CHIEF MEDICAL OFFICER SUMMIT
2019 RECAP

The Annual Gathering for Biotech CMOs to Exchange Best Practices, Benchmark Ideas and Work Through R&D Challenges

April 4-5, 2019
Boston, MA
By Jeannie Markowitz, MD, CMO Summit Reporter

Overview

The 7th Chief Medical Officer Summit, produced by the Conference Forum took place April 4-5 in Boston, MA. Over 80 CMOs from mostly emerging biotech, some large pharma as well as investors, CSOs and drug development support roles were in attendance.

Day One

Julie Krop, MD, CMO, EVP, Clinical Development and Regulatory Affairs, AMAG Pharmaceuticals, Inc delivered opening remarks. She pointed out that CMO’s play a unique role, in which they are “macro-doctors” who have to keep patients at the forefront and speak out on their behalf when necessary. She talked about the role CMOs play in the culture of companies, creating passion and purpose for employees, which plays a key role in job satisfaction. At the same time CMO’s must distill complicated clinical data and communicate with stakeholders at a variety of levels, which can be challenging. Dr. Krop noted that conferences like these can help with these challenges.
Steve Kanes, MD, PhD, CMO, Sage Therapeutics delivered the keynote address, How the CMO of Sage Therapeutics Positioned a New Indication for FDA Approval. He described how going from a small startup of 10 people to a public company with a drug that is FDA approved has been an incredible journey. Zulresso, the first drug for post-partum depression, was approved two weeks earlier. Dr. Kanes described the process of drug discovery and development that resulted in this approval. He reviewed the statistics regarding postpartum depression: 400,000 women affected, 25-30% severely, only 50% currently diagnosed and treated. Dr. Kanes pointed out that this disease had never been the focus of drug development at a large drug company. He described it as a problem “hidden in view.” Then he switched to mechanism of action. At Sage they were interested in the neuroactive steroid allopregnanolone, a positive GABA modulator that is made by the placenta. Allopregnanolone levels spike in the last trimester and decline rapidly after delivery. This drop can be associated with transient mood disruption (“baby blues,” occurring in 80% of women) but that is not the same thing as PPD. Sage developed brexanolone, an endogenous positive allosteric modulator of GABA receptors, which is a propriety formulation of allopregnanolone. This drug, now known as Zulresso, must be given intravenously. Dr. Kanes went on to describe the clinical trials that had been conducted with brexanolone. The PPD-201 study was performed in the only hospital in America that is dedicated to women’s behavioral health. This open label study with four subjects showed significant improvement in HAM-D scores within 24 hours of a 60-hour infusion. The PPD-202A study was a Phase 2, double-blind, placebo-controlled trial involving 21 women with severe PPD; they also showed significant improvement within a day and remained symptom free at day 30. After this study a breakthrough therapy meeting was held. The next set of Phase 3 studies, known as the Hummingbird Studies, involved women with severe and moderate PPD. The primary endpoint was response at hour 60, and significant responses were seen in both studies at this endpoint and at day 30 follow-up. Both the Phase 2 and the Phase 3 studies were published in *Lancet*.

Dr. Kanes said that with a new indication, it comes down to having strong data and a strong mechanistic hypothesis. There has never been a failed trial with Zulresso. When you have a new indication, challenges you might anticipate could become conversations rather than adversarial (like with the FDA). For example one patient had loss of consciousness, prompting a benefit risk discussion. An advisory committee voted 17 to 1 that it was preferable to get the drug out to patients. Other challenges include figuring out who administers the drug and where? Do you need a psychiatrist and does it have to be IV? It is important to enable Centers of Excellence where drugs can be delivered, support access and reimbursement, and focus on the patient experience.

**Steve Kanes, MD, PhD, Sage Therapeutics**
Case Study: Life of a CMO Pre and Post IPO, Tal Zaks, MD, PhD, CMO, Moderna Therapeutics

Dr. Zaks spoke about expanding the role of the CMO to meet the requirements of a public company. He said the changes needed are 2/3 communications, 1/3 operations, and none in strategy (if you are fortunate). He talked about the role of the CMO in articulating the data of clinical trials, how being public makes a difference. “You talk to investors differently in the public arena where you have to describe what is material. Materiality is not legislated, it is litigated.”

Dr. Zaks also described the personal implications of being a CMO in a publicly traded company as falling into three buckets: strategy, operations, and communications.

Strategy: risk management is essential to building a new class of medicines. Medicines can be thought of along two axes, technology risk and biology risk.

Operations: preclinical operations can be depicted using the spiderweb model showing different components such as Stats, ClinOps, Clinical toxicology, and CRO. If you have 1-3 Phase 1 studies in partnership with a CRO you are an ant and the CRO is an elephant. Dr. Zaks described how Moderna has 10 clinical programs, several moving to phase 2, and is soon to be launching a rare disease phase 1, increasing complexity exponentially. This platform requires internal integration and communication unlike in pharma.

Communications: Dr. Zaks said, now consider if you have 20 programs in development and 10 in the clinic, it will be a super-complicated story to distill for a broad audience. In a one-hour investor meeting, how do you get them comfortable with this level of complexity? As physicians we need to modulate the message in order to communicate with different audiences. The greatest behavioral challenge any physician faces is tailoring the message to the patient. Dr. Zaks also made the point that biotech is a team sport - you have to spend some time aligning with the team messages. Tailor the story language for PIs and patients to investors, analysts, and the lay public. Tailor the story content – as with patients, there is no absolute right answer for the balancing act between focusing on warts and focusing on cardiac reserve.
Mr. Getz gave a high level view of the current remarkable period of drug productivity, with 12,000 active compounds in the pipeline, 20% of which are immunotherapies, the majority of which are supported by small organizations. There is a record volume of approvals by the FDA, 58% to treat rare and orphan diseases, 27% that rely on biomarkers and genotyping. But there are implications for how we will continue to support this engine. The return on investment paradigm is being challenged.

