**GLOSSARY – Version 1.0 (status November 2020)**

The following glossary of terms is considered an introductory overview of specific terms used in the context of regulatory science and digital pathology. Some words in this glossary refer to specific settings, rules, or regulations. Please keep in mind that the information here is considered educational and provides a brief description of the typical context of use. If the provided context seems incomplete, we recommend using the primary source (i.e., peer-reviewed reference), official document, regulation, or legally applicable definition.

At the end of this page is an Appendix with additional resources and instructions for feedback

**Content: (available as .pdf download here).**

**Alphabetic index:** Regulatory science; Regulatory Guidance Framework…. (we will add this later)

**Thematic order**

**Regulatory Science.** The science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products.

**Regulatory Science (Medical Devices).** Regulatory science is the scientific discipline equipped with methods, tools, approaches, and standards for assessing the safety, effectiveness, quality, and performance of medical devices. By providing concrete scientific evidence for more robust, timely or lower cost evaluations of technologies, advances in this scientific discipline can reduce the time and cost of medical device development, assessment and regulatory review

**Regulatory Guidance Framework.** Here defined as rules & regulatory guidance documents pertinent to the field of digital pathology and AI/ML

**Regulatory Science Initiative (here the Alliance).** Collaborative community for the particular problem of digital pathology, working towards providing input into the regulatory guidance framework (LINK) and creating an integrated solution for digital pathology.

**FDA Authorization.** FDA decisions made on applications (e.g., PMA approval, 510(k) clearance, HDE approval, and De Novo granting order) are collectively referred to as marketing authorizations.

**Class I, II, III.** Three regulatory classes for medical devices based on degree of control necessary to assure safety and efficacy. Class I (=lower risk, general controls), Class II (=moderate risk, general and special controls; common with 510(k) and De Novo devices), and all devices placed into Class III are subject to premarket approval (PMA).

**FDA Clearance/cleared\*.** When a Premarket Notification application is cleared by the FDA; also known as 510(k) clearance. This is for new moderate risk devices that are “substantially equivalent” to existing FDA class II authorized products.

**FDA Approval/approved\*.** When a Premarket Approval (PMA) application is approved by the FDA; also known as PMA- or premarket approval; takes longer and more expensive than 510(k); used in context of new high-risk devices. The 510(k) Program: Evaluating Substantial Equivalence in Prematket Notifications

<https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443.pdf>

Guidance Document: Deciding When to Submit a 510(k) for a change to an Existing Device. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/deciding-when-submit-510k-change-existing-device>

**FDA De Novo/granted\*.** When a De Novo application is granted by the FDA. This is for new low or moderate risk devices that do not have a “substantially equivalent” FDA authorized predicate on the market.
Special controls accompany all de Novo classifications.
Special controls outline submission requirements for medical devices with similar IFU.
Special controls are defined for a device type that can be broad or narrow.
Link to special controls: <https://www.fda.gov/medical-devices/overview-device-regulation/regulatory-controls#special>

**FDA qualification/qualified.** Qualification means that the FDA has evaluated the tool and concurs with available supporting evidence that e.g., a tool produces scientifically plausible measurements and works as intended within the specified context of use.

**IFU:** Indications for Use. Part of the definition of a medical device are the indications for use. This is a very important topic and requires research to craft an IFU for a device.

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/device-labeling-guidance-g91-1-blue-book-memo>

**Intended Use.** Objective aim of medical products manufacturers related to the purpose of the products, processes or services; see GHTF/SG1/N70:2011 or 21 C.F.R. 801.4

**Device Advice:** A comprehensive FDA resource from the Center for Devices and Radiological Health (CDRH) for comprehensive regulatory education

<https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance>

**DHCoE Digital Health Center of Excellence.** The Digital Health Center of Excellence (DHCoE) is part of the planned evolution of the Digital Health Program in the Center for Devices and Radiological Health (CDRH) and will align and coordinate digital health work across the FDA. It marks the beginning of a comprehensive approach to digital health technology, setting the stage for advancing and realizing the potential of digital health. <https://www.fda.gov/medical-devices/digital-health-center-excellence/about-digital-health-center-excellence>

