CDRH Learn - Third Party X-Ray Systems

Slide 1

Hello, my name is Jabari Calliste with the Food and Drug Administration, Center for Devices and Radiological Health, or CDRH. In this presentation, I'll describe the basic process for how to review an X-Ray System to determine substantial equivalence.

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We expect Third Party Reviewers to have knowledge on the subject matter, which in this instance would be x-ray systems. You also should be familiar with the "How to determine substantial equivalence guidance document". This document identifies, explains, and clarifies each of the critical decision points. And finally, you should be aware of regulations, device specific guidance documents and standards.

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Here is a list of some FDA recognized standards and guidance documents that you should be aware of.

Slide 4

These are the learning objectives for this module. First, you'll understand the important components of the review and documentation for x-ray systems. You'll become familiar with the applicable regulations and guidance documents specific to X-ray systems. And third, you'll identify the potential premarket review items important to these devices. To achieve these objectives, we'll walk through an example review memo, showing how the review and documentation of a device is done to determine substantial equivalence.

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Before we get started, here's a brief overview of our example new device that we'll be reviewing during this training. A picture is included on the left side of this slide. Our new device is a stationary x-ray system which is comprised of an x-ray tube, a high voltage generator, and collimator. Our device also features a wireless digital detector, a floating table, and a bucky stand. Moving over to our written description of the device on the right side of this slide, note that the device also contains software features and claims.

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Before beginning the review of the device, it's important to ensure that the listed product codes and regulation numbers are correct, and applicable for the device under review. This is important, as different regulation numbers may have differences in review strategies.

This chart categorizes the x-ray systems in their respective regulation numbers and product codes. 21 CFR 892 broadly covers radiological devices. Subpart 21 CFR 892.1680 addresses stationary x-ray systems, and subpart 21 CFR 892.1720 addresses mobile x-ray systems.

Under the regulation for stationary x-ray systems, we see that there are two product codes, MQB for solid state x-ray imagers and KPR for stationary x-ray systems. Under the regulation for mobile x-ray systems, there is just one product code IZL for mobile x-ray systems. However, there are no major differences in the review of stationary x-ray and mobile x-ray devices.

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Based on the preliminary description of the example stationary x-ray system, we are already aware of the correct regulation number and product code applicable, that is KPR.

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The review and documentation of x-ray devices can be broken down into three main steps:
First, documenting and highlighting critical components of the review to ensure the provided information addresses any new questions of safety and effectiveness of the device.
Second, using the device specific guidance documents, to know what type of data is needed by CDRH to establish substantial equivalence. And third, focusing on the decision-making flow chart from the "how to establish substantial equivalence" guidance document. This document shows how to apply the information from the regulations, guidance documents and standards to answer pertinent questions in determining substantial equivalence.

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Here is an excerpt of the 510(k) decision-making flow chart taken from the "how to establish substantial equivalence" guidance document. It's a good framework in the 510(k) decision-making process.

Though this flowchart is being featured, please note that this is not intended to be used as a stand-alone document. When you use this flowchart, the decision questions should be answered in order, with decisions 1 through 4 answered with respect to PRIMARY predicate.

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Since we're focusing on the decision-making flow chart, we've color coded each decision step with an accompanying key at the bottom. This should make it easier to follow each step associated with our example review memo.

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For each decision-making step, we'll walk through the appropriate section in the example memo. You can identify slides with example memo documentation with the memo icon in the top left corner.

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To answer the questions to each decision point, we'll provide a table which points out where in the submission to look, what to do when reviewing the information in the respective sections, and what to document in you review memo. Before jumping into the decision-making flow chart, it's good to get acquainted with the submission. This information should be readily available in the sponsor's cover letter, the CDRH Premarket review cover sheet, and the 510(k) summary. You should also verify product codes and regulation numbers for both devices.

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Here are some hints and tips for conducting Medical Device Reports searches, using our publicly available Manufacturer and User Facility Device Experience database, also known as MAUDE.
When performing searches on this website, always enter the device product code and the manufacturer's name. If the manufacture's name consists of more than one word, use both partial and full names to conduct a complete search. In addition, pay attention to spelling.

