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Outlook 2019 Teleconference: Washington, D.C. Updates and Insights on Life Sciences and Health Care

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Al: Hello and thank you for joining our teleconference this afternoon. I am Al Cacozza, a partner in the Washington D.C. office of Ropes & Gray and a member of the firm's life sciences practice group. This teleconference is part of our ongoing Capital Insights series where we are capturing our latest thinking on developments from the federal government that might affect our clients — in this case regulatory and compliance issues in 2019 of particular interest to life sciences and health care companies.

Our Capital Insights page at www.ropesgray.com, includes alerts, analyses and podcasts, and we invite you to continue to visit that page throughout 2019.

Joining me again today are several of my colleagues from the D.C. office: Tom Bulleit from our health care practice group; Kellie Combs, Greg Levine and Beth Weinman from the life sciences practice group; and Colleen Conry, with our litigation and enforcement practice group. Welcome back everyone and welcome to Beth who recently joined our firm from the FDA Office of Chief Counsel.

Over the next hour, we will look to give you insights into critical developments we see emerging in 2019. But at the outset we cannot ignore the key current issue — the government shutdown now over one month old. Suffice it to say it is an unprecedented, unpredictable and dynamic situation. And, by the way, anyone who tells you they know when the shutdown will end does not truly know when the shutdown will end.

First, much of HHS, including CMS and NIH are not shut down because the HHS appropriations bill was enacted earlier in 2018. But FDA, even though it is part of HHS, for historical reasons gets its funding through the Agriculture appropriations bill and that bill was not enacted in time. From an FDA perspective, the agency is not allowed to spend "appropriated funds" during the shutdown, but user fees are not considered "appropriated funds" so the agency can spend the user fees collected prior to the shutdown to run certain operations. Reports indicate that 2018 reserve user fees, at least from the PDUFA program, will run out sometime in early to mid-February. In addition, FDA is not allowed to collect any user fees during the shutdown and therefore cannot accept any applications that require a user fee. Commissioner Gottlieb has been juggling his available resources to target essential activities deemed to "address imminent threats to the safety of human life," but it's unclear how long his current resources will last. Even in those essential situations, employees who are called back to work are working without pay. Finally, once the shutdown ends there likely will be a rush of applications filed that could create a backlog that FDA will have to work through in 2019.

Let's turn from the shutdown to today's conversation that 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, of course, some element of educated speculation. As you can all appreciate, however, given the results of the 2018 mid-term elections and what appears to be the early start of the 2020 Presidential campaign, it is unclear what, if anything, will be accomplished legislatively this year, although there still may be room for executive action.

We plan to save time at the end of the teleconference 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.

What's New in Health Care 2019?

Al: So, let's now begin with Tom Bulleit from our health care practice group. Tom, you spent 2017 watching very closely the efforts of Congress and the Trump Administration to "repeal and replace" the Obama Administration's signature domestic achievement, the "Affordable Care Act" or "Obamacare." You even wrote a monthly column for

Bloomberg BNA on this subject. I suppose everyone knows that the Congress failed to repeal the ACA that year. Were there important ACA developments in 2018 that continue to be of interest to health care stakeholders in 2019?

Tom: Thanks, Al. The only legislative accomplishment on Obamacare was the tax cut bill passed in December 2017, which, for ACA purposes, reduced the tax penalty for failure to have Obamacare-compliant health insurance to $0.00, starting this year. That led to a lawsuit by some state attorneys general to have the entire ACA declared unconstitutional, because, the theory goes, with the tax removed, the individual mandate can no longer stand as an exercise of Congress's taxing powers, and the individual mandate is so essential to the rest of the ACA that the entire act has to fall. A Texas U.S. district judge agreed with that, but has stayed his decision pending appeal. The issue will certainly end up in the Supreme Court, but the ACA will continue at least for this year. It's worth noting that if the ACA were to fall, it would strike down not just the law's insurance reforms and Medicaid expansion, but a variety of programs that were enacted as part of the ACA, including the pathway for FDA approval of biosimilars and the Center for Medicare and Medicaid Innovation (CMMI) that has launched many of the federal value-based health care initiatives, such as the Medicare Shared Savings Program for accountable care organizations and the Bundled Payments for Care Improvement initiative.

Obamacare signups in the 39 states using the federal healthcare.gov platform were down this year by about 4%. We still don't have all the data on state sign-ups but it looks like there will still be about 10 million who are signed-up through the exchange and another 17 million through the expansion of Medicaid. One of the things that the Trump administration has done that could be significant is to expand the availability of non-Obamacare compliant plans by promulgating final regulations allowing short term plans, which can now last for a year and be renewed, and association health plans, which would allow unrelated entities in the same area of business to be treated as a single employer. CMS has also recently suggested that states may be able to obtain ACA waivers allowing them to make subsidy dollars available to individuals buying one of these non-ACA compliant plans. The result is, as I and a lot of others predicted last year, fewer people will have comprehensive insurance, putting more pressure on hospitals and other providers to deal with the uninsured. But so far the effects have been marginal.

Value-Based Health Care

Al: Thank you Tom. Let's turn to another topic - value-based health care. Since the arrival of new HHS secretary Alex Azar, has there been more favorable movement in the area of value-based health care than under prior Secretary Tom Price? Will you remind us what value-based health care means, and catch us up on what's happening on that topic?

