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The AI Touch: Artificial Intelligence Could Boost Quality Systems, Cut FDA Inspections – But Is Industry Ready?

by Shawn M. Schmitt

As the medical device industry begins to push the boundaries of artificial intelligence – exploring ways to use advanced AI systems to review, sort and process big data to find quality systems or product problems that would simply take too long for human eyes to see – FDA is also looking at ways to use AI for its own advantage. "AI will reduce investigational time and increase FDA's speed in taking action on a problematic firm," one agency official says. Meanwhile, a new Artificial Intelligence Initiative has been launched by Xavier University to better determine how AI can be used in the quality and regulatory space. Also: J&J subsidiary Janssen explains how it uses AI for quality and regulatory applications, and an expert from Shire tells how top management can be convinced that using artificial intelligence can save their firms money.

Pioneering device-makers that use advanced artificial intelligence systems to analyze their vast streams of data to pinpoint predictive outcomes for quality systems and marketed products could one day see fewer US FDA facility inspections, an agency official says.

Art Czabaniuk, program division director/district director for the Division of Pharmaceutical Quality Operations III within FDA's Office of Regulatory Affairs, foresees "great benefit from AI in the regulatory environment" – especially for ORA, which handles all of the agency's inspectional activities in the field.

"This is how I see artificial intelligence unfolding: AI will reduce investigational time and increase FDA's speed in taking action on a problematic firm, and promote preventative action and speed with regard to corrective action," he said. AI will also "elevate quality because firms

will understand the quality of their products and their manufacturing systems to a greater degree if they monitor all of their many data points."

Czabaniuk's conclusion? "AI is everything we're looking for."

> ***"That's what our investigators would like to see: an AI model in place in the regulated environment that would take the place of some of their investigational activities and determine the root cause of some of the problems they see in the field," FDA's Art Czabaniuk says.***

Most device companies have already dipped a toe into more rudimentary forms of artificial intelligence, using AI systems to help spot trends in, say, the number and types of complaints they receive.

But industry is looking to push artificial intelligence even further, exploring ways to use AI to review, sort and process extremely large quantities of quality and manufacturing data to find problems that would simply take too long for human eyes to see – if they could even spot them at all – and "training" AI systems to self-correct and create more positive outcomes. In other words, machine learning.

The topic has become so hot that Cincinnati's Xavier University launched an *Artificial Intelligence Initiative* earlier this year to better determine how AI can be used in the quality and regulatory space in the device and pharma industries. The initiative's core team is made up of officials from Xavier and FDA, IBM Watson Health, and experts from device and drug firms. (Also see "*Artificial Intelligence Center To Offer Quality, Regulatory Solutions*" - Medtech Insight, 13 Apr, 2017.)

At the first-ever AI Summit at Xavier in August, Czabaniuk explained how artificial intelligence could make a difference in how FDA investigators approach inspections, and how audit outcomes could prove to be more favorable for manufacturers.

"On the medical device side, we've had cases where we've seen several MDRs [Medical Device Reports] – serious ones – and we followed up immediately, inspected the firms, and determined there was a failure with their supplier. So, it was a faulty component – the supplier changed the specifications without notifying the manufacturers," he said.

"So, from an investigator's point of view, the first questions they are going to ask are, 'How and why are *we* catching this? Isn't there some sort of a control or system in place where this could be caught before we get here?'" Czabaniuk said. "Unfortunately, models to predict those kinds of failures are not always in place at companies, and it can be complicated, especially for large firms that probably have millions of inputs."

But device-makers could mitigate problems by using AI to more easily detect such troubles before an investigator even arrives at their facility.

"From my view – from the regulatory point of view – AI is a solution," he said. In the near term, "AI in its entirety and its scope may not be achievable, but an incremental approach might be worthwhile – just focusing AI on those risk-based potential events that could occur in a manufacturing environment.

"I think all manufacturers know what those risk-based events are," Czabaniuk added. "For example, if you make implantable devices, an event is probably going to be infections. So, how can a firm weed out infections that occur from an unsterilized product or a sterilization failure, from those that occurred in the practice of medicine? Firms could focus AI in those areas that would reduce the risk in the fastest possible manner.

