interview

Steve Carney talks to Vincent Lee on the pharma industry, the FDA and public education with respect to drugs and their development

Interviewed by Steve Carney

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Vincent H.L. Lee joined the Office of Pharmaceutical Science, US FDA in March 2004, after serving on the faculty of the University of Southern California (USC) in Los Angeles for 24 years. While at USC, Lee and his research team were recognized for their research contributions in three interrelated areas. These are: defining the biochemical barriers to peptide and protein drug delivery; elucidating the structure–function of drug transporters, notably the oligopeptide transporter PepT1; and characterizing the pharmacokinetic barriers to drug delivery in treating retinal degenerative diseases, including macular degeneration. His research has been recognized by several international honors and awards, including the Young Investigator Award of the Controlled Release Society, Research Achievement Award in Pharmaceutics and Drug Delivery of the American Association of Pharmaceutical Scientists, and Pharmaceutical Scientist of the Year award sponsored by the FIP Board of Pharmaceutical Sciences. In 2003, he was awarded an Honorary Doctor of Science degree from the University of London, United Kingdom. Lee served as Past President of the American Association of Pharmaceutical Scientists (1996) and of the Controlled Release Society (1993). He is presently editor-in-chief of *Pharmaceutical Research* and of *Advanced Drug Delivery Reviews*. He is a member on the editorial advisory boards of several journals, including *Drug Discovery Today*.

How do you think that publication of clinical trial data will affect public perception in the drug industry?

For the record, I am here to express my own opinion on your well-thought-out questions. Furthermore, my opinion is not necessarily reflective of the FDA's thinking or opinion.

Public disclosure, certainly, and, upon peer-review, publication of clinical data by sponsors are long overdue. This is a powerful statement of transparency in all aspects of conducting a clinical trial. It will not only inspire confidence in the public but, I hope, it might set the stage for disclosing all relevant data, including non clinical data, in the development of a drug product. A major hurdle to progress in research is access to the entire knowledge base, of which negative data is a part. As a member of the scientific community, I feel obligated to inform other members of every dead-end I encountered, so as to increase the probability of zeroing in on the critical path to target. But in reality, no peer-reviewed publications today or tomorrow would encourage the publication of negative results. So, finding a way to authenticate and then archive negative results is what the scientific community must grapple with. I hope we can learn from the human genome project the merit of depositing the data in the public domain. It is essential that all users of the knowledge space fulfill their obligation to add to the knowledge base as well.

Do you think that the information should be universally accessible or do you think it is of little value to the general public?

Yes, in principle, the information should be available to the scientific community at large. The question is how can we be assured of the integrity of the data? As for the general public, I am not so sure of the value of the information, given its technical nature.

'A major hurdle to progress in research is access to the entire knowledge base'

In view of the recent issues related to various COX-2 inhibitors, how do you feel the issues of drug safety will affect the process of drug discovery?

Balancing safety versus efficacy is always in the consciousness of the pharmaceutical

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interview

community in the development and regulatory approval of drug products. But as a society, we tend to accentuate the positives while downplaying the negatives. The time has come to address the side effects of drug products as well, but in a 'personalized' way. As you already knew, there is usually a laundry list of side effects in every package insert. But pharmacists should put that information in the context of the genetic profile and life style of the patients to identify only those side effects that are relevant. As to whether drug development time would increase due to the concern of drug safety, it would depend on how we look at it. Personally I don't think drug development time will increase dramatically, provided we are willing to build innovative thinking into the design and conduct of clinical trials.

Is there a reliable means to estimate the 'gestation period' of a drug product? Should pharmaceutical companies working on the same therapeutic target for the first time be motivated to form a consortium? Do you see what I am trying to drive at?

To pool data and find out adverse effects?
That's correct. We must realize that if one member of a therapeutic class fails, all members of that class may also be at risk. Also, if we truly embrace that science drives drug product development and regulatory approval, then we should acknowledge the reality that progress in science is highly dependent on our access to prior knowledge. Hopefully, the path of a second drug product in a class would benefit from what was learned in the first drug product in the class. I am not sure whether the current business model does encourage this type of scientific exchange. If not, then we need to find a way to make it happen.