Tom: Well, value-based health care means paying for quality outcomes rather than quantity of procedures. Both HHS and the private sector have been pursuing this agenda since Secretary Price's departure and Secretary Azar's arrival. A significant event demonstrating the government's position on this is an OIG advisory opinion from September that allowed a medical device seller to offer a warranty equal to the aggregate purchase price of all three products in the product suite that wouldn't have been protected by the warranty safe harbor to the anti-kickback law, and in doing that said some favorable things about manufacturer guarantees like that.

In 2018, OIG also put out three notable requests for information, soliciting public comment on ways to reduce impediments to value-based care under the Anti-Kickback Statute, the Stark Law, and HIPAA. Many groups including PhRMA and AdvaMed submitted comments. The noise we are hearing is that HHS is favorably inclined towards doing something to make it easier for drug and device makers to stand behind their products' performance, though as of now there have been no new regulations.

CMS has rolled out a new Bundled Payments for Care Improvement Advanced (BPCI Advanced) initiative. This one is an improvement, or at least a change, from the prior program. The biggest change is that for BPCI Advanced, participants will now have to share downside risk in order to participate.

Probably the biggest value-based change also feeds into the next area of I think of as important: prescription drug pricing. We have seen drugmakers and payors explore innovative ways to pay for expensive specialty drugs. There is Bluebird Bio's proposed five-year installment plan, where the payor would make annual payments contingent on the drug's effectiveness; and Louisiana's proposal to enter into a "Netflix" model arrangement with a hepatitis C drugmaker where the state would pay an annual subscription fee for unlimited access to the drug.

Maybe the most surprising development in 2018 came from CMS, which has proposed a mandatory demonstration project for half of Medicare Part B that would use international reference pricing as the basis for payment for drugs administered in physician offices. The current system virtually guarantees doctors a markup on drugs they purchase and administer under a statutory formula. In the new system, if this goes through, beginning in spring 2020, doctors would no longer buy and bill. Intermediaries would bid to become contractors to buy the drug to be supplied to doctor offices and would be paid at the international reference pricing rate. By the way, we maintain a website on value-based health care at ropesgray.com with a number of the resources on this area that listeners can access.

Prescription Drug Pricing

Al: Thank you, Tom. You have now set up the next area of questions, which is around prescription drug pricing. You know, in the many years I have been practicing law here in D.C., I have never seen so much attention by policymakers across the spectrum, to the subject of prescription drug pricing. As you may remember, candidate Trump accused drug companies of getting away with murder. He has continued that rhetoric, but in 2018 he really turned up the heat. His administration issued a Blueprint in the spring of 2018 that addressed several areas where the administration intended to take steps to reduce the amount that payers and patients have to pay for drugs. Can you catch us up on those developments, Tom?

Tom: Yes, my experience is the same as yours. It has been a remarkable year for rhetoric on prescription drug prices, but apart from the Medicare Part B demonstration that I mentioned, which is still just proposed, little real action at the federal level. Some of the federal initiatives that are unlikely, I think, to have more than a marginal impact on drug pricing include:

- Proposing that manufacturers disclose a drug's list price in television ads;
- Allowing step therapy for Part B drugs covered by Medicare Advantage plans;
- Proposing that Part D plans can exclude certain protected class drugs from their formularies;
- Convening a working group to study drug importation;

And signing legislation to ban "gag clauses" on pharmacists, which in theory would have prevented pharmacists from advising patients of lower cost products.

A number of states have also enacted price transparency laws aimed at requiring drugmakers to disclose their prices and price increases and a whole bunch of states whose legislative sessions have just started have already introduced new bills that would begin to regulate drug pricing transparency and, in some cases, would attempt to regulate drug price increases.

Lastly, the 340B Drug Discount Program continues to be a source of dispute. Providers and drugmakers each have long accused the other of failing to live up to the program's purposes. More recently, the Trump administration has sought to reduce 340B reimbursement to providers by nearly 30%, but a federal court recently enjoined the cuts. It will be interesting to see what 2019 has in store for the long-running controversy around that program.

Medical Devices

Al: Thank you, Tom, for that detailed discussion of various pricing and value-based issues. Let's turn now to FDA. Kellie Combs, Greg Levine and Beth Weinman will address these issues. Greg, let's start with you. I know you spend a lot of time on FDA device matters so let's focus on that sector. Yesterday, for example, FDA published on its website (rather than the Federal Register, which is affected by the shutdown) final guidance on a new "Safety and Performance Based Pathway" for 510(k) devices and also issued a Request for Comments on a proposal to publish a list of devices that were 510(k)-cleared based on comparisons to "older" predicate devices. What is the urgency on these issues and what are their prospects for success in 2019?

Greg: Yes, thanks Al. I was interested in the face of that guidance. When FDA published it, they included a note that explicitly says that they did not put a notice in the Federal Register because of the shutdown, and the reason is because they are required, by their good guidance practice regulations, to publish a notice of availability of the guidance in the Federal Register and on their website at the same time. So, they are explicitly acknowledging that they are not following their rules - but they can't. They will publish that notice on the Federal Register presumably as soon as they are able to do so. But, I think the reason that FDA wanted to push this out anyways is because of the context of what has been going on with devices and, in particular, this broader trend that we saw through much of 2018 where FDA leadership in the device center, and Commissioner Gottlieb himself, has increasingly emphasized device safety, both pre-market and post-market with devices.

