

Radical Transformation of Bench to Bedside *Imperatives for Success*



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PDA/FDA Joint Regulatory Conference

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ON SEPTEMBER 14, CUBIST CEO MIKE BONNEY WAS PART OF THE KEYNOTE PANEL AT THE ANNUAL PARENTERAL DRUG ASSOCIATION (PDA)/FDA CONFERENCE IN WASHINGTON D.C. ALONG WITH FELLOW PANELISTS, MIKE PROVIDED PERSPECTIVE ON WHAT'S AHEAD AS THE PHARMACEUTICAL INDUSTRY MOVES TOWARD THE YEAR 2020. THE SESSION WAS OPENED WITH REMARKS BY FDA DEPUTY COMMISSIONER JOSHUS SHARFSTEIN. MIKE WAS THE CONCLUDING SPEAKER*, PROVIDING A CEO'S PERSPECTIVE ON THE CHANGES THE INDUSTRY IS FACING. MIKE'S REMARKS AND SLIDES FOLLOW.

Thanks Martin. And thanks to the PDA FDA conference organizers for the invitation to be part of this keynote panel.

All of the changes that my fellow panelists have alluded to –from the regulatory, policy, demographic and financial perspective -- are having a dramatic impact on how we as an industry continue the critical work of bringing new treatments to physicians and the patients they treat.

As CEO of Cubist, my perspective will be colored by our work in developing and commercializing anti-infectives and other therapies for the acute care setting, as well as my experience serving on the Board of a teaching hospital in the Boston area. And I should say at the outset that it is impossible for me to talk about the future of our industry without thinking about its vital role in the health and well being of my family and members of our community.

A Transformative Experience

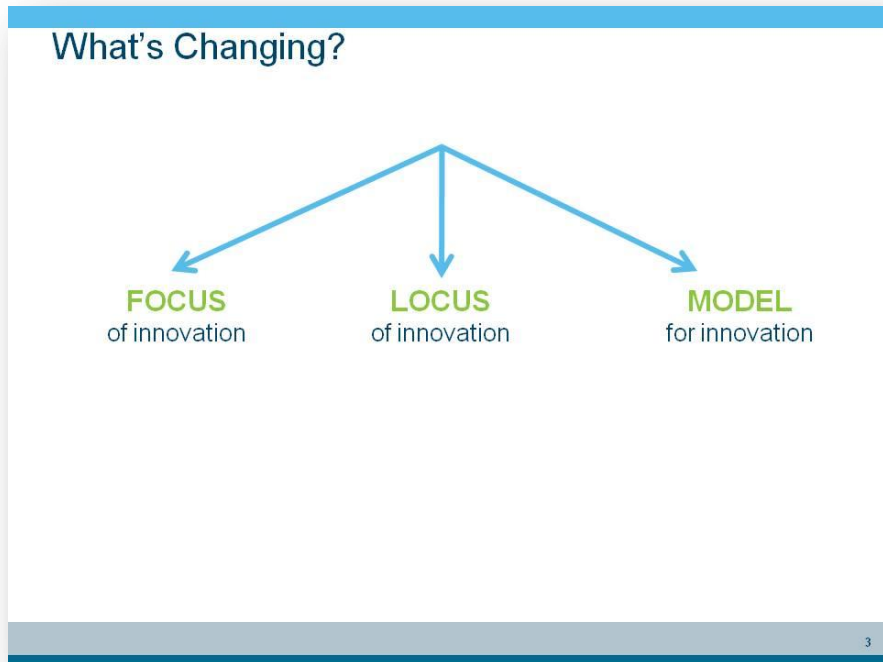


Before I share what I see as the critical components of the transformation the industry is experiencing, I want to reflect on a recent transformative experience of my own. In July, I joined members of my family for a great adventure, one we had been planning and training for over the past year. On July 21st we left base camp in Arusha, Tanzania to head for the summit of Mt. Kilimanjaro. I mention this not to bore you with tales of what I did on my summer vacation—though I'd be happy to do so, but because I see similarities to the great adventure on which we have all embarked as an industry. As you might take away from this photo of Kilimanjaro, my family's journey this summer was worth all of the detailed planning, the training, and the many steps of the climb itself over a period of seven days. But success was also contingent on a readiness to deal with much that was unknown or unexpected, and circumstances that were out of the comfort zone for most members of our family. We also had to rely on a support team of strangers to provide the critical expertise that we lacked.

