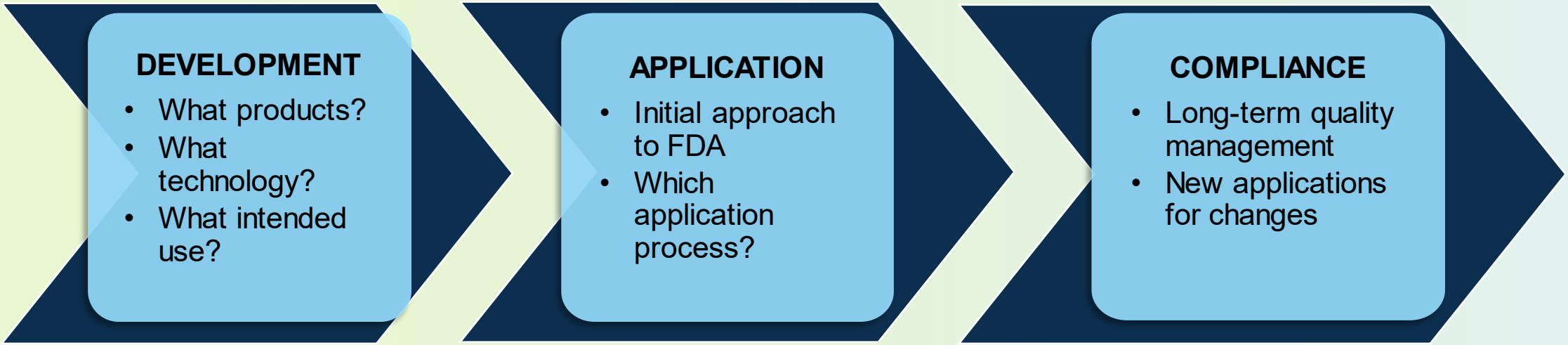
Medical Device Regulatory Case Study

Acoustic Imaging AI^2 Toolkit

Regulatory Overview

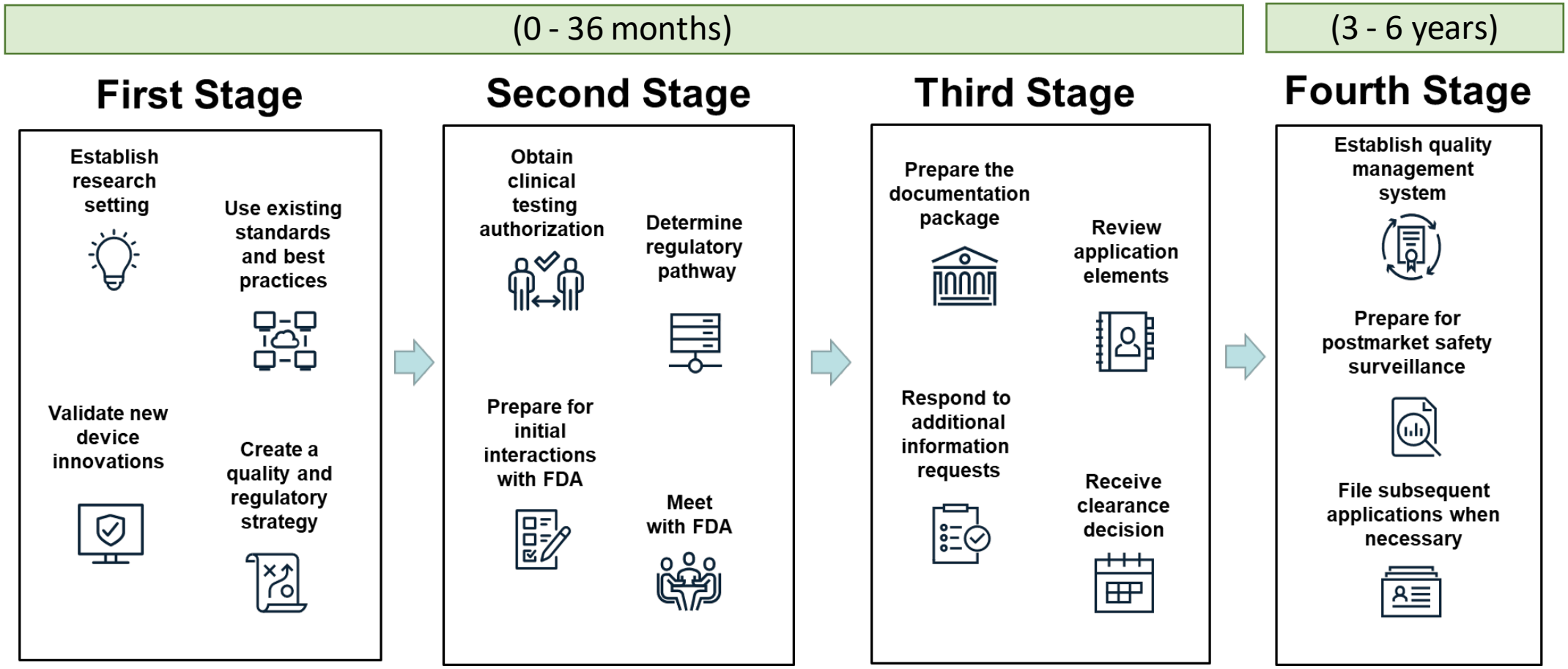
To bring a medical product to market, an innovator needs to understand the entire commercialization process and manage multiple tasks related to early-stage research and development, clinical trials, regulations, and reimbursement. The goal of receiving Food and Drug Administration (FDA) approval is a major milestone in leading a new technology to commercial success. Innovators developing new medical products need to become familiar with the regulatory processes that may be applicable to their drug, device, or biologic so they can successfully navigate the approval process.

Key Elements of a Regulatory Strategy



Regulatory Strategy Activities Roadmap

This case study breaks down the process described in our *Regulatory Knowledge Guides*. It will take you step-by-step through a process innovators may follow to develop a strategy for FDA market authorization. We'll walk through each step from the innovator's point of view. Aspects of the process may be conducted together, roughly in tandem. Each slide presents one aspect of a particular stage of the process.



Introduction to CEO and Product

Dr. Jade Murphy is an ultrasound imaging expert, and the principal investigator of an R01 grant from the National Institute of Biomedical Imaging and Bioengineering focused on biomarkers of liver damage. They recently formed a company called Acoustic Imaging Lab, in continued collaboration with their academic research lab and the University's start up incubator program. The first product that Acoustic Imaging Lab intends to commercialize is a suite of ultrasound image processing tools that leverage artificial intelligence to segment regions of interest and assess quantitative imaging biomarkers. Jade leads the technical development, while Mumtaz Kalb leads the business and operations as CEO/COO. Mumtaz has experience leading several software companies, but this is her first exposure to the healthcare space.

What will Acoustic Imaging Lab need to do to navigate regulatory requirements and legally market their device?

Here's some background on the software in development as part of the R01 grant:

Product Description:

- The software is called the Acoustic Imaging AI^2 Toolkit.
- AI^2 Toolkit provides common ultrasound image manipulation tools including contrast adjustment, measurement functions, and a semi-automated segmentation capability that is driven by machine learning.
- The unique innovation of AI^2 Toolkit is the accurate quantitative assessment of shear wave speed as an estimate of liver fibrosis.

Why liver fibrosis?

- According to the World Health Organization, each year over one million people die from chronic liver disease.
- By measuring the speed of propagation of a shear wave as it traverses liver tissue, stiffness of the liver (which is a biomarker for the amount of fibrosis) can be measured.
- The Quantitative Imaging Biomarker Alliance has reached stage 2 consensus on ultrasound shear wave speed.

First Stage

First Stage

- Establish research setting
- Use existing standards and best practices
- Validate new device innovations
- Create a quality and regulatory strategy

Second Stage

- Obtain clinical testing authorization
- Determine regulatory pathway
- Prepare for initial interactions with FDA
- Meet with FDA

Third Stage

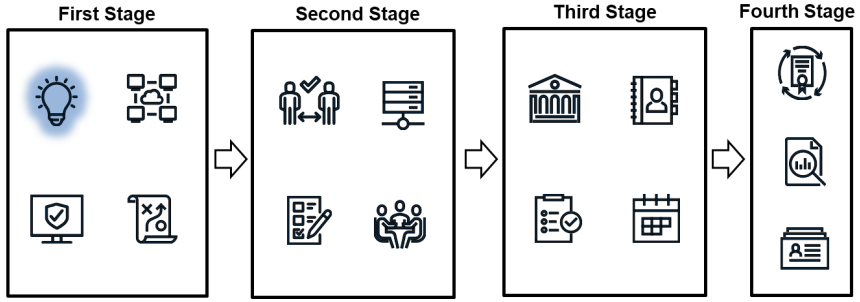
- Prepare the documentation package
- Review application elements
- Respond to additional information requests
- Receive clearance decision

Fourth Stage

- Establish quality management system
- Prepare for postmarket safety surveillance
- File subsequent applications when necessary

First Stage: Establish Research Setting

Jade and Mumtaz are initially focused on completing the first prototype of the AI^2 Toolkit. They need to ensure that their team has the necessary resources and directions to move toward commercialization. The grant proposal included an initial strategy, but now that the plan is in motion, they need to take inventory of their product development environment to anticipate any challenges ahead.



Jade evaluates the research tools they have at their disposal. An existing Institutional Review Board approval provides access to historical clinical data, as well as new data from healthy volunteers (typically students within their lab). A recent graduate from Jade's lab is the lead developer for the AI^2 Toolkit software – they have deep technical expertise on algorithm development but may need guidance when it comes to maintaining software quality.

Mumtaz assesses their anticipated business needs and resources. Because Acoustic Imaging Lab works through the University's incubator program, she has a several entrepreneurial resources including seed funding, mentorship and connections to industry leaders, and access to investors through coordinated pitch events/workshops. Furthermore, as an NIH grant recipient, the Acoustic Imaging Lab can contact their IC's Small Business Office, and the OER Small Business Education and Entrepreneurial Development office for commercialization support.

Key questions:

- Has an Institutional Review Board authorized research and development?
- Does the scientific/clinical team have access to the data and equipment they'll need?
- Has the team finalized the technological design and intended use?