Related to that, the relative lack of serious drug issues is perhaps a testament to the success of agencies such as the FDA. Maybe the public thinks that there is such a thing as a totally safe drug. Do you think it's time to educate the public with respect to the risk: benefits issues, and there should be an element of informed consent at the point of care?
Those are very good points. Your second point of informed consent is intriguing and merits further study. As for your first point, let's assume consumers of the future will be very much in tune with managing their own health, lifestyle and everything else by accessing the internet. But who on the health care team should be charged with assisting the consumers to interpret the deluge of information? Perhaps the time has come for a major restructuring of health care delivery as well. As I alluded to earlier, the pharmacist is that health care professional who should step forward, but she must have access to the consumer's genetics and lifestyle profiles in order to map a 'personalized' side-effect profile and engage the consumer to be on the alert for those side effects.

'Perhaps the time has come for a major restructuring of health care delivery'

On the basis that for very serious diseases, people are prepared to put up with significant side effects it is perhaps a case of what they are prepared to tolerate for the condition that they have?
I agree. To add to that, future drug development may opt for relatively homogeneous targeted populations with respect to drug pharmacokinetic and pharmacodynamics rather than the current heterogeneous population model, the so-called blockbuster model. I am optimistic that this more focused approach would be able to shorten drug product development time, allowing timelier introduction into the therapeutic space without sacrificing product quality.

How avidly do you think pharmaceutical companies will take up the invitation to submit pharmacogenomic data?
Well, amazingly enough, the trend is encouraging. But I don't have the exact numbers to date at my finger tips.

But do you envisage a time perhaps when such information will be mandatory rather than encouraged?
Let me put it this way. If that information is essential for the industrial scientists to render a decision on the drug products' safety and efficacy, then reviewer scientists should be granted access to it as well. Today, even though we are living in a knowledge society, sadly we are still operating as if we were in the bygone industrial era. That can't go on for much longer. What we are finding now is that the sponsors have access to the public database, their in-house database, but not their competitors' database. Won't our resources for drug product development be better utilized if we can learn from the experience of our peers?

'Pharmacists must be more proactive in educating both the consumers and the physicians'

What do you think about the trend to direct to consumer advertising? Do you think there needs to be some more legislation here or, in your opinion, would you ban it all together?
Well, the pharmaceutical companies are already addressing this very issue on their own. It is not so much about the overarching principle of direct to consumer advertising, it is more about the way advertising is done on television. A spot on TV in prime time has to be succinct because of the associated cost. Consequently, the context surrounding that claim may not be highlighted. But what about the internet, which is a marvelous tool to lead the user down a critical path. At the same time, pharmacists must be more proactive in educating both the consumers and the physicians of the context of whatever claims made.

Do you think that pharmacists could prove to be the point of information for patients more than they are at the moment?
Absolutely. Please allow me to speculate on the future of how consumers would prefer to have their prescriptions filled. So long as drug products are viewed as a commodity of commerce, consumers of the future may not hesitate to fill their prescriptions on line from the so-called 'internet pharmacies'. As a consumer, I am apprehensive about doing that right now because I am not sure of the quality of the drug product. But once that is done, I won't be surprised that I will order the drug product directly from the manufacturer, bypassing the pharmacy. What prompted that thought was my recent experience of ordering an iPod from Apple. I was amazed to notice my order was shipped directly from

interview

Shanghai (presumably the place of final assembly), and it came to me within 2 days. Can you imagine that your medications will be processed in the same way? And then it will be up to you (or your insurance carrier) to decide whether you wish to subscribe to professional oversight of your medication needs. Such a scenario, which in effect will formalize the separation of dispensing of drug products and rendering of professional services, challenges the definition of licensure of pharmacists and ultimately the geographical boundaries of where pharmacists can practice. On a related note, should the mission of faculties of pharmacy be solely in the domain of graduating pharmacists to practice in the conventional way? I don't think so. Society will need pharmacists as epidemiologists and authors of software to enable self-management of drug therapy, and the like.

