ROPES & GRAY

TELECONFERENCE TRANSCRIPT

Health Care ▪ Life Sciences

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Outlook 2018 Teleconference: The Trump Administration's Impact on Life Sciences and Health Care—the First Year

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Al: Hello, and thank you for joining our teleconference this afternoon. I'm Al Cacozza, a partner in the Washington, D.C. office of Ropes & Gray, and a member of the firm's life sciences practice. This is the third time we have convened this group to discuss the regulatory and compliance impact of the Trump Administration on life sciences and health care companies. We did so at the outset of the Administration, we did a check-in at the 100-day mark and now we are revisiting the topic on the first anniversary. This teleconference is part of our ongoing Capital Insights initiative. We are capturing our latest thinking on developments from the federal government, including alerts, analyses and podcasts on our Capital Insights page at www.ropesgray.com and we invite you to continue to visit the Capital Insights page throughout 2018. Joining me again today are several of my partners in the D.C. office: Tom Bulleit, from our health care practice group; Kellie Combs and Greg Levine from the life sciences practice group; and litigation and enforcement partner, Colleen Conry. Welcome back everyone.

It is an understatement to say that the regulatory and compliance landscape has been subject to change in the last year, although it is still unclear what the lasting impact of all that activity will be on the health care and life sciences sectors. Over the next hour, we will update some of the key issues we discussed in 2017 and then look forward to give you insights into critical developments we see emerging in 2018.

Today's conversation will be informed by a combination of publicly available statements, past behavior, and general trends we have observed in the life sciences and health care industries and some element of educated speculation. As you can all appreciate, however, given that 2018 is an election year, it is unclear what will be accomplished this year.

We plan to save time at the end to address questions from our listeners. If you have questions during the teleconference, please email them to rgevents@ropesgray.com and we will try to get to as many as we can. One further note, we are offering CLE credit for this teleconference. I will provide you with the necessary information to receive such credit at the end of the teleconference.

Repeal and Replace Efforts

Al: So, let's now begin with Tom Bulleit from our health care practice group. Tom, you spent the last year watching very closely the likely effects of the Trump presidency on the Obama Administration's signature domestic achievement, the "Affordable Care Act" or "Obamacare". In fact, the teleconference materials we have shared with the listeners include a monthly column you wrote for Bloomberg BNA, as well as several articles following the trajectory of the so-called repeal and replace effort. Can you start our call by bringing us up to speed on where we are with Obamacare?

Tom: Al, this is one of those areas where if you follow the mainstream national press, you will have a pretty good idea what's happened legislatively, but the real news on Obamacare is in the regulatory actions that the Trump Administration has taken. The headline here is that we likely are headed for a more bifurcated individual health care market, with older and sicker people signed up for increasingly expensive Obamacare policies - and the feds paying premium support for a large number of those - and younger, healthier people opting out of coverage altogether, or buying skinnier policies that don't have all of the Obamacare consumer protections. The effect is fewer people will have health care coverage that protects them in cases of unexpected or catastrophic health events.

Legislatively, probably everybody knows the current status: Congress was unable to get even enough Republican votes to pass one of the repeal bills, but did repeal, effective January of next year, the Obamacare provision that imposes a tax penalty on individuals who don't have insurance, the so-called "individual mandate". To repeal the individual mandate is widely expected to result in fewer people, especially young and healthy people buying insurance, with the result that the risk pool in the Obamacare exchanges will be older and sicker, and correspondingly, premiums will go up. Further efforts at legislative repeal are possible - Senator Graham in

particular has advocated for this - but Majority Leader McConnell has indicated little interest in pursuing further repeal efforts and his majority in the Senate has dropped from 52 to 51.

More important is that this likely migration of the young and healthy out of the Obamacare markets and the corresponding rise in premiums for Obamacare-compliant plans is likely to be exacerbated by some of the regulatory actions that the Administration has taken. The three most important are: (1) cutoff of the cost-sharing reductions, or CSRs, paid to Obamacare insurers to help patients with the costs of their medical care, essentially copays and deductibles; (2) actions that critics say were designed to reduce enrollment by removing helpful information from the CMS website; cutting the open enrollment period in half and reducing the budget for enrollment assistance; and (3) maybe most important, instructing federal agencies to expand the availability of alternative health plans.

The status of the CSRs are still in flux, but regardless of the outcome of the pending lawsuit by some states, most analysts are saying that Obamacare insurers built the loss of CSRs into their 2018 rates, and certainly will for their 2019 rates. So, plans going forward are correspondingly more expensive, but that may make the funding issue for the CSRs less important.

More important, the Administration has instructed federal agencies to expand the availability of alternative health plans that are subject to fewer Obamacare consumer protections, such as not having to include the 10 essential health benefits. The labor department issued a proposed regulation earlier this month that would allow so-called association health plans, plans formed by associations of small businesses with common interests like farm bureaus, to be treated as large group employers, which are exempt from the EHB requirements. All of that would likely further drain the young and healthy from more comprehensive Obamacare plans, and a similar result come from the expansion of so-called short-term plans, which could be available for up to a year. So bottom line, although fewer young and healthy people will buy comprehensive Obamacare policies, they may be satisfied with the skinnier alternative policies which could reduce the political pressure on Republican legislators to repeal. With the individual mandate gone and cheaper policies available, Republicans might find the efforts to repeal will be less popular, and that there's more pressure even from their own base to put more money into policies to stabilize the Obamacare markets.