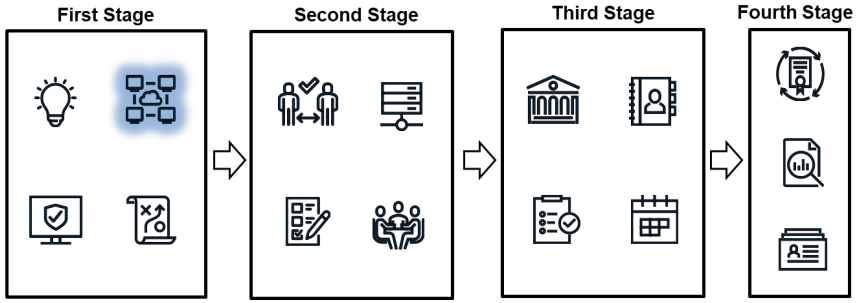
First Stage: Utilize Existing Standards and Guidances

Performance testing of the device is a critical part of regulatory approval, and the AI^2 Toolkit is no exception. Thankfully, there are several standards and best practices available to the imaging community through academia, trade organizations, and Center for Devices and Radiological Health (CDRH).

Jade reached out to CDRH's Division of Industry and Consumer Education (DICE) to find relevant guidance documents. DICE provided references to multiple resources, the most important for their testing plans being the Technical Performance Assessment of Quantitative Imaging in Radiological Device Premarket Submissions. Jade's team carefully includes the considerations outlined in the guidance including bias, precision, limits of detection, limits of quantitation, linearity, sensitivity, specificity, and uncertainty in their testing and development plans.

Because the AI^2 Toolkit's distinguishing imaging metric is the shear wave speed, the team also incorporated the recommendations from the Quantitative Imaging Biomarker Alliance, (QIBA) a large radiology trade organization. QIBA has produced a consensus profile on Shear Wave Speed for Liver Fibrosis, which Jade's team incorporates to ensure completeness of testing, as well as users correct interpretation of the measurement.

Many medical devices need to show the interoperability of the inputs and outputs with other devices in the ecosystem. In the case of medical imaging, this is facilitated by the DICOM standard. Jade's team ensures that DICOM metadata is appropriately written and read, so the AI^2 Toolkit can plug into existing hospital PACS systems.

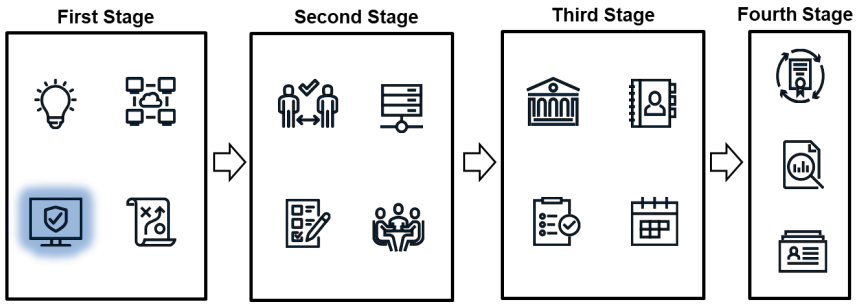


Key questions:

- What common aspects of the device's performance have well-understood test methods?
- Has FDA issued guidance relevant to the device?
- How does the device and its output integrate into the user's workflow and the broader device ecosystem?

First Stage: Validate New Device Innovations

While several device attributes can be validated using existing standards, any new device will include some innovations that may not be applicable. Therefore, Jade researches what validations may be needed for the AI^2 Toolkit's novel elements.



Part of developing a new device is identifying which elements have well established standards and testing methods and which elements are more novel and do not have clearly defined validation standards.

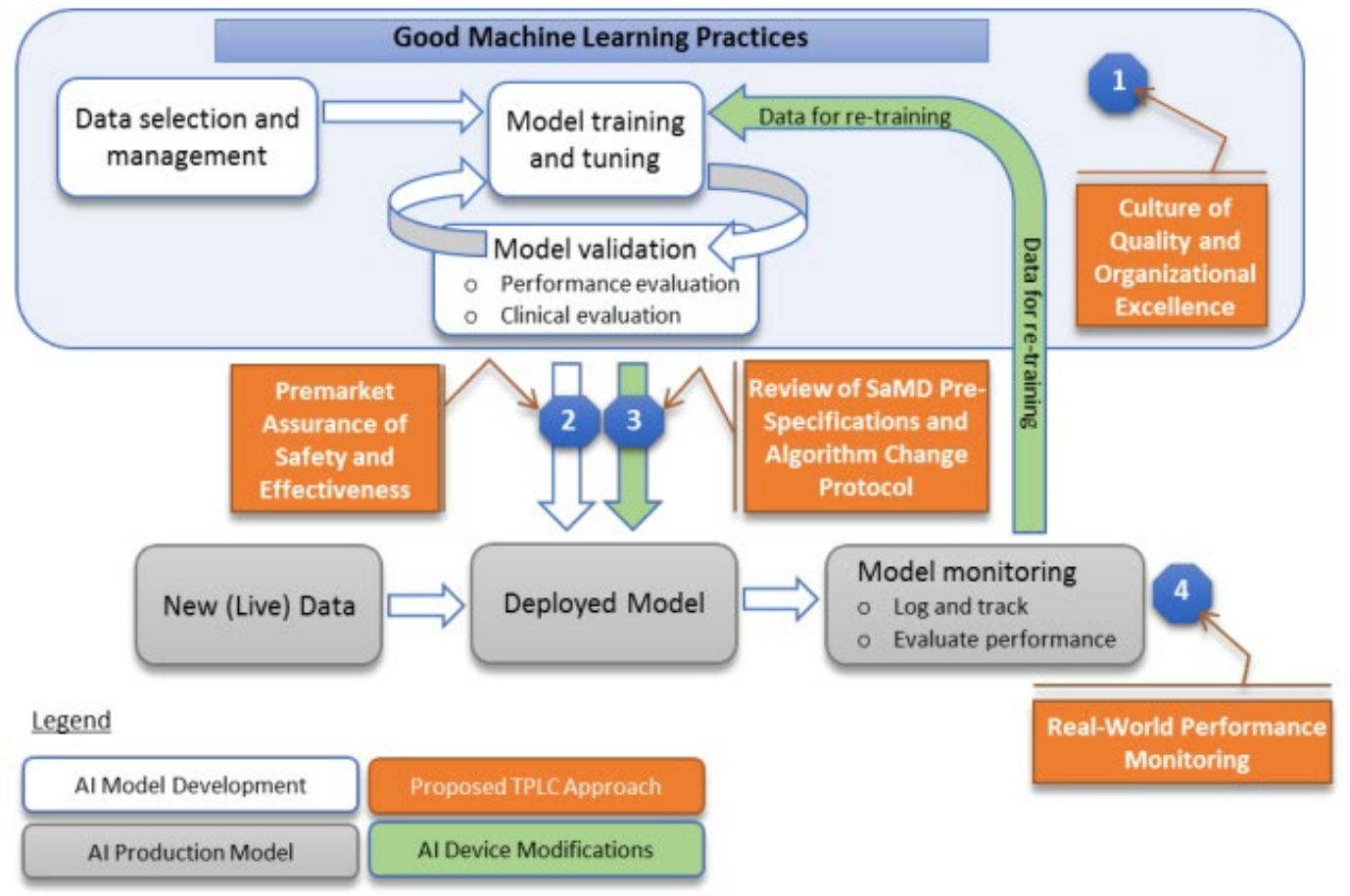
With AI-enabled modules in the AI^2 toolkit, Jade reviews the validation requirements of an AI-based healthcare application algorithm and an AI-enabled medical product. They find and review the Good Machine Learning Practices for Medical Device Development: Guiding Principles. Based on this, Jade reaches back to their team and ensures that these guiding principles were followed, including that the training and validation hold-out data sets were maintained separately, are representative of the intended patient population, and have similar clinical conditions of the intended use.

Furthermore, Jade knows that AI/machine learning is a rapidly evolving field particularly for Software as a Medical Device (SaMD). Jade sees FDA has published several resources on AI-enabled products. Specifically, Jade reviews the Proposed Regulatory Framework for Modifications to AI/ML-based SaMD and the AI/ML SaMD Action Plan AI white paper to understand FDA's current thinking on evolving AI-enabled medical devices.

Key questions:

- What validation measures need to be developed to demonstrate performance innovative device functionality, and support a marketing submission?
- Was the product developed with the appropriate data to address concerns of bias, generalizability of the model, and support clinical claims?

Total Product Lifecycle (TPLC) Approach to Good Machine Learning Practices



- To leverage the power of AI/ML learning algorithms while enabling continuous improvement of their performance and limiting degradations, the FDA's proposed total product life-cycle (TPLC) approach is based on balancing the benefits and risks and providing access to safe and effective AI/ML based SaMD.

- Jade understands now that the initial review will also establish clear expectations for AI Labs' AI/ML-based SaMD to continually manage patient risks throughout the AI^2 Toolkit's lifecycle, including review of SaMD Pre-Specifications and Algorithm Change Protocols.

First Stage: Create a Quality and Regulatory Strategy

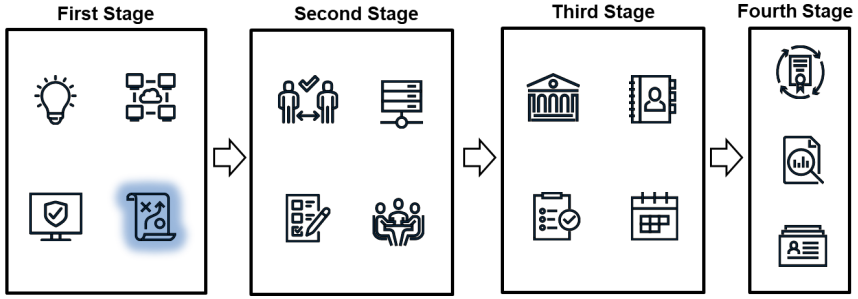
With other existing ultrasound imaging software available, the Acoustic Imaging team decides to use the liver fibrosis module as a market differentiator.

With promising results and confidence that radiologists would benefit from the AI^2 Toolkit innovations, Jade and Mumtaz begin to develop their regulatory strategy. They consider whether they can do it themselves using FDA's Regulation of Medical Devices or if they should hire a regulatory consultant.

After researching CDRH Learn, Mumtaz decides to hire a regulatory expert. As an NIH-funded innovator, Mumtaz consults with the NIH SEED Office and applies to the TABA Program for help in finding one. She works with Jade to outline the statement of work (including technical details, validation requirements, and intended use) that they need to identify the right consultant.