I think that everyone in this room who is working to bring important new treatments to physicians and patients is in the middle of a similar kind of journey – one that is both challenging AND transformative. Much that was familiar in the way we discover, develop and commercialize therapies is changing—sometimes in revolutionary ways.

As I see it, we have two choices—to opt out of a journey that appears daunting, or to embrace the opportunity to be part of this exciting, but very challenging transformation. In leading a company in an industry confronting these many changes, I find that our employees get their motivation from the seriously ill patients whose unmet medical needs we are seeking to address. I suspect that same inspiration is what brings most of you here today. But motivation is not sufficient. We need to forge a path that requires detailed preparation. Also required is a willingness to work in new ways in evolving business environments and with technologies that may be new to us, and with a recognition that we may need to rely on new partners to provide critical expertise.

If we were to choose to opt out of the transformative journey ahead, the consequences would be dire. Patents will expire, investors will walk away, innovation will be stifled and pipelines will go dry. Worst of all, the lack of the right treatments will impact and almost certainly shorten the lives of patients, including many of us in the room today. I'm going to take the leap of faith that we are all signed on for the journey ahead.



So what are the kind of changes that impact the way we go about discovering and developing new medical treatments? Quite simply - everything. From the FOCUS of innovation, that is the kind of therapies or diagnostics or devices we work on; to the LOCUS, that is, the places where an innovation is born; to the business models we employ, giving us the privilege of transforming the capital our investors entrust us with into new medical treatments.

Changing the **FOCUS** of Innovation

CURRENT

Broad based focus on common disease state



FUTURE

Tight focus on distinct needs of specific patient populations driven by emerging science

Blockbuster commercial opportunities



Highly differentiated niche products

Focus on small molecules, some biologics

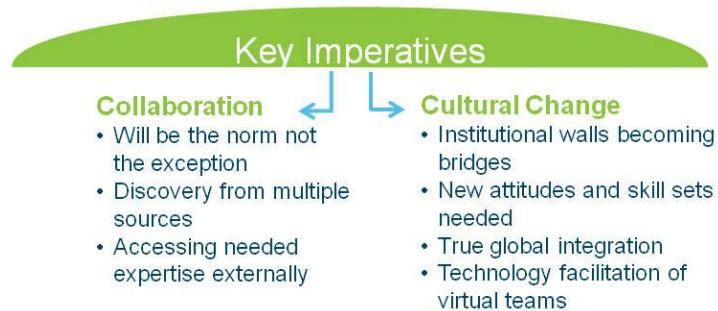


RNAi; gene-based therapies; stem cells; new delivery systems; diagnostic/therapeutic combos

This slide provides a top line view of how the focus of innovation is changing. I should point out that some of this shift is already underway— but you get the idea.

A human being is an incredibly complex set of biologies. But our history in developing medicines and diagnostics and prescribing treatments has been hindered by our limited ability to quickly and accurately translate symptoms. A patient who is febrile might be suffering from pneumonia, diverticulitis, appendicitis, or dozens of other diseases. Chest pain might suggest heart attack but could also be due to angina or even gastroesophageal reflux. Signs of illness can also mask the wide range of biological processes that may be involved. Recently though, the exploding understanding of our genetic makeup, and how that biology interacts with our environment, provides us with greater insight on the variety of disease etiologies that can manifest the same symptoms. This understanding also allows us to shift from a focus on broad-based disease states – like diabetes or cardiovascular disease – to being able to target medicines to more distinct patient populations with that disease – and even to the molecular pathways that may give rise to the symptoms. Our research today also benefits from a range of scientific advances that allow us to get beyond our crude ability to describe illness. Advances in stem cells, RNAi, gene sequencing and diagnostics, for example, open up new pathways and should allow us to target therapies for development more effectively, and develop them more efficiently. We won't see results overnight of course. Even with greater insight into our complex biology and with better tools from scientific advances, the outputs in terms of new therapies and treatment paradigms will likely advance at an evolutionary rather than a revolutionary pace. But these changes, along with the flattening of the world, are already leading to revolutionary changes in our business models.

