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# Adverse Events Stack Up At FDA; 2016 Warning Letter Data Show Troubles With MDRs, Complaints

by Shawn M. Schmitt

The US agency is inundated with adverse events through its Medical Device Reporting system with more than 1.4 million sent to FDA in 2015. Yet several industry experts – including from Eli Lilly and Implant Direct (Danaher) – say the industry overall may be underreporting adverse events, while some firms are overreporting. Preliminary 2016 warning letter data compiled by *Medtech Insight* also pinpoint problems with MDRs and complaint handling. Meanwhile, quality officials debate what makes a good complaint handling system, and tell what FDA expects from manufacturers. Plus: check out *Medtech Insight*'s new FDA Warning Letters Data Tracker.

Problems with a bevy of specific devices, better adverse event reporting by manufacturers, and enhanced industry and public awareness about what's reportable to FDA when a product fails are three possible reasons why the number of Medical Device Reports (MDRs) swelled to an all-time high of more than 1.4 million last year, the US agency says.

Yet several industry experts – including from Eli Lilly and Implant Direct (Danaher) – say not only is there underreporting going on, but adverse events are overreported in many cases, calling FDA's MDR count into question.

This comes as an analysis of *Medtech Insight*'s *FDA Warning Letters Data Tracker* discovered that 70% of 43 quality-related letters released by FDA on its website between Jan. 1, 2016, and Oct. 11, 2016, include MDR and/or complaint handling observations.

A record 1,409,841 adverse events were submitted to the agency via its MDR system in calendar year 2015, according to statistics provided by the Office of Surveillance and Biometrics (OSB)

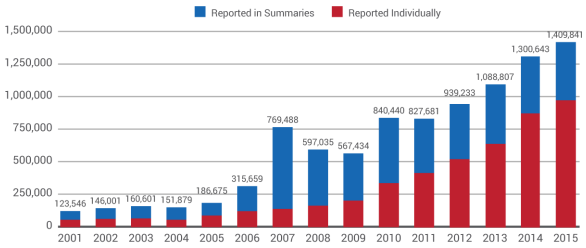
within FDA's Center for Devices and Radiological Health.

That's an increase of 8% from 2014, when 1,300,643 adverse events were filed with FDA. MDRs have been increasing year-over-year since 2011, when a mere 827,681 events were reported. (See Figure 1.)

"MAUDE is a passive reporting system, so it's difficult to pinpoint exact reasons for any increase ... in reporting, whether it's due to more devices on the market, more problems with devices, or better reporting by user facilities, doctors and patients," Isaac Chang, director of OSB's Division of Post-Market Surveillance, told *Medtech Insight*.

MAUDE is FDA's publicly searchable *Manufacturer and User Device Experience database*, where adverse event information is stored.

Figure 1




Source: FDA

"Public awareness of device issues can also increase MDR reporting by voluntary reporters such as patients and physicians, as well as by hospitals and manufacturers that receive reports of problems," Chang said.

Or the number of reports can rise because of problems with particular product types. For example, troubles with *uterine power morcellators*, *duodenoscopes* and *transvaginal mesh* likely played a role in the large number of MDRs last year, Chang pointed out. And difficulties with specific products – such as *Bayer HealthCare LLC*'s *Essure* permanent birth control device – added even more adverse events to the tally, he noted.

> ***US FDA's Isaac Chang says "it is indeed difficult to interpret" whether the number of MDRs will continue its upswing this year – but chances are it will.***

Also a probable factor in the increased reporting is that device firms better understand what types of events should be reported. Further, "we have received reports from patient groups that have not previously reported to FDA. That underscores the importance of FDA continuing to

receive MDR reports," Chang said.

In addition, "FDA has made several efforts to encourage better reporting by making adverse event reporting easier for both mandatory and voluntary reporters," Chang said.

FDA launched its *MedWatcher* app in May 2013 that allows for more convenient voluntary reporting through tablets, smartphones and other mobile devices. And the agency issued its eMDR *final rule* and *guidance* in February 2014 that requires mandatory electronic reporting for manufacturers and importers.