In interviewing regulatory consultants, she learns how CDRH is Structured and asks potential consultants if they have experience with the Office of Health Technology within the Office of Product Evaluation and Quality the office that reviews devices like theirs. For the AI^2 Toolkit, she identifies OHT8C: Radiological Health – Radiological Imaging and Radiation Therapy Devices. She also considers what consultant certifications may be useful (e.g., RAC certification by RAPS).

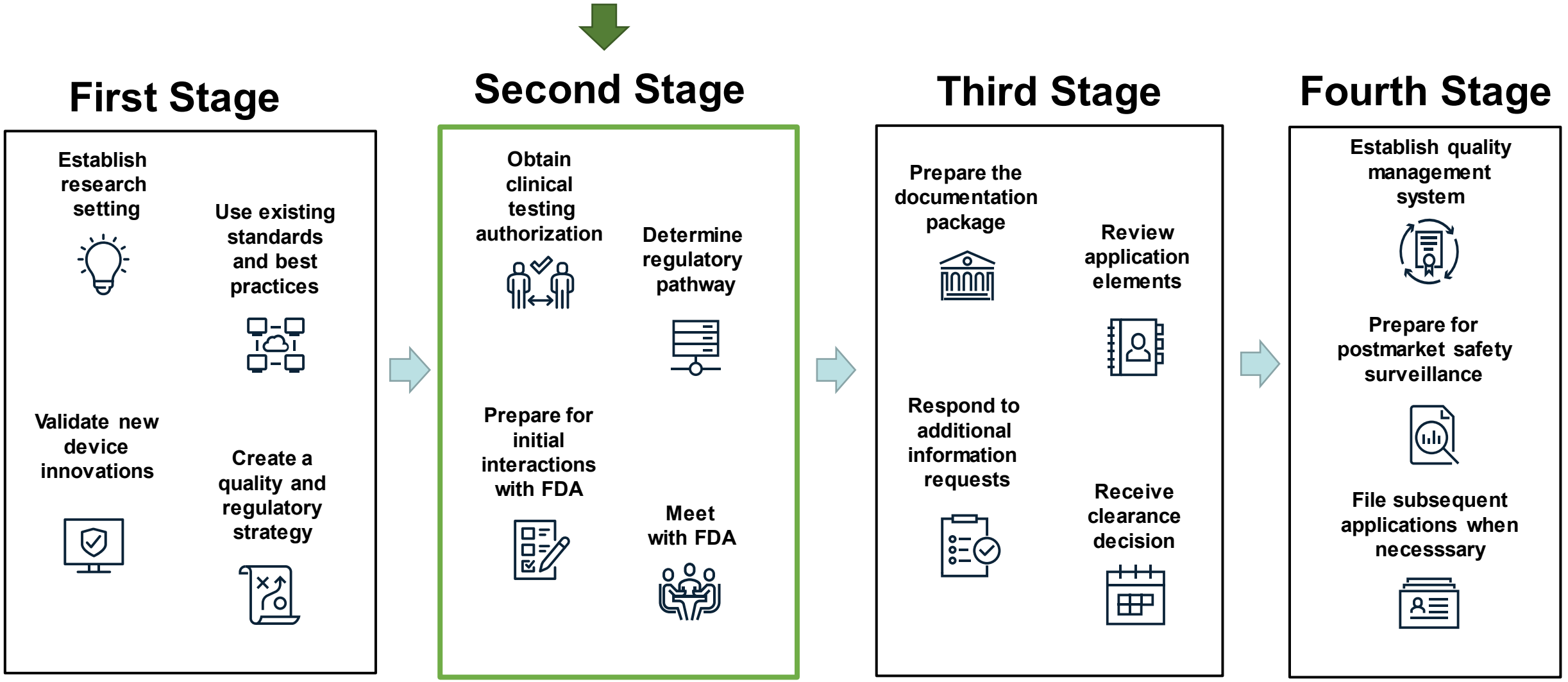
After a thorough search the Acoustics Imaging team brings in Dagmar Bauer, a regulatory consultant, and begins working with her to develop their quality and regulatory strategy.



Key questions:

- How does FDA regulate medical devices?
- What qualifications and certifications are needed in a regulatory consultant?
- What should be the scope of work of the regulatory consultant?

Second Stage



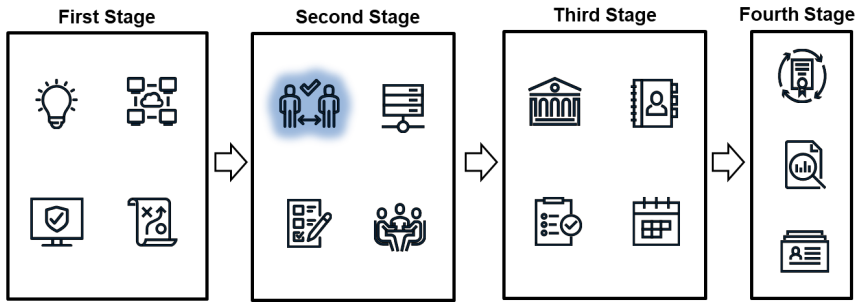
Second Stage: Obtain Clinical Testing Authorization

Dagmar Bauer, the team's regulatory consultant, recognizes that the first order of business is to ensure the human testing needed to verify the AI^2 Toolkit is compliant. Significant risk medical devices require FDA authorization for clinical testing, this is called an Investigational Device Exemption (IDE).

Dagmar charges the technical team with documenting the clinical test plan so she can conduct a risk analysis of her own. She cross references her understanding of risk with the CDRH guidance Significant Risk and Nonsignificant Risk Medical Device Studies. For the AI^2 Toolkit, the team needs to collect new data from patients experiencing liver fibrosis.

Though the team had an existing Institutional Review Board (IRB) approval for voluntary ultrasound imaging within their research lab, the new patient data collection constituted a separate study. They knew their first step was to obtain new authorization from the IRB, because the board would also determine whether an IDE or pre-IDE meeting with FDA is advisable. In this case, because the imaging study is non-invasive, and any disruption to the existing clinical workflow was minimized in the study plan, the IRB did not consider the risk significant.

Dagmar instructs Jade to coordinate with their NIH program officer to ensure the study is registered and clinicaltrials.gov information is up to date.

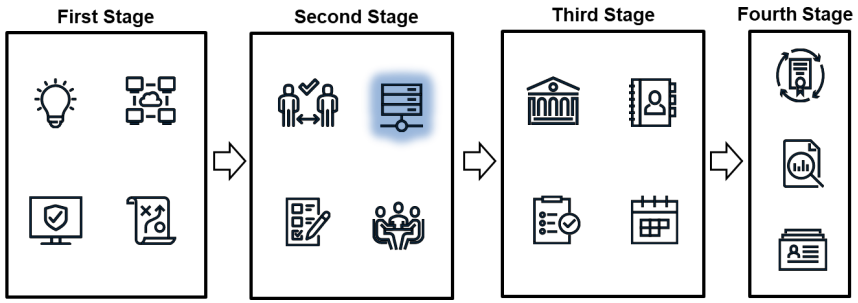


Key questions:

- How are risks to study participants being mitigated by the investigating team?
- Does the study require FDA oversight (IDE)?
- Has the IRB authorized the study?

Second Stage: Determine Regulatory Pathway

With clinical validation testing underway and device design near its final stages, Jade begins to investigate the regulatory requirements for marketing the AI^2 Toolkit.



Jade reads a recent announcement about how some clinical decision support software (CDS) may not be regulated by FDA.

After going through the online digital health policy navigator tool, they and Dagmar agree the product will in fact require pre-market application. Even though it might seem like it is exempt since it is intended to support clinical decisions, by proceeding through the steps of the policy navigator tool Jade notes that the AI^2 Toolkit is "intended to acquire, process, or analyze a medical image or a signal from an in vitro diagnostic device (IVD), or a pattern or signal from a signal acquisition system" and "perform patient-specific analysis and provide specific output(s) or directive(s) to users for use in the diagnosis, treatment, mitigation, cure, or prevention of a disease or condition", which therefore makes the AI2 Toolkit "likely the focus of FDA's regulatory oversight."

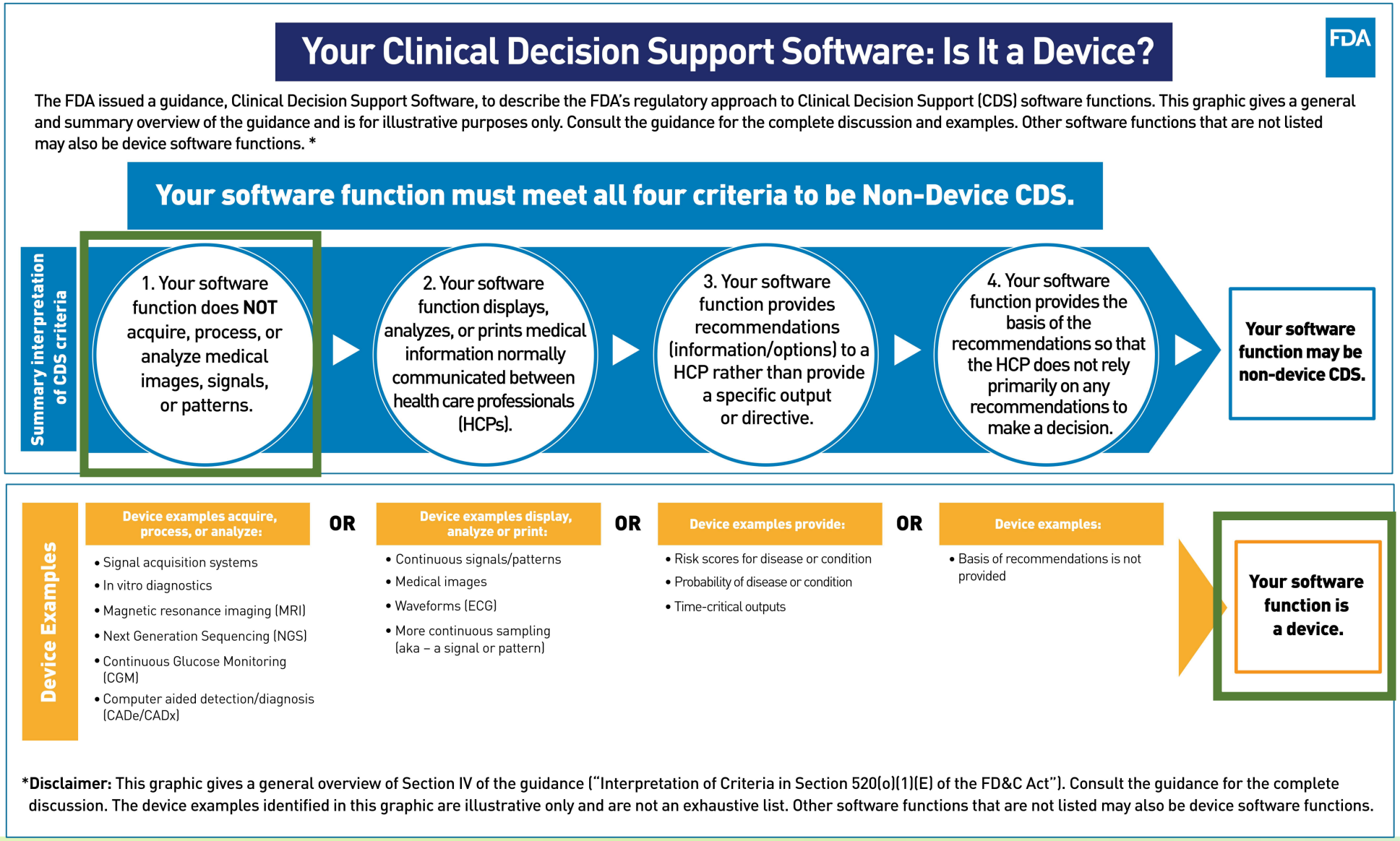
Dagmar outlines for Jade and Mumtaz the distinctions between device classifications and Class I and Class II exemptions as well as those devices that might fall under enforcement discretion.

