# An Overview of Clinical Decision Support Software from a Regulatory Affairs Historical Perspective

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## I. Development of Clinical Decision Support Software and Supporting Technology

Clinician Decision Support (CDS) tools, as the US federal government describes them, have existed as long as documents have supported medicine. A joint report by the FDA, the FCC, The Office of National Coordination of Health IT was published in 2014. It gives the following as examples of CDS: computerized alerts and reminders for providers and patients; clinical guidelines; condition-specific order sets; focused patient data reports and summaries; documentation templates; diagnostic support; and contextually relevant reference information. The development of user-friendly software applications allowed CDS to yield more valuable information than for example static clinical guidelines, or diagnostic supporting information, on a laminated card. Some of the software would be for lower risk clinical applications. The software might simply perform calculations for a clinician so that they did not have to do it manually; the calculations are well understood and straightforward to describe. Similarly, the software might provide clinical reference information that eliminates the need to maintain a library of physical books. Some of the software applications are for moderate risk information like an application that analyzes patient physiological signals to generate alerts for potential cardiovascular conditions. None of the successful early clinical applications would use highly complex calculations in part because the hardware to perform the calculations did not exist. Medicine did not generate enough interest in software applications to drive the hardware development needed to push CDS software to the next level. However, a perhaps unlikely source did drive the necessary technological breakthroughs: the gaming industry. Server farms grew and the availability of the new computing power provided clinical software algorithm developers and data scientists the opportunity to consider developing more powerful software applications.

Artificial Intelligence and Machine Learning (AI ML) models that required enormous of amount of data became feasible to design, development and implement. Now CDS software could do things like train on tens of thousands of images (e.g. images of the respiratory system), analyze tens of thousands of physiological signals (e.g. ECG recordings), and tens of thousands electronic health records (EHRs) which include routine vital sign measurement and more specific clinical laboratory test results. Medical software could always produce and display useful data. AI ML introduced the possibility of producing useful information. The combination of the need for CDS and the new power of AI ML has yielded major advances in medical technology; the FDA has authorized over 450 AI ML based device designs in the past five years with about 400 being radiological.

As the power of the devices increased, they grew closer to providing what might be called knowledge. Certainly, the outputs have begun to look like something more than just large calculations. Some in the cardiovascular business sector are even referring the device outputs as collaborative (link). As explained further in this article, the FDA responded in 2014 with a requirement that the indications for use statement, of an AI ML medical device, include a qualification statement communicating that the device output is only a part of the decision-

making process. This likely makes sense because the FDA cannot regulate the practice of medicine; there is no federal law giving the government the authority; the states have that right and responsibility. At some point, when AI ML medical devices consistently outperform humans, we as an American society will have to decide if we want our federal government to regulate AI ML medical devices in a way that is different from how it has regulated medical devices thus far. Will new federal legislation be needed, or perhaps a new agreement between the federal and state government? Whatever the answers, it is probably useful to review how we got to where we are today from a regulatory perspective before considering what comes next.

## II. The History of CDS Tools and Software in the United States from a Regulatory Perspective

The history of the development of regulations and FDA positions on CDS software is a traditional example of the application of checks and balances present in the US system of government. A timeline of Congressional and executive action appears in Figures 1 and 2 below.

