The FDA's Shift from Gate Keeper to Enabler

Moderator

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Panel Members

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Kineticos: Soon after Scott Gottlieb announced he was stepping down, he released a statement (Scott Gottlieb's March 14th, 2019 Statement) that talked about the clinical research landscape and we, at Kineticos, were quite shocked by some of the things that he said. Specifically, former FDA Commissioner Gottlieb stated, "Efforts to streamline medical product development based on advancing science can be frustrated by legacy business models that discourage collaboration and data sharing". He then goes on to say, "Without a more agile clinical research enterprise capable of testing more therapies or combinations of therapies against an expanding array of targets more efficiently and at lower total cost, important therapeutic opportunities may be delayed or discarded…"

I was quite taken back by this but before we address his strong comments, let's first think about the job the FDA has done to modernize our drug development system. When Scott Gottlieb was chosen for this position, the consensus within the industry was that he was a good choice. He is a physician, a cancer survivor, an investor, so he understands the space really well. Peter, starting with you, let's grade the FDA over the past few years. We're we right about Gottlieb?

PB: Our view at Worldwide Clinical Trials is that the FDA has turned from gate keeper to enabler. Traditionally, the agency was envisioned as an organization with a mandate to assure compliance with regulations, under the umbrella of protecting patient welfare, while ensuring that trial conduct fell within precedent compared to other approved therapies. Today, the FDA is an enabler. Across therapeutic areas and divisions, the agency's mission appears to be to accelerate the evaluation of innovative therapy through flexibility in program and study designs and to consider the utility of unique outcomes, particularly for diseases with significant unmet needs. In conversations with the agency for these illnesses, many of our sponsors have been encouraged to review the totality of data, rather than an isolated endpoint, to enable the next step in a program, even if the original objectives have not been achieved. Proactively

working with the FDA on the many different elements of programs is now a matter of routine. We are in a slow-moving and largely conservative industry, but the FDA is truly trying to bring new treatments and therapies to patients faster and more efficiently. They may not be the pushers but certainly the enablers.

Kineticos: They have had to be. Drug development has been changing significantly with all of the new technologies and advances, not only in oncology but with gene editing, RNAi, precision medicine, and biomarkers. So, they have had to rethink all of this. Trey, what are your thoughts?

TP: From gatekeeper to enabler to really even an advocate for the industry is how I would categorize it. You can look at it from a sports perspective – they are scoring more points with 22 innovative approvals in 2016, 46 in 2017, and 59 in 2018. So, they are certainly pushing the envelope from a mechanistic perspective. The even broader sense that Scott Gottlieb has brought is really forcing the industry to think differently about approvals and clinical trials. He's advocating that the industry should constantly think about how we can do it better, smarter, and in a more tech savvy fashion. We're starting to see a benefit related to all of this be intertwined within the drug development continuum. It will take some time to fully adopt but Gottlieb pressing on the accelerator has helped tremendously.

Kineticos: Rich, it seems like, historically, the FDA, similar to other regulatory bodies, has been reactive and relatively slow to respond. In the last few years they have turned that around and made it look like industry has been reactive. What are your thoughts on that, from the biotech and innovator side?

RS: As you alluded to Shailesh, my perspective is more on the sponsor side as that's where I've been over the last 10 years. That said, like any regulatory body, you can look at the macro trends. There's certainly more guidance coming out, so they're trying to provide more clarity to industry. Based on my personal experience, the term enabler is on point. However, I interact with a lot of folks across the sponsor community and it really depends on which division of the agency you talk to. As a sponsor, I'm also worried about continuity at the top. Since 2015, there has been a lack of consistent leadership over time. I'm not sure how that will play out but am concerned about the lack of continuity.

