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MTI's Top 21 Of '21: Omicron, Remote Reg Assessments, QSR Delays, US Capitol Insurrection Make Headlines

US Regulatory Roundup: 2021 In Review

by Shawn M. Schmitt

What a doozy of a year 2021 was in the medical device space – capped on one end by a deadly insurrection blasted by medtech heavy-hitters, and on the other end by news that the COVID-19 Omicron variant is wreaking havoc on some diagnostics (and many US FDA on-site inspections). Here are *Medtech Insight*'s Top 21 US regulation, policy, quality control and compliance stories of 2021, as determined by reader interest.

Omicron Headaches Abound For Diagnostics

At the close of 2021, there was one word on everyone's lips: Omicron. The latest COVID-19 variant – in particular, the negative effect it has on certain coronavirus diagnostics – was of most interest to *Medtech Insight* readers last year.

In our No. 1 story from early December, the US Food and Drug Administration said the DTPM COVID-19 RT-PCR Test made by Tide Laboratories LLC could fail to detect Omicron because of a "nine-nucleotide deletion in the N-gene, spanning positions 28370-28362. The single genetic target of this test covers the portion of the N-gene where the deletions occur."

Because the molecular diagnostic was a single-target test, a false-negative result was possible. But on 27 December, the FDA said in *our No. 5 story of 2021* that Tide Labs fixed the problem by changing the diagnostic to a "multiplex test with an added reverse primer."

"Bioinformatics analysis demonstrated a 100% match with Omicron variant sequences as well as Delta variant sequences," the agency said. "Initial laboratory testing also demonstrates the

ability to detect the Omicron variant." The FDA added that more lab testing is "ongoing as a condition of the EUA," or emergency use authorization, for the test. The agency reissued the EUA for the diagnostic to Tide Labs on 22 December.

The DTPM COVID-19 RT-PCR Test from Tide Labs was the first diagnostic that the FDA identified as having trouble detecting Omicron. Since then two other COVID-19 diagnostics, made by *Meridian Bioscience Inc.* and *Applied DNA Sciences*, have also been shown to also have problems with giving false-negative results. Those tests are still on the agency's *list* of molecular diagnostics that have trouble detecting the variant.

Meanwhile, on 28 December the FDA alerted the public that COVID-19 antigen tests will detect Omicron, "but may have reduced sensitivity." The agency said it's working with the National Institutes of Health's (NIH) RADx program "to study the performance of antigen tests with patient samples that have the Omicron variant" and pledged to keep the public updated of any additional findings.

The RADx – or Rapid Acceleration of Diagnostics – initiative was launched to "speed innovation in the development, commercialization and implementation of technologies for COVID-19 testing," the NIH *explains on its website*.

Pandemic Gives Birth To Remote Regulatory Assessments

Omicron – and COVID-19 in general – isn't just affecting diagnostics, however. On 29 December the *FDA decided to put the brakes once again* on conducting on-site surveillance inspections because of the disease variant.

While the FDA will continue to carry out domestic and foreign mission-critical inspections, the agency said it has "postponed certain inspectional activities" through at least 19 January. The FDA further said it's delaying the scheduling of foreign surveillance inspections that were slated to begin next month.

Industry has seen this type of pause by the agency before. The FDA put a stop to routine *domestic* and *foreign* surveillance inspections in March 2020. Domestic surveillance inspections weren't resumed until July 2021, and the agency is still inspecting overseas companies only when it's deemed mission critical.

> *"Remote Regulatory Assessments are here to stay." – Elizabeth Miller*

The unrelenting COVID-19 virus and its current (and future) variants have pushed the FDA over the past year to conduct a blend of in-person and remote inspectional activities, including the use of Remote Regulatory Assessments. The RRA program, which is voluntary for industry, helps the agency ascertain a manufacturer's general compliance with FDA rules and expectations via records requests and video interactions. RRAs are not considered by the agency to be official surveillance inspections.