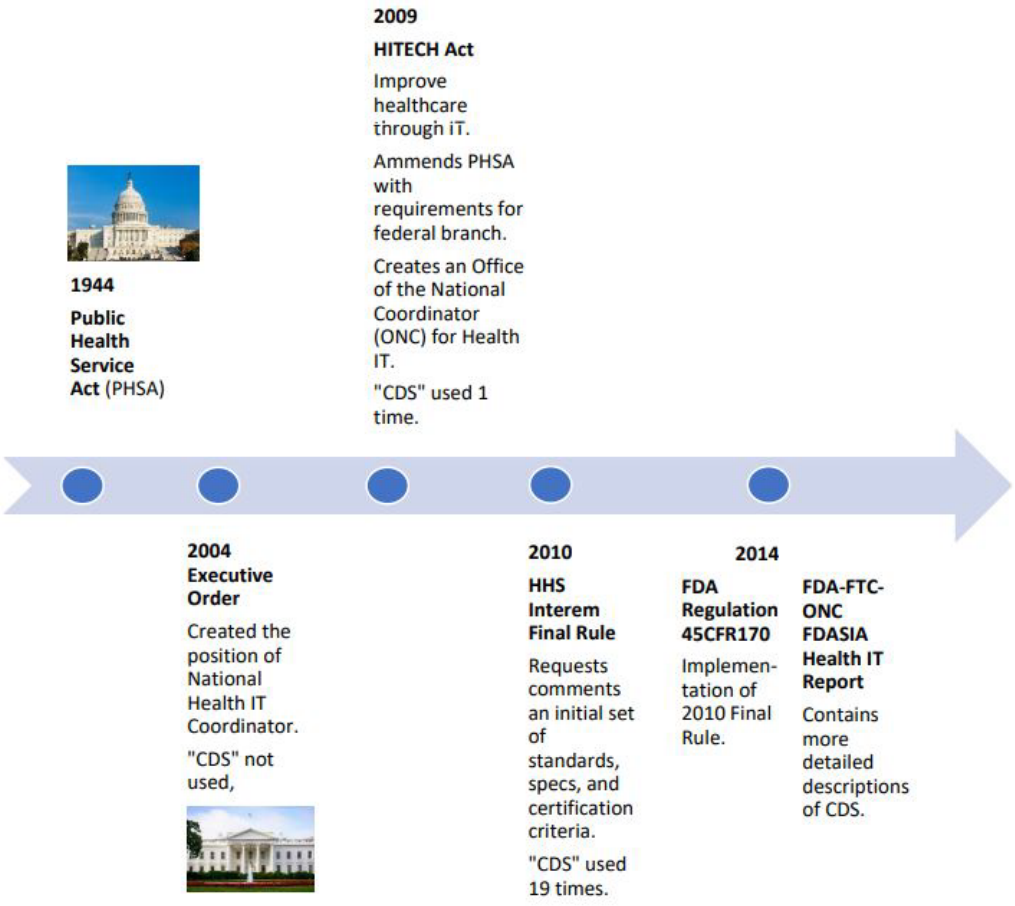


**Figure 1 – Timeline of US federal CDS-related activities from 1944 to 2014**

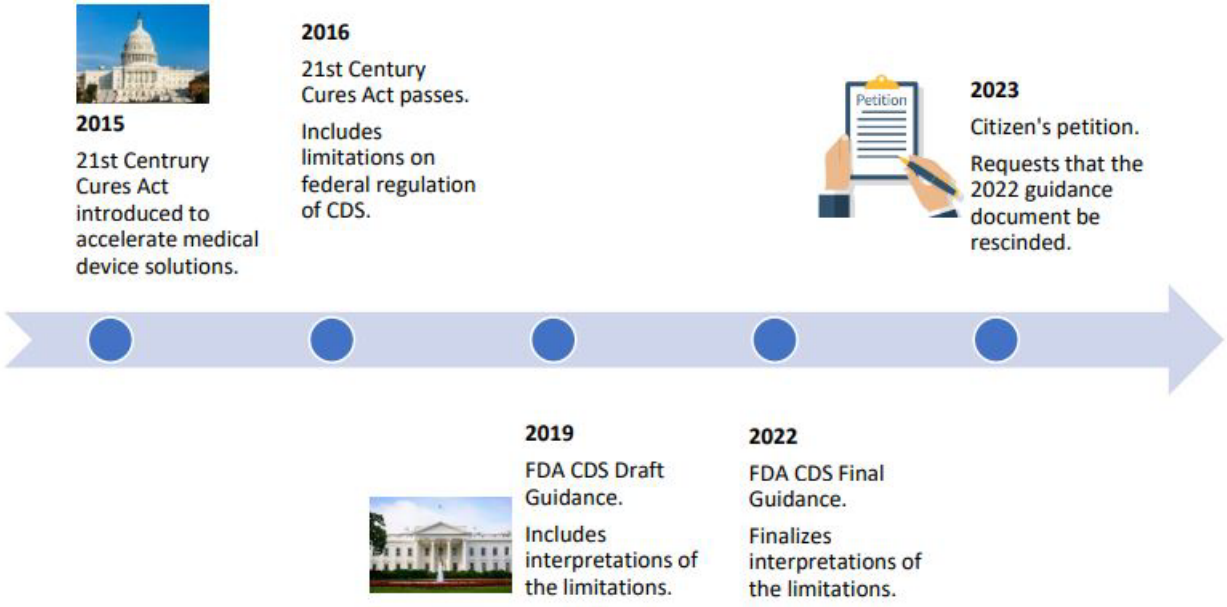


**Figure 2 – Timeline of US federal CDS-related activities from 2015 to the present**

The history begins with the Public Service Act of 1944 which was signed by president Franklin Delano Roosevelt and was "an important step in the toward the goal of better national health" (link). The advent of public access to the world wide web in the last two decades of the 21st century ushered in an explosion of technology development including health IT. It was now possible to improve public health more dramatically through harnessing the power of computing to begin to solve some of the harder challenges associated with the diagnose and treatment of diseases and medical conditions. It was therefore perhaps natural for the federal government to seek to support this new medical industry by creating an office to coordinate the underpinnings of the development of the new technologies.

In 2004 an executive order generated by George W. Bush created the position of National Health Information Technology Coordinator which does not mention CDS. However, in 2009, congress, created the HITECH Act which upon signature by Barack Obama established the Office of National Coordination of Health Information technology; this act uses the phrase "clinical decision support" and explains that some electronic health records may provide clinical decisions support:

> " (13) QUALIFIED ELECTRONIC HEALTH RECORD.—The term 'qualified electronic health record' means an electronic record of health-related information on an individual that—
> ''(A) includes patient demographic and clinical health information, such as medical history and problem lists; and:
>
> - ''(B) has the capacity—
> - '(i) to provide clinical decision support;…"

This is the only use of the phrase in the entire HITECH Act and no definition is provided. The Act also amended the PHSA to require the federal government to "adopt an initial set of standards, implementation specifications, and certification criteria by December 31, 2009 to enhance the interoperability, functionality, utility, and security of health information technology."

In 2010 the Department of Health and Human Services (HHS) issued an interim final rule, 75 FR 2013, with a request for comments on actions proposed to comply with the amended Public Health Service Act. The phrase "clinical decision support" appears approximately twenty times in the rule. It is used in relation to disease and medication management, definitions of EHR and EHR Modules, and rules for high priority clinical items. The rule also communicates (Section III.C.2) a desire of the executive branch to "…accelerate the adoption and use of clinical decision support." In Section V.C. of the act clinical decision support is provided as an example of a more sophisticated clinical capability.