**MDDT/MDDT program.** Medical Device Development Tools/Program. An FDA program to qualify tools that device sponsors can use in the development and evaluation of medical devices. The FDA’s Medical Device Development Tools (MDDT) program is a way for the FDA to qualify tools that medical device sponsors can use in the development and evaluation of medical devices. It is a way for the broader community (academia, health providers, and government scientists, not just industry) can impact the regulatory process. [Webpage: FDA page, “Medical Device Development Tools (MDDT)”](https://www.fda.gov/medicaldevices/scienceandresearch/medicaldevicedevelopmenttoolsmddt/%22%20%5Ct%20%22_blank)

**MDIC: Medica Device Innovation Consortium** is an independent organization that brings together the expertise and resources of Medical Device Stakeholders to address strategic, technical issues that affect the medical device industry and the public.

**DDT/DDT program:** Drug Development Tools/Program. An FDA program to qualify tools that drug sponsors can use in the development and evaluation of drugs.

**CADe/CADx** – Computer Aided Detection and Diagnosis: [Webpage: Software as a medical device](https://www.fda.gov/medical-devices/digital-health/software-medical-device-samd) Computer aided detection (CADe) guidance – Radiology [Webpage: Non-clinical=Stand-alone=No human in the loop:](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/computer-assisted-detection-devices-applied-radiology-images-and-radiology-device-data-premarket) [Webpage: Clinical=Reader Study=Human in the loop:](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-performance-assessment-considerations-computer-assisted-detection-devices-applied-radiology)

**Quantitative Imaging.** [Guidance Technical Performance Assessment of Quantitative Imaging in Device Premarket Submissions](https://www.fda.gov/regulatory-information/search-fda-guidance-documents/technical-performance-assessment-quantitative-imaging-device-premarket-submissions)
Quantitative imaging biomarkers alliance (<https://www.rsna.org/en/research/quantitative-imaging-biomarkers-alliance>)

**Continuous learning/Adaptive algorithms.** An algorithm that changes its behavior at the time it is run based on information available and on a priori defined reward mechanism (=criterions)
[Webpage, Artificial Intelligence and Machine Learning in Software as a Medical Device](https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-software-medical-device)
[White paper, Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD)](https://www.fda.gov/media/122535/download)

**Mock submission.** Representation of a premarket application (PMA or 510(k)) of a hypothetical device with hypothetical characteristics and companion information. Mock submissions provide a mutually beneficial way for the FDA and external communities to identify the issues that the field should address to clarify the regulatory pathway for a new device or device area.
 [Webpage: MDICx webinar that includes **a presentation on mock submissions to FDA/CDRH.**](https://mdic.org/event/computational-modeling-simulation/)

 [Slides: Mock Submissions to FDA/CDRH: History and Lessons Learned:](http://mdic.org/wp-content/uploads/2014/05/CMS-Summit-Myers.pdf) by Kyle Myers, Director DIDSR/OSEL/CDRH/FDA. This presentation was made as the agency was working with MDIC to pursue a mock submission about, “Augmenting a Clinical Study with Virtual Patient Models.” [Webpage: All the](https://webcache.googleusercontent.com/search?q=cache:C2Ru6HlIKEAJ:https://mdic.org/project/virtual-patient-vp-model/+&cd=7&hl=en&ct=clnk&gl=us&client=firefox-b-1-d" \t "_blank) **[mock submission documents](https://webcache.googleusercontent.com/search?q=cache:C2Ru6HlIKEAJ:https://mdic.org/project/virtual-patient-vp-model/+&cd=7&hl=en&ct=clnk&gl=us&client=firefox-b-1-d" \t "_blank)** [to and from the MDIC team and FDA.](https://webcache.googleusercontent.com/search?q=cache:C2Ru6HlIKEAJ:https://mdic.org/project/virtual-patient-vp-model/+&cd=7&hl=en&ct=clnk&gl=us&client=firefox-b-1-d" \t "_blank) Actually, this cached web link seems to now point to the updated Virtual Patient Page at MDIC which is missing the FDA submission feedback.
The mock submission was followed quickly by actual submissions.
Slides, Mock Submissions updated [20190412-HTTMockSubmissions.pdf](https://ncihub.org/groups/eedapstudies/wiki/DeviceAdvice/File%3A20190412-HTTMockSubmissions.pdf) (1 MB, uploaded by Brandon D. Gallas 1 year 6 months ago)
[Updated Virtual Patient Page at MDIC](https://mdic.org/project/virtual-patient-vp-model/)
 The virtual patients mock submission was preceded by [“Protein-Based Multiplex Assays: Mock Presubmissions to the US Food and Drug Administration”](http://clinchem.aaccjnls.org/content/56/2/165) , Regnier et al. [Supplementary Materials](https://academic.oup.com/clinchem/article/56/2/165/5622492%22%20%5Cl%20%22supplementary-data%22%20%5Ct%20%22_blank)