Value-Based Health Care

Al: Thank you, Tom. We continue to hear a lot about value-based healthcare. Former HHS secretary, Tom Price, was perceived as an opponent of some CMS initiatives in this area. Can you explain what value-based healthcare means, and will Secretary Price's departure make a difference?

Tom: Yeah, I would say reports of value-based healthcare's death were greatly exaggerated. Value-based healthcare means paying for quality outcomes rather than quantity of procedures and the Center for Medicare and Medicaid Innovation at CMS had rolled out several programs that would put some amount of payment at risk pending good outcomes. The main vehicle has been to "bundle" payments for episodes of care that make physicians, hospitals, and downstream providers share in a single payment that can be increased with good outcomes and reduced for bad outcomes. Secretary Price didn't like those and cancelled some of them. Alex Azar, who is likely to be confirmed as the new secretary, testified that he thought some mandatory programs in the bundled payment area were likely to be important, and a number of private payers and drug and device makers have announced that they are pursuing value-based initiatives. So, there's good reason to think that value-based healthcare is going to be alive and well in the next year. By the way, we maintain a website on value-based healthcare also at ropesgray.com with a number of the resources of this area that you can access.

Entitlement Reform

Al: Speaker Ryan initially indicated that he wanted Congress to pursue entitlement reform as a way of dealing with the cost side of the federal budget equation now that tax reform may, according to some analysts, reduce federal tax

revenues. That is a debatable position because others argue that an expanding economy will pay for that tax cut. Nonetheless, the question is, do you see any fundamental changes to Medicare or Medicaid in store?

Tom: This one is easy to answer quickly. Probably not. McConnell made clear that this was not something that he really wanted to pursue. And since one of the more unpopular aspects to the repeal bills was to eliminate the Medicaid entitlement and cap expenditures, even if that resurfaces I don't see it likely to get through the Senate.

Prescription Drug Prices

Al: And last question for you, Tom. Another issue we have heard about is the high cost of some prescription drugs. I will talk in a minute about what FDA might do in this area, but do you see any action in this area coming from Congress or CMS in 2018?

Tom: We may see a little bit of movement from Congress or CMS, but I don't think it will be dramatic. President Trump said that he favored letting Medicare negotiate directly with drug makers, something that the industry and secretary designate Azar have opposed, so I don't see that coming along. The real action here is likely to be at the state level. As of last week, six states have passed laws promoting drug pricing transparency. Four have passed laws requiring state agencies to collect data on prescription drug prices, and four have passed laws requiring drug manufacturers to provide justification for drug prices and price increases. The pharma industry is challenging some of these laws in federal district courts in Maryland, Nevada and California, alleging in all cases that there are unconstitutional constraints on interstate commerce. But despite the legal challenges, many states continue to introduce new legislation. In the first three weeks of 2018, 18 new bills were introduced across 13 states. Al, you mentioned that there might be some FDA initiatives on drug pricing as well?

Al: Yes I did, Tom. As you know, FDA does not have the authority to address drug prices directly, and historically has stayed away from any discussion of drug pricing issues. But, FDA Commissioner Scott Gottlieb has not shied away from this issue and, in fact, has made it one of his top priorities. Dspite the high profile of his rhetoric, FDA still has limited ability to influence drug pricing. Gottlieb's approach is to take steps to encourage and increase generic competition, which should then allow market forces to produce lower drug prices. In addition to trying to streamline and to speed up the generic application review process, Gottlieb seeks to identify those drugs, which are eligible for generic competition, but currently have no approved generic versions and prioritize approval of those applications.

One interesting recent development on this front is that just last week four significant hospital systems with over 300 hospitals led by the Intermountain system, that combined, count for nearly 10% of the hospital beds in the country, announced the creation of a non-profit joint venture to create their own generic drug company targeted at making those drugs that Commissioner Gottlieb has singled out - existing drugs that currently lack generic competition. The theory is these hospitals will then be able to buy these new generic drugs from their own manufacturers and sell them to others without the need to price them like a for-profit company. The VA system already has expressed interest in looking to purchase drugs from this non-profit venture. It will be interesting to monitor if this new venture has real world impact on drug prices.

One other indirect pricing initiative by FDA is an effort to streamline and encourage prescription to over-the-counter switches. Congress is considering over-the-counter user fees and over-the-counter monograph reform to make the cumbersome monograph process more effective and useful as a vehicle to introduce new OTC products. Commissioner Gottlieb also has signaled the need for FDA to be more open about using innovative technological solutions. For example, informative mobile apps to help consumers appropriately self-select a drug to ease the path for OTC switches. As a pricing mechanism, the theory is that OTC products tend to be less expensive then RX counterparts, although it is unclear if this is more of a cost shifting mechanism from third party payers that cover RX products to consumers who would be paying for OTC products out of pocket.

Now that we have opened up the discussion on FDA, let's turn to more details about that agency. Greg Levine and Kellie Combs will address these issues.

Commissioner Gottlieb

Greg, as I already noted, Commissioner Gottlieb, who was confirmed in June, has, unlike his predecessors, expressly raised addressing high drug prices as one of his top priorities. At a high level, what impact has the choice of Dr. Gottlieb as Commissioner had on the FDA from your perspective?