Changing the **LOCUS** of Innovation



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Evidence of this change in our business is apparent in the changing LOCUS of innovation. From large pharmaceutical companies to small biotechs and academic centers of excellence we are seeing a dramatic increase in collaboration for discovery and the early stages of development. Increasingly, I believe that the “Aha!” moments of innovation will occur when experts of different disciplines approach problems together. This change in turn also has implications for the culture of pharmaceutical companies.

Traditionally, we assumed that most of the innovation would happen inside vertically integrated pharmaceutical companies who did it all—bench to bedside. But now innovation increasingly is coming from outside – from academic science or emerging biotech. Increasingly as we move forward, externally-sourced innovation is going to become the norm, rather than the exception. We see evidence of this in the companies who have already downsized their large in-house research organizations. As this trend continues, pharma is going to find other ways to provide added value. For some that will be in overseeing development, others will choose to focus on commercialization, and some will have differentiating competencies in both.

At Cubist, we learned the importance of externally sourced innovation early in our history. Our first success was with a compound we in-licensed from Eli Lilly & Company. Today it is marketed as CUBICIN[®] (daptomycin for injection) and has been used to treat more than an estimated 750,000 patients in the U.S. with serious and sometimes life threatening infections. In-licensing is not new, but it is growing. It is estimated that in-licensed products already represent more than 30 percent of “Big Pharma” sales today.

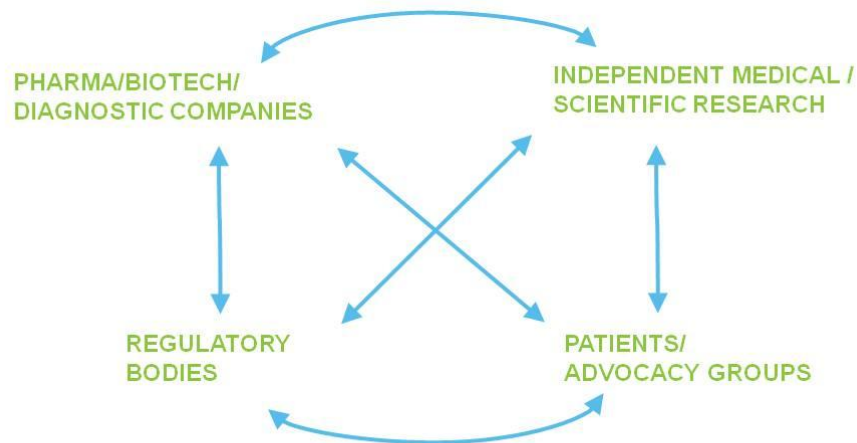
Another trend for external sourcing of innovation is collaboration--which can take various forms. The clinical pipeline at Cubist includes two programs that involve collaboration, and we also have several early discovery collaborations that complement the antibiotic discovery programs we continue in house. I guess you could say at Cubist we are true believers in driving innovation – but agnostic about where it actually happens.

We are not the only company that includes collaboration as a critical part of its pipeline development. As an example, earlier this year Merck and Astra Zeneca announced that they are combining two of their leading pipeline products to develop an innovative cancer therapy. This kind of collaboration does more than increase efficiency; it drives some very important cultural change for the organizations involved as it forces us to rethink the entire innovation ecosystem.



Traditionally, the industry viewed itself squarely in the center of this ecosystem – collaboration with academic scientists and other research groups was happening, but was not necessarily viewed as a central driver for the innovation engine.

