already been generated and may be amended to reflect the peer review outcome, a full validation of the digital peer review workflow including archiving of the digitized slides is expected.

b. Specificities for primary slide evaluation

For GLP digital primary reads, a similar thought process suggests that, since the digitized slides (although neither raw data nor specimens) are needed to reconstruct the study report, these should be archived. Glass slides should be archived as well, as specimens.

From the above, it can be concluded that digital slides used for primary histopathology evaluation and retrospective peer review (1) contribute to raw data, (2) are needed to reconstruct the study, and (3)

need to be retained, while digital slides used for contemporaneous peer review do not contribute to raw data (glass slides do and will be archived as specimens) and do not need to be retained.

3. General (technical) requirements for WSI

Based on the principles laid out in Section 2, in order for WSI to achieve a faithful representation of glass slides through hardware and software, the following technical requirements should be met:

- Files must not be modifiable without an audit trail and date/time stamps
- Compression must not alter the raw image files but be layered onto them
- Electronic records must be authenticated at the time of image generation

Details should be provided about how label information will be recorded at the time of image capture, and how the information will be transcribed into or linked to the image metadata file.

Authentication of WSI could be obtained by using a 21CFR Part 11-compliant system. [12,18]

Findable, Accessible, Interoperable, Reusable (FAIR) data principles should guide the archiving/retrieval processes, while image and metadata storage need to be developed within regulatory authority guidelines [19,20]. In order to ensure the readability of data over time, a particular Image format (DICOM) has been recommended for archiving, although not a regulatory requirement and not yet a technical standard in slide scanning technology. [21]

4. WSI system GLP validation recommendations

A full validation should encompass the point of data acquisition up to archiving. All steps in the data management life cycle, in addition to the hardware and software, need to be included in the validation effort.

A validation plan including vendor audit, user requirements and the relevant documentation (user acceptance testing, validation report) should be available to GLP inspectors and auditors.

WSI system validation should follow 21CFR part 11 and part 58 as guiding principles and be conducted by a multidisciplinary team.[2]

The scope of performance assessment should comprise both WSI system and imaging chain, including all steps from image acquisition to image display. This end-to-end approach has been designated as “the pixel pathway”, meaning that every component of the image chain as well as the pixel pathway as a whole need to be assessed. This would also encompass the copies or original WSI generated by softwares and the risk of loss due to compression (e.g., transformation of the original WSI into a proprietary format).

The validation should encompass a preliminary step of vendor assessment, both for the scanner and for the image management and visualization software. The aim is to confirm that the providers have a Quality Management System (QMS) and appropriate documentation in place. In this regard, software functional requirements should include: limited and authorized access to the system, definition of user roles, coding standards, (cyber) security assessment, personnel training, testing and system release plan, change control process, version control, problem reporting and resolution plans. [22]

As per 21CFR58, equipment used for the generation, measurement or assessment of data should be adequately tested, calibrated and/or standardized. Consequently, the scanner qualification should demonstrate its suitability to produce WSI evaluation in terms of color, focus, resolution, completeness of tissue represented, precision, reliability, and instrument-to-instrument reproducibility, while the WSI should be tested for its intended use and data integrity, including secured file exchanges. In addition, pathologists should be trained and confident that WSI delivers a faithful representation of glass slides.

In the clinical setting, a way to approach the validation of the whole system has consisted of running concordance (or "non-inferiority)") studies in order to demonstrate the absence of effect of WSI on the diagnoses. There is little regulatory guidance for the design of such studies.[2] However, comprehensive reviews are available in the literature to support this approach[23]. Concordance studies can either be vendor-driven (as for the scanners cleared as Diagnostic Medical Devices) or based on a system qualification in its specific laboratory environment, using a number of representative slides[24]. The main goal of any of these studies should be to include test cases that give a good representation of the tissues and diagnoses that will be commonly encountered in the respective institution, with optional addition of critical cases[11]. An adequate sample size of at least 60 diagnostic cases has been recommended to this effect in one publication in the clinical setting[24].

In the GLP space, integrating the comparison of an example glass slide (e.g., tissue microarray) with its digital counterpart has been proposed at each study level as a practical means to verify correct tissue outline and color rendition, but there is no official regulatory recommendation about it.

Finally, when artificial intelligence is involved in the workflow, it could be helpful to refer to published literature in the clinical field for further extrapolation (e.g., FDA validation of a breast cancer diagnostic system in radiology, AI-based retinal image analysis [diabetic retinopathy]) [25,26].

5. Standard Operating Procedures for WSI users

The use of DP in a GLP environment requires a specific set of SOPs[27]. These SOPs are applicable to all personnel involved in the digitization and evaluation processes, and must describe the individual workflow processes [28,29]. This includes the process for image generation as well as QC checks of digital image as part of study conduct.

It is recommended that SOPs mention that the glass slide remains the reference and can be used at any time during the process as a failsafe.

In addition, the SOPs describing the protocol/report generation should make clear that the use of digitized slides be mentioned in the protocol and report.