PB: Never in the history of the FDA has there been a more opportune time for clinical development and never has there been a more permissive and enabling regulatory environment. Not just the FDA but EMA, MHRA, across the globe, the word permissive is an appropriate adjective for current state. With things like gene editing, RNAi, and other examples of advanced therapy medicinal products, the possibilities for transformative therapies seems limitless from a drug development perspective, and regulatory bodies, in large measure, seem to be facilitating the process. I have never been more encouraged by the growth and expansion of our industry, and the amount of new therapies and treatments that may come to market over the next 10-15 years. A lot of that has been because of the FDA's change in position and style.

Kineticos: Soon after steppling down, former FDA Commissioner Scott Gottleib indicated we've done a good job with modernization, but he also indicates that there are some things holding us back. I read his statement as saying CROs are holding the sponsors back. What is he talking about here? How could CROs be holding us back?

TP: From a high-level perspective, in drug development, the incentives across sponsors, CROs, and everyone related to drug development are essentially aligned. A laser focus on bringing innovative therapies to patients is what we're all aiming for. If I put myself in the shoes of a sponsor selecting a CRO, the CROs that are more innovative are, in general, more attractive. These more innovative CROs are doing things

such as bringing innovative technologies and innovative trial designs in efforts to decrease patient burden and increase efficiency and effectiveness.

Another potential reason could be the fact that there are a number of large pharma companies with long-term relationships with a single CRO, and they are funneling all of their trials to that CRO. Not having to win the business on a trial by trial basis could be a deterrent for the CRO industry, or those particular CROs, to be as innovative as possible. That being said, this is probably only a small impact on innovation in the CRO industry. There certainly are instances where these relationships can be innovative. In fact, I believe that innovation is definitely becoming more pervasive throughout the industry itself.

Kineticos: That's really interesting. My initial reaction is that it would be the opposite in that if you have a strategic partnership, you don't have put so much energy into making sure you win the business and you can put that energy into being more innovative. Does that resonate?

TP: It certainly does in some aspects. If you look at the very large CROs vs. the smaller ones, you generally think about the smaller CROs as early adopters, or developers, of novel technologies. This is done in an effort to create a differential offering and to win business. Sometimes in these large, strategic relationships, I don't believe this drive to be an early adopter of innovative clinical trial practices is always observed. These strategic relationships can be a highly effective tool for the sponsor because there is often cost efficiencies and overall timeline efficiencies due to the close relationship between the CRO and the sponsor. I am just noting that there may not be as many innovative approaches when compared to the sponsor-CRO relationship where you have to win on a trial by trial basis.

RS: As a sponsor, there are two somewhat competing viewpoints on CRO innovation. First, a smaller CRO likely has the flexibility and willingness to adapt to specific needs, including an innovative approach to solving a problem. The flip side is, a lot of the enablers of today's innovation depend on resources that require scale, such as large datasets and technology. A small CRO might not be able to bring those resources under the umbrella. The capability to be innovative, in certain ways, may be a domain larger CROs have an advantage in.

We've used CROs just like any other professional services firm and I'm a strong proponent of a long-term relationship where each party imbeds themselves. I like that model more than a trial by trial transactional approach to doing business. In today's world, I believe long-term relationships are valued more and is the preferred approach, and larger CROs have the capability, by virtue of size and scale, to be more innovative. However, given that CROs are a process-based organization, they only have so much flexibility and ability to be creative while maintaining consistent standards across a global organization.

PB: If you go back to the history of CROs, this was a balance sheet transaction, originally. This was an industry dominated by a few large pharmaceutical companies. It began with pharma recognizing that they can pay lower wages and less benefits to an outside organization than what they would have to pay to run their own trials. That's where the CRO industry began. It's labor arbitrage, just like manufacturing and technology went through. We have come a long way from those beginnings. I believe that we, as CROs, are only limited by our imagination and ability to step away from established procedures, which is difficult to do for a risk averse industry. In this modern world of clinical research, we are truly partners to our sponsors. Yes, we are good at managing resources, as it's what we do. We're not selling a product; we are selling people and expertise.

