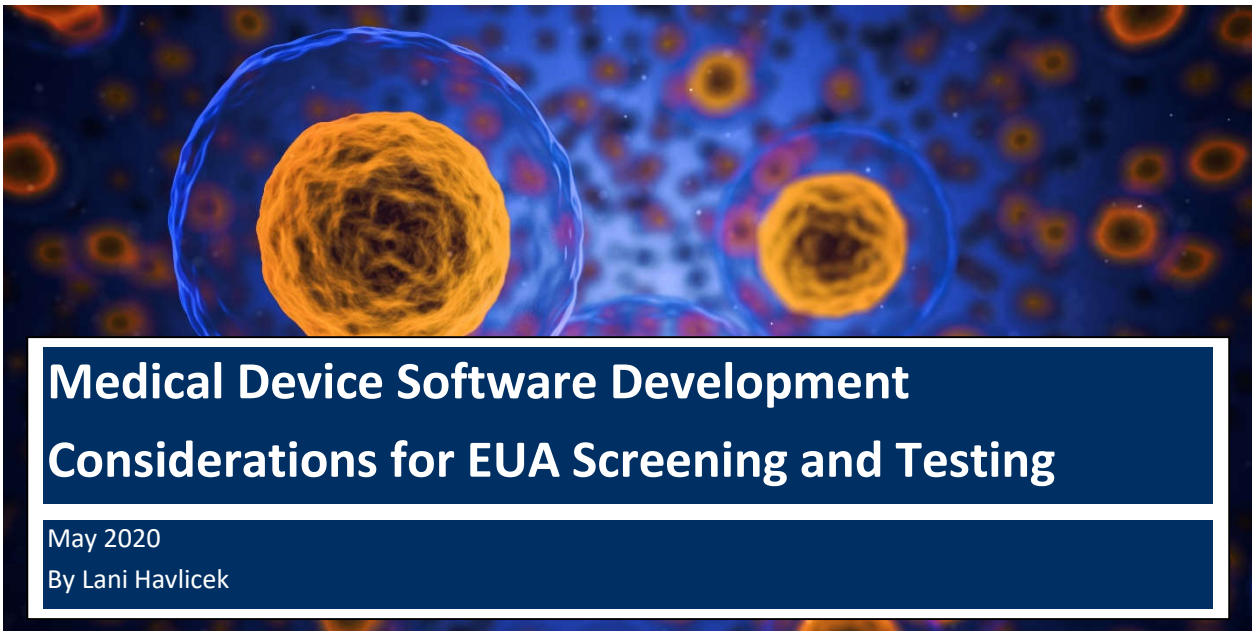

Medical Device Software Development Considerations for EUA Screening and Testing

May 2020

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It's May of 2020 and our lives have changed dramatically. The current COVID 19 pandemic has disrupted economies, supply chains, and daily life as we knew it only a few short months ago. We at Apartis echo a sentiment that we share with many when we state that we would like to see an effective cure for this virus as soon as possible so that the chaos caused by COVID 19 can be removed from our lives.

Worldwide, many professions are joined in the battle against COVID 19. Companies in the medical device software industry are doing our part to support the global diagnostics industry in the current fight against this virus. We do this by designing and developing software applications in accordance with FDA guidelines that ensure the software applications that impact health outcomes produce clinically significant and valid data.

In a pro-active response to the threat of COVID-19, the United Stated issued declaration that enabled the US FDA to grant Emergency Use Authorizations (EUAs) for medical countermeasures against COVID-19 on February 4, 2020 (U.S Department of Health and Human Services, 2020). This has sped up the development and commercialization cycles of COVID-19 screening, resulting in increased availability of testing. Products and technologies that would normally take 1-2 years to become available commercially are now becoming available within a month or 2 of development and validation. EUAs are limited in duration, but FDA guidelines for product design and development need to be followed to ensure clinical significance as well as test and data validity. This white paper details EUA medical device software development strategies for COVID 19 assays and Laboratory Developed Tests (LDTs).