An area of particular importance to be covered by these SOPs is the archiving procedure (see details in Section 6).

Finally, SOPs should mention the need for user training, disaster recovery, periodic refreshing of electronic records, disposal of archived records and materials as for any other information system within a GLP environment.

6. Storage and archiving

OECD GLP documents use different terminology (e.g. storage, retention and archiving) interchangeably, leaving room for some interpretation. In the context of this report, storage means storage during operational use as well as storage in the archive. This is reflected in OECD 17, section 3.2 (78).

Consequently, data storage should be considered for each computerized system used to perform GLP studies during the study phase and archiving period.

In case of format conversion across the data transfer chain, it is key that the validation process clarifies which file(s) will be archived. WSI should be archived in a format that 1) enables the system lifecycle management plan and, 2) is a faithful representation of the glass slide. Since the validation of the pixel chain has already proven that the WSI file format used for assessment by the pathologist is a faithful replica of the glass slide in the validated viewer, archiving this format is the easiest. However, other formats may be archived as long as the validation process showed that these were faithful replicas to each other and to the glass slide when visualized in the validated viewer.

In addition, from a data integrity perspective, there can be storage in an active system, followed by more restricted storage in an archived capacity later.

An area of particular importance is the archiving procedure for the record retention period, including not only the whole slide images and related metadata but also retention of specific software versions associated with the archived images to ensure readability over time, and/or universally readable image file formats. [10] A useful checklist to help prevent data loss, Lab Information System (LIS) interface shutdown/recovery and data preservation/destructive event has been published by the College of American Pathologists and could also be applicable to the nonclinical domain. [27] Storage and archiving of WSI can be achieved technically through network-based solutions, including cloud-based servers, remote servers, and/or local server-based networks, but there has not been any regulatory endorsement for a particular approach. [30]

21CFR58.195 recommends that documentation, records, raw data and specimens pertaining to a nonclinical laboratory study shall be retained in the archive(s) for whichever of the following periods is shortest:

(1) A period of at least 2 years following the date on which an application for a research or marketing permit, in support of which the results of the nonclinical laboratory study were submitted, is approved by the Food and Drug Administration.

(2) A period of at least 5 years following the date on which the results of the nonclinical laboratory study are submitted to the Food and Drug Administration in support of an application for a research or marketing permit for investigational new drug applications (INDs) or applications for investigational device exemptions (IDEs),

(3) In other situations (e.g., where the nonclinical laboratory study does not result in the submission of the study in support of an application for a research or marketing permit), a period of at least 2 years following the date on which the study is completed, terminated, or discontinued.

OECD recommendations differ from that approach. According to OECD No 1 it must be ensured that after completion (including termination) of the study, the study plan, the final report, raw data and supporting material are archived.[28] If slide images are not categorized raw data, they may still likely be considered “supporting material”. Archiving periods are not defined in the OECD documents, but may differ in national laws. (e.g. in Germany the Chemicals Act requires 15 years after study finalization.)

A process must exist and be described by SOPs for data retrieving per 21CFR part 11 and European Commission on Health and Consumers Directorate[31.]

It has also been recommended that searchability is a characteristic of the storage solution although no regulatory requirement supports it [32].

Achieving a sufficient level of security for storage and archiving can be obtained by a combination of administrative, physical and technical approaches[33] but these are recommendations without any specific regulatory guidance applicable to WSI in a GLP environment. [33]

Data integrity should be ensured during site-to-site transfer of digitized images and metadata for primary read, contemporaneous and retrospective peer reviews. This has been achieved so far by checksum comparisons, although no regulatory guidance currently supports this approach. A clear definition of the checksum comparison approach should be defined either in the SOPs, or in the study protocol, and should be a component of the validation effort.

Finally, a significant unknown pertaining to the server location remains, as there might be a need to inspect the GLP archive physically, which in the case of cloud-base services may be challenging, except for some company-specific private (on-premise) cloud installations.

As per OECD, the Principles of GLP require that a test facility has an archive to provide secure storage of records and materials[34]. This will usually consist of archive facilities within the test facility itself, but the use of contract archive facilities is not precluded. In this situation, the guidance contained within this document should equally apply to the contract archive facilities. Contract archive facilities are involved in processes dealing with GLP studies and thus should be subject to inspections by Quality Assurance

Programs, and by Monitoring Authorities, to assess the compliance with the GLP Principles. A pragmatic approach could thus be “on-premise” cloud storage solutions.

In any case archive location should be described in the study report, but whether location means a physical location or a logical one is not defined at the moment.

Conclusion

Although GLP have been in place for decades in nonclinical pathology, the recent technological evolution has allowed to replace glass slides by digitized equivalent. As the profession is embracing the change and relies on fundamental GLP principles to incorporate digital pathology in routine workflows, certain aspects such as storage duration, server access needs, and GLP categorization of digital images still need to be discussed with monitoring authorities to align on a common understanding of requirements to safely deploy this technology in compliance with GLP requirements.

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