In 2014 the rule led to the generation of federal regulation 45 CFR 170 "Health Information Technology Standards, Implementation Specifications, and Certification Criteria and Certification Programs for Health Information Technology." This regulation includes requirements for the items in its title and communicates that certification of health information technology is voluntary. Certification includes descriptions of the capabilities for health IT including five requirements for clinical decision support functionality (45CFR170.315). "CDS" or "clinical decisions support" appears ten times in the regulation.

2014 also saw the joint publication of a Health IT Report by the FDA, Federal Communications Commission and ONC which introduced CDS this way:

> "Clinical decision support (CDS) provides health care providers and patients with knowledge and person specific information, intelligently filtered or presented at appropriate times, to enhance health and health are.72 CDS encompasses a variety of tools intended to enhance, inform, and influence health care decisions. These tools include, but are not limited to, computerized alerts and reminders for providers and patients; clinical guidelines; condition-specific order sets; focused patient data reports and summaries; documentation templates; diagnostic support; and contextually relevant reference information. These functionalities can be deployed on a variety of platforms (e.g. mobile, cloud-based, installed)."

The report identifies three categories of health IT software functions: administrative, health management and medical device. The report states that most clinical decision support functions are health management and pose a low safety risk. Some may meet the FDA's definition of a medical device, but the benefits are high enough that the agencies state oversight focus should not be on these items (the FDA intends to use enforcement discretion). The report focuses on health management software functions (as opposed to the administrative and medical device functions) and states four areas are key: I. Promote the Use of Quality Management Principles; II. Identify, Develop, and Adopt Standards and Best Practices; III. Leverage Conformity Assessment Tools; and IV. Create an Environment of Learning and Continual Improvement. With respect to how the FDA will choose to focus resources, the report states that attention and oversight will be on higher risk software which the report identifies as medical device health IT functions; examples offered in the report are "computer aided detection software, remote display or notification of real-time alarms from

bedside monitors, and robotic surgical planning and control". "CDS" and "clinical decision support" are used throughout the report.