"Suffice it to say that Remote Regulatory Assessments are here to stay, even on the other side of the pandemic," FDA official Elizabeth Miller said in December. Miller is the assistant commissioner for medical products and tobacco operations for the agency's Office of Regulatory Affairs, the lead office for all of the FDA's field activities.

In our No. 21 story from 2021 we reported that device makers that agree to a Remote Regulatory Assessment are presented with a three-page explainer of how the RRA will be performed by the agency. The FDA's document advised manufacturers on how best to transfer electronic files to the agency and who to contact if they have problems with an investigator during an assessment, among other instructions and explanations. It further explained that an investigator's RRA report is not given to a manufacturer unless the firm requests a copy through the Freedom of Information Act (FOIA).

As expected, not everyone in industry was happy about the new RRAs. *Our No. 7 story from last year* detailed challenges that one device maker faced when it underwent such an assessment by the agency early on in 2021.

Korina Akhondzadeh, a consultant with Carlsbad CA-based KARA & Associates, told *Medtech Insight* that the FDA investigator working with her client during an RRA "caught them off guard." That's because the RRA began on the same day it was requested by the investigator, giving the manufacturer no time to prepare.

The investigator "told them this was not an inspection; it was just some kind of an assessment that the FDA was doing, and asked if they would want to be part of it. And so, because [the client] was afraid that there would be some repercussions, he said yes, which was his first mistake," Akhondzadeh said.

By beginning the RRA on the same day as receiving permission from the company, the investigator apparently flouted FDA process around the assessments. The agency told *Medtech Insight* at the time that a typical RRA begins roughly five days after a manufacturer agrees to take part.

The company in question – a small two-person firm that makes a moderate-risk class II medical device – was so flustered by its experience that it didn't consider redacting key documents before

sending them to the FDA investigator, Akhondzadeh said. Her client leapt an array of other hurdles during its RRA, but in the end the company was presented with five deficiencies found during the assessment. And to top things off, the manufacturer was later flagged by the FDA for an on-site inspection because of its RRA results.

The investigator "found that the responses [from the manufacturer] were not adequate, and therefore a subsequent inspection will be required," an angry Akhondzadeh told *Medtech Insight* in a mid-year follow-up call. "That's very much like an inspection response. But I'm not surprised. It's disappointing and frustrating that the agency is doing this."

In the inaugural episode of our new podcast series Speaking Of Medtech, Steve Silverman, a former director of the FDA device center's compliance office, said he believes Akhondzadeh's story is a "one-off," noting that the agency "has established clear lines for what an RRA is and is not, and investigators who blow past those lines are wrong."

Nevertheless, "the story raises an important point," said Silverman, who's now head of The Silverman Group consulting firm. "Too often, firms know that investigators or other FDA staffers are out of line, but those same firms are reluctant to release these issues for fear of FDA retribution. I'm here to tell you that I've never seen a firm put in the penalty box because they called out FDA staff misconduct."

Listen to Silverman's full comments on the FDA's move toward remote assessments in the Speaking Of Medtech podcast below:

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A Rough Year For Royal Philips

Last year was a difficult one for *Royal Philips*, which saw not only a high-risk class I recall of millions of its breathing machines, but also a scathing FDA inspection report and a *letter from a powerful lawmaker* who demanded to know more about the recall.

More than 2 million bi-level positive airway pressure (BiPAP), continuous positive airway pressure (CPAP), and other mechanical ventilator devices were recalled by the company last June because there's a risk that people could inhale broken-down sound-abatement foam.

That led to an on-site inspection at a *Philips Respironics* plant in Murrysville, PA, where an agency investigator handed the company a lengthy FDA-483 report that included eight observations, which we reported on in *our No. 4 story from 2021*. In one of the more damning observations made during the 26 August-9 November inspection, investigator Katelyn Staub-Zamperini wrote that Philips apparently opened no formal investigations after it received

hundreds of thousands of complaints of particles and other contaminants when the breathing devices were used.

The 483 form went on to say that a query of complaints from January 2008 to this year for the keywords "contaminants," "particles," "foam," "debris," "airway," "particulate," "airpath" and "black" returned more than 222,000 complaints. The investigator further said that no investigations or corrective and preventive actions were opened "in response to the at least 175,000 complaints potentially related to degraded foam."