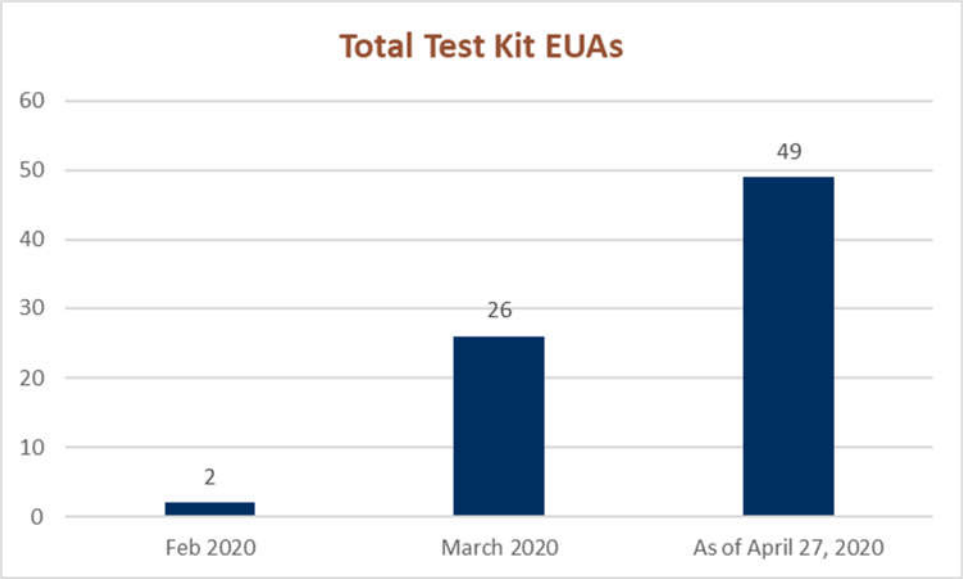
Rising to the Challenge: Widespread COVID 19 Screening & Contact Tracing

Screening of COVID 19 has been increasing at a rapid rate since the inception of the pandemic, but there is still a shortage. There are many benefits of widespread screening – it will answer several urgent questions that we keep asking ourselves – Do I have COVID 19? – Did I have COVID 19 in the past? - Can a person develop a COVID 19 immunity? – Do you have COVID 19? – What's my current risk of contracting the virus? – and the list keeps growing! If we have access to enough testing to support answering these questions at an individual level, there will be vast improvement to the health of the public at large.

The Current COVID 19 Screening Environment in the US

On February 4, 2020, the United States Department of Health and Human Services issued a Declaration under the Public Readiness and Emergency Preparedness Act for medical countermeasures against COVID-19 (U.S Department of Health and Human Services, 2020). This Declaration enables the US FDA to grant Emergency Use Authorizations (EUAs) for "qualified pandemic or epidemic product(s)" and "security countermeasure(s)" that are needed to diagnose, treat, and prevent COVID 19. This has sped up the development and commercialization cycles of these desperately needed products and technologies and resulted in an increased availability of testing.

At the publication of this white paper (search date 4/27/2020), there are EUAs for a total of 49 test kits available from manufacturers and commercial laboratories (US Food and Drug Administration, 2020).



In addition, as of March 31, 2020, the FDA has granted 21 EUAs for Laboratory Developed Tests (US Food and Drug Administration, 2020) for use in single laboratories as part of the effort to increase the availability of COVID 19 screening.

Types of Tests Available

The FDA categorizes COVID 19 tests into two types – Molecular and Serological. The two types of tests have different pros and cons. However, widespread availability of both types of tests are needed to help the world overcome the current pandemic. Molecular tests are generally more selective and specific but take longer and are more expensive than serological tests. Molecular tests tell if viral molecules were detected in a sample. Serological tests indicate if coronavirus attacking antibodies are detected in a sample. Both types of tests are critical to preventing the spread of COVID 19.

