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Janet Woodcock discusses the FDA and the drug development process

Interview by Christopher Watson

Janet Woodcock, currently Acting Deputy Commissioner for Operations and Director, Center for Drug Evaluation and Research, US Food and Drug Administration

Currently Acting Deputy Commissioner for Operations at FDA, Janet Woodcock has served as Director, Center for Drug Evaluation and Research at FDA since 1994. She previously served in other positions in FDA including Director, Office of Therapeutics Research and Review and Acting Deputy Director, Center for Biologics Evaluation and Research. She received her MD from Northwestern Medical School and held faculty appointments at the Pennsylvania State University and the University of California in San Francisco. She joined FDA in 1986.

How must/can the pharmaceutical industry change its adversarial approach to regulatory authorities?

I think we have been seeing a change for more than a decade, probably worldwide, in the approach of both the regulatory authorities and the industry. They recognise that there are many common goals and I think that there is a sense of collaboration that has come to the fore on technical matters, through forums such as the ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) and through other avenues. I think that there will always be conflict because that is the nature of regulation but the goal is to use science-based technical standards – that is our mantra – and this is the way forward for much of regulation.

It is often said that it is FDA bureaucracy that is responsible for the soaring costs of drug development. How do you respond to that?

There are two issues here. One is, yes, there are standards, and they aren't just FDA standards, they're societal standards. People who develop drugs have to be responsible for determining that they are reasonably safe and that they work – that they add value. Increasingly, firms are going to have to show the value of the products that they are selling and also that they can be made reliably. I think we all agree that we need to have the most reasonable, effective science-based standards possible, which are not excessive and that are targeted towards meeting regulatory and societal objectives. That is not bureaucracy, it has to be very mindful regulation. That is part of our obligation.

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What is the biggest threat to research-based pharma companies – is it patent infringement, cost control or their own operating model and subsequent lack of productivity?

I believe that the current development model is not completely successful. It has obviously brought tremendous benefits to the population over the past three decades but I believe that we are going to have to improve the model if we are to translate the next wave of new scientific knowledge into new products. This is what we at the FDA articulated in our Critical Path report. There are many opportunities for improving the discovery and development process. We didn't talk about the business model but this is definitely something that big pharma needs to look at.

Is the current clinical trial methodology sustainable economically – what other approaches could be used?

At the FDA Science Board meeting where we presented the Critical Path, Rob Califf said that with fairly straightforward measures the costs of clinical trials could be reduced by 50%. I believe that figure could be even greater with more systematic interventions. One of the things we will be focusing on in Critical Path over the next year is where the opportunities are to really bring down the costs, to reduce the cumbersome nature of clinical trials, and how to get these answers more efficiently and have the same quality of information. I think there is actually uniform agreement that this can happen but it requires a lot of cultural change. However, I definitely believe that it is possible. It is similar to the GMP (Good Manufacturing Practices) initiative for reforming the approach to regulating manufacturing that we started a year and a half ago. People said that there wasn't a problem, except for the FDA, and that the FDA will never change. But we have changed dramatically and there is widespread acknowledgement that there are problems in manufacturing and that there are scientific opportunities for improving the way that pharmaceuticals are manufactured. We are using this initiative almost as a prototype, I think, because it has been very successful in focusing people on applying science to how we make medicines and this will eventually really lower the costs and improve the flexibility and agility of the industry. The same kind of approach can be applied to some of the problems in development. However, each one requires a whole initiative so it's a big task, but doable. We have talked to some clinical research organizations (CROs) and I think that they all believe that there are opportunities.

There has been a marked dip in approval rates of drugs with novel chemical structures and new biologics applications. Is this a regulatory problem or a problem with the drug companies?

It's not a regulatory problem because we are approving the same percentage of applications as we have in the past, possibly even slightly higher. It is the submittal rate that has dropped. This is a much-discussed area and the reasons behind it are probably multi-factorial but it will probably be reversible over time. However, the downward trend is very disheartening – we should be seeing a marked acceleration in the rate of submission so something is very wrong.