In 2015 Congress introduced legislation, the 21st Century Cures Act, as part of an effort to help accelerate medical product development and bring new innovations and advances to patients who need them faster and more efficiently. This act included limitations on the FDA's ability to regulate some health IT software functions. If clinical decision support software functions met specific criteria, then the congress excluded the functions from the definition of a medical device; in other words, FDA lacks the authority to regulate them. The criteria are a bit cumbersome, difficult to summarize and can be read in full here: link (subtitle F Section 3060). They do include some gray area terms: medical information, recommendation, independent review, intent, and primarily. The proposed legislation was signed into law in 2016.

In 2019 FDA responded with a draft guidance on clinical decision support software which goes into a good amount of detailed assessment of the criteria. For example, one of the criteria is software that is "Intended for the purpose of displaying, analyzing, or printing medical information about a patient or other medical information." Here the FDA interprets medical information to be "demographic information, symptoms, test results, medical device outputs (such as heart rate or blood pressure), patient discharge summaries, and/or medical information (such as clinical practice guidelines, peer-reviewed clinical studies, textbooks, approved drug or medical device labeling, and government agency recommendations)". So gray areas in the law do require some detail in the guidance document to allow FDA to make practical recommendations. The guidance also provides about ten pages of examples of software functions that meet and do not meet the criteria, including software functions that are under enforcement discretion; the examples are very useful because they allow manufacturers and FDA reviewers to compare a given device description to the lists of examples to estimate the Agency view on that specific device description. Additionally, the CDS guidance document used factors from a 2014 International Medical Device Regulatory Forum (IMDRF) guidance document (""Software as a Medical Device": Possible Framework for Risk Categorization and Corresponding Considerations") to apply a risk-based policy for CDS software functions.

When the CDS guidance was finalized in 2022 the IMDRF factors from the international guidance document were no longer discussed except for a brief mention that the users of the guidance document should see the IMDRF for risk categorization and consideration that may apply to certain software functions. Also removed was a section on definitions. About ten pages of examples were again present as well as consideration of devices that would again be under enforcement discretion; on page 19 the reader is referred to four other guidance documents to better understand the enforcement discretion policies for some software functions although the phrase enforcement discretion is no longer used. In support of the 2022 guidance document, and related guidance documents, the FDA has created a website and downloadable graphic (link) entitled "Your Clinical Decision Support Software: Is It a Medical Device?" and more a more broad site (link) entitled "Digital Health Policy Navigator". Both are very useful references when beginning a regulatory strategy for a software function(s).

Digital Policy Navigator walks the user through a series of questions about their software function with each question based on a law, an FDA regulation or an FDA guidance document. Guidance is given along the way and the user is told at the end of their path, through their related series of questions, the general likelihood that the software function is (a) not regulated by the FDA, (b) under FDA enforcement discretion or (c) regulated by the FDA.

On February 6th, 2023 a Citizen's Petition was filed with the Center for Devices and Radiological Health (CDRH) to request that the 2022 guidance document be rescinded (docket # FDA-2023-P-0422; link). The rationale for the request is that the 2022 CDS guidance document violates law established by Congress. One conclusion in the petition is that the time-criticality, of the decision that CDS software supports, was misinterpreted by the Agency. The petitioners note that the FDA concluded time-criticality was a bar under the third criterion of the 21st Century Cures Act when it should be a under the fourth criterion. The fourth criterion can be met if a manufacturer is highly transparent; more specifically the software is intended for the purpose of "enabling such health care professional to independently review the basis for such recommendations that such software presents so that it is not the intent that such health care professional rely primarily on any of such recommendations to make a clinical diagnosis or treatment decision regarding an individual patient". Many more points are made in the petition to rescind the guidance document. On July 10th, 2023 a second Citizen's Petition was filed based upon a proposed violation of the software developers first amendment rights to speak freely about technological innovations (docket # FDA-2023-P-2808-0001; link).