The CDRH Product Classification Database provides some guidance and Dagmar concludes that the AI^2 Toolkit will likely be considered a Class II device and require a pre-market submission. As a Class II device there are two potential pathways available, the 510(k) pathway or the De Novo pathway. Additional research on selecting appropriate regulatory pathways & a regulatory consult with the NIH SEED office, leads Dagmar to determine the 510(k) pathway is most likely appropriate for the AI^2 Toolkit.

Key questions:

- Will the product need a pre-market application for FDA?
- What regulatory pathway will be most appropriate for the product?

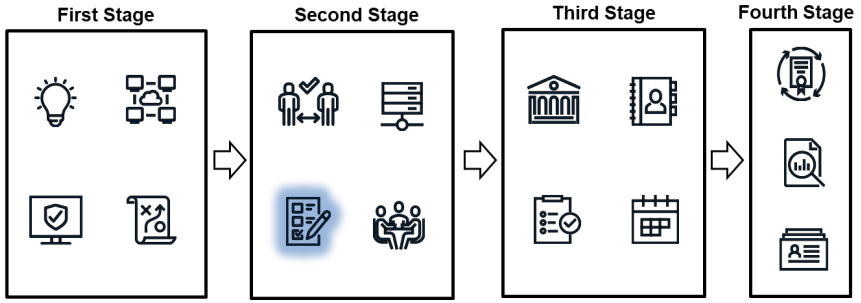
Is the digital health product a device?



- In addition to the online tool, Jade and Dagmar also review this more condensed flowchart to help determine if the AI² Toolkit is considered a medical device.
- Consistent with their earlier findings, since the AI² Toolkit DOES process and analyze medical images, it does not meet the definition of a non-device CDS and therefore is likely a medical device.

Second Stage: Prepare for Initial Interactions with FDA

Now that the Acoustic Imaging Lab team understands how their software is likely to be classified by FDA, they set out to form a detailed regulatory plan. Since the AI^2 Toolkit will most likely require a 510(k), they need to identify a predicate device. These planning activities will culminate in a pre-submission meeting request submitted to CDRH, to validate their approach.



By now Dagmar has sufficient understanding of the technical details and intended use to do some digging for potential predicate devices on the 510(k) Database. The AI^2 Toolkit falls under product code LLZ. Within the 510(k) database, she searches for image processing software systems that are especially tailored for ultrasound imaging and quantitative measurements. She finds a good candidate, but its functions measure another quantity of interest (amniotic fluid index) rather than shear wave speed.

Guided by the anticipated 510(k) process, Dagmar documents the following for the first FDA meeting:

- An "indications for use" statement using similar verbiage to the predicate
- A detailed device description including all functions of the software
- A preliminary substantial equivalence comparison between the devices, focusing on differences (unique capabilities of AI^2 Toolkit) and how those are validated. In doing so, the team refers to available FDA reference materials such as the Quantitative Imaging Guidance.

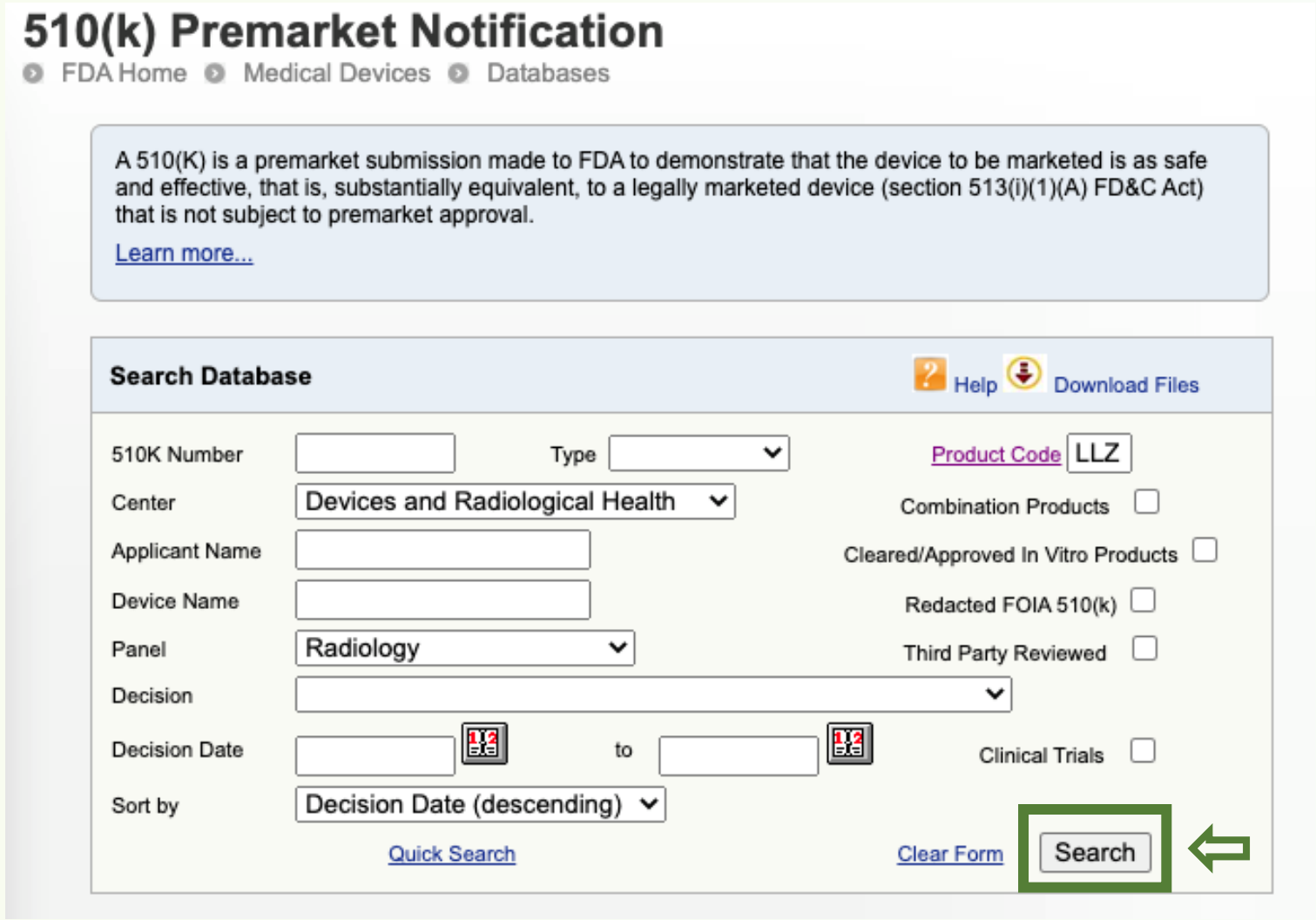
Lastly, Dagmar and the team prioritize which questions they *need* FDA feedback on during the pre-submission meeting. Dagmar advises them to keep it concise, sticking to two critical questions to confirm the upcoming 510(k):

1. Based on the device description and indications for use, does FDA agree that LLZ (21 CFR 892.2050) is the appropriate classification for AI^2 Toolkit?
2. Based on the substantial equivalence comparison, does FDA agree that the proposed validation plan supports the quantitative imaging claims?

Key questions:

- What relevant regulatory information can be gleaned from decision summaries in public databases?
- What information is most critical to receive from FDA before the upcoming regulatory application?

Browsing the 510(k) Database



- Based on Dagmar's experience and prior research, she uses the 510(k) database to identify an appropriate predicate device.
- She filters her search based on Product Code "LLZ," products cleared by the Center for "Devices and Radiological Health," and specifically those reviewed by a "Radiology" panel.
- The result produces a list, most recently cleared devices first, where she can review each device and the associated 510(k) Summary.

Indications for Use Statement

Blank until FDA receives application

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*

Device Name

AI² Toolkit

Indications for Use *(Describe)*

AI² Toolkit is a software-only device intended for diagnostic review and analysis of ultrasound images. It is only to be used by a license physician (or at their direction). AI² Toolkit allows post-processing and visualization of DICOM ultrasound images.

Ultrasound images are acquired via B, M, Color M, Color Power, Pulsed, CW Doppler, Coded Pulse, Harmonic, 3D, and Real time 3D modes.

Clinical applications include: Fetal/Obstetrics; Abdominal (including renal and GYN), Urology (including prostate), Pediatric; Small organs (breast, testes, thyroid), Neonatal and Adult Cephalic, Cardiac (adult and pediatric), Peripheral Vascular, Transesophageal (TEE), Musculo-skeletal Conventional, Musculo-skeletal Superficial, Transrectal (TR), Transvaginal (TV), Intraoperative (vascular), Intra-cardiac, and Intra-luminal.