"And that's what our investigators would like to see: an AI model in place in the regulated environment that would take the place of some of their investigational activities and determine the root cause of some of the problems they see in the field."

Czabaniuk theorizes that as more manufacturers use AI to catch current problems and predict future ones, the less time agency investigators will spend inspecting.

When it comes to artificial intelligence, "I think there's some value added for everybody," he said. "From the regulatory point of view, AI could in fact reduce inspections, and I know how important that is to everybody – not only to the regulated industry, but to FDA. We don't have the resources to inspect the global inventory we have. So, if we could reduce that inspection time, then I think that would give us the capacity to inspect a greater part of our inventory. Anything we could do to save time in the field would be critical from my perspective in the Office of Regulatory Affairs."

Further, AI could result in faster market action by device-makers when a nonconforming product results in a recall event.

"Historically, we've inspected firms once every few years, and we sometimes find a device failure that happened nine months previously, or even a year before we arrived at the firm," Czabaniuk said. "It would be great if firms could find that problem within a shorter timeframe by using AI

and taking an appropriate action."

FDA: AI Can Aid 'Case For Quality'

Francisco Vicenty – a program manager in FDA's device center compliance office, and a leader for the joint FDA/Medical Device Innovation Consortium (MDIC) *Case for Quality* – says artificial intelligence offers a host of opportunities when it comes to how – and how often – FDA might inspect.

"Can you imagine what something like [AI] could do to change [FDA's] oversight paradigm?" Vicenty said at MedCon 2017 in May. "If you use AI systems that are looking at all of the interconnectedness that's going on within your facility, that's really where your quality will show."

A Case for Quality initiative that's been underway since last year is focused on developing quality metrics for firms – measures that can be used to assess the overall quality of device manufacturing. FDA will use the metrics as another tool to help it determine which firms have gold-star quality systems. That, in turn, helps guide the agency's selection of facilities to inspect. (Also see "*At The Intersection Of Quality And Metrics: What's Ahead In FDA's Effort To More Objectively Measure Quality*" - Medtech Insight, 13 Jul, 2016.)

Vicenty says it's nearly impossible to have a one-size-fits-all approach to quality metrics. "That's a struggle we've had with the Case for Quality – determining what is the right metric when it's really dependent on the company. But AI would be something that would take [the guesswork] out of it" and give a much clearer signal of a quality system's health – and whether the agency should inspect.

To use AI is to go beyond using simple metrics, which can take a firm only so far. Metrics can help guide a manufacturer to become proactive after a failure has already occurred, but artificial intelligence can be predictive, which is much more valuable.

Another Case for Quality initiative – this one focusing on a maturity model assessment of quality systems – could also be strengthened by artificial intelligence, Vicenty said separately at the recent AI Summit.

Under FDA's upcoming Voluntary Medical Device Manufacturing and Product Quality Program, the quality systems and manufacturing processes of participants will be evaluated by third-party appraiser against the *Capability Maturity Model Integration* (CMMI) appraisal framework. Results of a manufacturer's CMMI assessment will be shared with FDA; the agency will then use the information to help shape its regulatory, compliance and enforcement decisions. (Also see "*Quality On The Brain: FDA Maturity Pilot Aims To Shift Industry's Compliance Mentality To A 'Quality Mindset'*" - Medtech Insight, 29 Sep, 2017.)

"How often does a regulator like FDA really need to show up at a facility to inspect if we've already done the high-level work of assuring that its AI systems are established well, and have pulse-checks we can do based on the data?" FDA's Francisco Vicenty says.

"The approach and the perspective in a company to start thinking in AI terms, enabling AI systems, starting to put them in place – that shows from a maturity appraisal approach that the firm is considering and asking the right questions, and it's delivering on continuous improvement," Vicenty said.

"It's not about what's happening right now – 'I met the compliance check, I met the regulation. Great. FDA, verify it, and please leave for two years.' Instead, with AI, firms have taken the onus on themselves to find ways to look for improvements."

And additional information that AI could provide to FDA about a specific firm would "help change what we at FDA consider to be the demonstration of assurance," he said. "Getting that extra data, and FDA being able to incorporate that into its decision-making – down the road we're talking about enabling a whole different paradigm in terms of checking in" by way of an agency inspection.