Mr. Getz then went on to say that scale no longer matters – 60% of approvals come from sponsors submitting applications for the first time. We are moving from the traditional R&D view of scaling infrastructure to scaling ability to leverage data and analytics. Mr. Getz described how the patient engagement and data analytics movement has been unfolding at a faster pace than we realize. We are moving from KOL-oriented to patient/patient data oriented, from great science to patient-engaged science. Meanwhile data and analytics are moving from insular to open, from basic and lagging to advanced and leading (seeing patterns in the data). We are moving from reactive use of the data to predictive analytics.

Mr. Getz also said that scaling infrastructure will continue to struggle because of intensifying protocol complexity, highly fragmented operating processes, outdated and reactive tactical practices. The focus on rare diseases will intensify these challenges. Rare diseases account for 58% of total drug approvals and 31% of the R&D pipeline; cycle times are longer, costs are not reduced, the market size is smaller, and success rates begin to approach the common level. Mr. Getz said this is a huge challenge unless we can find new approaches, like targeting patient populations more effectively.

Mr. Getz then went on to discuss leveraging data and analytics. He talked about flexible, integrated models oriented around patients and patient data that can accommodate process customization. He described a study modeling the impact of patient engagement on expected net present value of a program, which found that a patient centric program for Phase 2-3 trials was associated with 40x faster enrollment, 21% high likelihood of reaching market launch, and 10 percentage points higher accepted by formularies. But ecosystem complexity can be a critical reason preventing us from leveraging our data analytics.

Finally, Mr. Getz ended by discussing how real world data is informing development decisions. 70% of companies say they are using AI, primarily machine learning, more at a piloted level, for such functions as patient identification and recruitment, literature and market intel, and AE social listening. We must support a true health systems model, where every time the patient interacts with therapy there is more data.
Panel: Addressing the Talent Gap in Biotech – Recruit and Retain

Moderated by Julie Krop, MD, CMO, EVP, Clinical Development and Regulatory Affairs, AMAG Pharmaceuticals, Inc.

Panelists: Kara Coluccio Bern, Partner, Perspective Group; Donna Higgins, Founder and CEO, The Higgins Group, INC; James Lewis, Global Contract Director, Barrington-James; Chris Poshka, VP, Govig

The first question asked of this panel was, “how would you recommend a biotech company evaluate the firm?” Panelists replied that companies should look at the track record of firms with past clients. They said you want someone who can be evangelical on your behalf, who is the right fit technically and culturally. You should be able to share information readily and bring that to the marketplace. You should like the person you are working with. You need to have a level of trust and chemistry with the firm, making sure you are working as a partner with them. You should do your homework on who the firm is.

Panelists went on to say; when we get a difficult search we ask our companies to partner with us – who on the team can we pull in, to get further engaged? Having access to leadership of the organization can be important. The amount of competition is crazy; other companies are trying to say the same thing to the AAA candidate. You can’t forget the number of options they have.

What can you say that will differentiate you? It’s important to stay close to your search person because it’s amazing how quickly you can lose them. The search person will know which tool you need to pull out for which candidate. Sometimes the differentiating factor is the ability to move quickly. Panelists continued, saying that it’s important to help the company prepare for the interview. Early access to decision makers is also important. The CMO should send a message to the team with what they are looking for, the candidate’s background, and what we are looking for at the interview. The hiring manager then spends time listening to the client, finding out what really matters to them, understanding who that person is, and being willing to say, this is not the position for you. It’s important to trust your search partner to tell you when a candidate isn’t going to be the right fit. Search firms should also do all of the work to understand the universe of options for
the client, so as to get candidates on the far right of the bell-shaped curve. Donna Higgins talks to an average of 350 people per search.

Panelists also considered the issue of title inflation. Candidates are advised it has to be backed up by the data. It’s important to find people who have adequate experience to match the title. If you have someone who’s AAA and won’t move down on the title, it might be worth it to be creative and change the title structure for the right person – for example, bring in to a VP role at a small pharma company. Finally, when it comes to retaining talent, panelists said think about where this person can grow, what are possible different roles in a small company where this person’s skill set can evolve. It’s important to talk at least quarterly about where they are at, and important to have a great culture – as CMO you set the tone for your company.

Panel: Experienced CMO Insights on Building the R&D Team

Moderated by Jim Roach, MD, EVP, R&D, Clementia Pharmaceuticals

Panelists: Christophe Arbet-Engels, MD, PhD, CMO, Poxel Pharmaceuticals; Pedro Huertas, MD, PhD, CMO, Sentien Biotechnologies Inc; Ramon Mohanlal, MD, PhD, MBA, EVP, R&D and CMO, BeyondSpring Pharmaceuticals; John Paolini, MD, PhD, SVP, CMO, Kiniksa Pharmaceuticals

Dr. Mohanlal began by describing how initially it was just him and the CEO, now they are post IPO and in preparation for 2 NDAs. Building a program is a dynamic process, both science and art. Dr. Mohanlal’s company studies small cell lung cancer, which has changed a lot. Immuno-oncology was second line, now it is first line. He said one has to be adaptable to change. In terms of organization, BeyondSpring is built as a lean organization surrounded by resources externally. Dr. Mohanlal is responsible for R&D and clinical management, as well as medical affairs and pharmacovigilance. He mentioned that he used to work in big pharma in the past and looks to this to think about what makes different sized companies successful. Smaller organizations have out of the box thinking and a no nonsense approach. There is a flexible structure, no hierarchy, and sense of being on a team. There is an intolerance to politics. This empowers
everyone, and leaves everyone accountable in an open and transparent environment. Small companies are also process and metrics driven.

