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IN THIS ISSUE

Third Circuit: Hybrid Device Rules Apply to Individual Components

In a precedent-setting decision, a federal appeals court ruled that federal statutes on hybrid medical devices — products including components with different regulatory classifications — supersede state laws.

In a 2013 lawsuit, plaintiff Walter Shuker, who was implanted with components from Smith & Nephew's 510(k)-cleared R3 hip replacement system and an R3 metal liner in 2009, sued for negligence, fraud, and strict product liability, blaming the product for complications that eventually required further surgeries.

The suit was dismissed in September 2016, after which Shuker launched an appeal. Last September, the FDA filed an amicus brief with the Court of Appeals for the Third Circuit siding with the company. "Because the component is subject to device-specific federal requirements, [the FD&C Act] expressly preempts any state requirements 'with respect to' the component that are 'different from, or in

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Gottlieb: FDA to Continue Analyzing Safety of Bayer Birth Control Device

FDA Commissioner Scott Gottlieb said the agency is evaluating thousands of adverse event reports for Bayer's permanent birth control device Essure received in the past year.

The agency approved the device in 2002 and in February 2016 — responding to increased concerns about patients experiencing abdominal pain, device migration and abnormal uterine bleeding — ordered Bayer to conduct a postmarketing study to analyze the device's safety profile and to add a boxed warning to its labeling.

The agency received nearly 12,000 adverse events relating to Essure last year, the majority of which were submitted in the last quarter of the year, Gottlieb said, in a Feb. 7 statement.

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addition to,' those device-specific federal requirements," the FDA wrote.

In its March 1 opinion, the court ruled that the District Court was correct in dismissing the preempted claims of negligence, strict liability and breach of implied warranty. However, the court wrote, the FD&C Act's medical device amendments' preemption provision does not cover "parallel" claims, or those that hinge on state laws incorporating federal requirements.

The plaintiffs, in their appeal, claimed that the device at issue is the entire hybrid system, but the company and the FDA argued that "analysis at the component level is the only way to harmonize various provisions of the statute."

The court found in favor of the company for three reasons:

- The FD&C Act does not define devices as finished products and statutory precedent has always defined it to include components;
- The FD&C Act's provision for off-label use supports component-level analysis, as such uses are "an accepted and necessary corollary of the FDA's mission to regulate in this area without directly interfering with the practice of medicine"; and
- FDA enforcement of such issues has historically favored the component argument over the full-system argument.

"Taken together, the statutory definition of 'device,' the treatment of off-label uses, and the guidance of the FDA all counsel in favor of scrutinizing hybrid systems at the component-level," the ruling states. However, the court overturned the district court's dismissal of negligence based on off-label promotion claim but affirmed its dismissal of the fraud claim.

Read the ruling here: www.fdanews.com/03-08-18-Smith.pdf. — Zack Budryk

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"We're working to evaluate whether these cases reflect new safety concerns, as well as the extent to which they represent entirely new reports to the FDA or may have been reported in a prior safety filing. More than 90 percent of the reports in 2017 mentioned issues involving potential device removal, which the FDA is further investigating," Gottlieb said.

Some of the adverse event reports do not indicate if or when the device was removed. "We're actively working to gain more information on these new reports and to better understand reasons for the device removal," Gottlieb said, adding that the agency will be following up on many individual reports to gather the additional information.

He said the agency will provide ongoing updates on its assessments of the data and will consider peer-reviewed medical studies on the device's safety. Thus far, he wrote, such studies have generally aligned with agency assessments of Essure's safety profile.

The FDA also will consider regulatory options in line with the device's risks and benefits as it obtains new information, said. — Zack Budryk

483 Roundup: FDA Hits Five Firms For Complaints, Other Deficiencies

Five device manufacturers drew 483s for problems with complaint handling, medical device reporting, CAPAs and other nonconformances.

Philips Medical Systems: The FDA cited Philips Medical Systems for failure to investigate or properly review thousands of complaints in a Form 483 issued after a July/August 2017 inspection of the firm's Cleveland facility.