"While the [eMDR] rule did not change what must be included in an MDR submission to FDA, it facilitated more expedient and timely reporting by industry," Chang said.

Nearly 1 million of last year's MDRs – 967,839 – were sent to the agency individually on full MedWatch reporting forms. That's an 11% boost over 2014, when 867,754 individual reports were filed.

The remaining 442,002 reports were sent to FDA in 2015 as part of its Alternative Summary Reporting Program, which allows firms to submit abbreviated reports in a summarized, line-item format. That's up 2% from 2014.

> ***"Any increase you see in Medical Device Reports is probably based on industry's effort to collect that adverse event information. But I still think MDRs are very much underreported," Eli Lilly's Francis Blacha says.***

Chang said he can't predict whether adverse events will increase in 2016, and there is no preliminary data available from FDA to suggest that there will be a rise in reports. But if recent history is any indication, FDA's pile of MDRs will undoubtedly grow this year.

"As the increase in the number of adverse event reports may be attributable to several sources – including heightened awareness of how to report MDRs and more streamlined methods for reporting – it is indeed difficult to interpret" whether the number of MDRs will continue its upswing in 2016, Chang said.

## Adverse Events: Underreported?

Despite the continued mushrooming of recorded adverse events, Francis Blacha, global quality leader for devices for *Eli Lilly & Co.*, believes MDRs are actually underreported.

"In general, a lot of complaint information and complaint reporting is totally unreported. A lot of people – device users – oftentimes don't know they have an issue. Or, if they do understand they have an issue, they just don't know whom to tell," Blacha said in a Sept. 23 interview with *Medtech Insight*.

Although it is primarily a pharmaceutical company, Eli Lilly manufactures drug-delivery devices for some of its medicines, including the *Forteo* pre-filled syringe system for osteoporosis.

So how does Blacha's assertion that adverse events are underreported square with the all-time high number of MDRs reported to FDA in 2015? That is, how can it be said there aren't enough adverse events reported when they've peaked at 1.4 million?

That's because there has been an increased vigilance in reporting by manufacturers – but only by manufacturers – Blacha said. Other reporters, such as hospitals, user facilities and end users, aren't faring as well, leading to a depression in the overall MDR count, he posits.

"Device firms are doing a much better job of proactively going out and trying to collect [adverse event] information – contacting patients, contacting health-care professionals, contacting hospitals," Blacha said. "They're doing more than just one attempt to contact those entities. They're doing two or three attempts to be able to get the information back that they need to understand the device failure."

Therefore, "any increase you see in Medical Device Reports is probably based on industry's effort to collect that adverse event information," he said. "But the firms can't collect every piece of data. MDRs are very much underreported because, again, many device-users don't know how or whom to complain when a failure happens."

Hospitals are indeed dropping the ball when it comes to reporting adverse events, leading to underreporting, consultant and former FDA investigator Denise Dion claimed in a Sept. 23 interview. She is VP of regulatory and quality services for consulting firm EduQuest in Hyattstown, Md.

"The people that are working with the medical devices in hospitals never read the instructions for use. That is where they're getting hung up – not understanding how the device is supposed to work, so they don't really understand when the device is failing," Dion said.

"If hospital workers actually read the instructions for use to know how to properly use the

medical device, that would be perfect, but I don't think you're going to get them to do that," she said.

"In reality, the medical device companies should be supplying quick-reference guides for a lot of these medical devices to help the hospital understand that there has been an adverse event," Dion said. "It goes back to the medical device manufacturer. Some of their labeling is very long, and nobody is going to read a 142-page manual."

Dion suggested that firms would be wise to include in the back of instruction manuals a checklist of all information the manufacturer will need to conduct a thorough failure investigation into an adverse event.

"That would be a helpful thing to have from a medical device perspective so users know what information they need to fork over, and what physical items the firm needs to retrieve from the complainant," she said.

Kwame Ulmer, VP of regulatory affairs and quality assurance at Thousand Oaks, Calif.-based Implant Direct, agreed that underreporting occurs and said a lack of public awareness plays a key role – despite FDA's assertion that general awareness surrounding Medical Device Reporting has been heightened.