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One of the issues is that it takes 15 years for a new technology such as genomics and proteomics to really penetrate into drug development so it is probably over optimistic to assume that these will be revolutionary so quickly. Even in discovery they are finding that these approaches are not the panacea that they were first thought to be. Many targets are being discovered but are they valid targets? This raises a whole set of new questions rather than immediate answers. That's OK because we are learning more about disease and biology but I think that everybody understands now that we are going to need a more systems and whole organism focus rather than a strictly reductionist focus on the genome or the single gene. So that is one factor – there are also mergers, the big pharma model, the costs, people say many of the easy targets are gone and so on – there is a whole long list and many of these are probably true and are part of the problem. What we need to do is to focus on solutions and a way forward because it is clear that we are currently not in a period of rapid production of new therapies.

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What is the long term future of big research-based pharma given their poor productivity and pipelines filled with the same targets?
I think they will diversify down different pathways. Corporations must change and evolve. It's the nature of economic competition. So, we'll see multiple strategies followed and it will be a survival of the fittest strategy. A large number of new molecular entities (NMEs) that CDER approves every year are from smaller companies and this will probably continue as a trend.

The NIH Roadmap is attempting to address clinical research infrastructure problems. What is your opinion on the Roadmap and how will the FDA be collaborating with these efforts?
I have an extremely laudatory opinion of the Roadmap and we are working very closely with the NIH now on regulatory issues relating to this. So we will be collaborating very closely.

What are your views on the increasing number of biologicals coming through approval – do you see this trend continuing?
I think for the foreseeable future, yes. Eventually, you want to design molecules for a purpose. Right now, biologicals use nature's design. This is because nature is a better designer than we are right now. We are increasingly seeing engineered biologicals and I think that the distinction between biologicals and small molecules, which are all basically organic compounds, will be eventually eliminated.

What will be the impact of the FDA reorganisation of the Center for Biologics Evaluation and Research (CBER) so that new biologicals will be reviewed at the CDER?
The review practices will gradually become merged. There are certain statutory differences under the Public Health Services (PHS) Act but we will be gradually reviewing and standardising our review practices.

What is the current FDA perspective on generic biologics?
Legally, the Hatch-Waxman Act is available for proteins that are approved as drugs but we do not believe that a protein could now be approved as a generic. Physical and chemical characterization alone is not sufficient to show sameness for these molecules. For products approved under the PHS act there is no generic pathway legally, which means that, other than publicly available information, there is no way for a follow-on to get the information of the innovator and use it. So there cannot be generics through that pathway.

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In silico ***modeling is becoming more commonplace in drug discovery. Do you think the FDA will ever mandate simulation-based screening of therapeutic agents?***
I think it will be a long way into the future before we mandate it. We have a small internal program where we are trying to introduce quantitative disease modeling into our reasoning when looking at early drug development and the construction of end-points and recommendations.

On a related note, simulation in clinical trials has been around for some time – thinking some way out, do you ever see a time when the majority of a drug discovery development programme will be done **in silico** ***with a small amount of in-life testing – if yes when?***
This might become best practice once there is enough data to construct good models but I think that you will always require clinical confirmation because biology always throws you!

How do you see the advent of personalised medicine (as a cover-all for some combination of pharmacogenetics, biomarkers, diagnostic bundled with a therapeutic) impacting regulation.
It is clear from our recent pharmacogenomics guidance and related programs that we are trying to be at the front-line of this because drug safety and effectiveness obviously impacts the population. We don't want to have regulation be a perceived barrier to the development of targeted therapies because there are many other barriers – economic, scientific and so on. This requires a lot of regulatory flexibility and construction of new models of regulation, and that's a good thing.