Investigators found that out of 133,845 complaints from July 2016 to July 2017, more than 129,000 were closed based only on the assigned hazard/harm symptom code without further investigation. Nearly 1,800 complaints were not properly escalated and forwarded to the complaint-handling unit.

The Form 483 further faulted the company for its CAPA and complaint-handling procedures. The facility's procedures for entering complaints do not describe how and when failure codes are entered, nor does the company have any procedure defining the codes. The firm only evaluated complaints and non-conformances for potential CAPAs when they meet an escalation threshold, which is not adequately defined or consistent.

The inspection also found that of 36 complaint records and associated MDR files, 21 of 36 complaint files did not list all possible associated hazards.

In addition, the firm's procedures did not ensure control of suppliers and procedures for acceptance of incoming product were not properly established. The company's process for handling duplicate anomaly reports was also inadequate. Lastly, the company's written MDR procedure lacked an internal system providing for a standard review process to determine whether an event meets the reporting criteria.

Nevro Corporation: Failure to submit medical device reports, inadequate risk analysis and CAPA procedures that failed to detect recurring quality issues were just a few of the nonconformances cited on a Form 483 handed to

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Medical Device Reporting Requirements

MDR requirements are an outgrowth of complaint management regulations. The FDA's regulations in 21 CFR Part 803 – Medical Device Reporting require that companies evaluate all device complaints to determine if they involve an adverse event that must be reported to the agency.

Malfunctions must be reported when the chance of death or serious injury resulting from recurrent malfunctions is not remote. Malfunctions also need to be reported when the consequences of the malfunction affect the device in a catastrophic manner that might lead to a death or serious injury.

Manufacturers often have the most trouble determining when the likelihood of a future malfunction resulting in death or serious injury is not remote. One of the factors the FDA looks at is whether or not that particular type of malfunction has caused a death or serious injury in the past two years. If it has, the agency concludes that the risk is not remote and the event must be reported.

In addition, manufacturers must report malfunctions when:

- They cause the device to fail to perform its essential function, compromising the device's therapeutic, monitoring or diagnostic effectiveness, and could cause or contribute to a death or serious injury, or other significant adverse device experience;
- They would prevent a long-term device implant from performing its function;
- The device is considered life-supporting or life-sustaining, and thus essential to maintaining human life; or
- The manufacturer takes or would be required to take action under Section 518 or 519(f) of the Food, Drug and Cosmetic Act, which deals with recalls and tracking products.

Excerpted from the *FDAnews* management report: *Complaint Management for Devicemakers: From Receiving and Investigating to Analyzing Trends*.

FDA Expert Panel Considers Trial Designs for Neurological Devices

Most members of the FDA's Medical Devices Advisory Committee panel on neurological devices said patient age should not be a consideration for inclusion in a clinical trial, but life expectancy should, and patients with less than one year of life expectancy should be excluded from studies.

The FDA asked the experts to consider whether there are specific rates of adverse events that would raise serious concerns about the safety of a specific device. Some panelists argued there should be a 3 to 5 percent rate limit for death and disabling strokes for unruptured aneurysms and a 10 percent rate for ruptured aneurysms. All panel members said it was important to differentiate between ruptured and unruptured aneurysm cases.

The panel members generally agreed that the widely-used Raymond classification scale, which assesses the degree of aneurysm occlusion, should be used in intracranial aneurysm device trials, but that "novel technologies" may require alternative assessment tools.

In terms of follow up, the panel recommended that for a premarket decision, one-year assessment of treatment is appropriate, provided the aneurysm is stable (Raymond I for flow diverters and Raymond I or II for intrasaccular devices).

Some panelists recommended that two-year long-term follow up is "reasonable for devices similar in technology to something already marketed" while five-year follow up is necessary for "novel intracranial aneurysm treatment devices."

In cases where a post-approval study may be warranted, the panel suggested differentiating between unruptured and ruptured aneurysms. Recommendations for follow up of ruptured aneurysms ranged from two to five years.

In cases where retreatment is necessary, the panel agreed that this may be considered a "failure of initial treatment," depending on the device type.

The majority of the panel agreed that a Raymond III result would not be acceptable for device treatment.