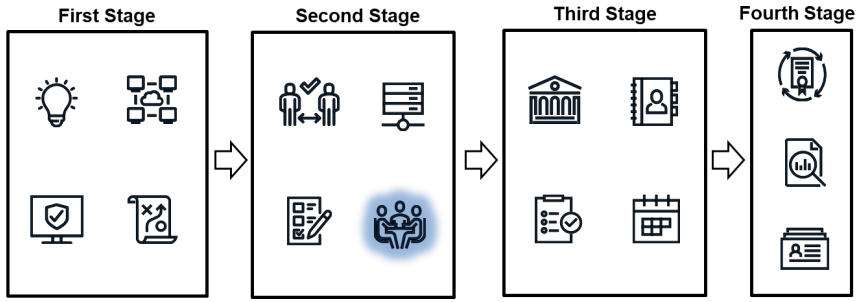
Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

- AI Labs drafted their IFU based on similar devices found within the 510(k) database.
- The intended use is often included within the IFU statement (first paragraph).
- They found that IFU statements for ultrasound tools typically contain a complete list of imaging modes and clinical applications.

Second Stage: Meet with FDA

After thoroughly researching regulatory requirements and aggregating all the necessary documentation it's time to submit the pre-submission package to CDRH and meet with FDA.



Dagmar prepares the Pre-Submission and submits it online to CDRH. Shortly after receiving the documents, FDA proposes a few one-hour meeting options, roughly 75 days out, for FDA and the team to meet after the pre-submission feedback is provided.

Two days before the scheduled meeting with FDA, the team receives written feedback from their Q-submission. The short timeline was expected, and the team is ready to address FDA's feedback! FDA responds to Question 1 by generally agreeing that the LLZ classification is appropriate for the device description and indications for use. However, for Question 2, FDA does not completely agree with the substantial equivalence comparison and provides several suggestions of how the comparison and testing plans can be improved to support a future 510(k) submission.

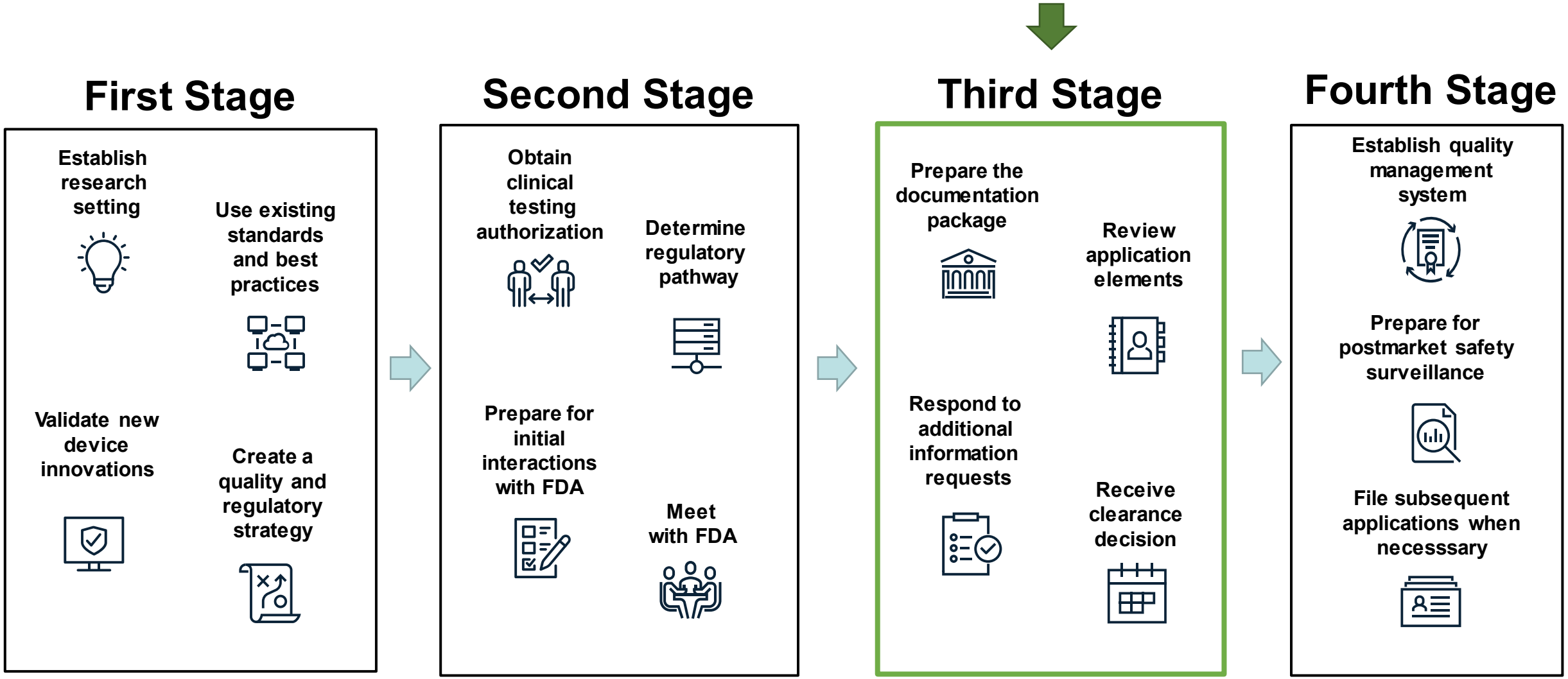
The Acoustic Imaging Lab team prepares a presentation deck outlining FDA's responses and poses clarifying questions based on FDA's feedback of Questions 2. Based on Dagmar's experience, they focus on getting as much clarity and additional feedback on the materials they provided in the pre-submission. FDA has thoroughly read through the submission, and it is not good use of time to re-present content. The team also do not try to propose new plans to address FDA's feedback since they know that FDA will generally not be able to provide feedback to new materials presented in the meeting.

After the meeting, the team convenes to consolidate and submit minutes of the meeting to FDA for addition to the pre-submission file. FDA will reply either accepting the minutes or with any amendments to reflect differences in meeting take aways.

Key questions:

- What to expect for the pre-submission?
- Based on FDA's written feedback before the meeting, what is the best use of time for the face-to-face discussion?

Third Stage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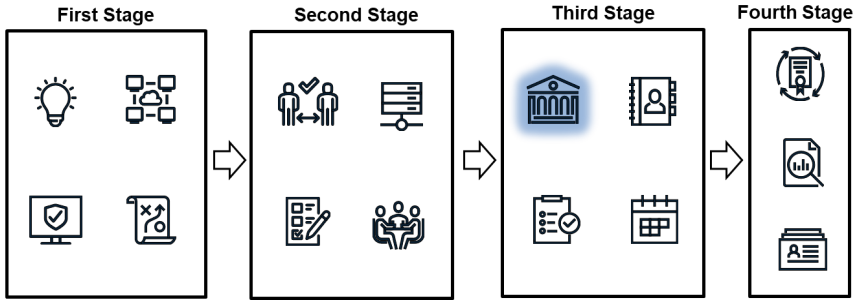
Third Stage: Prepare the Documentation Package

With input from FDA via the pre-submission meeting, Acoustic Imaging Labs have all they need finalize their studies and prepare to submit for market authorization. Dagmar, the team's regulatory consultant, is not solely responsible for writing the documents – but she is able to direct the team's best-suited subject matter experts to prepare each section, while she reviews them. After the team sends the 510(k) application to FDA, Dagmar meets the lead reviewer, Dr. Nicholas Reid.



Nicholas Reid, an FDA Biomedical Engineer, is appointed to lead the review the AI^2 Toolkit 510(k). That means he will coordinate a team of experts, in this case primarily a software specialist, to ensure the device is substantially equivalent. This 510(k) happens to be one of five applications that Nicholas is currently in charge of: there is another 510(k), two pre-submission meetings, and a recall that he is reviewing simultaneously,

Nicholas begins by ensuring that the documentation is administratively complete. This means there are no missing sections that would be relevant for an acoustic image processing tool. Nicholas uses the Refuse-to-Accept (RTA) Checklist to determine if he needs to "refuse to accept." Thankfully, Dagmar instructed Acoustic Imaging Labs to include an RTA Checklist of their own. The included checklist indicates that all materials are present, and even includes page numbers so Nicholas can verify content easily.

Upon verification, he sends a formal email to Dagmar letting her know the application has been accepted and he is proceeding with his review.

Key questions:

- Has all pre-submission FDA feedback been incorporated into the application?
- Has the RTA checklist been completed before submission?

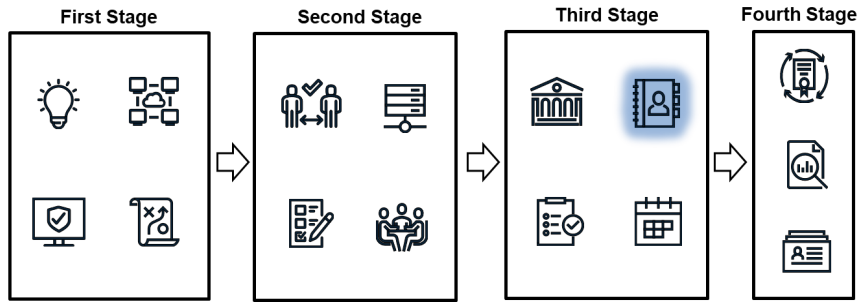
Excerpt from RTA Checklist

Check "Yes" if item is present, "N/A" if it is not needed and "No" if it is not included but needed. ***Submitters including the checklist with their submission should identify the page numbers where requested information is located. Use the comments section for an element if additional space is needed to identify the location of supporting information.**				**Yes**	**No**	**N/A**	***Page #**
A.	**Administrative**						
	1.	All content used to support the submission is written in English (including translations of test reports, literature articles, etc.).		☑	☐		
		Comments:					
	2.	Submission identifies the following (FDA recommends use of the CDRH Premarket Review Submission Cover Sheet form (Form 3514, available at https://www.fda.gov/media/72421/download)):					
		a.	Device trade/proprietary name	☑	☐		Executive summary
		b.	Device class and panel OR Classification regulation OR Statement that device has not been classified with rationale for that conclusion	☑	☐		1 - 1 Executive summary 1 - 1
		Comments:					

- The RTA Checklist is used by reviewers as a tool to ensure an application is administratively complete.
- The blank checklist is available to the public and can be included within the 510(k) by companies to ensure completeness and aide in administrative review.

Third Stage: Review Application Elements

Now that Nicholas has accepted the 510(k) application from the Acoustic Imaging Lab, he assesses the subject matter expertise within FDA he may need to consult with in order to complete his review. In this case, he decides to talk to a Medical Officer to discuss the diagnostic utility of shear wave speed, as well as a Software Specialist to evaluate the AI/ML aspects of the device.