In summary CDS software law and regulations has its origin in an act from 1944 that was amended in 2009 to begin to address the development of more sophisticated health information technology. Since then, more detailed descriptions of what CDS software is, and which CDS software is regulated by the US government, have been generated by Congress and the FDA. Some gray areas still exist and cause a good deal of discussion and sometimes concern. It might make sense for manufacturers to engage the FDA before making decisions on regulatory strategies for CDS software applications. The 2022 CDS guidance document is likely a very important reference for FDA staff as they review premarket submissions including Q-subs, 510(k)s and De Novo classification requests.

## III. CDS Indications for Use Statements, and the Past and Present State of Premarket Authorizations

The FDA has authorized the distribution of several CDS medical devices through the 510(k) and De Novo processes. The indication for use statements of the devices includes statements that are perhaps somewhat unusual for non-IVD medical devices; the user is informed, or perhaps reminded, that a device cannot practice medicine or make decisions. Only qualified health care providers can do that. Table 1 contains a sample of devices that include a qualifying statement within their indications for use statement. The earliest year that one of these statements was found is 2014 and is part of the Indications for Use statement of the CVI42 device submitted by Circle Cardiovascular Imaging, Inc. The qualifying statements are varied but all put the responsibility of decision making firmly on the user of the device and not on the

device itself by using terms and phrases like "as part of", "in conjunction with", "adjunct", "assist" and "reference only". A health care provider must lead on the decision making and is responsible for the decision. Put in more general and current AI ML terms: There must a be a "human in the loop".

It is interesting to see that some devices were cleared under existing regulations while other are cleared under new regulations generated through the De Novo classification request process. Where new regulations were generated, one finds the FDA sometimes putting very specific CDS medical device verbiage into the regulation itself and sometimes making a softer statement; two examples are seen in the last two entries in Table 2:

- 21 CFR 870.2210 (created for the Accumen HPI Feature Software) describes a covered device as "…intended for adjunctive use with other physical vital sign parameters and patient information and is not intended to independently direct therapy." Adjunctive, independent and direct are strong clear terms here.
- By contrast 21 CFR 882.1491 (created for the Cognoa ASD Diagnosis Aid) describes a covered device simply as "…intended for use as an aid in the diagnosis of Autism Spectrum Disorder in pediatric patients." Aid is a softer term, and perhaps open for greater interpretation, but the described device falls within the FDA's broad stated understanding of what CDS means.

**Table 1 – CDS verbiage within sample Indications for use statements from public FDA website**

| **Device Name** Manufacturer | **21CFR Regulation #** | **Qualifying statement(s) within the Indications for Use** | **Submission #** |
|---|---|---|---|
| **Viz SDH**<br>Viz.ai, Inc. | 892.2080 | Notified clinicians are responsible for viewing non-compressed images on a diagnostic viewer and engaging in appropriate patient evaluation and relevant discussion with a treating physician before making care-related decisions or requests. Viz SDH is limited to analysis of imaging data and should not be used in-lieu of full patient evaluation or relied upon to make or confirm diagnosis. | K220439 |
| **CVI42**<br>Circle Cardiovascular Imaging, Inc. | 892.2050 | It shall be used by qualified medical professionals, experienced in examining and evaluating cardiovascular CT or MR images, for the purpose of obtaining diagnostic information as part of a comprehensive diagnostic decision-making process. | K213998 |
| **CVI42**<br>Circle Cardiovascul | 892.2050 | It shall be used by qualified medical professionals, experienced in examining and evaluating cardiovascular CT or MR images, for the purpose of obtaining diagnostic information as part of a | K141480 |

| | | | |
|---|---|---|---|
| ar Imaging, Inc. | | comprehensive diagnostic decision-making process. | |
| **Cognoa ASD Diagnosis Aid**<br><br>Cognoa, Inc. | 882.1491 | The device is not intended for use as a stand-alone diagnostic device but as an adjunct to the diagnostic process. | DEN200069 |
| **CLEWICU**<br><br>CLEW Medical, Inc. | 870.2210 | The product predictions are for reference only and no therapeutic decisions should be made based solely on the CLEWICU predictions. | K200717 |
| **Acumen HPI Feature Software** | 870.2210 | The Acumen HPI feature is considered to be additional quantitative information regarding the patient's physiological condition for reference only and no therapeutic decisions should be made based solely on the Hypotension Prediction Index (HPI) parameter. | DEN160044 |
| **DeepRhythm AI**<br><br>Medicalgorithmics S.A. | 870.1425 | Interpretation results are not intended to be the sole means of diagnosis. It is offered to physicians and clinicians on an advisory basis only in conjunction with the physician's knowledge of ECG patterns, patient background, clinical history, symptoms and other diagnostic information. | K210822 |
| **Minuteful - kidney test**<br><br>Healthy.io Ltd. | 862.1225 | Results are intended to be used in conjunction with clinical evaluation as an aid in the assessment of kidney health. | K210069 |