After all, "how often does a regulator like FDA really need to show up at a facility to inspect if we've already done the high-level work of assuring that its AI systems are established well, and have pulse-checks we can do based on the data?" Vicenty wondered.

AI: It's For Quality And Regulatory

Marla Philips, director of Xavier Health at Xavier University, says the mission of the school's Artificial Intelligence Initiative is clear: to use AI to augment quality and regulatory systems to better predict QA/RA decisions and outcomes.

A major theme of the initiative is to determine "how we can use artificial intelligence to give us more information as quality and regulatory professionals to make better decisions about our products before they get out on the market and we find out, 'Oh, gosh. We didn't realize that problem was related to what we've been experiencing for the past five years. Somehow we missed that thread,' Philips said at MedCon.

She offered an example of how quality and regulatory professionals could use AI to their advantage.

"Imagine the vast amount of structured numerical data that comes in for any single product you have, starting with the components coming in the door. They can be in a spec range, sometimes so wide that you could drive a truck through it," she said. "Components could come in on this end, or that end, or somewhere in the middle, or anywhere in-between. The component then passes inspection and it goes into your product, and your product goes out the door.

"And that's just one variable," Philips continued. "Just think of all the variables that go into your product: the room temperature, the humidity, the operating speed, the operators themselves. There are so many variables that go into getting your product out the door. Now, imagine if you could train your system, through AI, to look at all of those variables and to see what lines up with success – or what led to the edge of failure. Then, you could say, for example, 'My gosh. Every time Marla is involved with that product, we're on the edge of failure.'"

AI can pick up on those types of troubles because it looks across all product variables, and detects what works and what doesn't.

"AI can pick up trends in a variable that you might not even be connecting with your release decisions, or ever bring into an investigation when you have a product failure," Philips said.

> ***"With AI you can very quickly gain the power to see the 'small things' and say, 'Hey, maybe there's something there that we should look into,'" IBM Watson Health's John Daley says.***

John Daley, VP of quality and regulatory affairs for IBM Watson Health, noted that artificial intelligence excels at pattern recognition, which can give device-makers a leg-up when trying to find product or manufacturing nonconformances.

Daley is a veteran of device giants Boston Scientific and Johnson & Johnson, where he held various senior quality positions.

"If your firm could partner with others to get data, that would be helpful," he said at MedCon. "Let's say you make artificial hips and partner with providers such as Kaiser, Blue Cross and Blue

Shield. You get access to their data for your devices and you start to see, 'Hey, for this new hip, we're noticing that people are on narcotics longer,' or something else that might be such a low signal that you'd never see it without AI.

"If it's a low signal, there's a good chance that no one would complain," Daley said. "They might not think, 'Hey, everybody else is on narcotics for nine days but my patients are on them for 11 days.' But with AI you can very quickly gain the power to see the 'small things' and say, 'Hey, maybe there's something there that we should look into.'"

Separately, at the AI Summit, Philips pointed out that siloed data is an issue for many QA/RA experts – a problem that could be solved by using artificial intelligence systems.

It can be troublesome "if you're not pulling all of your quality data together because it's in different siloes or different systems – or even different divisions – of your company," she said.

"If you have a centralized organization, and there's information that some of your sites have that your other sites aren't seeing – is that getting linked to what's happening in R&D? Does it ever cycle back enterprise-wide to inform the way the next product is being developed?" Philips asked.

AI can break down walls that surround data by pulling from many different streams of information.

"There's a lot of opportunity for AI to do things that we don't have the bandwidth to do today, but are so important in giving you the competitive edge, the efficiency, the speed to market – all of that is something that's there but can't be taken advantage of because most firms aren't set up for AI systems," Philips said.

J&J Subsidiary Janssen Digs Into AI

Artificial intelligence systems can also analyze textual information – written language – and put it into context to detect trends. While numerical data is known as structured data because it's highly organized, textual data is unstructured – and can be a bit unruly.

AI can analyze unstructured data from internal audit reports, giving quality and regulatory experts a better view of quality and manufacturing systems.