As it relates to pricing models and penalties, we are still stuck with rate cards. No one pays based on the value the CRO creates; they pay an hourly wage based on rate cards. These proposals and rate cards are overly complex. I am not sure if that is the fault of the CRO or the sponsor, but we, as an industry, have created a monster when it comes to getting into the details and nitty gritty of how many minutes per page, meetings per week, calls, copies being made, etc. We somehow got to a level of granularity and insanity that is meaningless in the overall design and execution of a clinical trial.

The industry is evolving rapidly and we're seeing more demand for sponsors, primarily small biotechs, that need consultative support such as an aggressive yet informed regulatory strategy, for example, or help thinking through a specific penetration plan that will allow them to get a trial up and going faster. Back to Gottleib's statement, I can tell you that CROs aren't out there trying to figure out how to make this slower to make more money. That just does not exist. Even if you are in that 1-1 strategic relationship, you are still going to try figure out what is the most efficient and effective design and operational footprint to get the data that you need as fast as possible. We are not working at odds anymore; CROs are collaborative with their sponsors.

One final point - there is an inverse relationship into the creativity, risk-taking, and risk-sharing that smaller companies have. You still require a little bit of scale. You can be a three-person biotech, but you can't hire a 13-person, or even a 130-person CRO. If you are going to do a phase 2 trial, much less phase 3, you need an organization that has enough scale and resources, with a full suite of tools and processes to go execute. Mid-sized CROs offer a lot of creativity. Small CROs certainly offer creativity, but they don't have the scale to be able to execute efficiently. Indeed, Worldwide's experience has been that predictable and sustainable execution usually trumps brilliant planning.

That was the most provocative statement by the commissioner. His statements don't reflect the tone and tenor of relationships that we have with our customers and partners and the work that we do daily, but I recognize the sentiment from days of old.

Kineticos: I agree. The industry he described is not what I've seen. Perhaps he was trying to be a bit provocative to push the industry and get people talking and reacting to this. If so, it worked!

Earlier in our discussion, the general consensus seemed to be that Scott Gottlieb is an advocate for innovation and was a great FDA commissioner. While his recent statement indicated we've come a long way in terms of modernization, he is also pushing us all to do more. Turning to the panel, what can the industry do to become more efficient, faster, less expensive, and more innovative in such a highly regulated environment?

RS: I would start from a sponsor perspective and make sure I run the right trial and get a clear answer to the scientific question being asked. A couple of Commissioner Gottlieb's comments really get at that point, e.g. the focus on precision medicine and applying new tools such as AI and machine learning. The most expensive trial you run and the one that creates the least value is the one that you have to shut down because you cannot recruit the patients, or you don't get a clear answer because of a poor trial design. We need to be thinking about which patients are going to benefit clinically based on the biology. That gets to precision medicine – targeting the optimal patient population and building a trial enrichment strategy into the design which enables you to get an answer with a smaller sample size. We all know patient recruitment is the biggest challenge in terms of cost, timeline, and execution so ensuring you are enrolling the right patients is critical.

That said, I've heard other sponsors push back because that approach may limit your label, but that's a short-term view based on the historical pharma mass marketing paradigm. Moving forward, the healthcare system is increasingly going to focus on paying for value created, so you'll be expected to demonstrate outcomes but be rewarded through favorable reimbursement. Treating non-responders should not be rewarded, so trial enrichment is important. However, in practice, it can be tough to implement because for many disease states, we don't have well validated biomarkers to tie back to the biology and help us to pinpoint the patient population most likely to benefit from a treatment. It's conceptually appealing but can be harder to execute depending on the particular development program.

There are some things AI will bring to the table. This is where CROs can come in and provide real value if they have access to large sets of longitudinal patient data. One example of this value is allowing you to test inclusion and exclusion criteria on an actual patient sample set. Some criteria sound good on paper when the protocol is first drafted but if a few are going to eliminate a large portion of the population, it may not make sense to be that restrictive. It allows you to weigh benefit and risk of a trial design early on, not after enrollment is lagging. Bottom line, there are ways to become more efficient with tools and resources that didn't exist 5, 10, 15 years ago to design and run better trials and to get therapies to patients quicker and more efficiently. We're still in the early days here but the potential is significant.