On the pre-market side, for around a decade the primary focus both at FDA and in Congress has been improving the timeliness and consistency of the FDA review process and, in particular, the 510(k) process where most device pre-market reviews happen. And there has been a lot of criticism and, I think, a pretty widely held view starting from 2009 when a lot of these issues started being looked at seriously, that there was a lack of consistency in device reviews, that device reviews often focused on irrelevant questions and that many reviews were overly burdensome. This caused the delayed introduction of devices to the U.S. market, making the U.S. market increasingly unattractive for device innovation and investment. But in 2018 it seems that the pendulum began swinging pretty hard the other way, both in the U.S. and in Europe as well. A couple of events I think may have precipitated that, first in the spring and then again in November.

First, there was a Netflix documentary and then a series of print, TV and internet news stories that broke both in the U.S. and in Europe. These focused on cases in which marketed devices were allegedly associated with adverse reactions. Many of those devices involved women's health, such as gynecological devices and contraceptive implants. These really weren't new stories. Some were frankly pretty old. For example, there were stories about metal-on-metal hips, which have been known for years. Some of these devices have even been off the market for years. But, I think a lot of the reaction has to do with the manner in which these stories (like the Netflix documentary) were publicized – there was a particular focus on regulators. They had interviews with people like former FDA Commissioner, David Kessler, who spoke out about alleged deficiencies in the regulatory process for medical devices. This was somewhat novel and seemed to have captured the attention of FDA and regulators overseas as well.

Another significant development on this side of the pond, happened in November 2018 when the Democrats took over the House of Representatives in Congress. I think we can expect to see heightened oversight of the executive branch of government and there is no reason to think that FDA is going to be an exception to that. In this environment it is not surprising to see FDA emphasizing a commitment to device safety while, at the same time, continuing to work on its efforts to improve the efficiency of the device review process. Many of the efforts that FDA has underway and in process in the area of efficiency are happening because it has been mandated by Congress under a series of laws such as the 21st Century Cures Act enacted in 2016 and the medical device user fee reauthorization law that was part of the FDARA, which was enacted in 2017. So FDA had many initiatives in process that they have to continue to work on to improve and speed-up the device review process.

We are also seeing increased efforts by FDA to focus on device safety. There were a number of examples of this throughout the year. In April, just a few days before that Netflix documentary came out, FDA published a medical device safety action plan that had a number of elements to it. It talked about working with the National Evaluation System for Health Technology (NEST) to enhance active surveillance and signal detection by using electronic health records and systems and Unique Device Identification (UDI) on device labelling to try to associate adverse reactions with devices in the real world. There is also the potential ability of FDA to streamline the imposition of closed-market device safety mitigation when adverse reactions are observed in devices, without having to go through notice and comment rule-making. And then potentially spurring innovation towards safer medical devices by adopting an expanded version of the Abbreviated 510(k) program to increase the use of consensus standards for bringing new devices to market, rather than comparing new devices to older predicate devices.

I mentioned that in April there was this series of news articles and TV programs that ran both in the U.S. and in Europe. That month, a few days before those started running, FDA came out with an update to its Medical Device Safety Action Plan. Here, FDA announced an ambitious new goal for device safety. The goal is to ensure that FDA is consistently first among the world's regulatory agencies to identify and act upon safety signals related to medical devices. FDA again emphasized that it is going to try to use active surveillance techniques. It mentioned its budget request to the administration for that program and some other efforts it has underway, with a particular emphasis on women's health and some other kinds of devices which were included in these publicized stories.

Then in November, FDA came out with an announcement that it wanted to modernize the 510(k) pathway with a particular emphasis on movement toward more modern predicate devices. FDA said that the most impactful way they can promote innovation and improve safety in the 510(k) program is to drive innovators towards reliance on more modern predicate devices or objective performance criteria. To promote the use of more recent predicates, FDA would consider publishing a list of cleared devices, or marketed devices, that have demonstrated substantial equivalence, or gone through the 510(k) process, by comparing them to predicate devices that were more than ten years old. I'll skip over the details of that, but suffice it to say this was extremely controversial when it was announced. In fact, the very next day the FDA Commissioner felt the need to release another press statement of his own, justifying why he felt this was important and talking further about why older predicates might not reflect the newest performance standards and might not have the latest features related to cybersecurity, biocompatibility, etc.

In regards to the announcement published yesterday, there were two main items that came out of this. The first was the Safety and Performance Based Pathway, which is the new name that FDA gave to that expanded Abbreviated 510(k) program they had announced months before. As a final guidance, instead of comparing your device to a predicate device, or an older device, you would instead compare your device to a set of performance criteria that would be identified by FDA. FDA, in theory, is going to have to, on a device type by device type basis, issue guidance documents that identify a set of objective performance criteria that would be reflective of devices currently on the market. Instead of comparing your device to a particular device on the market, you would show that your device meets these objective criteria to get your device on the market. Clearly, FDA thinks this is a better way to go. One among many criticisms of this program is that this is a very burdensome process. How do you come up with these performance criteria? Is it really going to happen? Is it realistic? So there are a lot of questions about that. But that is now final guidance, although it didn't really follow FDAs good guidance practices.