As a result of the meeting, "we'll soon be able to bring this technology that we created in the United States to patients here in the United States," said Italo Linfante, president of the Society of Vascular and Interventional Neurology.
— Donna Scaramastra Gorman

TGA Issues Alert For Blood Treatment Device

Australia's Therapeutic Goods Administration is investigating a safety concern involving Therakos' Cellex photopheresis system.

The device treats patients' blood with a photosensitizing agent and returns it to the patient's body, a process that can be used to treat cutaneous T-cell lymphoma and graft versus host disease.

Over the past nine years, the TGA has received 13 reports about the system, one of which concerned a severe allergic reaction linked to either the device itself or a drug associated with its use, and the other involving broken, leaking or missing components of the device.

The FDA published an alert for the devices in February, warning of pulmonary embolisms in patients who recently used it. While two patient deaths are included in the alert, it remains unclear whether their deaths were the result of pulmonary embolisms.

The TGA called on patients and providers to report any potential problems associated with the disease, particularly cases of venous thromboembolism and pulmonary embolism. Hematologists and oncologists should educate patients on the signs and symptoms of both conditions.
— Zack Budryk

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implantable devicemaker Nevro following an October 2017 inspection of the firm's Redwood City, California plant.

During the inspection, the firm's chief medical officer told the FDA inspector that the company "only reports medical device reports for complaint cases where [implantable pulse generator] pocket infections require IV antibiotics and/or hospitalization." The inspector noted that many complaints documented Nevro's implantable products being removed due to infection complaints, and many of these were not reported.

When the inspector asked for a list of complaints that were not reported as medical device reports for which the firm's product was explanted due to infections, he received a list of 129 complaint case files.

The inspector reviewed 123 complaints related to reports of infections and/or deaths for which the company had not yet opened corrective or preventive action files.

While reviewing the failure mode and effects analysis (FMEA) documentation, the inspector observed that levels of harm were inappropriately rated. In one case, a patient was hospitalized and diagnosed with sepsis and the Nevro IPG tested positive for staph infection. The firm's FMEA documentation did not list the injury as life threatening even though the patient suffered multiple organ shutdowns. The FMEA also indicated that a new CAPA did not need to be initiated for the event.

Similar incidents were cited by the FDA inspector. He noted that of the 123 complaints reviewed, roughly 75 percent received only a cursory note documenting the lot history records associated with the complaint.

Other nonconformances included validation failures for the firm's sterilization processes.

Arrowhead Dental: Class II device manufacturer Arrowhead Dental was cited for failure to develop design control and medical device reporting procedures among other quality failures in a Form 483 issued following a December 2017 inspection of the firm's Sandy, Utah facility.

The firm lacked design control procedures for sleep apnea devices it had been selling since April 2012, the 12-item 483 said. It also did not have a design history file for its Elastic Mandibular Advancement device, and it failed to address planning, inputs, design reviews, risk, or design verifications for design changes.

The inspector observed that Arrowhead didn't develop written MDR procedures and it lacked approved procedures for handling and evaluating complaints for the Class II devices.

Also missing were CAPA procedures and procedures to ensure that equipment is routinely calibrated, inspected checked and maintained. The firm also lacked acceptance procedures for raw materials as well as procedures to control products that don't conform to specifications.

In addition, Arrowhead had no device master record for documentation associated with specifications and manufacturing requirements. The facility also lacked written procedures for device history records, management reviews, quality audits or training.

A Cute Baby: Class II breast pump manufacturer A Cute Baby failed to establish written medical device reporting procedures as well as procedures for evaluating complaints, according to a Form 483 the firm received following a Dec. 7, 2017 inspection of the firm's Orem, Utah facility.

The FDA inspector said that the firm didn't have any approved procedures in place for handling adverse events or for evaluating complaints.

The 483 also highlighted deficiencies in training and identifying training needs.

The firm lacked procedures for training employees in MDRs, complaint handling, and servicing for the devices. In addition, employees

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Czech Republic Struggles With EU Device Regulations, Reimbursements

The Czech Republic expects the new EU medical device and in vitro diagnostic regulations will pose a significant regulatory burden to its domestic devicemakers.

The country's transition is particularly difficult because it already introduced new device regulations in 2015 and is currently developing a new reimbursement system for devices that is scheduled to go into effect on Jan. 1, 2019.