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Searching the recalls database is synonymous to the Medical Device Reports searches. Remember to always enter the product code, include the partial and full name of the recalling firm, and pay attention to spelling.

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At this point, you should have a high-level understanding of the components of the new device, its intended use, features, and differences between the new and predicate devices. If your device features a computer-aided diagnostic, that is, CADe, or detection, that is, CADx, or a combination of both, stop your review and contact the FDA, as the submission may not be eligible for third-party review. These features will likely require clinical evaluation.

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Now let's review our example device by using the SE Flowchart. We start with Decision 1, which asks "Is the predicate device legally marketed?" We addressed this question earlier in Slide 12 as we researched the classification of the new device and predicate device.

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Once we've established that the predicate device is legally marketed, we now go to Decision 2: Do the devices have the same intended use?

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To answer this, you should start with looking at details about the IFU statement, intended population, and Rx/OTC information. This information is located in the FDA 3881 form and can also be found in the sponsor's proposed labeling. We recommend that you review the IFU and proposed labeling in detail for any new indications for use, intended population, and prescription information. In general, you should describe any major differences of the new device's IFU and its predicate in this section. If you observe any differences, please highlight the differences and provide an explanation why it does not change the intended use of the device. If the IFUs are identical, state this. At this point, check the proposed labeling for consistency with the IFU and the intended use of the device.

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On this slide, there are some hints and tips to consider when reviewing labeling information for the review of x-ray devices. The user manual should contain an indication for use section, and an Rx icon or prescription statement. For x-ray systems, you should verify whether a quality control section was included. Likewise, image quality and dosimetry performance testing information should be present. The manual should also indicate which devices and other components are compatible with appropriate indications for use. Lastly, evaluate all device specific claims.

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Here are some further labeling tips specific to pediatric information. The user manual should contain a section describing all pediatric features, as well as all labeling information for pediatric use of x-ray imaging devices, according to the pediatric guidance document. You should check for appropriate cautions, warnings, and contraindications as well as instructions specific to pediatric populations. And the manual should include the caution statement "Use special care when imaging patients outside typical adult size range."

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We'd like you to document all these finding in your review memo, highlighting any risk assessment for pediatric use. A sample summary of what this section should look like is provided in Appendix A of the pediatric guidance.

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Let's look at our example memo. If we compare the new device's IFU to the predicate, we see that the new device explicitly states adults and pediatrics as their intended population, whereas, the predicate device is intended for adult use only. This difference is noted and accompanied with an explanation on why it does not change the intended use. Other attributes, such as anatomical sites and prescription information, are the same between the devices. As I previously mentioned, it's critical to review the proposed labelling at this stage to ensure that the intended use is consistent. In the labeling of our new device, a CAD feature was discovered.

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Here, you should typically begin by answering these questions in the box. Since we have begun reviewing the labeling information for our new device, we have enough information to answer these questions. In addition to answering these questions, it is crucially important that you document whether the sponsor has satisfied the regulation requirements and addressed the suggested labeling information by FDA Guidance on Solid State X-ray Imaging Devices, or SSXI Guidance. For our example, the bullets below summarize the information in the user manual. These points address requirements by 21 CFR 801, but only some labeling recommendations from the SSXI Guidance.

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According to the SSXI guidance, our new device's user manual should include performance and quality control information. This information is missing from the submission and is documented in the review memo as a deficiency. In addition, since the new device is intended for pediatrics, we expect to see information as recommended by the Pediatric X-ray Guidance. This is absent and is noted in the memo as a deficiency.

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We review all device claims in the labeling of the x-ray device. For our new stationary x-ray device, four claims were provided on a product brochure. Let's use the first example to walk through step-by-step how this was resolved with the sponsor. For the other examples, I'll just touch upon the highlights.