The other thing that FDA came out with yesterday was a call for comments on this idea of publishing a list of older predicates. I do not see any alternative, but to see this as naming and shaming. The concept is, FDA is going to come out with a list of devices that are on the market based on a comparison to predicates that are more than ten years old. FDA says they are not saying that every device that is more than ten years old is necessarily bad. There may be devices that are older that do not need innovation and do not need to be newer. They are old, established technologies that are perfectly fine. But, they have come out with a series of four questions about whether this is a good idea or not, and, if not ten years, then what should the criteria be? So FDAs website asks for comments by April 22. But, according to the

attached instructions, it says you *must* comment by April 22. So it is a little unclear whether that has any binding force, given that it is not actually in the Federal Register. So, that is where that stands.

Digital Health and the Pre-Certification Pilot Program

Al: Thanks, Greg. It sounds like 2019 is going to be a very busy year in the device sector. Can you give us a high-level review on another device topic that has come up - the rapidly-developing field of "digital health" and in particular the progress FDA has made on its "pre-certification" pilot program that was initiated in 2017. A number of Democratic Senators raised questions about FDA's legal authority to even implement a pre-certification program. Can you give us a high-level overview of what the latest thinking is on that area?

Greg: Sure, Al. FDA came out with an announcement earlier this month to say that they are moving from the first stage of the pre-certification pilot program. They started the pilot program in 2017 with nine companies designated to look at this idea of "pre-certification", which was undefined. The idea is that FDA is going to pre-certify certain companies and create excellence criteria that, if met, asserts these companies are excellent at developing software as a medical device. This program is limited to software that itself serves as a medical device. Companies in this program are going have streamlined benefits and there is going to be some streamlining of the regulatory process for that kind of software. But, what that streamlined process would be and what the criteria would be was unclear. So these nine companies were helping develop the program in its entirety to bring some clarity and come up with a working model. This was the "development phase".

Now they are moving from that phase into the "testing phase". The companies developed a testing plan and this year, in 2019, they are going to start testing how this program might actually work. They actually came out with three documents: one is a testing plan, the other is an update of the model to walk through what it would contain, and the last, very interestingly, is a regulatory framework for conducting the pilot program within current authorities. This is clearly a response to the concerns and criticisms raised about whether FDA has legal authority to do pre-certifications. And essentially what it says is that, for now, the only things FDA will do will fall within their current legal authority and will be done under the De Novo Program. It is still the nine companies in the pilot program and they can do De Novo device submissions for software. Then FDA is going to do a comparison – they are trying to come up with a streamlined form of De Novo submission. Their test is going to be a hypothetical pre-sub De Novo versus a traditional De Novo. But the devices that come to the market under the program in the real world are going to have to go through the traditional method. So companies do not actually get a break if they are in this pilot testing program. This year, in 2019, there is a focus on testing to see what the program benefits are and also showing and validating that having a streamlined submission process actually provides the same level of safety and effectiveness and assurance to public health as the traditional process. They are going to do some other testing as well, like how to establish the Excellence Appraisal and whether it is a good process. So, 2019 is going to be another year of testing under this pilot program.

Biosimilars

Al: As I said, it sounds like 2019 is going to be a very busy year in the device sector. Thanks for that thorough discussion, Greg. I'm now going to turn it over to Kellie Combs so we talk about drugs and biologics. And in that area, what about biosimilars Kellie? What's the current landscape for biosimilars? Are there any significant regulatory developments for biosimilars in store for 2019?

Kellie: Yes, absolutely. So, FDA Commissioner Gottlieb has been extremely vocal about his support for biosimilars, and he views a robust biosimilar market as critical to addressing the Trump administration's larger objective of bringing down drug prices, which Tom talked about before. Last summer we saw the release of the agency's biosimilar action plan, which focuses on improving efficiency of biosimilar development and approval, increasing scientific and regulatory clarity for development, ensuring that doctors and patients understand biosimilars and the role they may have to play in treatment, and then finally supporting market competition in general. The agency also released guidance on biosimilar

labeling, guidance and Q&A on development, and guidance and Q&A on the biologics previously regulated as drugs for historical reasons, such as insulin and human growth hormones, that will ultimately transition to regulation as biologics in March of 2020. It was also a banner year for biosimilars approvals. There were seven approvals last year. Now, keep in mind that only nine biosimilars in total had been approved prior to last year, so we are certainly starting to see a major shift here. Additionally, of the seven that were approved last year, four have already launched. That more than doubles the number of biosimilars that are now commercially available in the U.S.

As for what's to come in 2019 based on publicly available information, there are five biosimilar submissions with action dates this year, plus at least one that is going through a second review cycle at FDA. There are also upwards of seventy products enrolled in FDA's biosimilar development program. So again, we are certainly going to see an uptick in the biosimilars market this year.

Aside from additional biosimilar approvals, we are also expecting clarity from FDA on interchangeability, with the agency expected to release final guidance by this May. And FDA Commission Gottlieb has committed to the development of what he refers to as a structured interchangeability application. As you may know, we have yet to actually see an application or approval for an interchangeable biosimilar, and the expectation is that with the guidance and with the new application, that those things will in fact facilitate development. Among other things, the interchangeability final guidance may address whether manufacturers could use foreign versions of reference products in their clinical switching studies that are required for an interchangeability determination. That was one of the controversial topics not addressed in the draft guidance, and that we expect to see some movement on in 2019.