Let's say a device manufacturer conducts a quality audit of its facilities once a year. "Usually when you're auditing, you can probably look at about 2% of your documents. That means you're reviewing only 2% of your documents yearly and determining if you're in control or not, which can be dangerous," Xavier's Philips said.

But by using natural language processing, or NLP, "AI can look at more than just that small number of documents and be better positioned to give a clearer representation of how your quality system is operating," Philips said.

Natural language processing allows AI systems to extract and evaluate human language data, which can be tricky.

At *Johnson & Johnson*pharma subsidiary Janssen, a team of 37 data scientists are working to bring advanced AI systems and approaches to its quality, regulatory, supply chain and clinical trial spaces. That includes work with NLP, extracting textual data from various reports, including FDA-483 inspection observation forms and documentation related to corrective and preventive actions (CAPAs).

"We can use natural language processing to take those unstructured sources and use them as data, and put them into a structured format where we can use them in machine learning models and in other types of big data analytics to derive some insights," Ryan Schoenfeld, Janssen's director of data sciences, said during an April Xavier University webinar on artificial intelligence.

> ***At Janssen, "what we can do is leverage machine learning, artificial intelligence and big data analytics approaches to automate workflows, and look for new business opportunities, as well," Ryan Schoenfeld says.***

Schoenfeld said the firm uses AI to tackle more traditional problems, revisit old issues, and even question assumptions the company has made in the past that were based on using older types of analytical techniques.

"The ability to leverage capabilities such as high-performance computing really expands the realm of what's possible and what's economical from a computational perspective, versus just a few years ago," he said. For Janssen, "AI is going to have an impact on a number of areas. Certainly, and probably most importantly, it's going to impact our decision-making. We can make more data-driven decisions and reduce bias in our decision-making by allowing the data to drive things."

Schoenfeld stressed that "artificial intelligence is not machines thinking for us. Rather, AI is

going to be leveraging the technology to help us make better decisions, and it's going to also help us automate workloads. There are a lot of manual processes that go on [at firms] today across all areas, in clinical development, manufacturing and the supply chain. What we can do is leverage machine learning, artificial intelligence and big data analytics approaches to automate workflows, and look for new business opportunities, as well."

Robert Studt, Janssen's senior director for data quality metrics & reporting, said the firm's quality and compliance group is fiddling with NLP to identify trends, better determine the root causes of product problems and be more efficient in handling nonconformances.

"We want to leverage the knowledge that we have sitting in many years of audit reports, CAPAs, and corrective and preventative action plans, where a lot of the data that is in those reports is a lot of pretext," Studt said during the AI webinar. "What we're developing are algorithms – mechanisms – to take all of that historical knowledge that is encompassed in pretext, and all of our audit reports and root cause analyses, and analyze it."

Janssen also plans to roll out this year a software portal that can be used for inputting and analyzing textual data.

"If we receive an inspection report and it has a description of the observation or what's gone wrong, the user can paste that observational text into the portal and use natural language process algorithms to look for similar situations that have occurred in the past, hopefully reducing the time we spend developing a plan" to fix an issue, Studt explained.

"Within a company like J&J, we have multiple large therapeutic areas. So, imagine you're sitting in the oncology group and receive an observation from FDA. Well, someone in the cardiovascular group may have received a very similar inspection observation two years ago, and may have developed an approach – a response – that was either effective or not," he said.

"That would be very useful for you to know as the current-day oncology person who is developing a plan to respond to the agency."

While Janssen is a drug-maker, Robert Studt foresees the firm's parent company, Johnson & Johnson, using AI systems in its other commodity areas, including medical devices.

Janssen's quality and compliance group is working with colleagues in the firm's supplier control group to figure out how it can leverage a similar approach to nonconformances in its supply chain.

"You can use advanced analytics and predictive analytics for things like reducing stock write-offs and for optimizing processes in different ways. Or, better ways to catch label mismatches. There's a long list of potential applications for advanced analytics in the supply chain," Schoenfeld said.

Janssen also wants to add external information to its collection of data. "For example, FDA warning letters that may have been issued to other companies in certain areas – we can bring those into our knowledge base and supplement the data that we've gathered internally over the years," Studt said.

And while Janssen is a drug-maker, Studt foresees the firm's parent company using AI systems in its other commodity areas, including medical devices.