The first claim is a dose reduction claim. It states, "At equivalent image quality, the device results in 50% less dose to the patient". Dose reduction claims need to be validated with appropriate performance testing data. In our example, the sponsor provided inadequate performance testing. They provided a Likert-type scoring of clinical images which is not adequate to support the claims, as this study did not take any physical parameters into consideration. For a quantitative dose reduction claim, we typically expect a more carefully designed clinical study, with a clearly defined baseline and endpoints. Therefore, based on the review of the performance testing section, which is not shown here, the claim is unacceptable.

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A deficiency was issued explaining what the sponsor provided, what is deficient about the information, why we need additional information, and what we need. In response, the sponsor removed the dose-reduction claim from the submission. This is adequate, and the deficiency is now resolved.

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The second claim is a quantitative image quality claim, which states "at equivalent dose, the device results in 41% improvement in image quality." However, the provided performance testing to substantiate this claim was not adequate and was documented as unacceptable.

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The third claim is a qualitative image quality claim, which states "AutoGrid is an optional feature that improves visibility of diagnostic x-ray images by decreasing scatter radiation when a physical grid is not used." For this claim, the provided performance testing was adequate. Therefore, this claim is acceptable.

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The last claim was discovered in the promotional brochure for the new x-ray device. This claim implies that there is a computer-aided detection and diagnosis feature, capable of detecting fractures, and whether it has led to a pulmonary contusion. Devices with CAD features have different intended uses and belong to another product code. This intended use was not previously specified in the 510(k) summary, device description, or substantial equivalence sections. So, the only way this new intended use of the device was discovered was by a review of the labeling. For your review, if such a claim is discovered, please contact the FDA immediately as CAD features require clinical testing, rendering the submission inapplicable for third party review. However, for the sake of our example, a deficiency was issued to the sponsor seeking clarification on this feature, and the sponsor chose to remove it. Without this feature, the device is eligible for third party review, and we can continue.

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Now that we've established that the new device has the same intended use as the predicate device, we now transition to Decision Point 3 of the flowchart, which asks "Do the devices have the same technological characteristics?"

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To answer this question, we expect you to adequately describe the new device, and evaluate the differences in the technological characteristics between the subject and predicate device. In the memo, we typically describe the x-ray system, specifying both hardware and software components, and a more detailed description of new and or modified features, focusing on those that are different from the predicate device. For new features, we sometimes provide an accompanying flowchart describing the workflow of the device. This is helpful. Also, if the sponsor indicates that any of the components have been previously cleared, provide the accompanying 510(k) numbers.

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Let's look at the device description review section of our memo. We usually begin by answering these simple questions in the box. Since the sponsor's submission identifies that the device uses cloud and wireless networks, we'd expect to see appropriate cybersecurity documentation in the submission. Below the table, you can see a summary of the device description, accompanied with a diagram on the right.

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This section of the memo focuses on the differences in technological characteristics between the new and predicate x-ray devices, stating whether they are new or modified. Here, we see the new stationary x-ray device has a wireless detector, which is new compared to the predicate. Also, we see the addition of the two new features to the modified software package.

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Here are a couple common occurrences and practices to use when reviewing the software of x-ray systems. If the sponsor states that the software is identical to the predicate, clarify with the sponsor that nothing in the software is changing to accommodate the new or different hardware components. Also, if the hardware components are different to the predicate but the software is identical, this is an indicator that you should pay special attention to integration testing.

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Decision Point 4 is asking whether the differences in the technological characteristics raise different questions of safety and effectiveness compared to the predicate device. A "different question of safety or effectiveness" is a question raised by the technological characteristics of the new device that was not applicable to the predicate device and poses a significant safety or effectiveness concern for the new device.

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We typically go about answering this question by explaining why the new and or modified features do not introduce any issues of safety and effectiveness to the new device. The information to answer this question is usually available in the device description, substantial equivalence and software sections. For any new or modified components, assess whether there are any new questions of safety and effectiveness. In your review memo, document all major differences in the technological characteristics against the predicate, and provide an explanation on why the new or modified components do not introduce any different questions of safety and effectiveness. For the comparison of characteristics, we suggest providing a table.