"Underreporting is happening. Now, I haven't heard of a specific number of adverse events when we can say, 'Yes, everyone is reporting properly,' but there's just a general sense in industry that there is indeed underreporting," Ulmer, an ex FDA official, told *Medtech Insight* on Oct. 3.

> ***"All I've heard are some really smart people say that there is underreporting. But I haven't seen a thoughtful approach as to, 'These are the reasons why we're underreporting, this is how we could get to proper reporting, and these are the steps it would take,'" Implant Direct's Kwame Ulmer says.***

Implant Direct, which makes dental implant products such as the *Legacy* system, is a joint venture partially owned by diversified scientific and industrial instrument conglomerate *Danaher Corp.*Before taking his position at Implant Direct in 2015, Ulmer was director of strategic regulatory affairs for Danaher from 2014-2015.

Ulmer began his 12-year FDA career in 2002 as a biomedical engineer and reviewer in the agency's Office of Device Evaluation (ODE). He moved up the ladder to chief of ODE's pacemaker and defibrillator branch, and eventually was named an ODE division director, overseeing anesthesia, general hospital respiratory, infection control and dental devices.

Although FDA's Chang said increased public awareness is helping to drive the high number of Medical Device Reports, Ulmer questions whether it's sufficient.

"Is there *enough* awareness – not just with the device companies, but with patients, clinicians, *et cetera*? And are they educated and fully aware, and do they have a regulations translator so they can say, 'Ah, yes. This is reportable'? So that's why you'll see in the public health community this consistent meme of, 'there's underreporting,'" he said.

But there are other reasons why events might be underreported.

For example, Ulmer says problems with diagnostic products are not reported nearly enough because "there's not always a crystal-clear connection between a device failure and its reportability just as a diagnostic," unlike a therapeutic device where the linkage between a nonconforming product and an adverse event is likely easier and quicker to spot.

Nevertheless, he concedes that he hasn't "seen any peer-reviewed literature that says there is underreporting – that 'These are the explicit reasons why,' or 'This is the number of adverse events we should be at,' *et cetera*." Instead, "all I've heard are some really smart people say that there is underreporting. But I haven't seen a thoughtful approach as to, 'These are the reasons why we're underreporting, this is how we could get to proper reporting, and these are the steps it would take.'"

Larry Kopyta, head of consulting firm KRC Group LLC, suspects that practices of some smaller firms contribute to the problem of underreporting.

"Some companies are perhaps start-ups or less-mature companies, or are companies that are willing to take the risk not to report," he said. "They'll tend to say, 'We don't think this is a potential safety hazard that could harm someone or kill someone, therefore we're not going to report it. We'll justify it, but there's a risk that the agency will disagree.' So I think that's part of the issue."

Until recently, Kopyta was VP of QA/RA for Omnyx LLC, a Pittsburgh-based manufacturer that this year was purchased by – and absorbed into – *GE Healthcare*.

## Adverse Events: Overreported?

There are manufacturers, however, that choose to be extra cautious and submit adverse events to

the agency even if they aren't technically reportable, Kopyta said in an Oct. 3 interview.

"There may be some degree of overreporting for companies that don't want to take a chance. They don't want to take the risk that they might not report something that they should have," he said.

But that doesn't mean overreporting is necessarily a bad thing.

"FDA would want to know about any potential issue. So I think in the agency's mind, overreporting is preferable to a firm not alerting them to potential safety or health issues," Kopyta said.

Further, "companies that are more aware and want to do the right thing are probably going to overreport," he said. "They're going to report something that maybe they hadn't in the past because FDA has become stricter on requiring firms to report incidents that perhaps they may not have reported previously. Also, firms are more averse to their risk of getting a warning letter from FDA."

Yet overreporting is a double-edged sword because firms that overreport might catch the attention of FDA, which might then choose to inspect if agency officials believe there could be significant troubles with particular products.

And a manufacturer's competitors "might be underreporting, which could be a competitive disadvantage," Kopyta said. "If a manufacturer is reporting pretty much everything or anything they think is even a potential adverse event and their competitor is not, their competitor might say, 'Look, that other firm has a ton of issues with their product. We don't have issues with our version of the same product.'"