The 2015 law brought important changes in areas such as performance evaluations, registration and inspections, according to Tomas Cihula, an attorney with law firm Kinstellar based in Prague.

In the past, for example, the country's postmarket surveillance was fragmented. The new regulations included a new register of medical devices and the Czech Ministry of Health is now responsible for registering devices and postmarket surveillance. The new law introduced more stringent penalties and sanctions, as well as price checks.

The Czech healthcare system is mostly financed by the public sector, and securing reimbursement from public and private health insurers has been a longstanding industry struggle. The Czech Constitutional Court has ruled that the current reimbursement system must be replaced with a more transparent system by the end of 2018.

"This will certainly be a challenge considering that previous attempts to change the reimbursement system failed and that the current government still does not have sufficient support in the Parliament," Cihula said.

A new draft law on reimbursements will be proposed in the coming months.

Switzerland Models Revisions of Its Device Law on EU Requirements

The Swiss Federal Office of Public Health issued an update on the alignment of the country's medical device legislation with the new EU requirements adopted early last year.

Although not an EU member, Switzerland is part of the European Free Trade Association and wants to ensure that its device manufacturers continue to have full access to the EU market.

Revisions to the country's Therapeutic Products Act and to the Human Research Act will be followed by a complete overhaul of its Medical Devices Ordinance and a new ordinance for in vitro diagnostics.

In force since Jan. 1, 2002, the Medical Devices Ordinance integrated the European medical devices directives on active implants, classical and in vitro diagnostic devices into Swiss law.

Revisions in April 2010 harmonized the Swiss law with the EU's revised medical devices directives, and requirements for conformity assessment bodies were increased as of Apr. 15, 2015 to align with those of the EU.

The regulatory authority is inviting comments on the proposed amendments by June 11, 2018. Entry into force of the legislative changes is scheduled for the first half of 2020.

The new regulations for medical devices and in vitro diagnostics will introduce stricter requirements, making manufacturers prove the effectiveness of high-risk devices through clinical studies on a more frequent basis.

In addition, criteria for clinical trials and performance testing will be strengthened, and the EU now expects clear identification of all devices to allow full traceability.

The regulations also require that relevant data to be made available to the public by means of Eudamed, the centralized European databank for medical devices.

The adjustments to the Swiss medical devices law will occur in stages, in line with the transitional periods that apply to the EU member states. — James Miessler

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do not have documented training records for these activities.

Smith & Nephew: Smith & Nephew drew a Form 483 for multiple issues at its Memphis, Tennessee facility, including a faulty procedure for the control of nonconforming product and inadequate corrective and preventive action procedures.

The firm lacked an adequate procedure for the control of nonconforming product or to ensure that assessments of nonconforming products were properly documented. For example, the procedure required an investigation of discrepancies, including missing laser engraved batch numbers, but provided no method to ensure investigations were performed or recorded.

The FDA investigators observed that a corrective and preventive action was also not adequately established. The firm failed to conduct or record activities in a timely and effective manner. For example, a request to initiate a CAPA took over a year to be evaluated by the review board and was not signed as approved until three months after its evaluation. No investigation was performed into the cause of the problem or any subsequent impact on product.

In addition, the firm lacked an adequate complaint handling unit. Specifically, its orthopedic instrument repair processing specification procedure required information to be shared when a device could not be repaired or a deficiency became evident, but multiple device repair orders were not shared.

Read the Philips Medical Form 483 here: www.fdanews.com/03-09-18-Phillips483.pdf.

Read the Nevro Form 483 here: www.fdanews.com/03-06-18-nevrocorp483.pdf.

Read the Arrowhead Dental Form 483 here: www.fdanews.com/03-07-18-arrowheaddentalinc483.pdf.

Read the A Cute Baby Form 483 here: www.fdanews.com/03-07-18-acutebabyinc483.pdf.

Read the Smith & Nephew Form 483 here: www.fdanews.com/03-08-18-smithnephewinc483.pdf.