It's important to note that just because a company is issued an FDA-483 doesn't mean the agency will also send a warning letter – although a case like this that involves a class I recall and a less-than-stellar inspection outcome does up the chances that Philips could find an enforcement missive in its mailbox. Nevertheless, the company stressed in a November recall FAQ sheet that "an FDA investigator's list of inspection observations does not constitute a final FDA determination of whether any condition is in violation of the Federal Food, Drug, and Cosmetic Act or any of its implementing regulations."

And in *comments to reporters in late November*, Royal Philips CEO Frans van Houten pushed back, claiming that complaints were wildly overcounted by Staub-Zamperini during her inspection.

"The complaints that were referenced by the FDA are the result of a very broad search. Therefore the complaints did not necessarily relate specifically to the issue that led to the recall," van Houten said. "Not all entries in the database actually are a safety issue or a defect. Together with the FDA we have to go through the details and demonstrate what is related to the particulates and what were innocent queries."

More recently, Philips said on 23 December that a first round of toxins testing on its DreamStation breathing machine found that the level of volatile organic compounds (VOCs) put off by the recalled device probably won't cause long-term health effects for users. The company says the first-generation DreamStation represents the majority of affected recalled product.

Philips said its December update "covers the test results and assessment to date of the VOC emissions" of DreamStation. "Review of this assessment by an outside medical panel and Philips Respironics has determined that exposure to the level of VOCs identified to date for the first-generation DreamStation devices is not typically anticipated to result in long-term health consequences for patients," the company explained.

Philips – along with "certified testing laboratories and other qualified third-party experts" – is leaning on guidance from the International Organization for Standardization, ISO 18562, as it carries out testing of the recalled devices. ISO 18562, "Evaluation of Breathing Gas Pathways," offers "guidelines and general principles to evaluate and test the biocompatibility of breathing

gas pathways in health care applications," the American National Standards Institute (ANSI) *explains* on its website.

"At the time the recall notification was issued, Philips Respironics relied on an initial, limited dataset and toxicological risk assessment," the company said. "Since then, using ISO 18562 guidance, VOC toxicological risk assessments were performed … based on the initial and new VOC testing performed to date. Philips Respironics has made this data available to the FDA and other competent authorities, and is in the process of sharing this data with health care providers and patients."

The manufacturer stresses, however, that the tested DreamStation devices weren't exposed to ozone cleaning, which is called for in the product's instructions for use. Further, "this new assessment is limited to the evaluation of VOCs for first generation DreamStation devices, and does not evaluate the risks of potential foam particulates or cover other devices affected by the recall," Philips said.

Quality System Regulation Harmonization: Four Years Later

If you're a medtech regulatory enthusiast you've likely been champing at the bit to see the FDA's draft of its new Quality System Regulation, which the agency has been harmonizing with international quality systems standard ISO 13485 since early 2018.

The director of the agency's device center, Jeff Shuren, spent much of 2021 ensuring industry that the draft QSR would be released by the end of the year, even noting *in our No. 15 story* that it was "full-steam ahead with that proposed regulation." But he began *walking those comments back* in mid-October.

But things are looking up: *On 5 January the FDA sent its draft reg to the White House Office of Management and Budget for review.* While this is a major step forward for a proposed rule that's been worked on for nearly four years, industry shouldn't expect to see the draft until perhaps later this year, after the OMB completes its review.

In the meantime, check out *our No. 17 story from 2021*, wherein longtime industry experts Kim Trautman, Vincent Cafiso, Steve Niedelman, Kwame Ulmer and Josh Levin answered six questions about the future draft rule.

And for more on the FDA's Quality System Regulation rewrite, check out our recent Speaking Of Medtech podcast below:

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Medtech Industry Denounces Insurrection

Exactly one year ago heavy-hitters in the medtech community came together to denounce the insurrection at the US Capitol. Our reporting on industry's reaction to the insurrectionists' attempts to thwart members of Congress from tabulating electoral votes from the November 2020 presidential election was *our No. 8 most popular story in 2021*.