**Q-sub/Q-submission:** A mechanism for sponsors to obtain FDA feedback on:

* Potential or planned medical device Investigational Device Exemption (IDE) applications,
* Premarket Approval (PMA) applications,
* Humanitarian Device Exemption (HDE) applications,
* Evaluation of Automatic Class III Designations (De Novo requests),
* Premarket Notification (510(k)) Submissions,
* Clinical Laboratory Improvement Amendments (CLIA) Waiver by Applications (CW),
* Dual 510(k) and CLIA Waiver by Application Submissions (Duals),
* Accessory Classification Requests, and
* Certain Investigational New Drug Applications (INDs) and Biologics License Applications (BLAs) submitted to the Center for Biologics Evaluation and Research (CBER)) (specifically, INDs and BLAs for devices that are regulated as biological products under section 351 of the Public Health Service (PHS) Act).

**PreSub/Presubmission.** An official inquiry process to obtain regulatory feedback prior to an intended submission.

Pre-submissions and Meetings with FDA Staff

<https://www.fda.gov/media/93740/download>

Guidance document: Requests for Feedback onMedical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff.

<https://www.fda.gov/media/114034/download>

**Submission Issue Request (SIR):** A SIR is a request for FDA feedback on a proposed approach to address issues conveyed in a marketing submission (i.e., PMA, HDE, De Novo request, 510(k), Dual, or BLA) hold letter, a CW hold letter, an IDE Letter, or an IND Clinical Hold letter. It is intended to facilitate interaction between FDA and the submitter to quickly resolve or clarify issues identified in these letters. <https://www.proximacro.com/faqs/what-is-a-submission-issue-request-sir>

**Study Risk Determination:** a request for FDA determination for whether a planned medical device clinical study is significant risk (SR), non-significant risk (NSR), or exempt from IDE regulations <https://www.fda.gov/media/75459/download>

**Informational meetings:** a request to share information with FDA without the expectation of feedback. This information sharing can be helpful in providing an overview of ongoing device development and familiarizing the FDA review team about new device(s) with significant differences in technology from currently available devices.

**Other Q-submission types:** the Q-Sub program provides a mechanism to track interactions between the sponsor and FDA. Currently, in addition to the Q-Sub types above, the interactions that are tracked in the Q-Submission program include the following:

* PMA Day 100 Meetings
* Agreement and Determination Meetings
* Submissions associated with the Breakthrough Devices Program
* Accessory Classification Requests

 **Breakthrough Devices Program:** A voluntary program for certain medical devices and device-led combination products that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions. This program is intended to help patients have more timely access to medical devices by expediting their development, assessment, and review, while preserving the statutory standards for premarket approval, 510(k) clearance, and De Novo marketing authorization.
<https://www.fda.gov/medical-devices/how-study-and-market-your-device/breakthrough-devices-program>

**WSI/VM.** Whole slide imaging and virtual microscopy is largely synonymous and refers to the digitization of microscopic slides.

**WSI system.** Defined as Whole Slide Imaging system. The FDA-cleared WSI systems include three components: (a) an image acquisition subsystem (scanner) that converts the content of a glass slide into a digital image file, (b) an image management and viewing system (workstation environment or “viewer”), and (c) the display for viewing the digital images. The image management system and display could be treated as individual medical devices if and when a company is successful with a premarket application.

**Device/Medical Device.** A medical device is a technical device (e.g. a WSI system) in combination with an intended use for a specific regulatory agency (here Technical Device + Intended Use + Country, here U.S./FDA). ”…an instrument, apparatus,…, machine,…, in vitro reagent,…, including a component part,…, intended for use in the diagnosis of disease or other conditions,…”.

**SaMD/**Software as a medical device is defined ads software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device.