Dr. Arbet-Engels described having a Phase 1 program, a Phase 2 program, a Clin Ops team in Lyon, a team in Tokyo, and a CMO in Boston. They have 1 NDA. For their program his company needed to have a clinical operations, safety, regulatory, and biostatistics. The Clin Ops team in Lyon is through local and global CROs. The Phase 1 and Phase 2 studies will need to have a global aspect. They are working through CROs for biostats, and have recruited a safety person for pharmacovigilance phase 4.

Dr. Paolini asked, who do you need to start a global team? He described the competing concerns of speed versus robustness and the need to make sure the work we do is the highest quality, and make sure we have the right people. We need a leader not just of a clinical trial but also a program leader. We are looking for clinicians who think at molecule level and researchers that can develop clinical programs.

Dr. Huertas touched on how we tend to outsource our activities that have to do with late translational medicine all the way to clinical trials development. You need somebody who has developed relationships with regulatory agencies.

Dr. Roach said don’t compromise on experience. You need experienced people who are senior enough to manage things well. From an order perspective we need an experienced operations person, an experienced regulatory person, and experienced statistician (although you don’t always have enough work for a statistician). It is absolutely critical in this market to act quickly; establishing relationships with recruiters is important. Having a seasoned person who knows how to engage with CROs is of critical importance. What drives through value, what will make you different as a company, other things can be found through outsourcing.

Optimizing Development with Model-Informed Decision Making

Tina Checchio, PhD, Associate Director, Quantitative Pharmacology and Pharmacometrics, Cytel

Dr. Checchio introduced model informed drug development (MIDD), which involves using models to inform drug development and decision-making. MIDD utilizes diverse
data sources (preclinical and clinical), helps decrease uncertainty, lowers failure rates, and develops information that cannot or would not be generated experimentally. It can streamline and accelerate clinical development.

Dr. Checchio then described how modeling can go beyond PKPD exposure:response modeling. Model-based meta-analysis (MBMA) can be used to benchmark the drug in a competitive environment. Noncompartmental (NCA) and population PK help understand underlying pharmacokinetic mechanisms. Translational modeling is used to optimize use of preclinical data. Models can also be used to answer strategic questions. For example, a team wanted to know whether they should run a Phase 1 dose ranging study using a biomarker simply to demonstrate proof of concept prior to Phase 2. The model shows the percentage of times the correct decision and dose would be made. A substantial difference in correct decision-making was demonstrated as N increases. Incorporation of model-based decisions results in significant cost savings. One study found Pfizer saved $874,000,000 by employing these methods.

Model informed decisions accepted by the agencies include: acceptance of model-informed trial designs, smaller sample sizes, recommended use of models, identifying target concentrations and therapeutic windows, working in fragile populations like kids or rare diseases.

Dr. Checchio then went on to describe a model equation: here individual response can be described by baseline disease status plus placebo effect (effect of being in a clinical trial) plus effect of being on a drug or biologic agent plus residual error (sampling error). She went on to demonstrate how this would work for a biomarker for receptor occupancy that correlates with efficacy. The model, used prior to use in diseased humans, was able to predict baseline effect and to help identify pharmacologic information about the drug.
The afternoon track sessions focused on addressing unique development challenges in novel therapeutic areas.

**Track 1A: Immuno-Oncology – When and How to Approach Strategic Collaborations and Partnerships**

Moderated by Beth Trehu, MD, FACP, CMO, Jounce Therapeutics

Panelists: Christina Coughlin, MD, PhD, EVP and CMO, Tmunity; Ildiko Csiki, MD, PhD, CMO, Sensei Bio; Wei Lin, MD, SVP, Clinical Development and Head of Oncology, Nektar Therapeutics; Ian Walters, MD, CMO, Intensity Therapeutics

Panelists were asked, why would a small biotech want to start a partnership? Dr. Coughlin replied, as a small company you can really lose your way with 10 programs and so you really have to focus. Be very strategic and patient. Sit back and if you know that you have something cool just wait. Pay attention to the middle. What am I doing? What do I need to focus on? Use your BD folks. Partner between clinical R&D and BD. Small companies fail when they try and do too many things at once.

Dr. Lin said, in immuno-oncology it is impossible to take a drug to market yourself because it is way too competitive. With checkpoint inhibitors, we have to move in parallel; only a big pharma partner can provide that as a resource. Nektar is a pegylation company. We are going to provide cytokines. We are the lead providers of IL-2 and IL-15, also pegylated, which expands cytokine activity. Looking ahead, IL-15 should help T cells expand, so we are starting dialogues with T cell organizations to see if partnership will lead to success for patients.

Dr. Walters said he partners with 7 small companies. It depends on how novel your product is. If you’re super novel it’s helpful to get pharma companies or potential future acquirers familiar with your organization. Partnering is a way to get resources, and help advance a backup program so that primary attention can be focused on a lead asset. Dr. Csiki discussed a tumor specific antigen that modulates notch, a cancer specific antigen that provokes a specific immune response. This antigen is very highly expressed across all cancers. She spoke about the development of cancer vaccines, which could be used alone early on, when there is low burden of disease. Later on, they could be combined with checkpoint inhibitors. She is collaborating with large
pharma to obtain these partners. Also, her company is entering the cell therapy field. They are partnering or having peer-to-peer collaborations with companies that offer T cell products.

Track 1B: Addressing Unique Development Challenges in the Microbiome

Moderated by Zain Kassam, MD, MPH, Co-founder, EVP, Clinical Development and Translational Medicine, Finch Therapeutics

Panelists: Jessica R Allegretti, MD, MPH, Attending Gastroenterologist, Brigham and Women’s Hospital Crohms and Colitis Center; Director, Fecal Microbiota Transplant Program; Assistant Professor of Medicine, Harvard Medical School; Aoife Brennan, MB, BCh, BAO, MRCPI, CEO and CMO, Synlogic

In the Microbiome session, panelists were asked about their interactions with the FDA. Dr. Brennan said that because we are an engineered bacterial strain, no one knows where we belong at the FDA. Thus far our interactions have been positive. Ultimately there’s an alignment – how much data, what the standards will be, how you can work together to meet expectations.