We are also expecting more biosimilar developers to pursue what are called "carve-outs" this year. And that's where the manufacturer would seek approval for some, but not all, of the referenced product's indications, omitting the indications that are protected by market exclusivity or patents. That's quickly becoming a trend as a practical matter, but unlike the Hatch-Waxman framework for drugs where there is a statutory mechanism and a regulatory process for carving out protected indications, there is no such clarity for biosimilar manufacturers. FDA has committed to issuing policy in 2019 so that manufacturers can really understand how the carve-out process works and, perhaps just as important, how the process would work to add those indications back in once patent or exclusivity has expired. Overall, we expect this year to be a really significant one in biosimilar development and approval. And it's likely that the biosimilar landscape will look drastically different when we meet again here next year.

Warning and Untitled Letters

Al: Thank you, Kellie. Let's turn to product communications. We saw a modest uptick in OPDP and APLB warning and untitled letters in 2018. What are the key themes you think will emerge from those letters and what do we know about where FDA might be headed in terms of ad promo regulation?

Kellie: Well, as you know warning and untitled letters issued by OPDP and APLB have sharply declined in recent years. We used to see several dozen letters issued each year. 2018 saw eight in total - seven from the OPDP and one from APLB. But this is up from five total in 2017. I am not planning to discuss the letters in detail today, but there are certainly a few notable developments.

First, the agency continues to focus on minimization or omission of risk and appears to be particularly focused on products with boxed warnings. As a result, it is absolutely critical that manufactures convey risk information appropriately, ensure fair balance and share any material limitations to the indication or use of the drug, especially where the labeling contemplates serious safety issues may result.

Second, FDA continues to be concerned about promotion of investigational drugs and last year called out one manufacturer for alleged inappropriate safety and efficacy claims on a product website and also in an exhibit booth at a

scientific conference. Even with the historical decline in letters that we have seen over recent years, FDA's attention to investigational drugs has never really waned. And accordingly, it is important that any communication about investigational drugs clearly discloses that the product has not been approved. Moreover, while it may be appropriate to share scientific information or data about an investigational product or use, provided that the information is objective and straightforward and presented in a neutral way, it is very important to refrain from any claims or characterizations about that data that would veer towards promotional language. And finally, of course, it is important to refrain from implying that FDA approval is ultimately certain.

Third, the agency, for the first time in many years now, issued an untitled letter that called a company out for off-label promotion. There, a company sales rep had given a presentation that allegedly promoted a drug for an off-label use in young children, including in babies. The product at issue had a boxed warning with very serious risks including homicidal ideation, and it is likely that the vulnerable patient population here, as well as the serious risks, factored into FDA's decision to issue the letter. This letter also serves as a teachable moment because it focused on the oral statements of the sales rep to a physician, so we are aware of many companies that are now using this untitled letter to refresh its sales reps on promotional compliance. In terms of what this all means and what's to come in 2019, we have heard now from a number of FDA and DOJ officials that the government is mindful of First Amendment limitations with respect to regulation of manufacturers' speech, and that rather than focusing on what FDA would refer to as a technical regulatory violation, the government instead is going to be focused on communications that are false or misleading or that otherwise implicate genuine safety concerns. Now, that's not to say that the government is no longer concerned with off-label communications, but the risk is certainly higher where off-label communications pose a real public health threat. We expect that approach to be borne out in the FDA letters again this year.

Advertising and Promotion

Al: Thank you, Kellie. Tom mentioned earlier in the teleconference that CMS had proposed a rule that would require drug manufacturers to include the "list price" in broadcast television advertisements. Can you talk briefly about what the rule would mean for drug manufacturers and how we might see TV ads change in 2019?

Kellie: Sure. As Tom mentioned, CMS proposed a rule in the fall of last year that was framed as an initiative by the government to combat rising drug prices. And, in that proposed rule, CMS would require all drug manufacturers to disclose the list price in direct-to-consumer ads that are broadcast on television. The government's rationale was that, by providing the price, both doctors and patients would have essentially a jumping off point to have a conversation about cost and potentially engage in conversations about price shopping and comparisons to alternative therapies. And, finally, there was a name and shame element here because, for companies that did not comply with CMS' rule, CMS would publish, presumably on a website, the name of all those companies. So the proposed rule, as you may expect, was hugely controversial when it was issued for a few reasons.

Number one, list price is not tethered to the actual out-of-pocket cost that consumers pay. And, in most cases, list price is significantly higher than what consumers actually pay. So the concern from industry and others is that the rule would in fact deter patients from seeking care and filling their prescriptions because they were misled about the potential cost. The result is a concern that the information, just by providing list price alone, would be misleading because there would not be enough context for consumers or doctors to understand how the average price would shake out for consumers and what alternatives could mean in terms of price comparison.

There were also constitutional issues associated with the proposed rule. The First Amendment case law provides that the government can only compel speech, as it is compelled in this case, if the speech itself is factual and uncontroversial. And for the reasons that I have just been describing, many believe that the compelled disclosure of list price does not fit the bill. There are also issues associated with CMS' statutory authority to promulgate the rule. Interestingly enough, very shortly before CMS proposed the rule, PhRMA had issued or updated its voluntary principles for direct to consumer

communications. In the PhRMA principles, members voluntarily agree now, that in all DTC branded communications on TV that they will direct patients where to find additional information about the cost of the medicine. And that additional information, which presumably would be on a product or company website, would provide the list price just like in the proposed rule, but would also provide information on the average, estimated or typical cost for patients as well as other context about potential costs of medication. So, PhRMA and its members have voluntarily agreed to provide more information than what CMS would require, but the idea is that this additional context, because it doesn't all have to be included in the body of the television advertisement itself, would actually help consumers and doctors make more educated decisions without deterring patients from seeking care.