COVID 19 Molecular and Serological Testing Pros and Cons (Society for Laboratory Automation and Screening (SLAS), 2020)

Type	Pros	Cons
Molecular	• Early detection • Quick processing (hours) • Highly selective & specific	• Skilled personnel & equipment needed • Detects virus presence, not whether virus is active or inactive • Cannot determine if an infected patient has recovered
Serological	• Rapid test available at point of care (result in <1 hour for some tests) • Low cost • Can be used to test large populations • Reliably detects exposure	• Cannot determine if patient is still contagious or infected • Prone to false negatives (not as selective or specific as molecular testing)

The Difference Between EUA and Normal FDA Submissions for COVID 19 Test Kit Manufacturers and Laboratory Developed Tests

In normal times, a COVID-19 assay requires FDA/CE-IVD premarket approval (De Novo/510(k) clearance) before it can be legally marketed. This is a process that typically takes 12-24 months for comparable molecular and serological assays. The normal clearance cycle is not short enough to deliver widespread COVID19 screening capacity in a timely fashion. For Emergency Use Authorization Diagnostic Tests, the FDA has issued nonbinding recommendations for standards and guidelines that should be followed in FDA Docket Number FDA-2020-D-0867, "Policy for Diagnostic Test for Coronavirus Disease-2019 during the Public Health Emergency" (US Food & Drug Administration, 2020) which was issued on the web on March 16, 2020. The EUA believes that this policy will allow test manufacturers to be able to prepare an EUA submission for a test that has already been validated in a timeframe of 15 business days.

The major factor that allows for this rapid release is the waiving of most of the 21 CFR 820 Quality System Regulation (QSR) Requirements for this Emergency Use Authorizations. These QSR requirements are a rigorous set of guidelines designed to ensure that medical devices are safe and effective. In the FDA's "EUA Interactive Review Template for Molecular-based tests for

SARS-CoV-2 that Causes Coronavirus Disease 2019 (COVID-19)" updated March 12, 2020 (FDA, 2020), the following statement appears:

> **Under the Emergency Use Authorization (EUA) most of the 21 CFR 820 Quality System Regulation (QSR) requirements can be waived for the duration of the EUA. FDA expects that developers follow comparable practices as much as possible and may consider previous compliance history when determining whether or not to waive certain QSR requirements for a specific product. Please note adverse events, as per 21 CFR part 803, have to be reported for authorized devices*

The FDA does not want to slow down the process of making COVID-19 tests available on the marketplace, but they also do not want test manufacturers to take any risks with the design, validation, and distribution of these test kits that will negatively impact public health. Whenever possible, the FDA would like test manufacturers to comply with 21 CFR part 803 requirements and EUA registration of test kits. In the same EUA Interactive Review Template (FDA, 2020) with the waiver above, the FDA states:

> *The EUA is not a pathway to permanent marketing of your device. Therefore, we strongly recommend that you consider, in addition to an EUA, a traditional premarket submission for your IVD so that your device can still be legally marketed after termination of the emergency declaration. We recommend that you identify as soon as possible in the Pre-EUA review process any consideration of moving your product forward towards De Novo/510(k) clearance. If so some of our feedback to you may take such a long-term goal into consideration in order to prevent additional testing where it may not be needed…*

It's important to keep in mind that even though some requirements are not fully enforced during an assay or LDT's EUA authorization, manufacturers and laboratories interested in keeping their products on the market over the longer term will eventually have to demonstrate compliance.

The FDA (US Food and Drug Administration, 2020) advises that manufacturers should be aware of the following standards when producing EUA medical devices:

- IEC 60601 group standards
- IEC 62304 (ISO, 2020) for medical device software life cycle processes
- ISO 10993 for biological evaluation of medical devices
- ISO 80601 group of standards for medical electrical equipment including ventilators and respiratory devices

The Importance of Medical Device Software to the COVID 19 Testing Effort

No matter the type of testing performed, software is a major component of testing. Software streamlines the process of delivering test results to patients and clinicians. Multiple software tools are used to

- collect samples
- track samples
- process tests
- manufacture tests
- calculate test results
- report test results

Software makes data gathering and recording faster with the use of automation techniques. It also reduces the potential for processing, transcription, calculation, and reporting errors. Time is valuable when it comes to providing care to patients and high-quality and high volumes of COVID 19 data are being used daily to influence public health measures.