APPROVALS

MemoryMD Gets FDA Clearance For Wireless EEG Amplifier

MemoryMD received FDA clearance for its NeuroEEG, a wireless amplifier that transmits EEG signals to computers and cloud-based databases via Bluetooth. The device is used to monitor concussions and traumatic brain injuries.

A separate component called NeuroCap, a disposable EEG cap, is still awaiting clearance. The combination of NeuroEEG and NeuroCap can enable neurologists to cut the time for EEG appointments by 20 minutes, the company said.

Alfa Scientific Wins 510(k) Clearance for Fecal Blood Test

Alfa Scientific Designs received 510(k) clearance for its iFOB with Driven Flow immunoassay for identifying human blood in feces, a possible symptom of pre-cancerous polyps and colorectal cancer.

The test requires just one drop of sample solution wand can provide a result in one minute, about five times faster than standard lateral flow assays.

Colorectal cancer is the third most common cancer diagnosed in the U.S. and the second leading cause of cancer death despite a high cure rate. Early diagnosis yields a 90 percent cure rate.

Stryker's Tritanium TL Lumbar Cage Gains 510(k) Clearance

Stryker received 510(k) clearance for its Tritanium TL curved posterior lumbar cage, an interbody fusion cage intended for lumbar fixation.

The device is a hollow implant that uses a material designed for bone ingrowth and biological fixation and complements Stryker's Titanium PL cage. It is shaped for steerability and is designed so the cage can be rotated.

The Tritanium TL is indicated for use with autograft and/or allogenic bone graft comprised of cancellous and/or corticocancellous bone graft.

Stryker said the product will be available in the second quarter of 2018.

Sky Medical Receives 510(k) Clearance for Edema Reduction

Sky Medical Technology received 510(k) clearance to market its geko device for edema reduction in clinical applications.

The disposable battery powered device is the size of a wristwatch and delivers neuromuscular electrostimulation, increasing blood flow equal to 60% of walking without the user having to move or exert energy.

U.K.-based Sky Medical is the developer of the OnPulse neuromuscular electrostimulation platform.

Quidel Receives 510(k) Clearance for Lyme Assay

Quidel received 510(k) clearance for its Sofia Lyme fluorescent immunoassay to aid in diagnosis of Lyme disease.

The assay detects antibodies to *Borrelia burgdorferi* in serum and plasma specimens from patients suspected of *B. burgdorferi* infection.

The assay works with Quidel's Sofia and Sofia 2 systems. It also comes connected to Quidel's Virena data management system, which provides aggregated, de-identified testing data in near real-time.

Synergy's BioSphere Putty Secures Regulatory Clearance in Australia

Synergy Biomedical received clearance from Australia's Therapeutic Goods Administration for its bioactive bone graft product BioSphere Putty.

The product uses spherical bioactive glass particles to create a moldable bone graft putty that improves bone formation.

The product previously received FDA and CE Mark clearances and has been marketed since 2013.

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Myoscience Receives 510(k)Clearance For Nerve Stim Enabled Smart Tip

Myoscience received FDA 510(k) clearance for its Smart Tip with Nerve Stim. The hand-held device uses disposable tips to deliver focused cold to targeted nerves.

The device enables physicians to access nerves in the shoulder, hip, and knees to apply cold therapy and block pain signals from peripheral nerves.

FDA Clears BD Onclarity HPV Assay

The FDA cleared Becton Dickinson's Onclarity human papillomavirus assay for marketing.

The assay detects DNA from 14 high risk human papillomavirus types that are associated with cervical cancer.

The automated laboratory test is used on BD's Viper LT system. The test specifically identifies HPV types 16, 18 and 45 while concurrently detecting types 31, 33, 35, 39, 51, 52, 56, 58, 59, 66 and 68.

iCAD Granted CE Mark for Breast Cancer Detection Device

iCAD received a CE Mark for its PowerLook Tomo Detection 2.0, the company's second deep-learning based computer aided detection device for breast cancer.

The PowerLook uses an algorithm that is trained to detect malignancies and determine the probability of cases having malignant findings. It provides radiologists a "certainty of finding" score for each detected lesion. The device is compatible with Hologic, GE and Siemens systems.