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Referring to our example memo, we've created a table comparing each of the major components of the stationary x-ray system with the predicate device. This table compares the specifications of the x-ray generator. We see that both kV, and milliampere ranges, highlighted in red, are different from the predicate, which is also noted below. However, this difference does not introduce any new questions of safety and effectiveness, as both ranges are well within acceptable ranges for imaging of the human anatomy.

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In comparing the stationary x-ray systems detectors, we see that the connection type, scintillator material, spatial resolution as quantified by the modulation transfer function (MTF) and detector quantum efficiency (DQE) are different.

The values for MTF and DQE show that the new stationary x-ray device's detector has worse performance than the predicate's. Since these parameters are indicators of the systems spatial resolution, we know that this new detector may affect the effectiveness of the device. This is a deficiency. A simple way of resolving this issue is to ask the sponsor to provide a reference device with similar or worse performance. If the detector was previously cleared, the review of performance data is not necessary.

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The last section of the table compares the imaging acquisition software and additional features. Though this software has been previously cleared, the new device's software package has additional features that the predicate device does not have. We will go through each feature separately. Let's look at the Autogrid feature. In the memo, we see a summary of the feature's purpose, and an explanation on why there are no new questions of safety and effectiveness.

This feature reduces the effects of scattered radiation on diagnostic x-ray images, which improves the image contrast. This does not introduce any new questions of safety and effectiveness, as the question of image quality at a reasonable dose is the same for all x-ray systems.

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The low dose protocol feature, not present in the predicate, utilizes a noise reduction algorithm. The memo further explains that this feature is intended to be used with lower dosage imaging protocols. These allow for low patient dose while maintaining image quality. This feature is similar to the previous Autogrid feature, as it concerns image quality at reasonable patient dose. Therefore, this feature also does not introduce any new questions of safety and effectiveness.

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Now let's move on to Decision 5a, where we ask whether the methods to evaluate the device characteristics are acceptable.

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To answer the question to decision point 5a, you need to determine whether the provided performance data supports the intended use of the device. This is not limited to bench testing only, but includes electromagnetic, mechanical, thermal, and radiation safety as well as sterilization, biocompatibility and software verification and validation. Therefore, these sections of the submission are reviewed during the evaluation of performance testing. For documentation, we typically focus on performance testing for new or modified components, especially detectors and post processing features as these can change the effective performance compared to the predicate. For any device specific claims, we confirm whether the sponsor has provided adequate performance testing to support them. If you discover any dose reduction claims, please contact the FDA.

Also, we ensure that the sponsor provides acceptable support for their testing methodologies by referencing the appropriate guidance documents, standards or literature. Once evaluated, we provide a conclusion on whether all concerns of safety and effectiveness have been addressed.

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Here's a list of performance testing to consider when evaluating x-ray systems. We'll review each of these categories of testing one by one.

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First, let's start with Software. Here are a few hints and tips for reviewing the software section of x-ray devices. First check the sponsor's justification for the software's level of concern. For our example device, this is moderate. So, you should expect to review documentation consistent with the moderate level of concern based on the FDA Software Guidances listed on this slide. Please note, in general, it's expected that the software level of concern for most diagnostic stationary x-ray systems will be moderate because failure of the device can lead to a delay in diagnosis.

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We typically also clarify and document whether the software is changing from the predicate when the sponsor indicates that they're identical. If the software is the same, but the hardware components are different from the predicate, we typically focus on software/hardware integration in the hazard analysis and verification and

validation testing. For any modifications to existing software platforms, focus on the corresponding risk analysis and V&V of these changes.
And, if features are entirely new, choose features that interact with a number of software and hardware components, analyze the risk assessment, and trace through requirements, design, and, lastly testing. Finally, we ensure validation testing is done on the finished device.