Greg: Well, thanks Al. If we go back to last year, in our spring First 100 Day teleconference, we talked about some of the candidates who were under consideration. There was a wide range of folks that we discussed at that time, some of whom held very unorthodox views or had very unorthodox backgrounds. The Administration went with Dr. Gottlieb, who's an MD, a fairly traditional background for FDA Commissioner, and someone who had held a leadership position in the agency before. So, I think the effect of going with this known quantity has been relative stability at the FDA. There has been some turnover at the agency, natural in a time of transition, but really nothing particularly out of the ordinary from that perspective. I think at a high level things have unfolded largely as we predicted, the sort of a cadence of the year. Until the new commissioner was confirmed, which happened in June, there was essentially nothing happening at the FDA on policy side of things. The FDA was doing its day-to-day job. They were reviewing product applications, they were conducting CGMP inspections, and issuing warning letters, and things of that nature. But there was very little published in the Federal Register. For those of us who look at the Federal Register every morning, there wasn't a whole lot to look at for a long time. But starting in the fall, the floodgates really opened, and these days you have to pay very close attention to what's coming out on a daily basis in the Federal Register or you'll miss some pretty important announcements. A lot of what has been happening has been implementing a lot of the requirements of the 21st Century Cures Act, which was enacted at the end of 2016, and then the beginning of work on implementing the new user fee law that was enacted in August of 2017, and the associated user fee agreements with industry. In terms of the trends of what we're seeing, and at this point I'll just talk at a very high level. I think what we're generally seeing is consistent with the Administration's philosophy, and also what was already happening in Congress, which was a trend towards lessening the burden of regulations and trying to be more flexible and even applying innovative regulatory approaches that haven't been tried before. The approvals of novel drugs, biologics, and devices are all up. You can argue whether that's the result or not of this. But one goal that the device center, for example, has made explicit in its recently published strategic priority document, is that by December 31, 2020, they would like to see more than 50% of manufacturers of novel technologies for the U.S. market intend to bring their devices to the U.S. first or in parallel with other major markets. So, the trend had been the other way. I think the FDA had gotten fairly conservative, arguably inflexible, perhaps in reaction to criticisms that its standards had gotten too lax, and now we're clearly seeing the pendulum go the other way.

Key Initiatives at FDA

Al: We have already mentioned drug pricing as one of the stated priorities of the current commissioner. What do you see as other key initiatives that the Commissioner has focused on?

Greg: There's a couple of things he's focused on. Two have a common thread, which is harmful addictions. The opioid crisis is obviously a huge public health issue for the country, so the Commissioner has put out a new strategy on that. A couple of elements on that worth mentioning. One is to expand labeling requirements that include warnings and safety information to immediate release opioids. Those requirements currently apply only to the extended release or long acting opioid products. And also to update the risk evaluation and mitigation strategy program, the REMS program, for opioids which applies to the extended release products currently and requires manufacturers to fund continuing medical education programs on the appropriate use of these products. Another focus is in the tobacco area. The Commissioner has announced a plan for the regulation of nicotine and the centerpiece of that would be a long-term strategy to use its authorities under The Tobacco Control Act to require a

reduction of nicotine in combustible cigarettes to less addictive or non-addictive levels. So that would be a multi-year effort requiring a lot of careful study.

A lot of what I've been following has been in the device area where I think there's a lot of innovative things happening. Just to mention a couple, there are several initiatives underway where the idea is to move away from approving or clearing individual devices on a product-specific basis and instead focus on the manufacturer or developer of the product. One example of that that is getting the most attention these days is the pre-certification pilot program for digital health software developers. The idea of that program, currently in a pilot with nine participants, is for the FDA to focus on the software developer and evaluate its systems for software design, validation and maintenance, and then at some point, hopefully certify or pre-certify that manufacturer or developer to introduce new digital health software products into the market without requiring FDA review for each product or some form of streamlined review. The details of this are yet to be developed. I've talked to some friends who work for companies that are in the program; they don't what the details are yet. There's going to be a public meeting on this in a few days, so there might be some more information forthcoming. But the FDA has talked about expanding this model to other product types as well. In November, the agency issued a notice seeking comments on a proposal to allow direct to consumer genetic health risk tests to be exempted from 510(k) review after the manufacturer of such a test has submitted a single 510(k) for one genetic health risk test to the agency, after which it could market new genetic health risk tests without further review from the FDA. So that's a similar type of idea; you look at the company, they go through the process once, the FDA signs off in that initial 510(k) and then the company has more flexibility to introduce further tests. I think a lot of the idea here is to try to foster innovation and not impede innovation in areas where there's a lot of iteration. Products are changing rapidly and the science is evolving quickly. And then one more, even more broadly, the FDA has said that they are considering applying this type of approach to laboratory-developed tests. That's been an area where the home brew tests or laboratory developed tests and how those are regulated in relation to FDA regulated in vitro diagnostic test kits, there's been a lot of controversy and uncertainty on how that's going to be resolved. So this idea that the FDA has at least floated is that maybe the agency will look at the lab and certify the lab and the lab could introduce tests without each one going through FDA approval or clearance. There is no concrete proposal on that one yet and we will see where that goes.