"J&J is a big manufacturer. Ryan and I sit in the pharma segment, but we also have consumer and device segments with a large footprint," he said. "We have, internal to the company, possibilities to expand this AI work there with data from other segments, and to expand the impact of some of our AI tools."

Validating AI Outputs

One hurdle that device-makers will have to jump is determining the best way to validate results generated from AI systems.

"The traditional validation of where you do something and then say, 'OK, I have full confidence in what I've got' is absolutely different in the world of artificial intelligence," Bakul Patel, associate director for digital health in FDA's Center for Devices and Radiological Health, said at MedCon.

When it comes to machine learning, "you can't train the system to recognize cats and then try to see if it can detect dogs," Patel said. "I think that's an example of

Might AI Replace Humans?

"The way we see artificial intelligence is, it's really a path forward to use more and more and more unbiased approaches based on data to make decisions. So, it's not a threat to the human decision-maker. We still need the human decision-maker," Janssen's Ryan Schoenfeld said.

"Maybe someday we'll be more in a state where we can assign more decisions to machines, but I can tell you as someone who sees the forefront of the current field today, we're not there. And I don't see us getting

the fundamental things that you must figure out as you use AI – and that's where validation needs to start from. You need to know what your features are that you're trying to identify."

The integrity and quality of data is also important when verifying AI outputs.

"If you have too much noisy information in your AI system, you will get indefinite answers. Then, when you test the system, you will still get those indefinite answers," Patel said.

IBM Watson Health's Daley agreed that using quality data is of the utmost importance to ensure adequate AI validation activities.

there anytime soon," he said.

"Humans are making the decisions, and these AI tools just help us make better ones, really. So, I don't think, from an AI perspective, that it's a threat," Schoenfeld said. "Now, some workflow automation can reduce the number of hours that people now need to spend on certain tasks. But those folks can focus on other areas where they didn't have time before to do things to push the frontier in other ways.

"So, that's the opportunity."

"I would say the quality of data is key, and then it's all about classic validation – knowing your predetermined outputs," he said. "Know very precisely what target you want to meet, and I would strongly suggest that it should be equal to or better than human performance in whatever you're starting out with. That's how it should be."

As manufacturers work toward AI validation, Daley also urged firms to know their products' risk profiles, and to understand "where and when humans may still be in on the decision-making."

Xavier's Philips echoed Daley's remarks, noting that AI outcomes should reflect, at a minimum, the same conclusions that humans would arrive at.

"But the important thing is that the system then continues to learn, and you have to make sure you're verifying that you agree with what it's learning before you just say, 'We'll take that information and make our decision based on it,'" Philips cautioned.

"Remember: AI can be used to help inform your quality and regulatory decisions with more information than you've ever had before, but validation is a key step," she said. (See sidebar story, "FDA-Industry Artificial Intelligence Teams Focus On Product Quality, AI Validation," below.)

For now, drug-maker Janssen is not implementing machine learning approaches in specific

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quality, regulatory or other areas that must be highly validated.

"The earliest places where we're implementing AI in our workflows are in areas that are support functions for the most validated and most regulated areas. That's where we're getting our feet wet," Janssen's Schoenfeld said.

And, although validating artificial intelligence outcomes may be different from traditional manual process validation activities, the same principles apply, he said.

FDA-Industry Artificial Intelligence Teams Focus On Product Quality, AI Validation

By Shawn M. Schmitt

25 Oct 2017
The Artificial Intelligence Initiative at Xavier University has formed teams to decide how to best scan for signals of device and drug troubles, and validate results generated from AI systems.

Read the full article here

"If you're going to put an advanced analytics tool into a workflow that's going to have an impact on decisions that have a direct impact on regulatory or regulated activities, such as releasing products to patients and clinical trial management, you must validate," Schoenfeld said.

"But the big question is, how do we validate down the road? As machine learning algorithms become more and more accurate in making various decisions, how will we validate those?"

Industry, Regulators Must Sing Off Same AI Song Sheet

Much of the answer, Schoenfeld says, lies in industry's willingness to work hand-in-glove with regulatory agencies on AI issues.