**Table 2 – Regulations used by FDA for the CDS devices in Table 1**

| 21CFR Regulation | (a) Identification |
|---|---|
| 892.2080 Radiological computer aided triage and notification software | Radiological computer aided triage and notification software is an image processing prescription device intended to aid in prioritization and triage of radiological medical images. The device notifies a designated list of clinicians of the availability of time sensitive radiological medical images for review based on computer aided image analysis of those images performed by the device. The device does not mark, highlight, or direct users' attention to a specific location in the original image. The device does not remove cases from a reading queue. The device operates in parallel with the standard of care, which remains the default option for all cases. |

| | |
|---|---|
| 892.2050<br>Medical image management and processing system | A medical image management and processing system is a device that provides one or more capabilities relating to the review and digital processing of medical images for the purposes of interpretation by a trained practitioner of disease detection, diagnosis, or patient management. The software components may provide advanced or complex image processing functions for image manipulation, enhancement, or quantification that are intended for use in the interpretation and analysis of medical images. Advanced image manipulation functions may include image segmentation, multimodality image registration, or 3D visualization. Complex quantitative functions may include semi-automated measurements or time-series measurements. |
| 882.1491<br>Pediatric Autism Spectrum Disorder diagnosis aid<br>(De Novo) | A pediatric Autism Spectrum Disorder diagnosis aid is a prescription device that is intended for use as an aid in the diagnosis of Autism Spectrum Disorder in pediatric patients. |
| 870.2210<br>Adjunctive predictive cardiovascular indicator.<br>(De Novo) | The adjunctive predictive cardiovascular indicator is a prescription device that uses software algorithms to analyze cardiovascular vital signs and predict future cardiovascular status or events. This device is intended for adjunctive use with other physical vital sign parameters and patient information and is not intended to independently direct therapy. |
| 870.1425 Programmable diagnostic computer | A programmable diagnostic computer is a device that can be programmed to compute various physiologic or blood flow parameters based on the output from one or more electrodes, transducers, or measuring devices; this device includes any associated commercially supplied programs. |
| 862.1225<br>Urinary protein or albumin (nonquantitative) test system. | A urinary protein or albumin (nonquantitative) test system is a device intended to identify proteins or albumin in urine. Identification of urinary protein or albumin (nonquantitative) is used in the diagnosis and treatment of disease conditions such as renal or heart diseases or thyroid disorders, which are characterized by proteinuria or albuminuria. |

## IV. Summary

In Summary, CDS has been used as a term by the federal government for over ten years. There are enough gray descriptions of what CDS is, that the Congress and the executive branch have issued laws, orders, reports and guidance documents to try to add clarity to support the development of innovative, clinically useful, safe and effective CDS software applications. It is not always clear what is and is not under the authority of the FDA to regulate and some controversy exists today. The FDA has on-line tools to help with the initiation of regulatory strategies, and guidance documents to help industry generate final regulatory assessments.

## V. The Future of Protecting Public Health with Respect to Safe and Effective CDS Medical Devices

Some futurists predict devices will practice some forms of medicine in the not-too-distant future. Some software will provide independent diagnoses better than some specialists. Some software will identify better treatment options than some clinicians. Will intellectual assessments, or the occurrence of unanticipated adverse events in the field, lead to federal action? For example, will new congressional legislation be necessary to grant FDA authority to regulate this future generation of CDS devices to the level needed to maintain an acceptable level of public health and safety? Will FDA instead use its existing authority to generate new regulations? That said perhaps the existing laws and regulations will prove to be sufficient. History has shown that the US federal government is engaged and is responsive. It will be interesting to see what happens.