Attendees networking

Dr. Allegretti said that regarding fecal transplant the FDA has been collaborative and helpful. They are easier on investigators than on pharma companies because we are not going for licensure. Many feel fecal transplants should have been classified earlier as a tissue and evolve as those products do, instead of as both a blood and a biologic product. Especially within the c. diff space, this is an area that might be evolving quite a bit in the next year or two. Hope we will have more engineered or synthetic products.
Panelists were then asked, how do you think about phase 1 and phase 1b in the PK PD path? Dr. Brennan mentioned the pillars of survival and asked, do they still predict late phase success for biologics? Yes, she said, they always have. She pointed out; we are looking at a non-biopsiable target organ. What is PK when you are administering a product to the gut microbiome. We invented a term, MK -- microbial kinetics. We did work to prove that we are getting to the target organ and now we have nice data from phase 1 showing that you can apply those principles of exposure and kinetics. For a small company that doesn’t have a lot of money, we’re thinking about how you de-risk and build the pillars of survival for this new platform.

Panelists were then asked; do you feel that the field is evolving to personalized microbial medicine? They replied, everything is evolving to precision medicine but I do not know when we will get to that level of precision. Could we identify individual bacteria or families of bacteria specific to C. Diff? All we have is stool profiling which tells very little about what is going on at the site of disease in vivo. C. diff will probably be first approved indication for microbiome. In the future Stool from responders to checkpoint inhibitors may be given to non-responders – requiring collaborations between microbiome therapy companies and oncology companies.

Track 2A: Designing Clinical Trials for Gene Therapy – a Paradigm Shift

Moderated by Martin Childers, DO, PhD, CMO, Asklepios BioPharmaceutical

Panelists: Edward Conner, MD, CMO and SVP, Sangamo Therapeutics
Kathleen Reape, MD, CMO, Spark Therapeutics

Among the topics discussed at the Gene Therapy session was designing clinical trials. According to panelists, patient safety is tantamount. Panelists said they felt that the pace of research was appropriate at this point, in order to maximize patient safety. They discussed how, when you are designing these trials, you have to create value for the regulators –clinical meaningfulness, demonstration of efficacy. When designing your own endpoint, it’s important to seek input
from patient advocacy groups. There needs to be value for patients and value for the payors. Depending on the drug this may be more or less difficult. For example, for vision, which has no direct cost, it can be hard. If you engage regulators, patients, and payors early and often and you will have an easier time on the back end with the commercial side.

Track 2B: Rare Disease - The Unique Challenge of Developing an Innovative Product When No Approved Product Currently Exists

Moderated by Cadmus Rich, MD, MBA, CMO, Aura Biosciences

Panelists: Shefali Agarwal, MBBS, CMO, Epizyme; Nerissa Kreher, MD, MBA, CMO, Tiburio Therapeutics; Heather Paden, Head of Clinical Operations, PROMETRIKA

Dr. Agarwal described her company’s development of a drug for epithelial sarcoma. She said when you talk to investigators the number of patients is always different from your database, so understanding the number of patients is really hard. Identifying patients is difficult.

Dr. Kreher talked about hypophosphatasia, a rare bone disease with a heterogeneous spectrum. Her company reached out to bone specialists who thought they had patients with the disease but it turned out did not. She said it is important to educate MD’s. She said you could use a well-established patient advocacy group but in this case one did not exist. So instead she helped to build one.

Others said, there is no one approach to how you can find out the unmet need. You may have to invest a lot in reaching out to a large group of individuals who have this genetic variant. Start with a reputable firm to do the epidemiology.

Panelists said, when developing a clinical strategy, if it is a small patient population, design the trial accordingly. Understand what the endpoint is. Explore the idea of using natural history or real world evidence as a comparator. It can help to have lots of interaction with the FDA – for example, obtaining fast-track designation.
Transforming Decision Making in Early Clinical Development

Moderated by Robert Grundy, PhD, Director of Business Development, Exploristics

Panelists: Aiden Flynn, CEO, Exploristics; Mark Trusheim, Visiting Scientist, MIT Sloan School of Management and Strategic Director, NEWDIGS, MIT Center for Biomedical Innovation

Dr. Trushein said that evidence generation has changed from a single trial over time to a full plan from a phase 2-ish to the bedside. But which information do you generate at what time? It’s an iterative process, where multi-stakeholder groups define the territory in which you have to make judgments and decisions. Dr. Trushein said the process of iterative data development, called the adaptive pathways process, is now available to all. He showed the example of Gilenya, where if a more iterative and staged process with more targeted precision medicine approach had been used, it could have gotten to market 2-3 years earlier with a high unmet-need population, and they would have seen the cardiac event sooner than in the smaller real world population and avoided the death that occurred after launch.

Panelists discussed how risk still looms increasingly large over clinical development – so how can we better exploit data? It’s important to consider what are the best endpoints to use, and how to use those endpoints. Statistics and statisticians could have a greater strategic impact.

Panelists said it is surprising how little available data sources that could prevent errors were used by large pharma companies. Such data sources include registries, electronic health records, or the traditional approach of any published data from the literature.

Panelists ended by talking about a virtual patient population based on multiple sources including natural history studies. Simulations let things be run through quantitatively and cut through hypothetical conversations. Within the study one can show pharmacodynamics markers, evidence of cure, beyond one single objective.
How to Make Clinical Operations as Lean as Possible in a Small Biotech

Moderated by Julie Krop, MD, CMO, EVP, Clinical Development and Regulatory Affairs, AMAG Pharmaceuticals, Inc.