## When Reporting An MDR, '30 Days Is 30 Days'

Under the *MDR regulation*, manufacturers must submit reports to FDA within 30 days when they receive information suggesting that a device may have contributed to a death or serious injury, or that it malfunctioned in a manner likely to cause death or serious injury if the malfunction were to recur.

### *Manufacturers Struggling With MDR Procedures*

Despite the extraordinary rise in MDR reports, some companies continue to have trouble developing, maintaining and implementing MDR procedures, which is mandated by 21 CFR, Part 803.17.

For events that require "remedial action to prevent an unreasonable risk of substantial harm to the public health," companies are

required to file a report to FDA within five business days.

But even though an adverse event might not be life-threatening or cause a permanent injury, FDA still wants to know about it, including device failures, malfunctions, improper or inadequate device designs, manufacturing troubles, labeling problems and use errors.

"The timeliness of MDR reporting is simple. Thirty days is 30 days. Not 31, not 32. Thirty," industry insider Steve Niedelman said. "I can't tell you how many firms out there think that this doesn't apply to them. They'll report at 35 days or 36 days, or even after a year. No. It's 30 days from the date that you became aware that an event is reportable."

"Firms still continue to fail to have MDR procedures, and when they do have procedures many of them don't follow them," consultant Steve Niedelman said.

"One of the worst things you could do is present to an FDA investigator a beautiful MDR procedure, and then go out on the manufacturing floor and determine that nobody even knows that it exists," he said. "You have to be able to demonstrate that you're following your own SOPs."

Companies are required to have MDR procedures that address timely and effective identification, communication and evaluation of events that may be subject to MDR requirements; a standardized review process or procedure for determining when an event meets the criteria for reporting; and timely transmission of MDRs.

Niedelman is a familiar face in the medical device arena, working at FDA for 34 years in both its Office of Regulatory Affairs and Center for Devices and Radiological Health. He is currently lead quality systems and compliance consultant at the law firm King & Spalding.

Problems can arise when company employees do not know that there is only a 30-day window to report MDRs.

"It's important that everybody at the firm is aware of the FDA timeframe – not just the MDR group, not just the complaint handling group, but every employee," Niedelman said.

"If one of your sales reps is at a party and learns that one of your devices might have been implicated in an adverse event, that rep needs to know that he or she has a responsibility to report that," he said.

"And if you're a multinational company, that responsibility extends to your multinational sites. So if somebody in Belgium becomes aware of a problem but your device is made in the U.S., then they have a responsibility to make you aware of that."

## Warning Letter Data: MDRs, Complaint Handling Dog Manufacturers

Meanwhile, an analysis of preliminary 2016 quality-related warning letter data appears to bear out that device firms are indeed plagued by problems with Medical Device Reporting and complaint handling.

*Medtech Insight* counts as a quality citation any alleged violation of FDA's *Quality System Regulation* (QSR), *MDR regulation* (21 CFR, Part 803) or *Corrections and Removals regulation* (21 CFR, Part 806).

Forty-three quality-related warning letters have been released by FDA on its website between Jan. 1, 2016, and Oct. 12, 2016. Thirty of those letters – or 70% – included violations of MDR and/or complaint handling requirements. The information was pulled from *Medtech Insight*'s new *FDA Warning Letters Data Tracker*. (Overall, 48 device-related letters have been released this year, including five with pre-market cites only.)

Figure 2

Taken separately, complaint handling is the third most-oft violated QSR subsection so far in 2016, with 45% of quality-related letters including that observation. MDR comes in fifth place, violations of which are found in 42% of warning letters. (See Figure 2.)

*Medtech Insight*'s tabulation isn't intended to replace official FDA calendar year numbers; rather, the publication aims to provide a general looksee at warning letter trends throughout in the year. It can take the agency significantly more time – roughly three to six months after a given calendar year – to crunch its own data. (Also see "*Domestic, Foreign Manufacturers Achieve Virtual Quality-Related FDA Warning Letter Parity; Missive-Counting Methodologies Explained*" - Medtech Insight, 28 Mar, 2016.)