'It may be prudent to consider the creation of an international regulatory agency'

Related to that, you mentioned about bringing drugs in from abroad, where the drug product is manufactured, do you think that the issue of the safety of parallel imported drugs is real, or is it a way that companies can maintain profit margin?
Well, in my opinion, the scenario you mentioned is a business model in transition, and the economic pressure will take care of that. At the same time, just like the mobile phone and other business, the pharmaceutical business is global. Soon, it will be rare to find the entire drug discovery development, clinical testing and manufacture process located all in one country, say, the United States. The process will be segmented and each segment will be conducted where the quality of the product can be achieved in a cost-effective manner. Countries with no pre-existing infrastructure will be positioning themselves to bid for the project. The implication is that, eventually, it may be prudent to consider the creation of an international regulatory agency, whose mission is to ensure that the quality of the products manufactured anywhere in the world or planet will be up to par.

Can you give me your views on how the interaction of globalization and consumerism, pressure on cost containment for example, synergies of nano, bio and information technologies can affect the future business model of drug discovery?
Globalization, consumerism, and pressure on cost containment are clearly the drivers for a structural rather than an incremental change in the way the pharmaceutical enterprise is structured and operated. Advances in the three technologies you mentioned would provide the fuel to accelerate passage into a new world, where consumers are whom the pharmaceutical enterprise is held accounted for. There is no question that we need leadership in every segment of the pharmaceutical enterprise to inspire the community to revolutionize the way drug products are discovered and developed. We must raise the bar for improving efficiency of the drug discovery and development process to better than the prevailing 10%. The inherent inefficiency of the process is because we don't have access to critical information. We are not learning from the present, we are learning from the (perhaps irrelevant) past.

'We must raise the bar for improving efficiency of the drug discovery and development process'

In ten years time, how much research will be being done by small biotechs compared with large pharma? Will the innovative discoveries be coming from the biotechs?
Innovations are more likely to come from the super biotech companies; another likely source is conglomerates of academic research investigators across departments or institutions with complementary research distinction and infrastructure.

How do you feel that you can leverage innovation in drug development and what part should the FDA play?
That's an interesting question. What is innovation? Innovation is not simply invention. Rather, it includes not only science and R&D, but also the adoption and implementation of new technologies, the development of new skills, and learning-by-doing. My personal observation is that, in drug development, we'll try our best to be innovative. We are likely to seed innovation in every box in the quaternary chain of drug development, from preclinical to clinical. But I wonder whether we would be better off to question the logic of the longstanding scheme and develop a new one that meets the present day's goals.

What role could the FDA play? My short answer is a key, if not a leadership role. First, the FDA needs to examine whether current regulations, which were legislated in a different era, are still valid today. Second, is there a climate of openness in scientific discourse between the sponsor and the FDA? Third, is the FDA prepared to categorize drug products based on a comparison of their profile with those profiles derived through data mining in the numerous drug applications in their archives? Of course, you already knew that the FDA is not at liberty to share product information. But then should the stakeholders champion for a change?

'There must be built-in incentives to stimulate the innovator to embrace the concept of continuous innovation'

In my opinion, continuous innovation should be encouraged and the commitment and an associated roadmap to do so could be part of the sponsor's original drug application. For this expectation to be fulfilled, there must be built-in incentives to stimulate the innovator to embrace the concept of continuous innovation. As you know, generic products are formulated to match the performance of the referenced drug product that was formulated a decade ago. Wouldn't the consumer be better off if scientific advances are translated into the design of innovative products?

What do you see as the most appropriate critical path topics to improve drug development? Do you think that the FDA is focusing on the most important ones?
Quality by design and identifying clinical trial tool kits for improving the quality of decision making, such as pharmacogenomics, biomarkers, and imaging, are excellent starting points. From there, my personal preference is threefold: (1) creating an open

interview

access knowledge base in drug discovery and development that enable the forecasting of hurdles to drug discovery, development and testing; (2) fostering an open scientific dialog among the stakeholders in the pharmaceutical enterprise. Thus, sponsors are encouraged to engage the reviewers at the FDA as early in the project as possible, so as to develop a common understanding on the management of risks and the measurement of efficacy; and (3) recruiting and retaining top notch pharmaceutical and clinical scientists and engineers who are forward thinking, pragmatic and team-oriented to staff the FDA. Towards that end, I hope to see FDA as much on the radar screen in the academic community as NIH in terms of intellectual pursuits and graduate and post-graduate education.