Panelists: Brandy Lind, Senior Director, Operations, Rho; Murray Stewart, MD, CMO, Rhythm Pharmaceuticals

Dr. Stewart began the panel by asking; the challenge is do you need clinical operations? I want someone to translate the strategy of the company to investors, and people want to see the face of the company and that is the CRO. I want a senior Clinical operations person who can link across all the studies and think strategically. Do we need internal people in this role?

When it comes to selecting the right vendor, you need to have the right chemistry. What is their capability at different levels? A larger CRO does have the depth. A smaller company may be very good in one area where they started but if they tried to expand beyond that they may not be ready to scale up. So think about where you are going in two years and if they are also ready to scale up with you.

It’s important to communicate properly, to have dialogue. You need to frame education up front about the protocol, nature of disease, why you are doing what you are doing. You should be upfront with accountability, where responsibility is shared. Be clear who is the point person for the CRO in your organization. Dr. Stewart forces himself to read the contract. There should be consequences for not meeting timeline requirements. You need an escalation process. Never assume what you’re thinking is what someone else is thinking. Sometimes face-to-face meetings are best.

Ms. Lind said that not all clinical operations people have experience managing vendors. Companies are looking for someone with flexibility, who can switch gears quickly and grow as their company grows. There needs to be chemistry, knowing the team that comes for the road show is the team you are going to get. There should be routine calls to say, what do we need from each other to make it go more smoothly, and if we are behind, what are plans to get back on track.
The Dynamic Trial Design: The Missing Step Between Phase I and Phase II
Jennifer Keppler, MBA, VP, Translational Medicine, Translational Drug Development

Ms. Keppler presented the dynamic Phase 1B clinical trial design. She gave an example of a standard 3+3 design, but with these patients you are already planning your expansion cohorts (the plan is to file a new protocol with multiple expansion cohorts when RP2D is determined). Here there would be 6-12 patients in each expansion cohort, closing arms for futility. It is a single protocol with multiple simultaneous and/or sequential expansion cohorts with cohort-specific endpoints, eligibility, monitoring plan, and statistical considerations. This dynamic phase 1B accelerates efficiently. It identifies patient populations and or disease subtypes to take forward into phase 2 or 3 more efficiently. It also provides valuable information used to design future studies. However, this type of trial is complex, operationalizing a multiple cohort design is not trivial, and data management requires forethought to adapt to future cohorts. Rapid enrollment could mean that a larger number of patients are exposed to the drug without a full understanding of its safety parameters. In combination studies may not be clear what is attributable to your drug. And, it requires a paradigm shift to real time interpretation of the data and statistical analyses so that failures are terminated quickly and successes are expanded upon.

How Can CROs Best Meet the Needs of Small/Emerging Biotech

Moderated by Jim Roach, MD, EVP R&D, Clementia Pharmaceuticals

Panelists: Lori Buckenmyer, Head, Clinical Operations, InSeption Group; Daniel Burch, MD, MBA, Global Medical Officer, PPD Biotech; Stacy Lindley, PharmD, VP Head of North America Emerging Biopharma Solutions Alliance Management, IQVIA; Zain Kassam, MD, MPH Co-Founder, EVP, Clinical Development and Translational Medicine, Finch Therapeutics

To address the question of how CROs can best meet the needs of small/emerging biotech, Dr. Burch said that big companies’ core competencies can become core rigidities. PPD changed its organizational architecture so that
biopharma and biotech both report to the CEO. Their biotech and biopharma business are the same size. People, culture and mindset are important. We want to curate teams that are emotionally aligned with the client. There needs to be executive engagement. It’s important to find people that want to work in partnership and not procurement mode, aligning with their own goals and objectives. The key issue is R&D productivity.

Dr. Lindley dove into biotech six years ago; now biotech customers want more flexibility and staff that is dedicated to biotech. IQVIA is focused on delivery for biotech. Dr. Lindley believes in working closely to start with a data driven approach and then using experience and intuition. She said, we are investing in data technologies and analytics that we can leverage.

Panelists were asked, how do you deal with behaviors that have come up because they may not be constructive, or other issues? Dr. Lindley said the problem is we dig in without asking questions or understanding where the other person is coming from. Large pharma may expect the CRO not to speak up, but biotech needs the CRO to speak up.

Panelists were then asked, what do you see as key behaviors that can lead to a
successful relationship? Panelists said trust, transparency, and communication. It is also important not to be afraid to bring up difficult conversations, like budgets, which are usually the elephant in room. Everyone should feel empowered to speak up when people are making decisions, and come up with creative solutions. When asked, how do you see the best way to resolve problems, Dr. Kassam reiterated the importance of communication, trust and transparency, the need for positive feedback, and for taking time. Dr. Lindley said a major success factor is to have both sides determine what accountability means. Dr. Burch said there should be no perverse incentives to make people do things too fast. Ms. Buckenmyer said that her people are hired for specific projects based on their experience and passion for that specific project. They have penalty and bonus language in the project and that is shared with the staff.

Day Two

In the Opening Remarks for Day 2, Dr. Kassam told the story of his father, who suffers from ulcerative colitis, and who was afraid to use a biologic due to the possible risk of cancer. This inspired Dr. Kassam to do his first fecal transplant trial, then to launch Finch therapeutics to study which bacteria engrafted and which did not, ultimately partnering with Takeda. He talked about putting patient safety at the forefront, and said that to change the hearts and minds of patients, safety matters. You can’t forget the patient, as they are at the heart of this journey.
What capabilities does the other organization have? Think about fit: can you work with these people? There are times when internally we say if we’re going to do a deal, we have to have a lot of control. So you have to have a common mindset.

Dr. Zeiher went on to say that all projects have bumps in the road. It’s important to take the time to understand the other organization’s governance and structure. Differences in governances and structure must be understood and managed. There are three levels of governance: protocol, development program, and corporate. Partnerships need strong and empowered leaders from both sides. Populate joint committees. Bring together the right people from both organizations with a joint plan to make the right decisions together. Make sure you have empowered people on committees. Agreeing on development strategy and key decision criteria early on supports quick decision-making, even terminating a project. Time is everything. Identifying factors to enable a seamless transition allows innovation to progress without delay.