While Nicholas' consultants focus on those elements, he handles the rest of the 510(k) review. He starts by familiarizing himself with the predicate device and its journey through FDA. With that in mind he turns to the AI^2 Toolkit's comparison of similarities and differences, which is cleanly formatted side-by-side in a table.

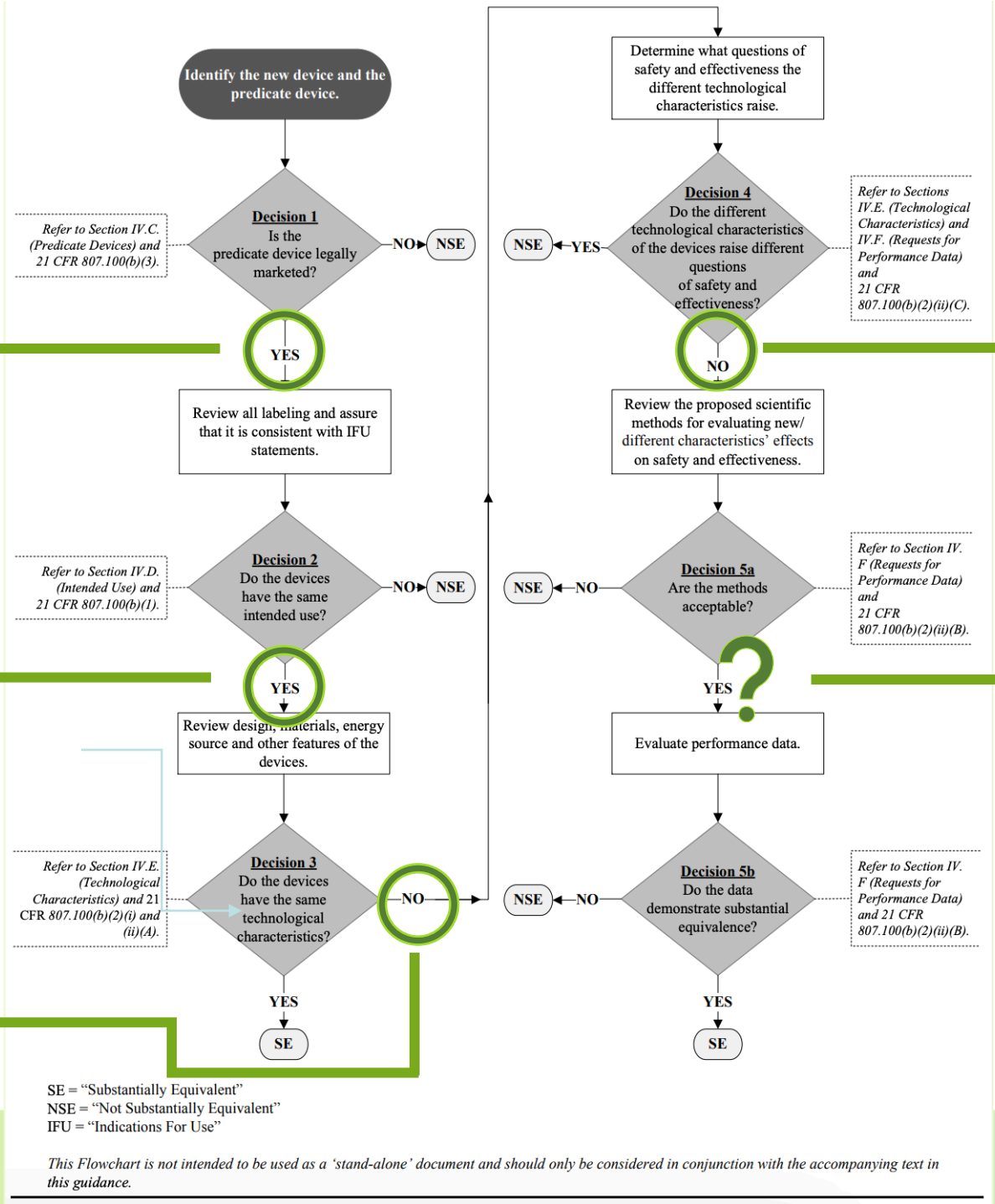
He then turns his attention to one of the novel quantitative imaging functions. In his review, Nicholas was not able to locate the default parameter values, nor the rationale for setting them as such. Rather than waiting to complete his entire review, he contacts Dagmar to request the additional details, this is called Interactive Review.

Because the AI^2 Toolkit is a moderate level-of-concern software device, the documentation of the software within the 510(k) is relatively comprehensive. These documents demonstrate that a software quality system is in place, and that the AI^2 Toolkit was developed accordingly.

Key questions:

- Does the submission include a justification for substantial equivalence?
- Have the appropriate standards and guidance documents been referenced within the application? (For example, *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices*)

510(k) Flowchart



SE = "Substantially Equivalent"
NSE = "Not Substantially Equivalent"
IFU = "Indications For Use"

This Flowchart is not intended to be used as a 'stand-alone' document and should only be considered in conjunction with the accompanying text in this guidance.

Predicate is suitable and legally marketed

Both devices are used for radiographic (ultrasound) image processing

The devices do not have identical software functions/algorithms, but that is ok because…

…despite the differences the overall safety/efficacy considerations are the same

Nicholas' software consultant reviewer raises some questions regarding the methods of updating/maintaining the AI^2 Toolkit.

Third Stage: Respond to Additional Information Requests

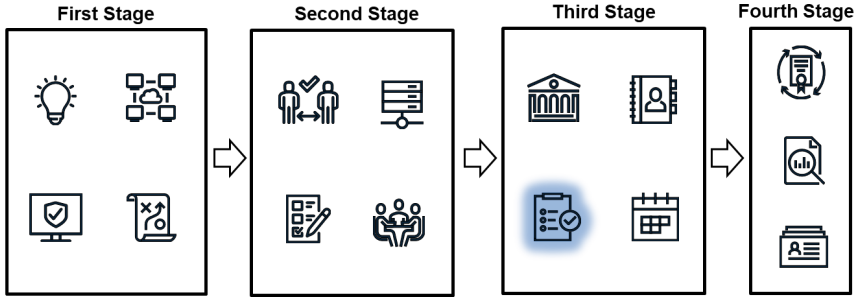
Nicholas has completed an initial review and has also gathered feedback from subject matter experts at FDA. He identifies several key points made in the submission that raise questions that cannot be answered by the materials provided in the submission.

Specifically, with the inclusion of machine learning-based algorithms, the Acoustic Imaging team mentions that as the AI^2 Toolkit continues to be used the additional available data will further improve the system's performance. However, the submission does not provide details on how exactly these improvements to the existing system will be validated before being implemented.

As with all FDA requests for information, as described in the guidance document on deficiency communication (an FDA request for additional information is known as a "deficiency"), FDA reviewers have a written communication formula found to be very effective when working with device manufacturers. The structure has four parts, as follows:

1. What was provided? Acknowledge the information submitted.
   - E.g., Acoustic Imaging states that the AI^2 Toolkit algorithm may be updated as more data becomes available.
2. What is deficient? Explain why that information is not adequate.
   - E.g., No specific plan on when and how the algorithm will be updated is provided.
3. What is needed? Request specific additional information.
   - E.g., A detailed plan of how changes to the algorithm will be validated and implemented should be included.
4. Why is it needed? Refer and connect to relevant regulations/policies and scientific evidence.
   - E.g., Though not finalized, plan should be compliant with draft guidance CDRH published Recommendation for a Predetermined Change Control Plan (PCCP) for AI/ML-enabled Device Software Function

Together this forms a complete explanation on what is needed for each of Nicholas' questions. Upon compiling all the questions, Nicholas sends a formal email to Dagmar letting her know of the additional information request and that the application has been put on hold for up to 180 business days or until a response to the questions and supporting documentation are provided.



Key questions:

- How does FDA communicate feedback and request additional information during review?
- How do you respond to FDA's feedback appropriately?

Acoustic Imaging Labs' Response to the Additional Information Letter

For each question included in an Additional Information Request, it is important to identify early on what the team will need to address the request. This might include additional management activities and decisions, research and validation, and understanding potential regulatory requirements and consequences.

With any of these plans, keep in mind the 180-day timeline and how long these activities might take.

FDA typically makes only one formal Additional Information request before making a final decision – so the team puts all-hands-on-deck to provide the most complete responses they can.

Responding to questions in an Additional Information Request

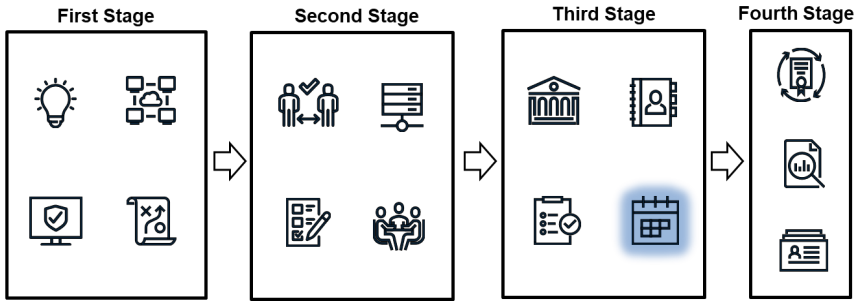
When responding to FDA, it is a best practice to use a response format similar to the following:

1. Restate the identified issue
   - For example: The precise conditions and plan on how the AI[2] algorithms will be updated was not was not provided
2. Provide one of the following:
   a. The information or data requested
      - For example: Acoustic Imaging outlines a thorough Predetermined Change Control Plan in line with FDA guidance and current thinking
   b. An explanation why the issue does not affect or impact the marketing authorization decision
   c. Alternative information and an explanation describing why the information adequately addresses the issue

Providing the specific information requested is the most likely way to enable FDA to make progress in the review of your device. Using well-organized, unambiguous written communication is often the quickest way to clarify the path forward for the product development.

Third Stage: Receive Clearance Decision

Dagmar and the rest of the Acoustic Imaging team submit their responses and provide supporting documentation to address the Additional Information Request.



Upon receipt of Acoustic Imaging's supplemental information, Nicholas reconvenes the original group of subject matter experts within FDA. They review the PCCP for AI[2] Toolkit along with other clarifications and supporting data. In general Nicolas and the rest of the review team find the information to support the statements made in the submission. However, Nicolas contacts the Acoustic Imaging team through interactive review process to discuss in more detail the PCCP. After some discussion, the PCCP is amended to only be applicable under more limited conditions as supported by the data.