One last thing that I think is interesting is also in this area of diagnostic testing, but is a novel approach that's different from the ones described before, involves next generation sequencing testing. In November, FDA used the De Novo classification pathway to authorize a tumor profiling test developed by Memorial Sloan Kettering Cancer Center. It's a test that can identify the presence of mutations in 468 genes. The idea of next generation sequencing is just looking at the genome as a whole at once. This would look for the presence of mutations in 468 genes as well as other molecular changes in the genomic makeup of a person's tumor. So you take a sample from the tumor, you compare it to a normal sample from the patient and do a comparison. What the FDA did in this case was they actually in a sense accepted a review of that product by the New York State Department of Health. New York State has its own program for reviewing in vitro diagnostic tests. The state agency had reviewed this test; traditionally this type of test would never go before the FDA. It would be considered a laboratory-developed test. But in this case, Memorial Sloan Kettering submitted the product to FDA through the De Novo program and what the FDA ruled there was they allowed the product on the market based on the same information and documentation that was submitted to New York State. At the same time they then accredited the New York State Department of Health as a third party reviewer of in vitro diagnostics, including tests similar to this test from Memorial Sloan Kettering. And now issued the De Novo ruling, which means moving forward, other laboratories who have similar types of tumor profiling tests that have been approved by the New York State Department of Health do not need to submit a separate 510(k) to the FDA. They could if they wanted to or they could chose to submit this third party review by New York State to the FDA in lieu of 510(k) clearance and the FDA will review that. The FDA may accredit others; it's not necessarily specific to New York State, but that was a pretty novel and interesting approach that the FDA took there.

FDA Enforcement

Al: Let's take a turn, Greg, and look at the enforcement issues. Do you see any enforcement areas that the FDA is likely to emphasize in 2018?

Greg: There are a number of them, but one that I'm focused on mostly because the FDA just came out with an announcement on this last week that was pretty significant I think, is drug compounding. In the drug compounding area we know there has been a lot of enforcement activity, a lot of FDA resources have been going to that since the NECC meningitis outbreak a number of years back now. But last week, FDA announced a compounding priorities plan and there's a couple of interesting elements of it. One is there seems to be an effort to kind of push and pull some of the smaller compounders have not signed on to this new category of 503B outsourcing facilities that was created in that drug compounding law to try to push them into that category or pull them into that category. The pull aspect of it is the FDA says it is going to promulgate GMP regulations for these outsourcing facilities. The outsourcing facilities don't need a patient-specific prescription, unlike the 503A entities, but the FDA says that they will consider the size of the compounder when they create these regulations and that they intend to be very flexible with respect to smaller entities. So that's the pull element. The push element seems to be that the FDA is signaling it is going to be stricter with regard to compounding from bulk drug substances. They are actually being sued right now by Par Pharmaceuticals with respect to the interim enforcement policy they've been taking on bulk drug substances while they're developing these statutorily required lists of drugs that can be compounded from bulk. Without getting into too much detail on that, I think that is the way they're going to say we're going to be stricter in enforcing the law, but we're going to make the law in certain other ways easier to comply with.

Biosimilars

Al: That's great. Thank you, Greg. I am now going to turn things over to Kellie Combs. We have already discussed a little bit about the FDA's efforts to facilitate generic competition for small molecule drugs. Let's turn now to look at large molecule products. What is the current landscape for biosimilars? Are there any significant developments at the FDA in store in that area?

Kellie: Thanks Al. Last year, FDA approved five biosimilars, and that brings the total number of approved biosimilars to nine. It's important to note that even though nine products have been approved by FDA, only three are actually on the market: Sandoz's biosimilar to Amgen's Neupogen, Celtrion and Pfizer's InFlectra, which is biosimilar to J&J's Remicade, and then Samsung and Merck's Renflexis, which is also a biosimilar to J&J's Remicade. The other six remain tied up in patent litigation, which will continue and where much of the action will occur in 2018.

Also relevant to note with respect to what happened last year at FDA, two guidance documents on biosimilars were issued in draft form. The first one was draft guidance on interchangeability that was issued now just over a year ago at the very start of last year. In that draft guidance document, FDA essentially says that when evaluating whether a biosimilar product is interchangeable with the reference product, it will consider the totality of the evidence. Also in that draft guidance, FDA laid out a number of factors for sponsors of biosimilar applications to consider with respect to what data must be submitted to FDA, and then also laid out some pretty detailed recommendations with respect to the design of switching studies, essentially studies that would be required to demonstrate that a patient could switch back and forth between the biosimilar product and the reference product without any adverse clinical consequences. The other draft guidance document that FDA issued last year involved statistical approaches to evaluating analytical similarity and as you can probably guess by the topic alone, it is a very technical guidance document that lays out some general principles for assessing analytical similarity. It goes through things like development of risk ranking attributes, development of statistical methods, and development of the overall statistical analysis plan.

So the key question is: what's in store in 2018? There are several other biosimilar applications currently pending review at FDA, with at least five of them having user fee goal dates in the first half of 2018, so I think we can expect

to see more approvals here in the next couple of months. In addition to the patent issues that I mentioned earlier, which will still be very much in play in 2018, coverage and reimbursement practices are also expected to have a significant place in the biosimilars discussion. For one thing, unlike with small-molecule drugs, you don't have generic substitution mandated or permitted by state law. Many states have enacted laws to cover biosimilar substitution, but as a general matter, they only apply to biosimilars that are interchangeable. At this point, and probably not for a couple more years, we don't have any products that are considered to be interchangeable biosimilars by FDA. Additionally, on the payer side, the payer policies with respect to biosimilars haven't been ironed out yet and it's still too early to tell how rebate and bundling strategies by the original biologic manufacturer, the reference product manufacturer, will ultimately impact uptake in the biosimilars market. Additionally at FDA, I think it's really interesting that there's no mention of any biosimilar guidance documents on CBER's guidance agenda that was issued just last week. And in the user-fee goal letters that were released last year, FDA says that the interchangeability and statistical draft guidances that I mentioned earlier won't be finalized until February of 2019 and the long-awaited guidance on biosimilars labeling isn't expected until May of 2019.