"We'll have to carefully work with regulators like the FDA to make sure everyone is aligned with the validation process," he said. "If we have to adapt it or modernize it in some ways, working with regulators ensures that everyone is on the same page."

No matter how industry chooses to move forward with advanced artificial intelligence systems, Philips says it indeed must happen in conjunction with regulators.

"The understanding of what's going on has to be done together. It's not best to have FDA going off and understanding something about AI, with industry having no idea what it's talking about, and vice versa," she said. "It has to be done in-step together."

David Lowndes, head of small molecule operations at biopharmaceutical company *Shire PLC*, sees eye-to-eye with Philips and Schoenfeld.

"We have a long journey to travel, and it's a journey that we need to travel in close conjunction with our regulatory agencies. There's a lot of learning to be done," Lowndes, who leads the supply chain for the firm's Specialty Pharmaceuticals Division, said at the AI Summit.

"We need to bring AI experts, manufacturing and production experts, and the agencies together, to travel this journey together so we're on the same page, aligning on how to leverage AI and how to regulate in the new environment where we're using AI," he said. (See sidebar story, "AI & Regulation: AdvaMed Aims To Mold Artificial Intelligence Policy For Device Industry," below.)

Use Purse Strings To Gain Attention Of Top Leaders

As artificial intelligence marches forward in industry, it's likely that top management will need to be convinced that using AI in quality and regulatory applications is worthwhile.

That can typically be done by explaining to senior leaders that AI systems can save their companies money, Shire's Lowndes said.

"Recently I was at an API [active pharmaceutical ingredient] plant for one of our contract manufacturers, and we toured the facility," he said. "We walked into a control room, and there must have been 15 or 16 screens in the room, each of which had huge amounts of data on it.

"I asked: 'How much data do you have?' And they said: 'For each lot, we have 20,000 data points,'" he recounted. "I then asked: 'How much of that data are you using to control the process, and to learn about the process, and to improve it?' And they said: 'We take about six to eight data streams and we use that to control the process.'"

That's when it dawned on Lowndes that an AI system could help the facility take fuller advantage of its big data.

"Presumably the original investment – the ability of this plant to get all of this data – had a reason or logic behind it. So, it is a lost opportunity that they aren't using all of the data they are capturing," he said. "That's a loss of value to the business – a loss of competitive edge, a loss of performance – and that's something that senior leadership needs to understand."

AI & Regulation: AdvaMed Aims To Mold Artificial Intelligence Policy For Device Industry

By Shawn M. Schmitt

25 Oct 2017

As AI becomes more prevalent in the medical device arena, thought-leaders in industry and US FDA are looking down the road at how artificial intelligence can be regulated in a way that doesn't stymie innovation. AdvaMed is helping to lead the charge by crafting policy points to address the issue.

Read the full article here

"There's an argument to be made that it's taken AI a long time to catch on because we've not been able to show how AI can save companies money," Shire's David Lowndes says.

Although Lowndes recommended an AI solution to top officials at that particular plant, he received pushback.

"The response I got from senior leaders was, 'Well, yes, AI would help, but AI's really expensive, isn't it?'" he said. "Well, expense is all relative to the potential savings and benefits you can get, and I would argue that if you're not using much of the data you're collecting, that means you've already spent a lot of money, and you're wasting a lot of money by not using [the data], and you're missing an opportunity to turn that into value for the company."

Lowndes is concerned that if the drug and device industries do not use artificial intelligence in a way that demonstrates a meaningful return on investment, then their efforts will fail.

"AI has been around for decades already and it hasn't really gotten to anything close to what its potential is," he said. "So, I think we've got to be looking for opportunities where there's a great return on investment. Because if we don't generate solutions that drive value, then potentially AI becomes a clever niche technology.

"There's an argument to be made that it's taken AI a long time to catch on because we've not been able to show how AI can save companies money."

Despite the potential savings, firms should nevertheless exercise caution when handling artificial intelligence.

"The loss of oversight and learning for us as human beings is an area where we need to be extremely careful," Lowndes warned. "If we let artificial intelligence take us from the data collection to the decision and the implementation of that, and we're sitting there saying, 'What just happened?' – that's when we start to lose the knowledge of our processes."

From the editors of The Gray Sheet