FDCA Enforcement

Al: Thanks very much for those insights, Kellie. For the remainder of the teleconference we're going focus on enforcement. So let's turn first to Beth Weinman who will be talking to us about FDA enforcement. Beth, where do you think FDA and DOJ will focus their Food, Drug, and Cosmetic Act enforcement resources and attention in 2019?

Beth: Sure. Well, in some ways that's an easy question because we heard directly from FDA and DOJ leadership back in December at the FDLI Annual Enforcement Conference. There, the Commissioner, FDA's Chief Counsel, Stacy Cline Amin, and DOJ's Deputy Assistant Attorney General for the Consumer Protection Branch, James Burnham, laid out their enforcement priorities. As some of you on the line may know, DOJ's Consumer Protection Branch is the part of Main Justice that has jurisdiction to enforce the Federal Food, Drug and Cosmetic Act both civilly, through seizures and injunctions, and criminally. At that conference the Chief Counsel suggested that FDA's focus in the coming year would be somewhat wide ranging, focusing on tobacco sales to youth (particularly vaping), opioids, compounding, food safety and high risk devices - primarily she spoke about duodenoscopes. The Commissioner added rogue stem cell outfits and bad actors in the dietary supplement space to that list. And James Burnham focused on, among other areas, opioids, compounding and general cGMP enforcement as priorities.

I'm going to talk about what seems to be the intense focus on manufacturing processes I think we'll be seeing in the coming year, both for compounders who are very much in the spotlight and for traditional drug, device and biologic manufacturers. As some are likely aware, compounded drugs are not FDA approved. They are not subject to pre-market review for safety or effectiveness. And, for a very long time, most compounders were not inspected by FDA unless something bad happened. And then, something very bad did happen. The fungal meningitis outbreak in September 2012 that sickened hundreds and killed more than seventy patients was tied to contaminated steroid injections that were produced at the New England Compounding Center. The country learned about entities that were compounding on a massive scale with little to no federal oversight, and were shipping products all over the country thus multiplying the risk of harm from poor manufacturing practices. And a lot changed after this outbreak. The Drug Quality and Security Act (DQSA) was enacted in 2014. The Act clarified what entities would be treated as traditional state-regulated 503A compounding pharmacies and the Act created a new category of facilities referred to as 503B outsourcing facilities. These outsourcing facilities are entities that compound or repackage drugs, but not pursuant to patient-specific prescriptions, and typically on a much larger scale than a mom and pop pharmacy. Since the enactment of the DQSA, these 503B outsourcers, like traditional manufacturers, are required to register with FDA and comply with cGMP requirements. And they are now subject to FDA inspection.

I'll note that in 2015, FDA issued 176 drug-related warning letters. Eighty-eight of those addressed manufacturing practices and nearly one fifth of those eighty-eight targeted compounding pharmacies or outsourcing facilities. In addition, in 2018, the government brought two civil injunction actions resulting in consent decrees against outsourcing facilities. Those were Delta Pharma and Cantrell Drug Company. Both of those outsourcing facilities were processing and manufacturing sterile injectables in violation, allegedly, of cGMPs, and according to the publicly available documents, under unsanitary conditions. Expect to see more on this front in the coming year.

In addition, we saw in 2018 the AmerisourceBergen criminal and civil settlement. I won't talk a lot about them except to say that, though this involved pre-DQSA conduct, the case involved the manufacturing of sterile injectables and cancer support drugs that were being repackaged in an unregistered facility and under conditions that publicly available documents suggested were insanitary. The repackaging facility called itself a pharmacy, but FDA thought differently and the charging documents charged the firm as the manufacturer. So while sterile injectables are front and center, James Burnham made it very clear that DOJ will also be looking to take enforcement action against all entities where manufacturing practices may have the potential to cause serious harm. So I think traditional drug, device and biologics manufacturers are also very much on the government's radar. Though I'll note on the device side that of the twenty-six device-related warning letters that went out in 2018, twenty of them dealt with CGMP violations.

Al: Thank you, Beth. In addition to those trends, are there any specific legal cases that implicate the Food, Drug, and Cosmetics Act that we should be keeping our eye on in 2019?

Beth: Sure, but before I do that, I want to note a couple other priorities that I didn't get to. I'll do that very quickly. DOJ focus is also on fraud, they said that they are looking at practices that will hurt people. I think that covers the cGMP practices, but also I think the fraud component covers data integrity issues, so I want to make sure to mention that. And also attempts to evade FDA scrutiny. And I think Kellie talked a lot about marketing practices in the administrative context. James Burnham spoke in December about marketing practices cases very directly, along the same lines as Kellie mentioned. He noted the First Amendment problems with truthful speech, but he did say that DOJ will be focusing on false and misleading speech, specifically in cases where there is significant public risk. So I think, like in the warning letter context, we will likely see on the drug side boxed warning cases and REMS cases where there is a minimization of risk or an ignoring of the REMS requirements. On the device side, I think risk and patient injury will be the driving force, both in the enforcement and the marketing practices side, and otherwise.

And, I just want to take a moment before we get to the cases to watch, to mention the rogue stem cell outfits that the Commissioner alluded to. We have seen a number of warning letters and two injunction actions filed against those entities in 2008, and the Commissioner promised a lot more activity on that front in the coming year.