TP: More targeted therapies in development, in a targeted patient population, can drive smaller trials and less overall costs to demonstrate efficacy. For example, co-development of companion diagnostics, associated with biomarkers, for those particular therapies can drive cost efficiency and overall effectiveness of clinical trials. Unfortunately, at this time, many of those bio markers are not validated and it takes significant work and effort to validate them. It is noteworthy how far we have come. As an industry, we are routinely considering things such as adaptive clinical design, technology in clinical trials, and surrogate endpoints as standard. This is a paradigm shift from where we were just a few years ago. Additionally, another paradigm shifting approach would be the further development and refinement of AI for simulation of clinical trials. This approach would provide better prediction of clinical trial outcomes. Predicting outcomes before we put patients at risk in clinical trials is the right place to be as an industry

PB: We continue to talk about patient centricity, and we know so much more about patients today regarding their phenotypes, genotypes, and underlying pathophysiology. We also know more about the effects of a trial on a particular patient based upon their demography and presenting disease characteristics. So, from a scientific perspective, we can design more efficient trials – facilitating the enrollment of optimal patients, while evaluating the impact of novel therapy on all. Still, the biggest waste of money is failed trials. Not always because of the hypothesis about the drug, instead, it frequently is because of design, approach, and execution – resulting in an inability to create an unambiguous interpretation of results. We're getting better about trial design because in the past, we weren't able to take all the successes and failures data and repurpose that information in the correct way to design a trial.

Today, the industry is so much more advanced. Patients, families, care-givers, advocacy groups understand so much more. It is mind blowing how involved patient advocacy groups are today. Fifteen years ago, advocacy groups were perceived only as a vehicle to promote study conduct and information sharers, but now some of them are helping design programs, the studies within programs, key measures, and frequently have been instrumental in shaping regulatory policy. All this to say that site procedures are being driven by more awareness and education than ever before. There is huge efficiencies in trial operations gained as we keep learning as much about the illness as we do about the disease – as much about the patients and

families sentiments as we do about the perspectives of an investigator or practicing clinician – and that process is getting more sophisticated and powerful. With the advent of precision medicine, which it feels like we are finally here but still on the forefront, we will continue to exponentially be more efficient and effective.

Kineticos: We frequently read about 2 issues that research organizations have been struggling with for the last 10 years: First, half the trials do not recruit enough patients. Second, half the trials do not start on time. That gets to efficiency issues, trial design, working with the right advocacy group, and precision medicine.

PB: It is frustrating how much delay and wait time we have in getting a trial started. I'm an ex-manufacturing engineer, so I'm always looking at tag time, touch time, and how much time people are actually working on something. Years ago, we did an experiment at J&J where we wanted to see how quickly we could get a trial started. We assumed we had everything necessary, which means we had all the drug product, the resources, no scheduling conflicts, etc. The calculation revealed that we could start up a trial in 72 hours – with a whole list of exceptions that would need to be done. However, so much time is wasted emailing a protocol among 18 different parties across an organization. Indeed, we frequently say that the process of finalizing a study design fundamentally represents an adjudication of the interest of multiple stakeholders within an organization – all of whom agree on overall in tent, but not always on the detail. I'm a believer in pizza and coffee and locking people in a room together until they get to something meaningful. The value in getting all the right parties together for collaboration is underestimated. Email volleyball, as I like to call it, frustrates me to no end. It's not the time it takes, but it is getting those people together in a timely fashion. I have a personal passion for speed and agility when it comes to start-up.

Kineticos: Our industry is very complicated and science oriented. There are things we can learn about industries that move quicker and are not regulated such as software. They have different issues, but getting an app going, a team going, and everybody aligned is much faster than what we are used to.