Once all the review team's concerns are addressed, Nicholas compiles a full review of the submission, including memos from each of the subject matter experts, and provides a recommendation to clear the device for the U.S. market. These review documents are kept internal to FDA.

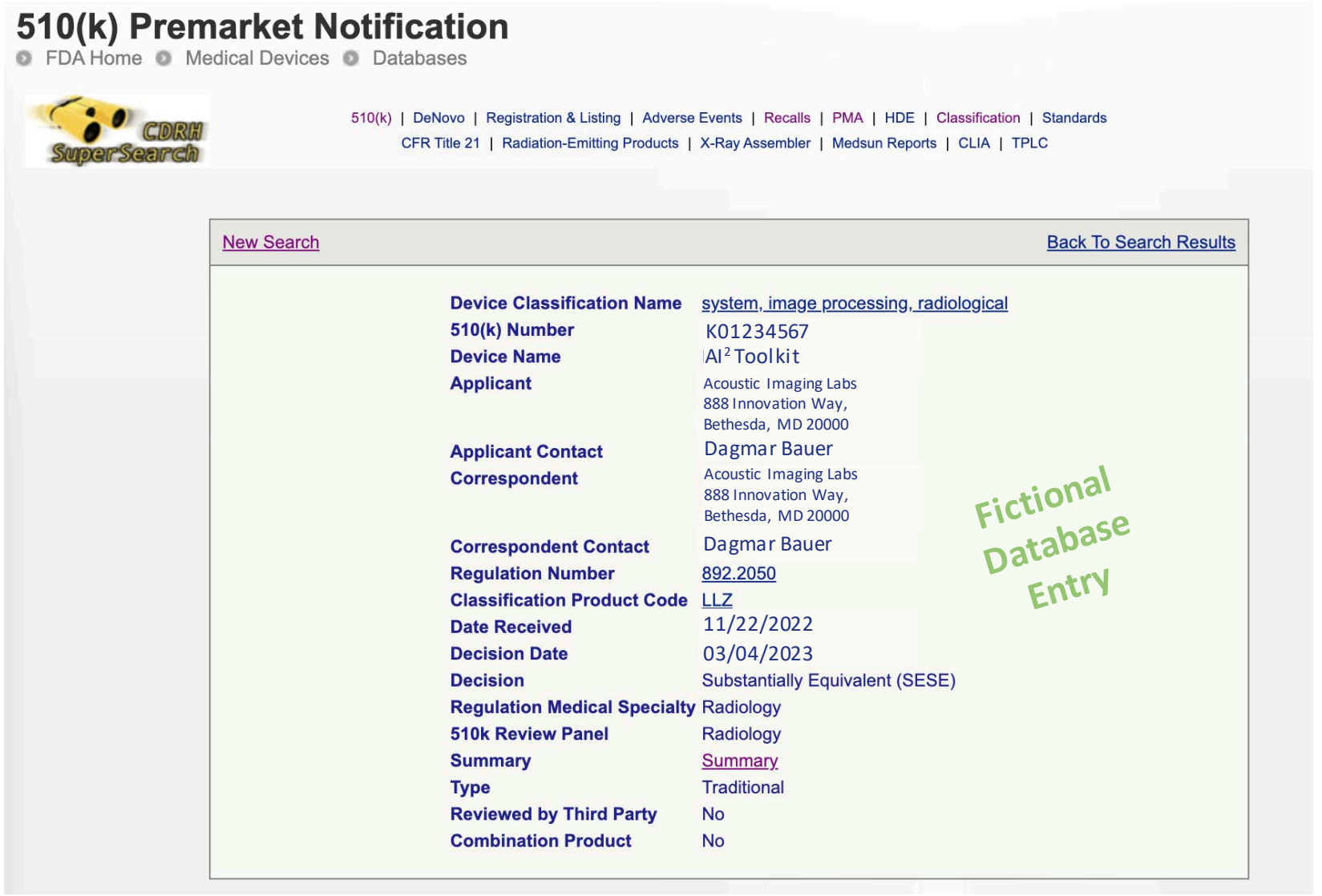
The completed file and recommendation is reviewed by managers and the director of OHT8C: Radiological Health – Radiological Imaging and Radiation Therapy Devices who signs off on the device clearance.

Within 90 review days of the submission, excluding the time between the additional information request and FDA's receipt of the response, Dagmar and the Acoustic Imaging team receive the clearance letter from FDA.

Key questions:

- Is there a plan in place for post-clearance regulatory and manufacturing activities (e.g., quality management, adverse event reporting, registration and listing).

Decision Letter and Addition to 510(k) Database



510(k) Premarket Notification

FDA Home ◉ Medical Devices ◉ Databases

CDRH SuperSearch

510(k) | DeNovo | Registration & Listing | Adverse Events | Recalls | PMA | HDE | Classification | Standards
CFR Title 21 | Radiation-Emitting Products | X-Ray Assembler | Medsun Reports | CLIA | TPLC

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Device Classification Name	system, image processing, radiological
510(k) Number	K01234567
Device Name	AI² Toolkit
Applicant	Acoustic Imaging Labs 888 Innovation Way, Bethesda, MD 20000
Applicant Contact	Dagmar Bauer
Correspondent	Acoustic Imaging Labs 888 Innovation Way, Bethesda, MD 20000
Correspondent Contact	Dagmar Bauer
Regulation Number	892.2050
Classification Product Code	LLZ
Date Received	11/22/2022
Decision Date	03/04/2023
Decision	Substantially Equivalent (SESE)
Regulation Medical Specialty	Radiology
510k Review Panel	Radiology
Summary	Summary
Type	Traditional
Reviewed by Third Party	No
Combination Product	No

Fictional Database Entry

- After the device is approved, Acoustic Imaging Labs receives an official clearance letter which will include the 510(k) summary.
- The 510(k) will then be added to FDA's 510(k) database along with the summary.

Fourth Stage

First Stage

- Establish research setting
- Use existing standards and best practices
- Validate new device innovations
- Create a quality and regulatory strategy

Second Stage

- Obtain clinical testing authorization
- Determine regulatory pathway
- Prepare for initial interactions with FDA
- Meet with FDA

Third Stage

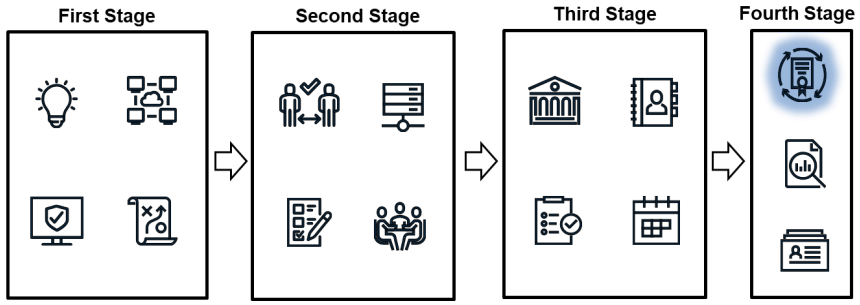
- Prepare the documentation package
- Review application elements
- Respond to additional information requests
- Receive clearance decision

Fourth Stage

- Establish quality management system
- Prepare for postmarket safety surveillance
- File subsequent applications when necesssary

Fourth Stage: Establish Quality Management System

While the Acoustic Imaging Labs team celebrates their first FDA clearance, Jade and Dagmar are examining the next steps in legally marketing their software. As a compliant medical device manufacturer, they are required by the Code of Federal Regulations (CFR) to utilize and maintain a Quality Management System (QMS).



In 1978, legal requirements for Good Manufacturing Practices were finalized into the CFR as 21 CFR 820 – titled the Quality System Regulation. The goal of the regulation is to ensure medical device quality by requiring manufacturers have robust processes in place for design, production, and delivery of their products. Dagmar explains to the team that as the registered manufacturer of the AI^2 Toolkit they may be inspected by FDA. The QMS, its documents and integration into manufacturing/management logistics, will be the focus of such an inspection.

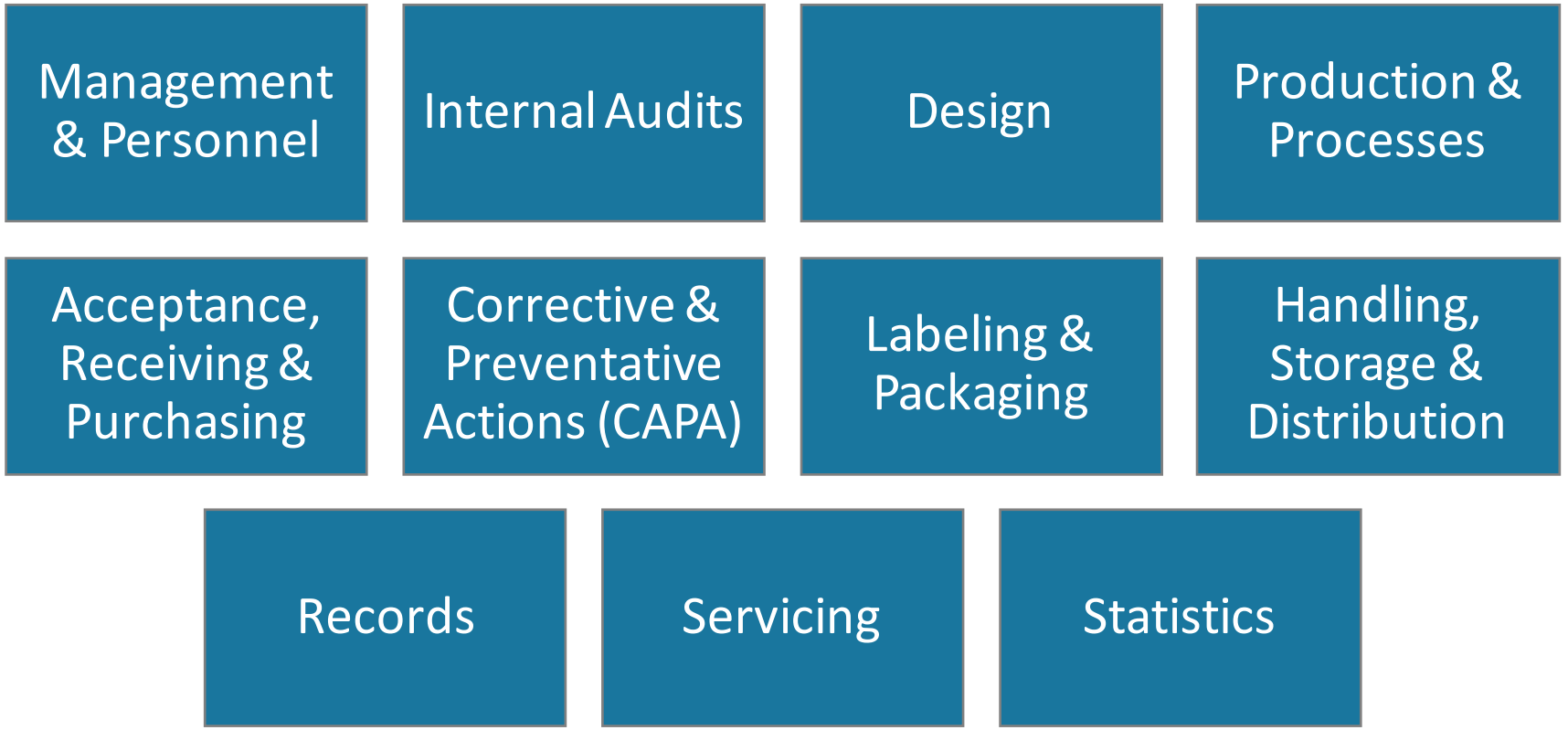
The Quality System Regulation contains 15 subparts that describe the required quality assurance processes. These cover a wide range including acceptance and receiving, complaint handling, design controls, packaging, and more. Dagmar emphasizes that each of these parts, if mismanaged, could negatively impact device's performance (and the company's reputation). Even as a purely-software device manufacturer, Acoustic Imaging Labs' QMS will ensure the software is designed, built, and delivered, to meet customer expectations.