So, if we want to talk about cases to watch, I would keep my eye on the stem cell injunction cases. I think these cases are fascinating. They are very similar, so I will just focus on one of them. And that is the injunction cased filed against the U.S. Stem Cell Clinic, Inc. out of Florida. The other case is the California Stem Cell Treatment Center, Inc. out of California. These cases are in some ways almost identical. The U.S. Stem Cell Clinic case involves the marketing of unapproved stem cell treatments for a wide variety of serious diseases, including Parkinson's, ALS, COPD and others. There has been a lot of press attention to this particular clinic after eye injections for macular degeneration led to a few patients becoming blind. After that, the clinic stopped doing those injections so they don't seem to be part of the injunction case, which is forward looking. But this firm did receive a warning letter arising out of an FDA inspection that found that the clinic was taking adipose tissue, which is fat, from patients through a mini-liposuction procedure and processing that into what is called stromal vascular fraction (SVF), which is a cellular product derived from the adipose tissue. Then the clinic would administer that product back into the patients via IV or directly into the spinal cord. The inspection found that the processing of these injectable products was not being done in a cGMP compliant sterile facility. So, the injunction complaint rests on the theory that the clinic is adulterating and misbranding drug products while held for sale. Adulteration rests on the lack of cGMP compliance. The misbranding theory rests on the drug's lack of adequate directions for use - they are unapproved new drugs so they de facto lack adequate directions for use. And the complaint hinges on the position that these products can, in fact, be regulated as drugs. Of course, the defense argument is going to be, no - these products are exempt from drug regulations. They are Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) subject only to statutory and regulatory provisions whose sole mandate is to control the communicable disease risk of these products. So in the clinic's view, FDA has no jurisdiction to regulate the products like drugs and at issue in the cases will be the regulatory exemptions in Part 1271 of the CFR. We saw a case similar case to this a few years ago, the Regenerative Sciences case. I think this case will deal with additional exemptions. The

authority to go after these clinics is very high priority for the Agency, and I expect we will see very motivated defendants arguing that this case reflects significant FDA overreach.

Al: Thanks very much, Beth. That's very interesting and we will keep an eye on those cases and those trends going forward. Now let's take a broader lens on enforcement. I want to turn it over to Colleen Conry to provide her enforcement insights related specifically to the general topic of fraud and abuse as well as opioids. Colleen what trends have you seen in this area in 2018 and where do you think the priorities will be, particularly for DOJ, in 2019?

Opioids

Colleen: Thanks, Al. So let me start with opioids first. So like many of its partner federal agencies, DOJ devoted substantial resources to addressing the nation's opioid crisis in 2018. Through both its criminal and civil enforcement actions, DOJ targeted a wide range of entities in the opioid space including drugmakers, suppliers, providers and even distribution networks. So on the criminal side, DOJ has targeted so-called "pill mills", where health professionals allegedly distributed mass amounts of opioids for non-medical purposes. Also, in June, DOJ announced its largest healthcare fraud enforcement action in U.S. history, charging 162 defendants including the 76 physicians responsible for prescribing and distributing more than 13 million illegal dosages of opioids.

On the civil side, DOJ also hit some notable milestones. In August, DOJ obtained the first-ever civil injunctions under the Controlled Substances Act, barring doctors who illegally prescribed opioids from writing prescriptions. DOJ also intervened in FCA lawsuits against a major opioid manufacturer, Insys Therapeutics, which settled for $150 million. The Department had earlier charged seven of the officers at Insys with, among other counts, racketeering and conspiracy to violate the Anti-Kickback Statute. So based on that, opioids surely will remain a top priority for DOJ in the foreseeable future.

Fraud & Abuse

Colleen: So shifting away from opioids briefly, let's look at recent FCA enforcement activity in other areas in the health care and life sciences space. Interestingly, if you look across all FCA activity across all industries, FCA activity actually declined in 2018. It was the lowest it's ever been since 2009. But despite that overall decline, FCA recoveries in the health care and life sciences entities actually increased by more than $300 million from the previous year. And in past years, qui tam actions were the primary vehicle for FCA enforcement, constituting nearly 90% of the new FCA matters in 2018. Consistent with prior years, the government intervened in approximately 20% of those qui tam actions.

So, other notable takeaways from this year is the fact that pharmaceutical and biotech companies were the most common targets of FCA actions. The largest single FCA recovery in 2018 involved a $625 million settlement with one of the nation's largest wholesale drug companies, AmerisourceBergen, for allegations related to illegal repackaging and distribution of cancer drugs. Drugmakers' patient assistance programs also continue to draw DOJ scrutiny, most notably resulting in a $210 million settlement with United Therapeutics at the very end of 2017. Providers, both large and small, were also common defendants. DOJ was particularly focused on cracking down on arrangements that violate the Anti-Kickback statute. And then, finally, managed care remains an area of scrutiny. For example, in the Medicare Advantage context, DOJ secured a $270 million settlement with DaVita for coding misconduct that took place among a physician group that DaVita had acquired in 2012. Litigation in the Medicare Advantage area against UnitedHealth Group also continues. So based on this recent activity, health care and life science companies can expect to continue to be prime targets for FCA lawsuits in 2019.