Alfa Scientific Wins 510(k) Clearance For Multi-Drug of Abuse Assay

Alfa Scientific Designs received 510(k) marketing clearance for its Simple Cup multi-drug of abuse urine immunoassay.

The test identifies thirteen drugs or drug metabolites and provides results in two minutes. The device maintains line integrity for at least two hours with 98.88% accuracy.

The assay is cleared for both professional and home use.

Cardiovascular Systems Wins Clearance for Coronary Balloon

Cardiovascular Systems received 510(k) clearance for the OrbusNeich 1.0 millimeter Sapphire II PRO coronary balloon.

CSI is the exclusive U.S. distributor of OrbusNeich balloon products.

It plans to launch OrbusNeich's full balloon product portfolio in the U.S. in 2018 and 2019.

PEOPLE ON THE MOVE

Millennium Health appointed **Andrew A. Lukowiak** as CEO. Lukowiak brings almost 20 years of management experience in molecular diagnostics. Most recently, he was chief operating officer and interim CEO of a commercial stage CLIA laboratory specializing in the combined use of genetics and algorithmic decision support to improve therapeutic outcomes. He previously held positions at GenMark Diagnostics, Hologic, and Third Wave Technologies. He has served in various roles including operations, R&D, quality/regulatory affairs, scientific/clinical affairs, customer service, and reimbursement.

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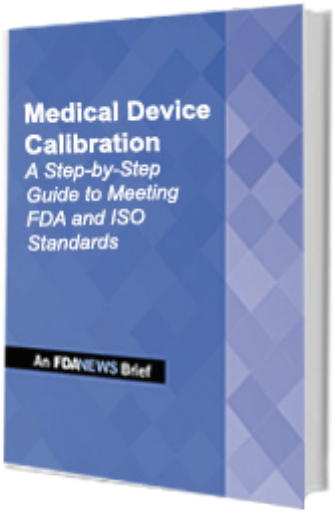

Medical Device Calibration: *A Step-by-Step Guide to Meeting FDA and ISO Standards*

Warning letter citing calibration failures are on the rise — indicating that the FDA is paying more attention to the issue.

Both the FDA and ISO have specific requirements for calibrating medical devices. And — they don't always line up. So devicemakers doing business in the US and abroad need a clear path to compliance if they want to avoid penalties.

Medical Device Calibration: *A Step-by-Step Guide to Meeting FDA and ISO Standards* provides a roadmap that walks devicemakers through each aspect of calibration requirements — showing where the FDA and ISO differ and where they match up — and explains how to combine them to endure full compliance.

You will learn:

- The role of monitoring and measuring in a medical device Quality Management System (QMS)
- Requirements for calibration in FDA's Quality System Regulation
- How to distinguish between accuracy and precision
- The role of traceability in a calibration program
- The audit requirements in both QSIT and MDSAP

The report defines key terms and concepts involved in calibration including proving that calibration practices can be traced back to recognized national and international standards.

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Risk-Based Monitoring of Clinical Trials 2017: *New Trends and Best Practices*

The biggest driving factor behind implementing risk-based monitoring (RBM) of clinical trials is savings. Centralized monitoring of trial sites based on risk profile is cheaper, less resource-intensive and, ultimately, more efficient.

But consider this: trials that are using RBM have found that it increases the effectiveness of quality control as well as data accuracy, according to a recent survey by QuintilesIMS. Here are some other key findings:

- The top therapeutic areas using RMB are dermatology, oncology, biologics and immunology;
- Use of RBM in Phase 2 through Phase 4 studies is increasing; and
- RBM users are increasingly shifting from 100 percent on-site monitoring to some degree of remote monitoring.

Most telling of all is that more than half of survey respondents not currently using RBM plan to implement it within the next two years.

The new FDAnews management report **Risk-Based Monitoring of Clinical Trials 2017: *New Trends and Best Practices*** will show you, step-by-step, how to properly design and implement your risk-based clinical trial monitoring program to fully satisfy the FDA's requirements.

You'll get specific recommendations about the 5 data points that you must always monitor … 9 essential critical risk factors your monitoring plan must consider … 5 key components that should make up your monitoring plan (and what they each should contain) … and all of the documentation requirements that are absolutely essential to every monitoring plan.

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