The New Innovation Ecosystem



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In the future, we there will be much more shared ownership of the drug discovery and development process among a number of players. There will be multiple paths to and through development and pharma will be a valued participant in what you might view as a horizontal or circular process—vs. the vertically integrated start to finish ownership of the past. In a recent New York Times story on a similar “open innovation” trend in high tech companies like HP, GE and IBM, it was suggested that the corporate lab is now becoming the “ringmaster” of the innovation process—although, as with our transformation, certain core areas of research will continue to involve tightly knit internal teams of scientists.

Changing the **MODEL** for Innovation

Are Mergers the Answer?

- Cost cutting can provide short term efficiency/EPS benefit but does not drive long term value creation
 - History has shown long term success is highly variable
- Silos of the past need to be replaced by nimble, fluid, collaborative thinking and processes
- Downsizing (of R&D as well as sales organizations) CAN provide opportunity to rebuild research based on new model for innovation

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Some of you might be directly involved with a number of high profile mergers that are happening among pharmaceutical companies and between pharma and “big biotech.” Many ask the question-- will these mergers help make the industry more productive and more efficient at driving innovation?

I think if you look at what mergers have achieved historically – the record is at best mixed. My view is that there may be some inherent conflict between the required systems, controls, and organizational structure in a large public pharmaceutical company and the drivers for an innovation culture—one that relies in part on what sprouts up in the spaces between disciplines. That said—I believe we will continue to see mergers of major companies. Independent of its impact on innovation, it is a tried and true strategy for increasing earnings while new sources and models of innovation are being devised and matured.

Cubist is a relatively young company. We’ve intentionally managed our growth to allow for differential funding of R & D—including in-licensing and collaboration programs, along with some core internal research. In the business model we are building, R&D would ideally represent about 25% of revenues—nearly 50% higher than the industry norm. We will get there only by carefully managing our investment in other areas. Striking the right balance presents challenges of course, but we are not on this journey because it’s easy. Among the challenges in creating a different model is meeting the expectations of both investors and employees, as well as the patients we ultimately serve—so communicating where you are heading, and why, is critical.

Changing the **MODEL**

Some challenging questions:

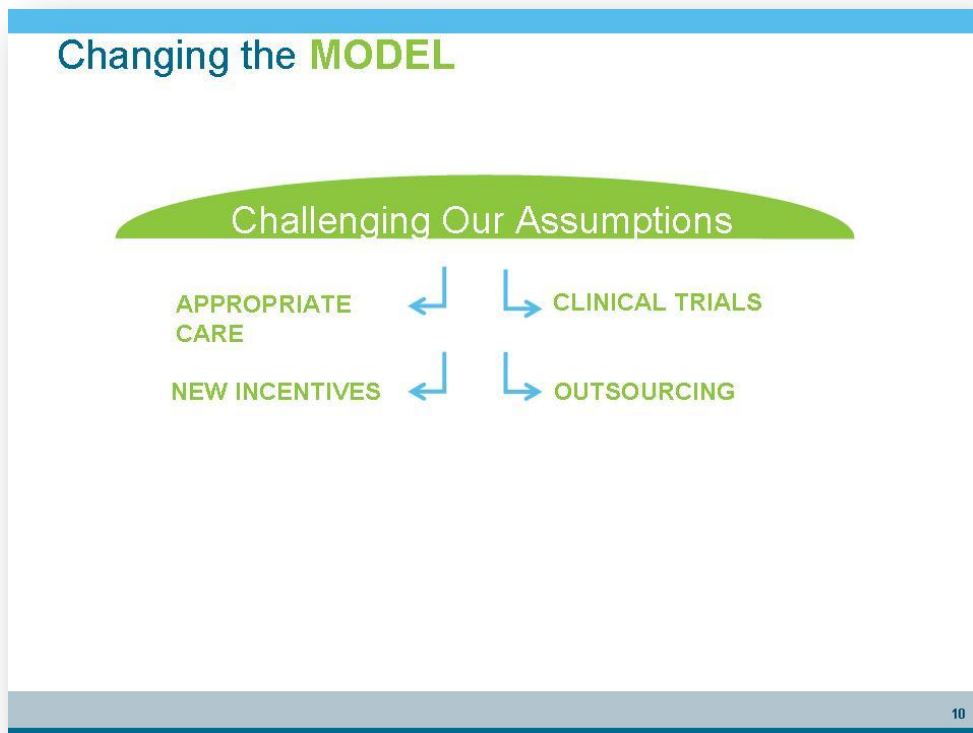
- Will regulatory, IP and reimbursement environment support true innovation?
- Will ROI be attractive for investors in a period of uncertainty?