**Computational pathology.** A branch of pathology that involves computational methods to analyze pathology that incorporate multiple sources of data for diagnostic decision-making and for the study of disease. <https://www.fda.gov/medical-devices/digital-health-center-excellence/software-medical-device-samd>

**Integrated solution for digital pathology.** A proposed term to account for an interoperable, modular, clinically integrated image-based workflow that includes all steps from specimen collection to diagnostic report. Specifically, this includes collection, specimen preparation, histologic processing, staining, image acquisition, metadata capture, storage, clinical decision support software (e.g., AI/ML algorithms), and diagnostic reporting.

**Digital pathology.** Tools and systems to digitize pathology slides/images and associated metadata, including image storage, review, analysis, and enabling infrastructure. To many the term also includes relevant workflow components.

**Pixel pathway.** Ill-defined term for pixel processing from image acquisition to display; e.g., “vendors are required to submit their manufactured device … as one system that encompasses the entire pixel pathway”
<https://www.jpathinformatics.org/downloadpdf.asp?issn=2153-3539;year=2017;volume=8;issue=1;spage=23;epage=23;aulast=Abels;type=2>

**Patient advocacy.** An individual or an organization typically focused on a specific, concerned with advocacy for patients, survivors, and caregivers. The Alliance aims to incorporate the patient-perspective related to improve accuracy and reproducibility of image-based diagnostics. <https://en.wikipedia.org/wiki/Patient_advocacy>

**CLIA/CLIA88.** Clinical Laboratory Improvement Amendments of 1988 (CLIA88) is the governing regulation for clinical laboratories that requires a laboratory to document that it has adequately verified or validated test performance characteristics for all clinically offered tests. A laboratory must, at a minimum, address all the performance characteristics required by CLIA, the specifics of how to verify or establish these is left by CLIA to the judgment of the laboratory director. <https://www.cdc.gov/clia/law-regulations.html>

**Verification.** A process, under CLIA, that the clinical laboratory performing the FDA authorized test must ‘‘verify’’ that the manufacturer’s performance characteristics, which were established during the FDA trial/precision study, can be obtained or exceeded by the laboratory. Specifies 4 performance characteristics: accuracy, precision, reference range, and reportable range as compared to those specified in the manufacturers package insert.

**Laboratory Developed Tests (LDTs).** Diagnostic assays, typically in vitro diagnostics, developed and used within a single clinical laboratory. <https://www.fda.gov/medical-devices/vitro-diagnostics/laboratory-developed-tests>

**Validation.** CLIA requires that laboratories performing LDTs, and modified FDA authorized tests, “establish”’ the same 4 performance characteristics that are required for verification of FDA authorized tests, as well as determine analytic sensitivity, analytic specificity, and any additional performance characteristics that may be important to establish (e.g., specimen stability, linearity). “Validation” is widely used by laboratorians to mean establishing all relevant performance characteristics of an LDT, but the term validation never appears anywhere within the CLIA regulations.

**Modalities.** Imaging modalities in the context of imaging in pathology include three broad groups: static images, dynamic images, and scanned whole slide imaging (WSI). The group of dynamic (assisted streaming video microscopy) can be subdivided into smart phone-based or robotic microscopy.

**System components (WSI).** Scanner (means of image acquisition or image acquisition system), image management system, and viewing system (=hardware). Other components are also important: Storage system (=PACS, including server configuration), interfaces to other systems (i.e., LIMS, HER, RCM), workload management software, reporting software, archiving systems.

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In case you have any suggestions or want to add a term or aspect of a definition – please see Appendix.

**Appendix**

1. Additional resources: links to other glossaries or standards

BEST (Biomarkers, EndpointS, and other Tools) Resource.

<https://www.ncbi.nlm.nih.gov/books/NBK326791/>

Developed by the FDA-NIH Biomarker Workgroup ([here](https://www.ncbi.nlm.nih.gov/books/NBK326791/)).

DICOM (Terms and Definitions)

<http://dicom.nema.org/medical/dicom/current/output/chtml/part02/sect_A.3.4.html>

Definitions

<http://dicom.nema.org/medical/dicom/current/output/chtml/part03/chapter_3.html>

Glossary of terms by the Royal college of Pathologists

<https://www.rcpath.org/discover-pathology/what-is-pathology/glossary-of-terms.html>

Etc….

1. Suggestions/updates/add-ons -please email us at:…