Software Considerations for the Design of Medial Device Software for COVID 19 EUA Applications

With over 20 years' experience in medical device software design, Apartis has the following recommendations that we are sharing with our customers on the development of software for COVID-19 EUA applications.

Define Product Goals

Determine if your product is one that you will market after the Emergency Use Authorization expires. This is important to determine because if the answer is yes, you should:

- make sure to notify the FDA of your intent to market product after EUA in your EUA submission
- implement a design and development plan framework that fulfills the immediate EUA submission requirements and at the same time be a framework that can scale up to encompass the full requirements of a De Novo/510(k) submission – the outline of a plan that you can elaborate upon after EUA approval. This will save you time in the long run because you can avoid duplicate work and rework.

Software Design Recommendations

Modular Design

Modularize software design as much as possible. Make software modules that can be reused and exchanged between different systems easily. Functionality that can be reused results in

less coding, documentation, and validation as well as makes your software more robust and manageable. Separate modules can be developed quickly allowing for the rapid development of flexible software solutions.

Standardize Modules

Modules with well understood functionality, interfaces, and dependencies are the reusable foundation of software applications. When software modules have standardized interfaces, you can build your applications rapidly and reliably. It's also easier to swap out or add modules.

Modular design and standardized module interface techniques also make your software applications more extensible. It's easier to expand the features of software that is built using these design concepts than monolithic software. If you are planning to move from an EUA to a traditional submission, it is very likely that you will be planning to add features to your software application.

Keep it Simple

Identify the key functionality needed in your software application and focus on delivering this functionality for the EUA phase. Focus on functionality that is essential to the basic safety and performance of your product. We need to get reliable COVID 19 assays on the market rapidly and report accurate test data quickly.

Look at your feature list – delivering 80% of the desired functionality in 20% of the time is more critical for an EUA than delivering 100% of the desired functionality in 100% of the time.

If you are moving on to a traditional De Novo/510(k) submission, you can plan for the development of additional functionality in a phased approach and release updates after your product receives EUA.

Software Documentation Recommendations

Consider Using a Software Lifecycle Management Tool

Using an online software lifecycle tool to manage software requirements, documentation, planning, testing, and tracking is something that we find extremely useful. Our integrated software application lifecycle management tool lets us track projects in real time and our customers can pull pertinent project information (requirements, testing coverage, issues, etc.) in real time as well as input information directly. Apartis has interfaces to our tool that allow us to generate design history file documents directly from the tool database.

Issue/defect tracking is required for EUA applications (FDA, 2020) and software lifecycle management tools are extremely useful tools to track these.

These tools are relatively straightforward and have numerous benefits to the software lifecycle process that help you manage your software development. Tools of note include:

- Jira
- SpiraTeam by Inflectra
- Jama
- Visual Studio Teams Services

Limit Design Depth

At Apartis, we implement a multi-layered design strategy that allows us to use the same basic process for design of IVD, RUO, and applications with minimal regulatory requirements. In a nutshell, we define a basic design depth common to all our software projects:

1. High Level Specifications that are verified at a high level (system testing). These are commonly referred to as Software Requirement Specifications.

For more critical (applications with higher risk/regulatory classifications) we add a layer of more detailed specifications based on the Software Requirement Specifications:

2. Design Specifications (which are more technical requirements that trace to the High-Level Requirements) and Integration Testing to ensure Design Specifications are met.

For even higher criticality applications, we add a 3rd level of design depth which we call:

3. Detailed Design Specifications – These are even more granulated requirements that are derived from Design Specifications and these are tested at the deepest, lowest level. In our process, Apartis refers to this as Unit Testing.

For an EUA, we recommend that you limit design depth to the highest level – keep as many requirements as possible at the Software Requirement Specification level.