RMAT and Gene Therapies

Al: Thanks, Kellie. In addition to that summary regarding biosimilars, there are other developments in the biologics area that carry over from 2017 to 2018. Greg mentioned that FDA has been implementing the 21st Century Cures Act. That act created the Regenerative Medicines Advanced Therapies or RMAT pathway and FDA has embraced this program and it counts as a major accomplishment of the Center for Biologics. The program focuses on gene and cell therapy and it is analogous to the breakthrough therapy designation for drugs. To date there have been over 40 RMAT designation requests and FDA already has designated a dozen RMAT therapies. The designation gives the sponsor early and frequent interactions with FDA in the hopes of streamlining the development process as well as eligibility for priority review and accelerated approval.

Along the same lines, 2017 marked the review and approval of the first three US gene therapies –two intended to treat certain cancers and one for genetic vision loss. This marks the beginning of the gene and cell therapy era, which will raise novel and complex issues around pricing, access and ethics. While FDA has taken steps to encourage these new therapies, it also launched an enforcement effort to crack down on providers of unapproved regenerative medicine products. The Center for Biologics targeted a number of stem cell clinics that were providing unapproved stem cell therapies to patients, including seizure of some of those products and announced it intends to continue that enforcement activity in 2018. We will have to monitor this carrot and stick approach to see its overall impact on gene and cell therapy.

Advertising and Promotion

Al: Changing course a bit Kellie, I know you advise a number of companies, on advertising and promotion matters. Can you give us an overview of where FDA seems to be focusing its attention of late?

Kellie: Sure. FDA's Office of Prescription Drug Promotion, or OPDP, issued only four warning and untitled letters last year. And keep in mind that a few years ago, we were seeing several dozen letters each year, so it's safe to say that enforcement continues to be on the decline, at least from OPDP. I won't describe all of the letters in detail today but on the whole, it's pretty clear that OPDP continues to focus on what it would consider to be the low-hanging fruit, and by that I mean on products that are associated with really serious risks and safety issues, and on promotional materials that minimize or totally omit safety information or that don't provide all the material facts necessary to use the drugs safely and effectively. So we're not seeing from OPDP like we used to a lot of letters focused on straight off-label promotion, we're not seeing references to broadening the indication, or failure to demonstrate safety or effectiveness by substantial evidence. I think that's likely not just due to some of the notable losses in the First Amendment space, but also due to a draft guidance that FDA issued about a year ago that permits companies to communicate information consistent with the labeling, but not clearly within the four corners of

labeling. So as a result of that draft guidance, companies have more flexibility to make different types of claims. Also, in that draft guidance FDA walks back somewhat from the substantial evidence standard.

I think the two key takeaways from the warning and untitled letters this year are that, one, to the extent you have a limitation to the indication, whether it's framed as an official limitation of use in your product labeling or it's just an important material fact included within the indication, it's absolutely essential that you share that information. Just as one example in one warning letter from OPDP about a product approved as a "short-term" adjunct for weight reduction in obese patients that also contained a specific instruction to weigh the benefits in light of the various risks associated with the drug, OPDP cited the manufacturer for summarizing the indication and omitting that key limitation about the short-term approval and that specific instruction about the benefits and the risks. I think the second key takeaway is just to ensure that your promotional materials have fair balance, which is a concept that I think most of us are familiar with, and that you discuss the serious and common risks associated with your product, and that you also ensure that the risk presentation is very clear. So one interesting example that comes out in an OPDP warning letter from this year is that the agency took issue with a broadcast TV ad where risk information was presented in the supers, so kind of in text running along the bottom of the screen of the ad, but not all the risk information was presented in the voiceover. In this particular case, not only was the information not presented in the voiceover, but the supers were also running at the same time the voiceover was talking about something that was totally different. So there, FDA determined that the risk information wasn't presented in a clear and understandable way to consumers.

Now in addition to those OPDP warning untitled letters, another trend that comes out of last year's enforcement activity from FDA is that we're starting to see off-label promotion framed as violation of a REMS, or Risk Evaluation and Mitigation Strategies. There were three interesting cases last year where the allegations were that companies were downplaying messaging required by the REMS or were attempting to circumvent REMS requirements related to restrictions on use or other provisions really intended to ensure that the use of a particular drug was strictly limited to its on-label use.

Off-label Developments

Al: Thank you, Kellie. Are there any other big-picture ideas of what we can expect in the off-label area this year?

Kellie: Yes. The first one is a very recent development. About a week- and-a-half ago, FDA proposed again to delay, indefinitely this time, the implementation of a revision to the intended use rule. The intended use rule describes what evidence the government can rely on when asserting that a company is promoting its products off-label. There has been a lot of action on intended use over the last couple of years. Starting back in 2015, FDA proposed to amend the regulation to remove language suggesting that knowledge of off-label use alone could be used to prove intended use. That was a move that industry had encouraged and was very supportive of at the time, and importantly, one that FDA said was consistent with its actual practice-- that even though the regulation referenced knowledge, the agency in practice wasn't considering knowledge alone as sufficient to prove intended off-label use. So then about a year ago, when the final rule was published in the Federal Register, the language in the regulation looked totally different than what was initially proposed. Instead of just removing reference to knowledge of off-label use, the regulation instead said that FDA can consider "the totality of the evidence," including knowledge, when determining intended use. Industry roundly criticized that departure from the proposed rule, both because it didn't provide fair notice so parties didn't know that FDA was considering this change and weren't able to share their comments, and then additionally because it departed from the established law of intended use, which makes clear that intended use has to be determined by reference to specific marketing claims, or promotional claims, by its manufacturer. The totality of the evidence standard would have potentially exposed companies to liability based on relatively normal business activities. For example, we know that prescribers are free in most cases to prescribe and use a product off-label. And if a company knows about that off-label use, anticipates the off-label use, and scales up to meet that demand, or even if they're speaking about the off-label use in a truthful and non-misleading way, even if that speech is protected by the First Amendment or various safe harbors, all of that potentially could have been covered by the totality of the