What is your take on a recent study from Harvard University and the University of Michigan claiming that the enactment of the Prescription Drug User Fee Act (PDUFA) has not made the approval process any more quicker than federal funding increases did?
I think that several articles have concluded that if you put more staff onto a program it's a faster process, irrespective of whether or not it's user fee dollars. Because the money comes from industry there have been a lot of accusations that this is the reason why the process has speeded up and that we have lowered our standards. We vigorously deny this – this is absolutely not the case and these studies support that. They show that additional funding, mainly in response to the AIDS crisis and prior to the introduction of the user fee program, resulted in a speed up of the review time. When the user fee program kicked in another speed-up occurred based on that incremental infusion of staff. It's strictly related to provision of greater workforce. So the money can come from any number of sources but you do need an adequate scientific workforce to accomplish the review in a timely manner.

Adverse drug reactions are still a major complication in drug therapy. What measures, both pre-approval and post-marketing, is the FDA implementing to tackle this problem?
With Critical Path we are trying to look at new pre-market tools to better predict some of these reactions. I also think that safety pharmacogenomics may be very helpful because many of these reactions are rare and it is not known why we have them. If we can predict who is at risk there will be a tremendous safety improvement. In the post-market arena we issued a report in 1998 on risk management and we have implemented under PDUFA more effort on managing risk, acknowledging that powerful pharmaceuticals are always going to have side effects and that what is needed is appropriate management of these risks. The Institute of Medicine and many other groups in the US have pointed out that many of these side effects, the preventable ones, are a consequence of problems in the healthcare system and medical error. So we are working with patient safety movements to try approaches such as automated prescribing and decision support systems for clinicians and so forth that are proven to cut down medical errors that lead to side effects and this could have a significant impact on safety.

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The accelerated approval process is used to speed promising new agents, particularly anticancer agents, to the bedside. It has met with some criticism though. Does the accelerated approval mechanism hinder a company's ability to perform definitive clinical trials with a new agent, reducing the opportunity to prove that a drug is truly safe and effective?
It has to be recognised that there is always a tension there. If there is a potentially life-saving drug and you are a patient who has a fatal condition, you are not going to want to be randomised – that's the bottom line. I would say to the critics that accelerated approval of HIV therapeutics transformed the HIV epidemic. Period. People have criticised CD4 counts and later surrogates but it is a fact that people are now living with HIV as a chronic disease and those drugs were all approved through accelerated approval and then they underwent more definitive studies later and they succeeded. The cancer area is more complicated because there are hundreds of different cancers. There is concern that tumor response alone is not an adequate basis for approving these therapies. Part of the problem with oncology at the moment is that the drugs are really not that effective. The dawn of pharmacogenomics will happen in oncology because tumors are mutated and have different functional genomes from normal tissue. Interventions will therefore be designed against these specific genomes. I believe that this will eventually be a very powerful and unequivocal approach.

What are your thoughts on the impact of direct-to-consumer advertising? Is enough information about side effects and complications contained in these ads? Do you think that the industry's advertising costs are now having an impact on the cost of drug development?
Well, I'm not a businessperson so I am not qualified to answer the last part. We believe that the current advertising is done within the law, and it's our job to make sure that it is balanced and not misleading. We are trying to do the best we can to make sure that this happens.

I would like to hear your thoughts on parallel importing of drugs. With drug companies such as Eli Lilly and GlaxoSmithKline stepping up their campaigns against reimportation and some states defying the law against importing drugs from Canada, what is the FDA planning to do to address this situation? Is the FDA perspective on reimportation going to change?
I can only say a few things about this. Importation of unapproved drugs from outside the US is against the law. There is no regulatory structure to make sure that this could happen safely. So people that are ordering drugs from outside the US have no assurance that they are getting a drug that is safe and effective.

One of the reasons why parallel importing has become such an issue is because of what is perceived as unfair prices for medicines in the US. Should the US government introduce price controls to address this?
This is not something that I could comment on.

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What would you like to have accomplished at the end of your career?
I don't see my career ending at FDA! What I have always been interested in accomplishing at FDA is making sure that we have a dynamic, science-based, innovative and flexible regulatory system that serves the needs of the population. I don't think that we are completely there yet but I think that we have made considerable progress. I am devoting my energies to moving down that path.

Janet Woodcock
Center for Drug Evaluation and Research
US Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
USA