After EUA approval, if you have plans to make a De Novo/510(k) product submission, you can add the needed depth of design and testing for your software.

Limit EUA Documentation to Testing Documentation

The critical documentation for your EUA submission is your testing documentation. This is the documentation you should focus on for the EUA submission phase of your software development efforts.

Software Validation Recommendations

Combine Design Testing into One Testing Group

Consolidate your EUA testing efforts to make the most of your limited time.

Limit Low Level Testing to Only Where Needed

You don't want your software testing to blow up your timeline for an EUA release, but you need to be conscientious and test modules and units that are critical to your EUA product performance (for example, modules that perform calculations, have direct impact on results/product validity). These modules should be identified and tested for EUA submissions.

Low level testing of noncritical modules can be deferred until after EUA approval.

Draft Higher-level Test Cases from ad hoc Testing

Test your software at the high level so that you can ensure your product functions reliably and reproducibly. In development, we employ an ad hoc testing strategy – this is informal undocumented testing that we use to see if the software is functioning according to specification. For an EUA submission, base your testing off ad hoc testing that represents the most common software processes – a limited number of high-level test cases that capture the bulk of software functionality and critical functionality. Again, the urgent need for your product outweighs testing formality, but it is important to implement due diligence.

Features to Consider Implementing in EUA Software Applications

Helpful features to implement in EUA software can include:

- Result tracing in log files (helps you prove that results are reproducible)
- Trace User Actions (helps in troubleshooting issues)
- Trace System Actions (helps in troubleshooting issues)
- Store all raw data (allows for reprocessing if needed)
- Data interface (you can add integrated analysis features later (perhaps even using this same interface), but often Excel can collect data from an interface and make necessary analysis calculations)
- LIS interface (consider a flat file or XML for a faster solution, add ASTM/HL7 after EUA is granted)
- If possible, support a REST API. A REST API is a commonly used architectural style/interface that supports flexible communications and interoperability between software applications.

Moving from EUA to FDA Submission: Software Development Tips

Keep the following key points in mind if you plan to move your software from EUA to FDA submission as they will prevent rework and duplicate work:

- Design Modularization and independency
- Keep software simple, don't develop a "spaghetti monster"
- Defined interfaces (internally and externally)
- Keep one level of design documentation up to date
    - Makes change control easier
    - Important for additional documents needed for FDA submission
    - Important for easier test case definition

Apartis is a software development partner specializing in OEM and customized software solutions for medical devices and the life sciences. We welcome any inquiries you have regarding this white paper or our software services in general. Please contact us at aiminfo@apartis.com or visit apartis.com to learn more.

Bibliography

FDA. (2020, April 30). *Emergency Use Authorization COVID 19 NAT Template.* Retrieved from FDA: https://www.fda.gov/media/135900/download

ISO. (2020, April 29). *IEC 62304:2006 Medical device software — Software life cycle processes*. Retrieved from ISO website: https://www.iso.org/standard/38421.html

Society for Laboratory Automation and Screening (SLAS). (2020, April 27). *Information: SLAS COVID 19 Infographic.* Retrieved from SLAS Web site: https://slas.org/resources/information/covid-19-infographic-resources/

U.S Department of Health and Human Services. (2020, April 27). *Office of the Assistant Secretary for Preparedness and Response.* Retrieved from Public Health Emergency: https://www.phe.gov/Preparedness/legal/prepact/Pages/COVID19.aspx

US Food & Drug Administration. (2020, April29). *FDA Docket Number FDA-2020-D-0987*. Retrieved from US FDA Regulatory Information: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/policy-diagnostic-tests-coronavirus-disease-2019-during-public-health-emergency

US Food and Drug Administration. (2020, April 27). *COVID 19 Emergency Use Authorizations.* Retrieved from Medical Devices: https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations#covid19ivd

Wikipedia. (2020, April 29). *IEC 62304*. Retrieved from Wikipedia: https://en.wikipedia.org/wiki/IEC_62304