evidence standard. At the time last year, the agency, in part due to the controversy of the totality of the evidence standard, had moved twice to delay implementation of the new intended use rule. Initially we heard that that delay would take us into March of 2018, however as we got closer and closer to that March deadline, it didn't seem like the agency was moving toward finalization of the rule. In fact, we heard just about a week-and-a-half ago that the agency needs more time to consider the public comments that were submitted by industry and patient groups and others and to address the implications of a change to the intended use rule. You know it's interesting that, although the agency was very careful in the Federal Register notice with respect to the delay that they weren't making any substantive determination about what is the right interpretation of intended use, there was a very clear acknowledgement by the agency that that totality of the evidence standard was confusing and that it could potentially have some pretty significant public health consequences. As a result, the agency, for the time being, is now reverting to the intended use regulation as it stood back in 2015. What that means is that even though knowledge is still included within that regulation, FDA will keep its long-standing practice of not considering knowledge alone as sufficient to prove intended use.

And one other interesting development with respect to manufacturer communications that has came out of Capitol Hill last week, House bill 2026, which is sponsored by Representative Guthrie from Kentucky, made it out of the House Energy and Commerce Health Subcommittee last week and now advances to the full House Energy and Commerce Committee. It was passed along party lines and had no support from Democrats, but this bill has been floating around in one version or another for quite some time now. It's called the Pharmaceutical Information Exchange Act; it expands upon FDAMA 114 and FDA draft guidance released last year that allows companies to communicate with payers prior to approval and in certain circumstances, both scientific information and health care economic information. This bill would essentially create a legislative safe harbor for companies that want to share those sorts of details. Some important limitations to be mindful of and keep an eye out for are that in the bill, unlike in the guidance, information has to be based on studies that the manufacturer could objectively anticipate could support approval of the new use or the new product, and the manufacturer must actually intend to submit the studies referenced to FDA to support an application for approval.

Enforcement and the Opioid Crisis

Al: Thank you, Kellie. We are now going to switch gears and talk about enforcement by agencies other than FDA and for that we are going to turn to our partner, Colleen Conry. Colleen is actually based in our DC office, but today will be talking to us from our London office. She will be giving us an update on health care enforcement and False Claims Act cases under the Trump Administration. What types of enforcement initiatives are you seeing now from the Trump Administration Department of Justice, Colleen?

Colleen: So Al, not surprisingly, enforcement actions that arise in one way or another from the opioid crisis continue to be a focus. In recent months, we've seen the federal and state governments increasingly move to target manufacturers of controlled substances. It's interesting – the theories underlying these actions are varied. On the one hand, we see traditional off-label promotion theories where a violation of the law comes from the way that a company markets it product, but then on the other hand we see cases that are really focused on distribution of controlled substances where companies are alleged to have committed acts of bribery or fraud in illegally distributing certain drugs. So DOJ has been explicit about its focus on the distribution angle with a recent press release underscoring the idea that manufacturers and distributors of controlled substances that can lead to addiction have a heightened obligation to operate in a transparent and trustworthy manner. In fact, in late November during his testimony before the Senate Health, Education, Labor and Pension Committee, Azar listed aggressive enforcement actions as one way that HHS will combat the opioid crisis.

Al: Colleen, can you give us a couple of examples of the kinds of cases you are seeing in this area?

Colleen: Sure, so in October 2017, Purdue Pharma disclosed that it was under criminal investigation by the U.S. Attorney's Office for the District of Connecticut. That investigation is focused on Purdue's marketing claims about

Oxycontin, namely, that it provides 12 hours of pain relief per dose. Purdue's October disclosure comes on the heels of its previously disclosed investigations by a number of state attorneys general into Purdue and other opioid manufacturers.

In another example, in July of 2017, one of the country's largest manufacturers of generic oxycodone paid $35 million to settle allegations that it violated provisions of the federal Controlled Substances Act. In particular, the government alleged that the company failed to report suspicious orders for controlled substances made between third-party distributors and downstream pharmacies. So the settlement really underscores the government's current position that manufacturers of controlled substances must use data available to them to understand events occurring down the supply chain.

Al: Colleen, you mentioned the state attorneys general are getting involved in these cases. Is that becoming a more common occurrence?

Colleen: Yes, you know they really are quite active in this space. We've recently seen, in fact, an announcement of a coalition of 41 state AGs that are working together to investigate some of the big opioid manufacturers. This coalition was announced in July of 2017 and in September, they publicly disclosed that they served document requests and subpoenas on pharma companies like Endo International, Janssen Pharmaceuticals and Allergan. So it appears likely that we're going to see a continuation of state and federal authorities investigating opioid manufacturers and distributors.