Finally, Dr. Zeiher shared some statistics: 57% of drugs approved by the FDA in the last 5 years originated in small companies. 49% of new drugs approved by the FDA in 2018 were from small pharma/biotech. 58% new approvals in 2018 were orphan drug designation. Orphan drug designations are on the rise. However biotech and pharma need each other to deliver innovation globally.
Fireside Chat with an R&D Veteran

Jeffrey Chodakewitz, MD, former EVP, Clinical Medicine and External Innovation, CMO, Vertex Pharmaceuticals with Julie Krop, MD, CMO, EVP, Clinical Development & Regulatory Affairs, AMAG Pharmaceuticals, Inc.

Dr. Jeffrey Chodakewitz, Former EVP and CMO at Vertex, spoke with Dr. Krop about his career. Dr. Chodakewitz specializes in infectious disease. He was at Merck for 23 years, where he worked on the HIV triple cocktail and infectious disease vaccine, and then moved to Vertex.

When asked about inflection points in his career, Dr. Chodakewitz described wanting to learn new things, taking the chance to do something different, to learn whether he would be successful or not, to be surrounded by people he’d like to speak with, occasionally to take a chance to make a big change. At Merck he was once told to swap jobs with somebody, running early development, where there were no guarantees. He was told this is a great thing for you, a great path, and if not you’ll find it somewhere else. Seizing those moments is really powerful. From that moment, he stopped thinking of himself as an ID person and thought of himself as a drug development person.

When asked about his move to Vertex, he described how he got a cold call one day and realized he wanted that kind of environment. He said there were a lot of points where he said no, which is hard. He said, it is important to carve out a little time and think about what it is that you want as your goal. Dr. Chodakewitz said the hardest thing to get used to was the experience level – there were smart people who had never seen what they were doing before, or who had only ever seen it the Vertex way.

Dr. Chodakewitz went on to describe the challenge of executing what you have on your plate that day but keeping in mind what you want to get to in 2-3 years. It’s important who you hire, and important to understand the environment.

Moving over to a smaller company was rewarding in that it provided a chance to grow and influence people, and a chance to share what he had seen over the years. He could provide some cover for people in
the organization so they could do their work. There was a huge need for the CMO role to influence their research colleagues. Having an advocate is extremely powerful in a smaller organization. As part of the executive team, they had freedom to ask questions of him, he learned a lot about the business, and he sometimes had to say I’m responsible for patient safety and I’m not going to do that. When you have to be cautious you are, but when you can push it, when you can accelerate, being an advocate, you do.

How to De-Risk a Development Program from a Regulatory Perspective

Moderated by Laurie Smaldone, MD, CMO, CSO, NDA Group

Panelists: Michael Needle, MD, CMO, AVEO Oncology; Shamim Ruff, SVP Regulatory Affairs and Quality, Stoke Therapeutics; Diego Cadavid, MD, SVP, Clinical Development, Fulcrum Therapeutics

Dr. Needle began the panel by saying that he was told never to ask an open-ended question, and never ask a question where you are afraid of the answer, but he has learned exactly the opposite: ask the questions. He said that you tend to make the most optimistic interpretation of your meeting with the FDA. Two days later, try thinking about it in the worst possible terms, which may be more representative of how the agency is thinking. Describing his own work he said, had we asked the hard questions earlier on, we would have gotten to the finish line sooner (working in parallel rather than sequentially). It’s important to ask the most direct question possible. Dr. Needle said he’d never been asked to do something crazy by the agency.

Dr. Cadavid echoed that fear of the agency is the wrong approach, and it’s important to engage the agency from the very beginning.

Ms. Ruff said that medical people often fear asking a question they don’t want to hear the answer to. Questions need to be crafted carefully. Consider, is the pre-IND meeting worth it? If you are a small company with limited experience the FDA and EMA can be more sympathetic. If you are in the rare disease arena, or your indication is in pediatric patients, discussion with FDA can help with inputs, and with expedited approaches. In these areas you want to get as much out of your trial as possible. Ms. Ruff said that she likes face-to-face meetings. You can ask
direct questions and develop relationships. If you want to do accelerated development then that is the time to begin this, early on.

Dr. Needle went on to say that a lot depends on who else is on your executive team, on how much experience they have. This is a good place for consultants. They can deliver a message to the CEO that they don’t want to hear from you.

Ms. Ruff said it depends on the management team, especially the CEO; a lot of time they don’t want to spend time talking to the agency, so bringing in consultants helps. Panelists were then asked about de-risking development in the European environment. Ms. Ruff said that it depends on company culture. You can get conflicting feedback between Europe and the FDA. Dr. Cadavid added, if you focus only on the FDA you are taking a serious risk. Getting your EU approvals early on is a goal. In Europe they don’t have the internal expertise that the FDA has so they rely a lot on clinical investigators. Keep in mind that what you get in the US may not work elsewhere. Dr. Needle said that Europe doesn’t necessarily view things the same way as the US. He gave an example of a drug that had been rejected by FDA, but was later approved in Europe with same data.

Ms. Ruff then pointed out, when you have an accelerated program and potentially surrogate endpoint, you can go to the FDA and ask about an accelerated program and then go to Europe with a more defined clinical endpoint.

Case Study: Why it is Crucial for a CMO to Have a Deep Understanding of Regulatory Affairs

Adrian Senderowicz, MD, SVP, CMO, Constellation Pharmaceuticals

Dr. Senderowicz said that regulatory understanding is a crucial strength for CMOs, especially in small biotech, as they need to integrate and lead drug development. Failure to understand regulatory affairs may lead to great drugs being delayed or blocked, leading to frustrations and potential abandonment of indications. He went on to describe the case of a novel oral tyrosine kinase inhibitor, gefitinib, also known as Iressa, which demonstrated rapid durable radiographic clinical responses in some patients with non-small cell lung cancer, including women, Asians, non-smokers, and those with adenocarcinoma. Iressa underwent accelerated approval. Two large phase 3
trials failed to show survival, but there was a 10% response rate. All postmarketing gefitinib studies failed to show benefit. Ultimately the gefitinib IND was withdrawn.