The Quality System Regulation explains *what* needs to be done by the QMS, but not *how* to do it. Acoustic Imaging Labs management team must develop – and iteratively improve – a QMS to meet their needs and ensure consistent quality. There are also commercially available third-party services to help establish a QMS.

Key questions:

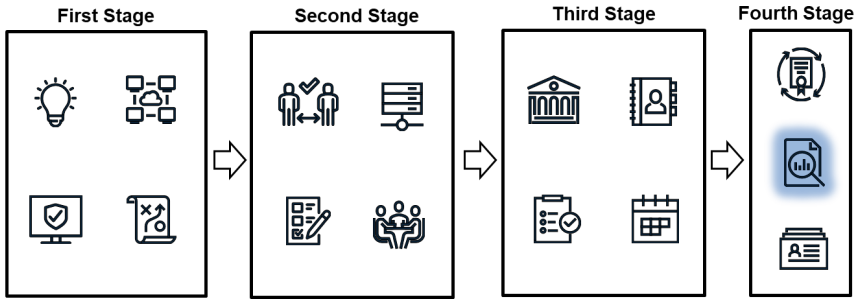
- Is the QMS compliant with 21 CFR 820, ISO 13485, or both?
- Will the device be on the international market?
- Who will certify/audit the QMS?

Overview of QMS Elements Required by 21 CFR 820



Fourth Stage: Prepare for Postmarket Safety Surveillance

Now that the AI^2 Toolkit has been cleared and they are about to begin marketing their device, the Acoustic Imaging team needs to be sure to implement systems for post-market monitoring requirements.



All medical device manufactures involved in the distribution of devices must follow postmarket requirements once a device is on the market. This includes having systems and protocols in place for documenting adverse events.

FDA has outlined Mandatory Reporting Requirements that all manufacturers must be aware of to understand when an event they are aware of must be reported to FDA.

FDA aggregates these reports in the MAUDE database. They are publicly available and searchable for transparency and accountability of reported adverse events involving any medical device on the market.

Along with plans and procedures for adverse events, it is also important to be familiar and have a plan in place to address any potential recalls. FDA publishes recall guidance that should be reviewed and followed should a recall need to be initiated.

Key questions:

- Is there a plan in place for post-clearance regulatory and manufacturing activities (e.g., quality management, adverse event reporting, recalls)?

Acoustic Imaging Labs Receives a Complaint related to AI^2 Toolkit

After a year of being on the market, there has been significant adoption of their new AI^2 Toolkit. Acoustic Imaging Labs receives their first complaint and immediately assesses the complaint to understand the issue and reporting requirements.

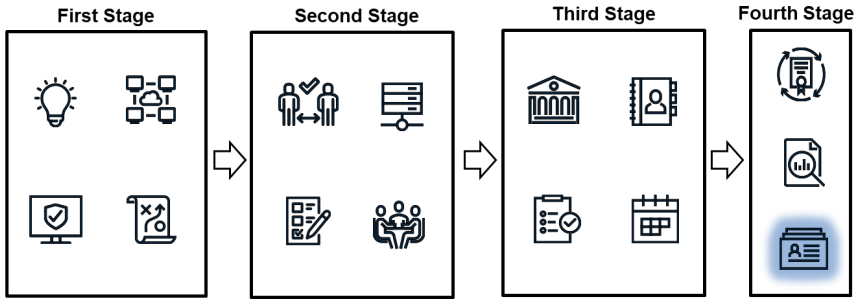
Each complaint received should be evaluated to understand any corrective actions or follow ups to resolve the issue. These complaints should also be tracked and recorded as part of a QMS.

Steps for addressing a complaint received by a consumer

1. The complaint received describes an incident as follows:
   - "While imaging was being conducted the data was lost and could not be recovered. The physician reported they saw the AI^2 Toolkit beginning to work before the file could not be found and believes the software was the reason the files were deleted."
2. Acoustic Imaging opens an incident report, investigates the issue, and follows up with the customer to better understand the problem and its impact.
   - After investigation, the Acoustic Imaging team determines the issue was rooted in a user configuration that had the files save to a location that did not exist on the system.
   - To avoid future incidents like this one, Acoustic Imaging will include additional validations of file saving configurations in a future software update.
3. Based on FDA reporting requirements, this incident does not need to be reported to FDA through an MDR since there was no patient harm.
   - Should the incident have met the FDA reporting requirements, FDA outlines How to Report Medical Device Problems along with the ability to submit electronically through eMDRs.

Fourth Stage: File Subsequent Applications When Necessary

With the initial 510(k) clearance in place, CEO Mumtaz Kalb has been busy identifying new customers and learning about their needs. Accordingly, Jade has been leading their developers to augment the AI^2 Toolkit with additional software functionality. With their fully functioning QMS in place, changes to the software are comprehensively documented, including their potential regulatory consequences.



The key aspects of deciding when to submit a 510(k) for software changes are fully described in the corresponding FDA guidance document. For the AI^2 Toolkit, the changes introduce new functions for image manipulation which have low, but nonetheless new, risks for Acoustic Imaging Labs to mitigate. Thus, they decide to file a new 510(k).

For these changes, it appears the Special 510(k) Program would apply because:

- The change is to their own device (so they can use their own 510(k) as a predicate).
- The data related to the change can be concisely summarized.

In comparison to a traditional 510(k), the Special 510(k) allows for a relatively smaller documentation package and a faster timeline to a clearance decision.

Key questions:

- Does the change introduce new risks or does it necessitate a modified risk control measure?
- Could the change significantly affect clinical performance?
- Can the data (related to the change) be evaluated with concise or well-established methods?

AI² Toolkit Press Release

The following is a fictional portrayal of what success for the AI² Toolkit may look like

For Immediate Release

FDA Clears Acoustic Imaging Lab's AI² Toolkit

College Park, Maryland, March 12, 2023–

Acoustic Imaging Lab Inc. is pleased to announce their AI² Toolkit. AI² Toolkit is the first and only FDA-cleared tool for the accurate quantitative assessment of shear wave speed for estimating liver fibrosis. The innovative AI² Toolkit provides common ultrasound image manipulation tools including contrast adjustment, measurement functions, and a semi-automated segmentation capability idriven by machine learning.

"Today's announcement marks an important step forward for technology-assisted ultrasound imaging," said Mumtaz Kalb, Acoustic Imaging's CEO. "By measuring the speed of propagation of a shear wave as it traverses liver tissue, the stiffness of the liver—which is a biomarker for the extent of liver fibrosis—can be accurately measured. This will help healthcare providers more accurately diagnose and treat their patients with liver disease."

Acoustic Imaging Inc. is part of University of Maryland's startup incubator program. Established in 2011, they are collaborating with their academic research lab to develop a first-of-its-kind suite of ultrasound image processing tools that leverage artificial intelligence to segment regions of interest and assess quantitative imaging biomarkers….

SUMMARY

Summary: By Stage

First Stage

- Establish research setting: Leverage existing connections and funding resources when setting up research team and environment.
- Use existing standards and best practices: Existing standards and documentation can reduce design burden and streamline future evaluation of the device.
- Validate device innovations: Though a device can rely on many existing technologies with known validation methods, novel aspects of the device should be designed with a validation aspect in mind.
- Create quality and regulatory strategy: Having the right regulatory strategy developed by an experienced subject matter expert can be critical in navigating these requirements.

Second Stage

- Obtain clinical testing authorization: Maintain IRB approval and contact FDA if significance of risk is uncertain.
- Determine regulatory pathway: Conduct landscape analysis and consult with regulatory specialists until there is high confidence in the applicable requirements and timelines.
- Prepare for initial interaction with FDA: Document the approach to testing the device for safety/efficacy and/or substantial equivalence and ask several questions of FDA for concurrence.
- Meet with FDA: Obtain direct feedback from FDA on the highest priority areas of uncertainty. Focus on outstanding issues.

Third Stage

- Prepare the document package: Do not underestimate the volume and complexity of documentation required to justify safety/efficacy and/or substantial equivalence.
- Review application elements: Be direct and focus on aspects of the device that are unique.
- Respond to additional information request: Expect that FDA will need some additional information and have the team prepared to quickly and comprehensively respond.
- Receive clearance decision: Celebrate a successful market authorization! Or in the worse case, meet with FDA to ensure the next submission goes smoothly.

Fourth Stage

- Establish a quality management system: Ensure that the manufacturing and management and quality processes are compliant. Anticipate future FDA inspections.
- Prepare for postmarket safety surveillance: Report adverse events to FDA and providers as necessary to ensure safety.
- File subsequent submissions when necessary: Resubmit market authorization applications when the device has substantially changed.

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