False Claims Act – General Enforcement

Al: Let's turn now to the False Claims Act, which has traditionally been at the heart of DOJ's health care enforcement efforts. Have things dropped off or changed at all since the start of the Trump Administration from your perspective?

Colleen: Yes, Al. I think the top-line takeaway really is that we're still seeing robust enforcement action in this space. When we spoke back in May, I gave my opinion that we had not seen a drop off at that point and that carried through for the rest of 2017. In fact, we've seen a couple of U.S. Attorney's Offices really pounding the table a bit in this space. For example, in announcing the $7.5 million settlement with Pine Creek Medical Center, which is a physician-owned hospital in Dallas, there are allegations that it was paying for advertisements on behalf of physicians to induce referrals. The U.S. Attorney for the Northern District of Texas, Erin Nealy Cox, went out of her way to note that her office, in partnership with HHS and Main Justice would continue to aggressively pursue the Anti-Kickback Statute violations. And in some respect, this continued focus on healthcare enforcement is unsurprising, right? These cases bring in a ton of money for DOJ. In fact, DOJ obtained more than $3.7 billion in settlements and judgments from the False Claims Act during fiscal year 2017. And $2.4 billion came from some corners of the health care industry. And then $900 million of that came from drug and medical device companies. So this is a big winner for DOJ and other government entities.

False Claims Act – Patient Support Services / White Coat Marketing

Al: So let's drill down to some of the specifics. What sort of cases are you seeing cropping up under the Trump Administration?

Colleen: So one area that's really interesting and is getting increasing focus from the government in what we call the "white coat marketing" cases. Broadly defined, those refer to matters arising from patient support services that are provided by the manufacturers of pharmaceuticals. In essence, drug companies often offer doctors nursing and other administrative services to assist their patients who are prescribed the manufacturers' drugs. So one example is where a nurse may go in and assist a patient in administering the drug — particularly if it's an injection that required a nurse's skills — or they may host informational sessions for patients on how to manage and treat certain chronic

diseases. Another example of this kind of service is where manufacturers contract with third party service providers to assist patients in determining whether their insurance covers a particular type of treatment and then helps the patient determine how they may obtain financial assistance to afford certain drugs. DOJ has recently brought a number of cases against both manufacturers and third-party providers, alleging the provision of these services is in effect an illegal kickback that's provided in order to induce physicians to prescribe certain drugs.

Al: Now these "white coat marketing" cases do not sound like traditional kickback cases that we have seen in the past from the FCA. What's the theory of liability that the DOJ is relying on here?

Colleen: Yes, they are looking at a novel approach to liability under the FCA. The theory basically is that by providing these "white coat" services, drug manufacturers have "assumed and underwritten" is the phrase the government uses, the prescribers' administrative responsibilities and costs that are otherwise associated with starting a patient on a drug. So per the government's theory, when these costs are outsourced to a third party paid for by a drug manufacturer, the doctors then see a decline in administrative costs and then are freed up to see more patients and subsequently generate more revenue throughout the day. The government contends that manufacturers provide these valuable services as an inducement to push practitioners to prescribe more of a certain product.

Al: And these cases have gotten increased traction under the Trump Administration? Is that what you are saying?

Colleen: You know Al, it's hard to say. I would assume so but the challenge we have is that the *qui tam* suits remain under seal for a significant period of time. But that said, we know that a few cases in this area were recently unsealed and the dates on those indicate they were filed in mid-2017. So at least a handful of these cases are FCA theories that the DOJ has pursued entirely under the Trump Administration. Among these cases are matters under Eli Lily and Bayer, as well as major service providers like Amerisource, Bergen, Lash and United Biosource. So it's a really interesting area of the law to review. We've got our eye on it, looking forward.

Al: And what about the effect on the industry writ large? How does this effect industry practices from your perspective?

Colleen: Time will tell but I think industries, or at least manufacturers, are looking at these arrangements because they are so common throughout the industry, right? So on one hand, it would not be a surprise to see more cases of this type unsealed in the coming months. But secondly, depending on how these cases proceed, there may well be a shift within the industry away from these types of arrangements because they generate so much regulatory scrutiny.

Al: Now aside from these "white coat marketing" cases, are there any other increased areas of False Claims Act enforcement that you have seen under the Trump Administration?

Colleen: Yes, we've seen a lot of action in the patient assistance arena. That is where the manufacturers make donations to these 501(c)(3) charities to provide financial assistance to patients, many of whom are on Medicare and cannot afford their copays or coinsurance. This is especially true when Medicare patients are taking brand name medications on the specialty tier. So the government has been using subpoenas and collecting settlements under the theory that manufacturers who are significant donors to these co-pay assistance foundations have sought to influence these foundations to promote the manufacturer's own drugs.

Al: How does the government allege that the manufacturer is influencing co-pay assistance to promote the manufacturer's own products using these charities?

Colleen: So it's interesting - the foundations typically allow donors to earmark their donations for a particular disease state, so there will be a fund that might treat something like Rheumatoid Arthritis or Renal Cell Carcinoma. They are meant to be broad enough to cover a wide variety of products, so just not that manufacturer's products, other companies' as well; however, the government is arguing that the manufacturers are pressuring co-pay

assistance foundations to limit the scope of the disease fund to include only that manufacturer's products. For instance, by limiting the disease fund to particular symptoms of a disease or method of drug administration. In this way, the government has alleged that a drug manufacturer can channel funds to Medicare patients through patient assistance charities, which is something the manufacturers couldn't do directly.