*Medtech Insight*'s data will never wholly mirror FDA's count. That's because there can be a delay of weeks or months (and, in rare cases, years) between when the agency writes a letter and when it's finally posted online.

Therefore, some warning letters written before the end of last year weren't cleared and posted online by FDA by Dec. 31, 2015, and were instead released in 2016. Seven warning letters fit that bill this year, and were therefore included in *Medtech Insight*'s count of 2016 missives.

## Complaint Handling: What FDA Wants To See

When it comes to complaint handling activities, FDA foremost wants to see an expeditious approach to handling

***New! Warning Letters Tracker***

complaints based on risk, former FDAer Ulmer says.

"The agency would be interested in how you tier complaints and categorize them based on risk and making sure you have robust internal policies and procedures to handle them correctly," the Implant Direct RA/QA VP said.

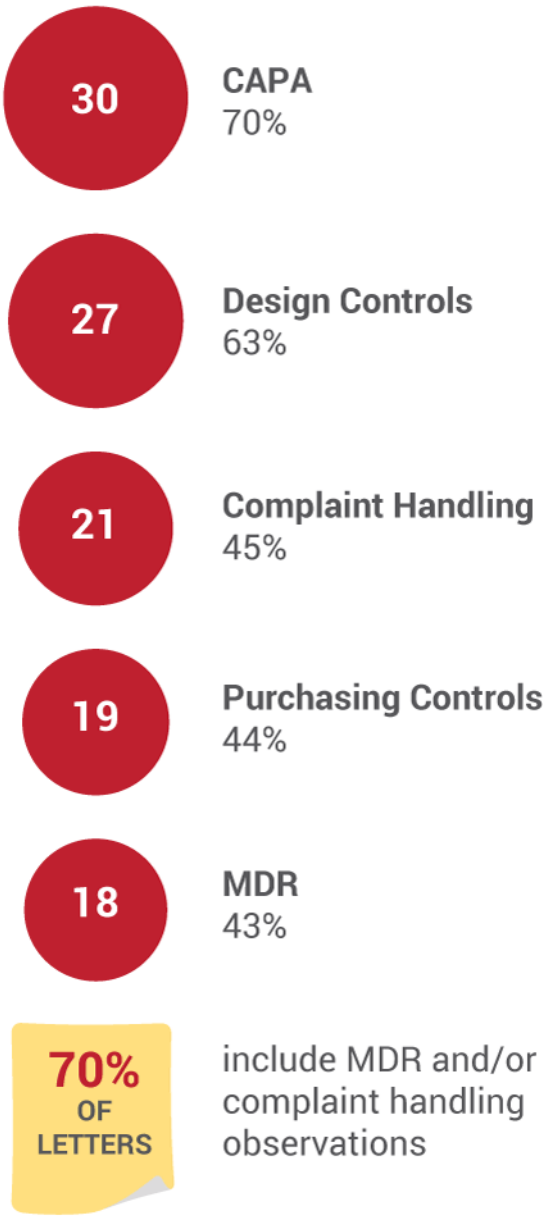
To help manufacturers avoid running afoul of FDA requirements, the agency wants to make sure firms have well-thought-out complaint handling procedures with corresponding work instructions, Ulmer said.

"Start with a procedure that maps to the relevant regulations, and to the best of your ability make sure you clearly understand at a fairly high level, but operationally, how complaints are handled and screened for things like potential CAPAs [corrective and preventive actions] or MDR adverse event reporting, or trending of data for discussion during management review," he said. "Firms should understand at a conceptual and at an operational level how that data is collected and used, and how it touches other parts of the quality system.

"At the end of the day, you should have your managers understanding – particularly your quality leaders and your regulatory leaders – how the pieces work together, and also the actual people who are executing complaint handling activities. I know that at a start-up that might be the same person, but try to have a fairly good grasp on how the pieces fit together."

Having a team that specifically works on handling complaints is of the utmost importance, Ulmer said.