Do you think that children and the elderly should be part of testing strategies for future drugs especially if there's an intention for them to be used in those populations?
The answer to your very timely question will depend on further definitive studies. A key aspect of such a study will be to identify conditions that will trigger the need for clinical testing in those two age groups and then to design clinical trials rationally without exposing the subjects on the study at extraordinary risks. Here is where the knowledge base that I have mentioned several times already would find utility.

Do you think that should be done by simulation or by actual testing?
Actual testing guided by simulation.

Do you think that, and at what level, should the FDA become involved in the NIH roadmap?
An extremely pertinent question that is very close to my heart. The NIH Roadmap Initiative seeks to identify the critical scientific gaps in basic discoveries and their translation into modalities that will lead to improvement in health. The three major themes – New Pathways to Discovery, Research Teams of the Future, and Reengineering the Clinical Research Enterprise –resonate very well with the tenet of the FDA's Critical Path Initiative. There are unique regulatory questions, which merit NIH funding to support research in the academic sector under the auspices of the NIH Roadmap Initiative. I think there is room for coordination.

What would you like to have achieved by the time you leave the FDA? Presumably that's part of it but would there be something else?
My answer obviously depends on the timeframe of my affiliation with the FDA. Thus far, I am having a fun time, there is so much to learn and so much to contribute. I learned firsthand the multitude of factors that shape the rendering of decisions on drug applications. I also witnessed the leadership role the FDA has played in improving the quality of medicines to consumers. Were I to leave the FDA tomorrow, I will be in a better position in advising graduate students to consider the FDA as an institution of choice to launch their career. I also see a need for graduate programs that will prepare regulatory scientists of the future to lead the march of transformation rather than perpetuating the status quo. I do hope that my tenure at the FDA has sparked discussion in the community on wide-ranging issues: (1) re-examining the mission of the Agency, (2) redefining its interaction with other stakeholders in the pharmaceutical enterprise, and (3) re-shaping this complex entity as a facilitator of bringing innovative therapeutics to consumers. We have to be ready for the consumers of tomorrow, who will be far more sophisticated in their knowledge in medications than the current generation. I won't be surprised that these consumers would, someday, become a significant driver for future innovations in therapeutics. This is certainly true in the electronic business.

So they can make informed decisions of their own?
To a certain extent and hopefully in consultation with the pharmacist. I am excited at the prospect of having my genetic information, health history, medication record, indices of life style and similar pertinent information on a chip. This is a marvelous tool from the standpoint of monitoring compliance, minimizing the occurrence of drug–drug and drug–nutrient interactions and, if necessary, identifying potential subjects to enroll in drug studies. When implemented on a community-wide basis, I can envision the possibility of forecasting the emergence of disease, particularly infectious diseases, thereby prompting early preventive measures.

My favorite scenario of the future is drug dispensing via an inkjet in your own home. Consider patients with chronic conditions stabilized on a fixed number of medications and assume that home-based diagnostic kits based on a color change upon exposure to a specific drug are available. If that color image can be scanned, the information captured on-line and analyzed, the dose readjusted and then dispensed via an inkjet. This kind of information, when integrated on a community basis, may lend insight on drug efficacy and/or toxicity in a diverse population. Can you imagine the impact this will make in drug development when such an arrangement is propagated worldwide?

I remember once talking to somebody with a similar idea where people in remote areas could actually use the internet to report their systems from chip based diagnostics and then the appropriate medicine and dosage could be shipped out to them rather than them have to go through pharmacies and physicians so I think maybe other people are thinking along similar lines.
Yes, this is truly personalized medicine. The skeptics might dismiss this therapeutic goal on the ground of costliness. This may be true in the current business model of drug development. Nevertheless, I am optimistic that if we look at cost on a broader scale, the actual cost to a community may in fact be reduced were patients to be prescribed drugs in accordance with the relevant information on their chip.

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