As we move forward and test new business models we will need to deal with new sets of risks as well as challenges in the macro environment.

Some of the newer approaches to innovation for our industry involve emerging or unproven science, or populations that are difficult to study. So these new approaches can add significantly to risk. That's OK as long as there is clarity around paths forward, and, where needed, the right incentives are in place.

Investment is the lifeblood of our industry – whether you are a publicly traded company or a private one looking for venture capital. And right now, some investors whose bets have fueled innovation in the past are pulling back or becoming more cautious. They have questions about the potential for financial return in sectors where regulatory pathways for approval are becoming less clear or more costly, where reasonable periods of exclusivity for innovators are being challenged by Congress.

Developing a single new therapy costs somewhere between 800 million and 1.2 billion dollars. It is difficult if not impossible to imagine where the capital of this magnitude will be found, if not through funds that must generate returns commensurate with the risks of these investments. If we want the kind of investment that is necessary to bring new therapies to market, we are going to have to make sure our regulators and legislators understand the value creation process. If we don't, investors will leave the sector and companies won't have the resources necessary to develop the new treatments that patients need.



We in industry also need to do our part to improve the drug development process—and reduce overall cost by reducing late stage development failures—a significant part of escalating R & D expense. For example, we can find ways to improve the type of research we do before investing in Phase 3 registration trials. Making a Phase 2 program more robust, for example, can both help gain investor confidence while providing regulators and investigators with better understanding of a disease state, or the level of risk or benefit with a particular patient

population. These insights in turn will help with Phase 3 design. Industry can't do this alone – we need to work with the FDA and others to make the process better so that we can focus on the most promising compounds, reduce time and money spent on failures, and potentially move more quickly into and successfully through Phase 3 programs. Industry also has the responsibility for ensuring that we are clear and transparent about both what we know about our products and what we don't know. We must refrain from advocating use of our products that goes beyond what has been rigorously studied.

At Cubist we are now involved in a Phase 2 program that is targeted to enroll several hundred patients across two different trials that allow us to study patients with different risk profiles. As a result, ecallantide, our therapeutic candidate to reduce blood loss in patients undergoing on pump cardiac surgery, will have been exposed to the complex biology of about 500 patients before we get to Phase 3. While we are investing more in our Phase 2 program, we believe it will pay off with a more informed approach to Phase 3 design.

We also need to work with regulators and clinicians to improve transparency around the risk/ benefit equation. This can both help to encourage well-informed patients to participate in important clinical trials, and generate renewed public support for the investments necessary to produce groundbreaking innovation.

Challenging Our Assumptions

CLINICAL DEVELOPMENT

- Transform Phase 2 of clinical research to produce learning that is richer, earlier, faster and less costly to inform path forward with greater ROI potential
 - Smaller, multiple trials to enable optimization of the innovation
- New tools must be embraced: diagnostics, biomarkers, imaging, toxicogenomics, to supplement traditional clinical endpoints
- Industry can lead here and add tremendous value, but partnership with regulatory bodies and the medical community is critical as we move forward

I want to elaborate a bit on the importance of rethinking how we move into and through the clinical trial process. In some cases we can gather more information at the preclinical stage to better inform the work we do in the clinic. But we also need to re-think the conventional model for clinical trials, especially during Phase 2, so that they produce more information, earlier, and also find ways to generate information about how a drug

candidate works with specific patient populations. As part of this transformation, we need to embrace new tools like diagnostics, biomarkers, diagnostic imaging, toxicogenomics, and use them to supplement traditional clinical endpoints.