Dr. Senderowicz then described how FDA approval requires substantial evidence of efficacy and safety in a well-controlled clinical trial. It does not require improvement over available therapy. Regular or standard approval is based on direct measure of clinical benefit or effect on established surrogate of benefit. Accelerated/ subpart-H approval is used for serious life threatening conditions and when we are reasonably likely to predict clinical benefit. It requires meaningful improvement over available therapy and may require post-approval clinical trials.

Dr. Senderowicz said, when you have enough resources, time and conviction, always go for the controlled trial. This has saved many sponsors and drugs from failure.

How to Navigate the Development Path from CMO to CEO

Moderated by Zain Kassam, MD, MPH, Co-Founder, EVP, Clinical Development and Translational Medicine, Finch Therapeutics

Panelists: Aoife Brennan, MB, BCh, BAO, MRCPI, CEO and CMO, Synlogic; Greg Fiore, MD, CEO, Sollis Therapeutics

Dr. Fiore opened by saying that he has an interest in learning new things. McKinsey taught him to think and present logically. His top-level advice is to be interested and find the opportunity.

Dr. Brennan said she had learned three things. First, there is actually no required step between CMO and CEO. People mistakenly think they have to be head of R&D or go through some other intermediate step. Secondly, it’s all about people. You can be bad at hiring and still be a great CMO. You can step in for most of the sub-functions. When you become a CEO that option is off the table. You need to develop a skill of hiring and surrounding yourself with great people. Third, the role of the CEO is to be a sponge when dealing with the board, with investors, absorbing all that uncertainty and risk.

Dr. Fiore added: everything is a test of the CEO, and everything is a negotiation with the CEO. When investors are pressuring – it’s a matter of knowing what you can be firm about.
Dr. Brennan said she is still on a learning curve, and at every board meeting she tries something different. It’s not a board; it’s 8 different individuals. Each one has things that are important to them; each one has a different depth that they want.

Dr. Fiore said you can run everything by them and try to figure out what about each topic individuals are interested in, but when they get to the meeting they can’t remember what they were asking. There they are looking to the CEO at the meeting to corral the group.

**Mechanisms for CMO Performance Improvement**

**Zain Kassam, MD, MPH, Co-Founder, EVP, Clinical Development and Translational Medicine, Finch Therapeutics**

When talking about CMO performance improvement, Dr. Kassam led an audience discussion. A few highlighted issues included:

Organizations can be better at giving more feedback more regularly and audience members chimed in on some suggestions such as using 360s, independent coaches and at minimum having quarterly meetings. Reviews should be required, written and signed by both the employee and management. Often 360s are used only if someone is on a performance improvement plan. For some smaller organizations it can be shoved to the side, until they have the time to do it. This is very shortsighted. When asked, how do you solicit feedback on a day-to-day basis from your juniors and your peers, audience members said that the best way to get feedback is to give feedback. Do that for other people and it will come back to you.

**Wei Lin, MD, Nektar Therapeutics**

**Going from Big Pharma to Small Biotech Leadership**

**Wei Lin, MD, SVP, Clinical Development & Head of Oncology, Nektar Therapeutics**

Dr. Lin spoke about his work on pegylated IL-2 combined with checkpoint inhibitors. He said it is about drug development and managing people. He described how he had to build a clinical team, a safety team, and a medical affairs team. Previously the old portion of Genentech hired people directly from fellowship and academia, which developed a sense of loyalty. When they transitioned to late stage they did not like to hire inexperienced people at all. At Nektar they hired several people with no direct experience. They had great enthusiasm because they were passionate about making...
a change. These individuals brought a fresh perspective. When hiring someone it is important to look for integrity (find someone who will not take short cuts), intelligence (find someone who is interested in learning new things), and initiative (find someone who is willing to take initiative so you can delegate).

Dr. Lin spoke about how it is important in a small company to have all kinds of processes in place. For instance, each week have one representative from each function (e.g. biostats, safety, clinical) come together and review the role together. This is the product team that is directly answerable to the executive committee.

Dr. Lin also discussed the goals of partnership, and the importance of short and long term communication, early and often. There should be respect, with honesty and transparency.

**Featured Session: Navigating Academia-Industry Partnerships: The View from Partners Clinical Trials Office**

Stephen Wiviott, MD, FACC, Executive Director, Clinical trials Office, Partners HealthCare; Senior Investigator, TIMI Study Group, Cardiovascular Division, Brigham and Women’s Hospital; Associate Professor of Medicine, Harvard Medical School with Barry Ticho, MD, PhD, CMO, Stoke Therapeutics

The panelists described how, on industry average, the time between when site selection begins and when sites start enrolling is 8 months; for academic centers this can be a year and a half. Much of that time is actual contract process. When asked, what is Partners doing to make that better? Dr. Wiviott described the creation of the Clinical Trials office where all the lawyers and budget staff sit under Dr. Wiviott and the operations director. This allows them to cut to the very specific things that tend to be problems. The number one issue is intellectual property, then data and publications, then indemnification language. Dr. Wiviott said it is most useful when we can get a master agreement in place that covers most of those things, rather than 5 different agreements with 5 different lawyers.