General Enforcement Trends

Al: So if we take a step back, it seems like these enforcement actions, particularly in the False Claims space, are expanding to go beyond the traditional type of case to include novel theories. Is that your sense?

Colleen: That's absolutely right. And if you think of it Al, it makes sense. The big players in health care and pharmaceutical companies, they by this time have robust compliance programs designed to catch the obvious kickback or off-label promotion type of activity. So relators and the government have to get a little more nuanced and look at more complicated relationships within the health care industry, like the "white coat" services. And even in the opioid space, many of these enforcement actions arise from increased scrutiny and relationships within the supply chains, which is really unprecedented in many ways.

Al: So as these actions continue to evolve, looking forward, do you expect any changes in DOJ enforcement policies under the FCA?

Colleen: It's interesting, Al, and the short answer is maybe. So in October of last year DOJ's Civil Fraud Director indicated that DOJ would more aggressively seek dismissal of clearly meritless *qui tam* suits. That kind of initiative would really be a departure from DOJ's historical practice of rarely moving to dismiss *qui tam* suits on its own motion. But, DOJ later walked back its prior statements on this and indicated that the Department has no plans to move to dismiss more relators' complaints. So you know we're all trying to read the tea leaves on this and we cling to every little DOJ rumbling. But there is a cost to DOJ to monitoring the *qui tam* suits, even those in which the Department doesn't intervene and I would look for DOJ to focus on that. If you look at it, less than 1% of the DOJ's total FCA recoveries came from these non-intervened cases and there is a cost for the government to monitoring, so stay tuned on that front.

Cybersecurity Enforcement and Medical Devices

Al: Thanks, Colleen. That concludes our discussion, but we have received some questions from our listening audience so we want to turn to those now. Greg, I want to give you this question, which we got from one of our listeners: "What agency will be leading any effort, if at all, regarding IT security concerns related to both direct and indirect hacking into medical devices? Would it be the FDA, DOJ or both? For example, sometimes ransomware is introduced into a program such as a Microsoft product and makes its way into the medical device stream. Another more direct risk is hacking, seeking ransomware in order to permit the device to function. What's your sense of the enforcement in this emerging area?"

Greg: Certainly, there is a role for the FDA with respect to the device itself and sort of the robustness of the security of the medical device. Since around 2013 the FDA has been pretty active on this issue. They put out draft guidance that year dealing with pre-market submission, so when you submit a 510(k) or PMA, you have to describe the cybersecurity controls you have for that device and the design of the device. I know from dealing with clients, they have gotten a number of questions back from the FDA on cybersecurity issues. They finalized that I believe in 2014 and at the very end of 2016, the agency came out with guidance in the post-market setting, dealing with cybersecurity medical devices already on the market. They had a number of recommendations there. There are a number of other agencies involved, the Department of Homeland Security is involved and the National Institutes of Standards and Technology is involved. The FDA has recommended that manufacturers follow a NIST framework for designing a device with cybersecurity controls. And in that post-market guidance, which I find extremely hard to follow to be honest, it's very complex, they provide recommendations for not only how to monitor the surveillance

for and react to cybersecurity threats or breaches, but also when these things have to be reported to the FDA and that's the piece that I find is a little bit hard to follow. But one of the elements of that is they encourage manufacturers to participate in these entities and be an active participant in an ISAO, an Information Sharing Analysis Organization, which are entities out there that share information among various players about cyber threats and so forth. The FDA has tried to do some things, but I think it is still the early days on this as you mentioned Al. I would not say the FDA is the only player here with respect to devices, but obviously they have a key role and they have put out quite a bit of guidance.

Prescription Drug Prices

Al: Thanks, Greg. I think we have time for one more question that has come in, which I will direct to Tom. In his testimony, Secretary designate Alex Azar said something about controlling drug prices for Medicare Part B the way it works under Medicare Part D. Can you provide some insight into how this would work if it comes to pass?

Tom: Yeah, I read that also and I'm a little perplexed. Part D is administered by private insurance companies and they negotiate a tiered drug formulary with manufacturers. They often use a pharmacy benefit manager to do that. Part B however doesn't have a formulary, it doesn't have any negotiation. The Medicare Administrative contractors just process claims for any drug administered in the physician office or a hospital out-patient department. But I was thinking maybe he's saying that CMS could avoid the prohibition in the Affordable Care Act on Medicare doing price negotiation by allowing the MACs, the Medicare Administrative contractors, to contract with pharmacy benefit managers and let the PBMs do the negotiating as they do under Part D. I'm not sure if that would be in the agency's discretion, and it likely would face litigation from the pharma industry but it's certainly something that Congress could do that might be perceived as a compromise.

Al: Thank you, Tom. I think our time is up so I want to thank everyone for joining us today and sending in your questions. I want to thank our Ropes & Gray partners, Tom Bulleit, Kellie Combs, Colleen Conry and Greg Levine. As I mentioned at the outset, we are offering CLE credit for this teleconference. For those seeking CLE credit, you will need to fill out the attorney affirmation form that was included at the bottom of the registration confirmation email you received yesterday. The CLE course code for this program is 3397, again that is 3397. Please submit the completed form to CLE.team@ropesgray.com within 48 hours. We will continue to provide additional news and analysis about regulatory enforcement issues emerging from the federal government throughout 2018. You can access that information by visiting our Capital Insights page at www.ropesgray.com. Once again, thank you all for your participation and attention.