"The peaceful transition of power has been a hallmark of American democracy for more than 200 years. As someone who has benefitted immensely from the freedoms we enjoy in the United States, I am deeply troubled by the images … from our nation's capital," *Medtronic PLC* CEO Geoff Martha *wrote on LinkedIn* at the time. "We all deserve better than the chaos we are seeing in Washington, DC – as a society and as a nation. I … stand with my fellow CEOs supporting a peaceful transition of power."

And *Johnson & Johnson* CEO Alex Gorsky said at the time that he was "devastated" by the "assault" on "fair and peaceful elections": "Now is the time to stand shoulder-to-shoulder in unity – not face-to-face in conflict – and to chart our path to a better and healthier future," *his statement* read.

The largest medtech lobby group, AdvaMed, also chimed in on the insurrection. In a series of tweets, CEO Scott Whitaker said the "violence at the US Capitol does not represent who we are or who we should be as a nation. We condemn it." It's rare for AdvaMed to make political statements, but not unprecedented. *In June 2020, Whitaker remarked* on the murder of a Black man, George Floyd, at the hands of Minneapolis police.

Meanwhile, Medical Device Manufacturers Association (MDMA) CEO Mark Leahey *denounced the insurrection* as "horrific and shocking," noting that it was "a tragic reminder that there needs to be more compassion and thoughtfulness in the United States as we debate our differences."

The 21 most popular US regulation and policy stories in 2021 are listed in the table below:

Rank	Story
1	*COVID-19 Omicron Variant Could Cause False-Negative Results In Tide Labs Test, FDA Says*
2	*Sweeping Executive Order Puts Hearing Aids Over The Counter; Cracks Down On Internet Providers*
3	*Damning FDA-483: Philips Didn't Investigate 222,000 Complaints Of Possible Degraded Foam In Breathing Devices*
4	*After 3 Years Of Work, FDA Says It Will Release Its Revamped Quality System Regulation This Month*
5	*Omicron Variant: Tide Labs Resolves False-Negative Problem With COVID-19 Tests*

6	*Proposed Medicare Code Change Could Affect Reimbursements On Glaucoma Devices*
7	*'We Were A Victim': How An FDA Remote Regulatory Assessment Took One Device Maker By Surprise*
8	*Medtronic, J&J, AdvaMed, MDMA Denounce Attempted Coup At US Capitol*
9	*Woodcock To Be Acting US FDA Commissioner, Leaving Agency in Stable, Capable Hands*
10	*Adverse Event Codes From IMDRF Now Used By FDA's eMDR System*
11	*Overflow Issue With Abbott COVID Tests Could Result In False Positives*
12	*Senator To Philips CEO: Fork Over Info On Class I Recall Of Sleep, Ventilator Devices – Pronto*
13	*Italian Sterilization Firm Falsified Certificates Since 2016; 97 Device Makers May Be Impacted, FDA Warns*
14	*FDA Will No Longer Regulate Certain Medical Software*
15	*After QSR Delays, 'It's Full-Steam Ahead With That Proposed Regulation,' FDA's Shuren Vows*
16	*FDA's Shuren: Staff Overburdened, Review Times Seeing Negative Effects*
17	*QSR Q&A: 5 Top Medtech Experts Answer 6 Burning Questions About FDA's Coming Quality Reg Redo*
18	*Lucira Health's Unexpected Sprint To A First-Of-Its-Kind EUA From FDA: The Inside Story*
19	*Securing FDA Approval For Novel OPRA Prosthetic Wasn't A 'Slam Dunk.' Here's How Start-Up Integrum Made It Through The PMA Maze*
20	*A Chat With Jeff Shuren: FDA Device Center Chief Worries About Agency Staffing; Talks MDUFA V, Pandemic, More*
21	*From Electronic Docs To FOIA Requests, FDA Lays Bare Its Process For Remote Regulatory Assessments*