By using improved tools and generating more robust information in Phase 2 we can then not only design better registration trials, but we have the potential to more quickly identify paths forward for multiple indications. This can mean that much needed treatments get to market sooner. That's important for patients and also for investors who pay a lot of attention to the returns generated within the life cycle determined by the patent expiration "clock" for an innovation.

We all need to work closely with leading clinicians and regulatory bodies to address some of the most challenging areas of unmet need today—for conditions or patient groups that may be particularly difficult to study. When Cubist decided, in 1999, to study CUBICIN for the treatment of patients with serious bloodstream infections caused by "*staph aureus*", there were no trial protocols, and no precedents. The etiology of the disease is varied and the patient population is heterogeneous, with a variety of potentially confounding co-morbidities. By engaging very early on with both clinical thought leaders and the FDA, we created a clinical path that, while challenging, was do-able and ultimately successful. Some wonder if such collaboration would be possible in today's environment and, as I stand here today I share this concern. I can't emphasize enough that we need to continue to be able to get out of our boxes to tackle challenging problems together. We can't let the norms of the past create barriers to innovation. And while pursuit of perfection is noble, we all need to be vigilant to ensure that this pursuit does not create impenetrable barriers to advancing human health.

Challenging Our Assumptions

APPROPRIATE CARE

- Focus on the right treatment, at the right time, administered in the right way.
- Provide clinicians with information to make evidence-based treatment decisions

We also need to work with all parts of the healthcare system to improve care based on providing the right treatment, to the right patient, administered at the right time, and in the most appropriate way. Research on comparative efficacy can be part of the solution here. But it will be important to look at this in a real world manner, and focus on getting physicians the information that is needed to make appropriate treatment decisions. As a company that has focused initially on developing antibiotic therapy, at Cubist we are quite aware of the importance of making evidence based treatment decisions, both for patient outcomes, as well as for the long term utility of an antibiotic agent. We also see that a therapy that can deliver a similar outcome, but in a less costly setting, or in a shorter treatment window may be better for patients, the medical delivery system and payers.

Challenging Our Assumptions

NEW INCENTIVES

- Lawmakers need to encourage investment in areas such as prevention and treatment of new global menaces (pandemic flu, super bug pathogens)

As I mentioned earlier, we need to create incentives to encourage investment in critical areas. This has been done very successfully in the past for HIV and orphan diseases. Cubist is supportive of the Infectious Disease Society of America, for example, in their push for incentives that will encourage the development of antibiotics for the growing number of infections caused by multi-drug resistant bacteria.

Challenging Our Assumptions

OUTSOURCING

- Has been common practice for clinical trial execution, but will increase in areas of discovery, with more broad scale adoption in manufacturing, and greater use for commercialization/sales
- Changes in the way we work will put a premium on both companies and people that are able to integrate processes and manage effectively across a variety of organizations, cultures and geographies

Finally, companies need to think strategically about outsourcing across the value continuum. Outsourcing has been embraced across the industry for many years for the execution of clinical trials, and, for smaller companies like Cubist, for manufacturing. Today, companies are increasingly looking across the drug discovery, development and commercialization process to see where they can add value with internal resources, and where an activity should be outsourced.

You've heard quite a bit this morning about some daunting issues and the need for transformative change. There is a lot to think about, and much to do.

A Journey Worth Making



It is important for us to all keep our eye on what lies ahead on this journey, for I believe it is a journey without end. By bringing to the bedside the treatments needed to support a more patient-focused healthcare system—we are renewing a vision of the future where our children can lead more productive, healthier lives. Some of them in turn will play critical roles in driving innovation to benefit future generations.

For this journey to be productive, and to meet the needs of all our constituencies, we'll need all the people and organizations represented in this room to pull together. The journey is challenging, but I think we are on the right path.

As we reached the summit of Kilimanjaro, my family's memories of the daunting journey ahead of us just a week earlier, and the strains of the climb we had just experienced, were instantly replaced by the inspiration and satisfaction we felt standing at the summit. It is with that spirit that I join my fellow panelists in encouraging us all to keep moving forward.