Barry Ticho, MD, PhD, Stoke Therapeutics and Stephen Wiviott, MD, FACC, Partners HealthCare
Panelists were then asked, what are successful interactions in academia-industry partnerships? Dr. Wiviott said that honesty is important. Also, when bringing together scientific leaders to discuss a pipeline for a given company and they end up with people relatively low level at company clinical affairs, which ends up being frustrating. Things that make collaborations difficult are lawyers and doctors, and lack of transparency. But overall the panelists felt that they have a positive interaction. The people who want to do the work are all frustrated. There are administrative intermediaries. We sometimes have these very prolonged negotiations that don’t result in clinical research projects. As an investigator when interacting with people I feel much better about an interaction when someone says that is not our priority or it is not what we want to do instead of stringing things out.

Panelists went on to stress that we need to find a way for clinical trials to be done more cheaply and efficiently. They mentioned a project called digital care transformation, a way to provide patient management at Partners through algorithms, which can be used for clinical trials.

The Role of the CMO When Interacting with the Board

Elliot Ehrich, MD, CMO, Expansion Therapeutics and John Paolini, MD, PhD, SVP, CMO, Kiniksa Pharmaceuticals

Panelists began by noting, there is not a single rule or a single type of board, and that boards morph over time. Dr. Ehrich said that board members can have extremely different goals. You always need to be transparent, open and authentic, but it’s how you communicate that also matters. The same issue can be heard quite differently, so your delivery needs to be quite thoughtful. Dr. Paolini said that in large pharma you are used to going to management meetings. Now with VC-backed pharma the board is not your management – they are interested in meeting milestones, but when it comes to actual scientific content the assumption is that the company has that figured out. You run into challenges when as boards evolve there are activist board members who start engaging on actual content.

Next Dr. Paolini asked, what is the role of the board? Is it or should it be a source of technical direction? He said, it is really tricky when it moves from higher guidance to getting into your shop. In the context of a board meeting you may not have the
opportunity to get into the level of depth that the conversation needs to go after these comments are made. At this point you can say, I hear what you're saying and we're going to take that back and look into it in a thoughtful fashion. As you get advice and guidance from the board the appropriate response is thank you. You can’t make decisions on the fly. Say thank you, try to reframe what it is you thought you heard, and then take it back and work on it. Use board calls in between meetings to follow up. All communication should go through the CEO.

Best Practice for Preparing for Investors and Q&A

Moderated by Julie Krop, MD, CMO, EVP, Clinical Development and Regulatory Affairs, AMAG Pharmaceuticals, Inc.

Panelists: Greg Fiore, MD, CEO, Sollis Therapeutics, Christopher Heery, MD, CMO, Bavarian Nordic Inc and Beth Trehu, MD, FACP, CMO, Jounce Therapeutics

Dr. Fiore began by pointing out that alignment of the team is very important, especially for the face-to-face setting. Dr. Trehu said they have a core team that puts together investor relations materials. They bring in regulatory and legal heads early. She brings the data to the table and the team talks about how to present and position it, but they could give each other’s parts of the presentations. She said that FAQ’s are where she plays the biggest NO role, like when they don’t want to give an update about something.

Dr. Krop said it’s important to spend a lot of time preparing for these calls, to review what has been disclosed publicly previously, bringing in legal and regulatory early. It’s important to develop FAQ’s to anticipate what investors might ask, and then practice those, keeping in mind body language and tone of voice.

Dr. Heery added that one should make sure data is accurate and true.

Panelists were then asked about key pitfalls. Dr. Trehu described her boss getting excited about a new piece of data which she did not think was ready for public consumption. She emphasized using the FAQ’s to make sure we agree on what we are not going to say, because investors will push and try to get you to say things you are not ready to say. Dr. Krop said
interactions with the FDA can be a pitfall – one should be careful never to speak for the FDA, and to try not to give out details about meetings with the FDA.

Dr. Fiore added the pitfall of not being aware of some things that are happening in the landscape, including up to the minute.

Dr. Krop added, try to keep things as simple as possible, because when you get a layer deep they don’t fully understand. It is much easier to lose credibility than to gain it. Other panelists echoed, take them along the journey, make sure they understand the complexities of the study, so when the data comes out, they are already there. The CMO’s role is to be as realistic as possible and not to over-promise. In the early stages of developing timelines we’re learning what will drive the deadlines and later on we are investing in meeting what we have committed to. Boards expect realistic timelines. Make sure that anything you give investors has been double QC’d.

Other panelists talked about putting in some rules, such as for open label trials putting in a DMC, trying to give investors as much information as you can without disturbing the integrity of the trial. Investors should know not to disclose this information.

The panel was asked about their relationships with investigators and KOLs. They responded, what do investigators in my trials and KOLs think about the data?

If the investigators are still engaged, they still believe in the drug, it helps them feel credible. Perhaps to educate the investment community, KOLs could do talks and webcasts.

Proving Value to Payors: Best Practices

Harry Leider, MD, MBA, Gelesis

During the last session, Dr. Leider posed the question, how do payors think? He answered, payors really like drugs if they reduce total medical spending. And reduced total medical spending for payors means keeping people out of the hospital. Right now specialty drug costs are driving increased spending. In terms of return on investment, the average turnover for <65 years old is 20% per year (different for Medicare advantage plans).

Health plans rely on PBMs (pharmacy benefit managers) to manage drug
spending. PBMS review efficacy and safety of drugs, construction of formularies with tiers and copay structures. Rebates are really important where there is a lot of competition in a class. Use of step-therapy algorithms (they won’t cover your drug until the patient has tried another drug), implementation of PA processes for low volume high cost drugs.

Dr. Leider went on to ask, so how do you prove value to payors? If you have a unique drug that has no real competition it will usually be covered. You need to have strong clinical data on efficacy and safety that sets you apart from competitors. Plan for HEOR studies to prove ROI if you believe it exists. Advocate to have your drug part of well-established clinical guidelines – this typically takes several years. Fully understand PBM/payor dynamics and how your asset will be evaluated and managed.

Thank You

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The 8th Annual Chief Medical Officer Summit will take place April 6-7, 2020 in Boston.