"In my experience, most medium-to-large companies have people dedicated to complaint handling," he said. "That's what those people should do on a regular basis. They must be familiar with FDA regulations, know how to screen for MDRs, and know how complaint handling data should be




The numbers and percentages of 43 quality-related warning letters that included the five most common citations between Jan. 1, 2016, and Oct. 11, 2016.

Source: FDA

trended."

Ulmer suggests that a quality expert is typically best-suited to lead the complaint handling team, but ultimately it depends on the size of the manufacturer. And there is wiggle room depending on how big the firm is.

A firm "might have a regulatory person who handles complaint handling, but generally speaking I would say a quality leader should be in charge," he said. "At a smaller start-up that might be the same person – the quality and regulatory person maybe have both responsibilities.

"Complaint handling, per se, is typically handled under the quality function, but that's not a hard-and-fast-rule, and at larger companies there might be multiple complaint handling teams," Ulmer continued. "Obviously it's a function of the size of the organization and making sure you scale it appropriately."

Ulmer recommended that manufacturers pull together its cross-functional complaint handling team when needed.

"It could be weekly; it could be monthly," he said. Now, that's dependent on the adverse events that are stimulating the need to meet, but I would say the team should probably get together at least monthly to conduct some sort of cross-functional assessments."

## Resources: An Absolute Must

Ensuring adequate complaint handling resources is an absolute must, consultant Kopyta says.

"One of the areas that a lot of companies struggle with is applying resources to do the complaint investigations, to basically identify the root cause of the problem," he said. "Generally, in most cases – or a lot of cases – you're pulling from your engineering team or your manufacturing team to conduct investigations of an issue that's been reported to determine if corrective action is necessary. The investigation may actually determine that it's reportable. Initially, it may not be

Want to monitor how your peers are faring when it comes to FDA warning letter observations? Then explore *Medtech Insight*'s new *US FDA Warning Letters Data Tracker*, updated weekly to include missives posted online by the agency.

The tracker not only includes information about device manufacturers that were recently sent warning letters, but also the particular violations that each company must address, from corrective and preventive action (CAPA), to complaint handling, to design control – and beyond.

Users can sort and search for specific information, such as company names, dates warning letters were written, devices manufactured by the offending firms and observations noted in each letter, and more.

And, as always, you can check out our weekly *Warning Letter Roundup & Recap*.

obvious, but once they get into the investigation and find out the issue, it may turn out that it should be reported to FDA.

"That's one of the biggest struggles: getting the right resources from the investigation side applied to the complaint process."

*"If you don't have good alignment, your resources may be constrained in the complaint handling area, and/or your procedures or work instructions might not be crystal clear," Ulmer says.*

It's often difficult, however, to bend top management's ear when it comes to providing adequate resources.

"One of the things that can raise the awareness of senior management is communicating what the potential risks are across the board for failing to properly handle complaints," Kopyta said. "But the other is providing metrics. So provide routine reporting on complaint handling in terms of what the turnaround time is to get complaints, how long complaints are open, how long it takes for them to close, and then providing management with some trends.

"Another way you can gain the attention of upper management is to say, 'This is direct information we got from a customer,'" he added. "So then it becomes a customer satisfaction piece, and now management will look at it from a business perspective – 'These are things that, if we could address them, would make our product better and provide higher levels of customer satisfaction."

Implant Direct's Ulmer says it's crucial for a firm to have all its ducks in a row so complaints are handled efficiently and adequate resources are appropriated.

"If you don't have good alignment, your resources may be constrained in the complaint handling area, and/or your procedures or work instructions might not be crystal clear, or as clear as they could be," he said.

"When I say 'alignment,' I mean that everyone – particularly senior leadership – clearly understands the importance of complaint handling and adverse event reporting," Ulmer said. "And then there's this quintessential question of, 'Are you adequately resourced to execute

against FDA's regulatory requirements? Do you have a robust quality system at a very high level?' And those are key questions that, as managers, you have to decide on a regular basis to manage your resources appropriately.

"So 'alignment' means that a firm has adequate resources and specifies the people who have responsibility for executing complaint handling; that you can point to a particular person or a group of persons, and there's accountability and performance plans, or developmental plans, or both."

*From the editors of The Gray Sheet*