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Let's look at our example memo. As documented, our example device includes modifications to an already cleared software platform. Therefore, the review did not go through a full traceability assessment. Instead, the review focused on the risk analysis, and corresponding verification and validation of the new software features, together with the integration of hardware components with the software. The memo also includes a table, mapping a hazard from the hazard analysis, to the mitigations and verification of the new AutoGrid feature. First, a hazard is chosen related to the AutoGrid feature, with its associated potential hazard, cause and effect.

Here, the hazard is that the Autogrid feature is not successfully applied to the diagnostic x-ray image post acquisition. Next, this hazard is traced to its respective mitigations. The sponsor provided a specific software requirement, which is to prompt the user for use of the feature prior to imaging, and user manual instruction requirements as mitigating factors for this potential hazard. These requirements are then traced to their respective verification test, indicating its acceptance criteria. We typically see this level of documentation for a few features. Please note, that this is not the end of the review for this feature. Since this feature impacts image quality, we need to verify that the output image is appropriate for diagnosis. You, as the reviewer, need to know when basic Verification and Validation is appropriate, versus when something might be affecting the output image.

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Remember! The review of the software section includes reviewing all cybersecurity information. As seen in the memo, the documentation of this section addresses five subcategories: risk management, plan for continuing support, plan for malware-free shipping, appropriate labeling, and interoperability. Provide an explanation of what the sponsor had submitted for each subcategory to address all cybersecurity concerns.

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Next, let's look at electrical safety, electromagnetic compatibility (EMC), and radiation safety. For this, sponsors usually conform to the appropriate international electrotechnical commission standard, IEC 60601-2-54. This standard addresses the basic safety and essential performance of X-ray equipment for radiography and radioscopy.

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Let's go back to our memo. Before we go into how this was documented, here, on the left side of this slide, are a few tips to use when reviewing this section. First, ensure that the completed testing was performed on the final finished device. Second, ensure that all testing is completed at the time of the submission, as promissory notes are typically not sufficient. And finally, ensure that the sponsor has conformed to the correct FDA recognized version of the standards, or provided a justification for taking a different approach. On the right, we see how this was documented using template language. It's essentially stating that the sponsor has conformed to the correct standard which covers EMC, electrical, mechanical, thermal, and radiation safety.

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Next, there is cleaning, disinfection and sterilization. For x-ray systems, we expect sponsors to provide appropriate cleaning instruction. These instructions are usually reviewed in the labeling material. We typically document whether the cleaning instructions contain appropriate methods of cleaning and indicate whether the sponsor suggested an appropriate cleaning agent.

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In our example device, the sponsor's user manual clearly stated that no components of the system are packaged as sterile, and they provided appropriate cleaning instructions with the suggestion of a cleaning agent. This is documented in the memo and deemed acceptable.

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Then there is biocompatibility. Biocompatibility testing is typically negligible for x-ray devices seeing that "patient examination paper" is usually used between potential patient contacting components and patient skin.

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When reviewing, confirm there are no patient contacting components, and include whether the sponsor has recommended the use of some separating material between the patient and potential patient contacting components. The sponsor proposed the use of a barrier, such as a sheath or drape. As a result, there are no patient contacting components. This is acceptable.

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Finally, there is the review of the non-clinical and clinical performance testing. For this, you need to determine what tests are necessary based on the predicate, and the new or modified features. This can be determined by the following questions listed in the box: Are there standards or well accepted test methods for evaluating the device? What performance testing methods were used for predicate and secondary or reference devices? Are these methods appropriate for new device?
For different features, are there any additional tests needed for the new device?

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Once we have determined whether the performance testing is adequate, we move to decision 5b. Here, we need to evaluate whether the data demonstrate substantial equivalence to the predicate.

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At this stage, we typically have the necessary information to identify the risk analysis methods, and the performance testing used to evaluate new and modified features. We summarize and document all verification and validation activities for these new or modified features. These include test plans and acceptance criteria. This should also be done for any performance testing of the new or modified features that impact the output of the x-ray device. This summary should be followed by a conclusion.