PB: I have heard software terms in some development companies. I think I recall a small, nimble biotech having a daily 'scrub' meeting but the process from software development goes back to rugby and football, in that everyone huddles in the morning, agrees on what needs to be done and they go off and do it. This daily debriefing and recalibration within a highly efficient project team lays a foundation for brisk execution and excellent data integrity. You must either be face-to-face or pick up the phone and have a conversation with someone. There are simple things that could take significant amounts of time out of our process still today.

RS: It's harder to execute in a large pharma organization because of the complex processes underlying decision making, but at the end of the day if you are in a small biotech, it's your timeline and you own the start-up. If start-up time is delayed, it's ultimately the sponsor's fault and, to an extent, sponsors aren't owning that and are not fulfilling their obligations. That puts the CRO in a bad spot.

TP: The ones that put CROs in bad spots are typically those that are coming out of other industries and naïve to the drug development process. It really highlights the need to have good tenured drug development experts in all parts of pharma, large and small, that really understand the levers of efficiency and effectiveness within a trial. If that skill set is not in the base management team, they need to go out and get it.

Kineticos: What new technologies are out there that really intrigue you in terms of making drug development more efficient and innovative, with shorter times and better outcomes?

TP: The new mobile technologies such as wearables and sensors that keep sponsors, patients, and CROs closer together will only help inform everyone about the therapeutic, the patient experience, as well as the risk and benefit of the drug. Obtaining real time insight into the patient experience is particularly important. Technologies can also help with understanding patient compliance with drugs and overall protocol aspects. I really do think that using AI and machine learning to simulate trials will be a huge paradigm shift in the industry. Using this approach, we'll be able to decrease the number of ineffective trials, or trial failures, which is critical as they are the costliest and have the most negative impact for any business. This is especially true with smaller firms who often don't have the capital to survive a failed major trial. Additionally, this approach will also decrease the number of patients we put at risk in drug development.

RS: New technologies offer great potential, but it's early days. Clinical trials are mainly white space. Patients have a certain number of visits, you collect data, and you don't know what happens in between. You have a very limited view in terms of the medical history of a patient before the trial. It's hard and expensive to follow up after the trial to assess long-term outcomes. In the long-term, technology can help us answer those questions better. Electronic Medical Records can help us understand the before and after for a patient. During the trial, you can be greatly informed by wearables. Mobile technologies don't fit everywhere, and it remains very early. There are also regulatory and HIPAA issues regarding who owns patient data. Does the patient own it or does the company own it? There are privacy issues as well. All this to say, it is highly complex but could potentially change the data sets that are used to understand how a particular intervention is going to impact a specific patient population.

Any technology that can help match patients, then bring patients to trials will be helpful. It is really early days to try to understand which technology within a portfolio of possibilities will help speed up trials. I'm not sure the wearables and these types of systems will really expedite the process, but they remain intriguing and a subject of active review by our organization.

There is value in compliance, and we must execute, but to date, the things that really have helped are mobile phones. Knowing all our CRAs can take pictures and send directly to sponsors is extremely helpful. It personalizes the drug development experience and connects the monitor to the sponsoring organization. As an example, it wasn't that long ago that we were taking a paper receipt, taping it to another piece of paper, scanning, key punching, etc. and we've come a long way despite issues of adoption, which always present impediments to introduction of new technologies. These technologies have been available for a long time, but the industry is finally adapting. Some of the simple things we've done in accounting, finance, and expense reporting have been extremely valuable to our organization and enable us to focus more on the important things like running a trial. Tools like Skype, Office365 and other document management systems are also really valuable. These operational functions are really speeding things up in my opinion, while simultaneously enhancing data quality and integrity, and permitting our site and patient facing staff the opportunity to provide a truly differentiated service. Making anything mobile is important to me. Having all information relevant to the execution about a trial at your fingertips is essential. Every assumption made about a trial could end up being wrong but being able to react and execute throughout the trial requires having all the right data at your fingertips in real-time, so you can make quick decisions.

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