So just to wrap it up, I want to point to two more interesting issues that we should all be following in 2019. I want to start with the Granston Memo, first. This was issued in 2018 and the memo provided a framework for DOJ to invoke a rarely used FCA provision to seek dismissal of non-intervened qui tam cases that conflict with the government's interest. In November, DOJ first signaled its willingness to seek dismissal in an amicus brief to the Supreme Court. Last month, DOJ

went further and moved to dismiss 11 qui tam actions, rejecting the plaintiffs' novel Anti-Kickback Statute arguments. These developments suggest that DOJ may be more active in seeking similar dismissals in 2019.

And then, finally, I think it is worth noting how courts continue to work through implications of the Supreme Court's landmark Escobar case. In particular, the circuit courts continue to grapple with Escobar's materiality standard, which may soon prompt the Supreme Court to wade back in and provide additional clarity on that front.

Off-Label Promotion and Marketing Cases

Al: That's great. Thanks for that overview, Colleen. We have a few minutes left, and we have a few questions that have come in from our listeners. So I want to use the expertise of the people around the room to help address those questions. First of all, Beth, you talked about a number of specific cases, but are there any cases percolating in the area of off-label promotion or marketing that people should be aware of?

Beth: I guess we can think about the criminal convictions, in July 2016, of Patrick Fabian and William Facteau in connection with their marketing and distribution of a steroid delivery device that, according to the papers, was cleared only for use of a sinus stent that had saline eluting capabilities, but was in fact distributed for unapproved uses. Those defendants were convicted on ten misdemeanor, adulteration and misbranding counts. And at the end of the trial in the summer of July 2016, the defendants moved for a judgement of acquittal or a new trial. That motion was fully briefed in the fall of 2016, but no decision on that motion has yet issued. So, if 2019 is the year that the judge in the District of Massachusetts decides to rule, this would definitely be a case to watch. Both the government and the defendants will have the right to appeal to the First Circuit. This case involves significant First Amendment issues and will also likely involve the Park doctrine.

ACA and the Biosimilars Title

Al: Thanks, Beth. A question has come in for you, Tom, related to the challenge to the whole ACA. Any thoughts on whether the ACA could have been drafted or has been drafted such that the biosimilars title could be severable from the other more focused insurance provisions of the Act?

Tom: Well, I sure would have thought so. I mean it's in a different title of the law. It's very hard to see how the individual mandate and the tax or not has anything to do with the biosimilars pathway. So I would have thought that even if the individual mandate had to fall, that and some of the other titles of the ACA, would have been severable. My best recollection of the principles of statutory construction are that when you're interpreting a statute, you're supposed to look first to congressional intent, and since Congress reduced the tax to zero but did not repeal any of the other provisions of the Act, one can think that Congress did not intend that result. But, the Supreme Court is a wild card these days and we are not sure where this is going to end up. That would still be my suspicion, however.

Laboratory Developed Test Debate

Al: Thanks, Tom. I have one last question. This is for you, Greg. Can you give us a quick overview of the developments in the laboratory-developed test debate, which has been ongoing for many years. What's going to happen in 2019 from your point of view?

Greg: Well, the action right now is in Congress. FDA, under the Obama administration, moved forward with a proposal. It put forth a framework to begin regulating laboratory-developed tests. Some background for those who don't know is that with diagnostic tests that are developed within a laboratory, FDAs position has been that they have the authority to regulate those as if they were developed by a manufacturer and distributed and sold like test kits, but they have chosen not to do that as a matter of enforcement discretion. But over the years, tests have shifted from being developed within one lab and used within one lab with people sending the samples in and the lab running the samples on their tests and sending out the results, to essentially mass-produced tests. And it is hard to tell the difference between that and

something that is developed by a big test manufacturer. Now that these tests are being used for very high risk diseases, and given the importance of what is going on with personalized medicine and testing, FDA thinks this is something that they need to be regulating.

Beginning in 2010, FDA said that the intent is to start regulating the tests, and by 2014 they came out with this framework to do so. But, it was so controversial that by the end of the Obama administration, FDA could not get it done so they threw up their hands, published a white paper and left it for the next administration to do. There was a bill that was going around Congress last summer. FDA then came out with their own draft of legislation, which interestingly had a pre-certification type of model that was similar to this idea of pre-certification that they have been working on in the digital health and software area. So the developer of the test - what they are calling an in vitro clinical diagnostics test - if they get pre-certified by FDA, would be able to get certain low-risk tests or potentially moderate-risk tests on the market without having to get FDA approval or going through a streamlined approval process. High-risk tests would have to go through FDA approval, so there would be different levels of tests. There are various exemptions in their proposal for orphan products and tests for smaller groups of patients and things like that. So, the idea has now been picked up in a bill that is being sponsored and drafted by Diana DeGette who is on the House Energy and Commerce Subcommittee on Oversight Investigations, which has a lot of oversight over FDA. I do not think it has been introduced in the current Congress yet, but of course nothing has been happening in the current Congress. But, I think there is some chance that things can move on that front.

Al: Thank you, Greg. That wraps up our teleconference. Thank you to my colleagues here today: Tom Bulleit, Kellie Combs, Colleen Conry, Greg Levine and Beth Weinman. As I mentioned at the outset of the call, 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 in the registration confirmation email you received yesterday. The CLE course code for this program is 3254. Please email the completed form to professionaldevelopment@ropesgray.com or fax it to 617-235-9606 within 48 hours. We will continue to provide additional news and analyses about regulatory and enforcement issues emerging from the federal government throughout 2019. You can access that information by visiting our Capital Insights page at www.ropesgsray.com. Once again, thank you for your participation and have a good afternoon.