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Similar to the predicate the device, the sponsor of our stationary x-ray device provided nonclinical performance data as recommended by the SSXI guidance. We would like to see this clearly stated, as shown in our example memo. In addition, the memo states methods used for the calculations of performance characteristics, and that the sponsor provided sufficient documentation as recommended by the wireless guidance.

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Now, if we refer to the comparison table from slide 37, you should remember that the comparison of the system MTF and DQE for the new stationary x-ray system is worse than the predicate's. Since these characteristics have an impact on the device output, this was highlighted in the performance testing section. Here, we see what was provided, which is the MTF curves in both x and y directions. Why it's deficient, which is the MTF values were lower for the new device in both x and y directions. And, why it's not acceptable, which is the new device's performance is not as effective as the predicate.

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Similar documentation was provided for the detector's DQE. The sponsor provided the DQE graphs and the integral DQE. This is deficient because the DQE performance rapidly deteriorates at increasing energies. This is not acceptable because the DQE performance in the new device is worse than the predicate.

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Now remember, the new stationary x-ray device has new features compared to the predicate. These features have not been evaluated by any of the previously reviewed performance testing.
Since the sponsor provided additional acceptable testing for evaluation of the two new features and associated claims, this was highlighted in the documentation as well. For the Autogrid feature, we see what type of study was conducted, which is an anthropomorphic phantom study. The memo documents the phantom type with size ranges, as this is important since the new device is intended for pediatrics and adults. Next, we see the acceptance criteria, which is a review by a board-certified radiologist. Also included is a statement that any associated revised claims in the submission are acceptable.

For our low dose protocol feature, we see what was provided; a clinical image evaluation report; what study was conducted, which is an image comparison of chest x-rays with and without the LDP feature. And the acceptance criteria, which is a statement from board-certified radiologists deeming the images clinically acceptable. Remember, all of the quantitative dose and image quality claims have been removed. So these features are now acceptable.

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Now that we've reviewed all the performance testing, let's revisit the questions at each decision point in the flowchart. Just like in the example memo, we would like you to state each question, and provide a summary answer where applicable. For question 2, which asks for an explanation of how the intended use of the new device is similar to or different from the predicate, we see a summary statement that says the devices are both intended for general projection radiography of the human anatomy in general diagnostic procedures. For question three, which asks to describe the different technological characteristics, we see a summary statement that lists the differences in detector communication; wireless vs wired, detector scintillator material; Gadox vs CsI, and software features; AutoGrid, and LDP.

Finally, there is question 5b, which asks to explain how the data do or do not demonstrate substantial equivalence. We see a summary explaining that the sponsor conformed to the correct FDA-recognized standard, IEC 60601-2-54, which addresses all basic safety concerns. It also states that the sponsor provided adequate performance testing as recommended by the SSXI, wireless, pediatric, cybersecurity, and software guidance documents. To address deficiencies with the new device's detector performance, the sponsor provided a reference detector, and

finally, the sponsor supported both post-processing features with anthropomorphic phantom studies, removing all quantitative claims.

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Referring to our color-coded flow chart, we see that we have satisfied all the decision point questions to result in a substantially equivalent final decision.

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Now that we've finished our review and determined that the new stationary x-ray system is substantially equivalent, it's necessary to revisit the 510(k) summary to ensure that it reflects the documentation of the substantially equivalent device. Here are some tips to use when reviewing the 510(k) summary at the end of the review process: Confirm that all administrative information is correct, like the 510(k) numbers, trade or proprietary names, classification name, regulation number and product code. Verify that the differences from the predicate are included in the substantial equivalence section.

Make sure that the performance data section is adequately described, with appropriate references to the standards and guidance documents utilized. This section should also reflect the performance testing provided for the software level of concern.

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The key steps for a successful review of x-ray devices include: identifying and comparing new or modified components of the new x-ray device to the predicate; using the 510(k) decision making flow chart, and knowing how to use the relevant resources for your review of x-ray devices.

Slide 65
For your reference, we've provided the definition of all the acronyms we used in this presentation.

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And here is an additional list of resources for your reference.

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We hope you found this presentation helpful.
Thanks for watching.

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