Janet Woodcock – Director, Center for Drug Evaluation and Research (CDER), US FDA

We have worldwide citizenship obligations. As we did with ICH, we are trying to bring everybody up to a certain level and be fit for purpose

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In an exclusive interview, Janet Woodcock, head of the Center for Drug Evaluation and Research (CDER) at the US Food & Drug Administration (FDA) outlines how the world's gold-standard agency for regulatory science is adapting to game-changing and often extremely expensive new therapies, why a sizeable impact from data and artificial intelligence on the US drug approval process is still some way in the future, and how the FDA is collaborating with other regulators in an increasingly globalised system of drug development and approval.

Janet, you are one of the FDA's most seasoned staff members, with over 30 years of experience. As head of the Center for Drug Evaluation and Research (CDER), what objectives have you set for yourself and your department?

My focus has been on ensuring that we do the very best for the public. We are public servants, so we have to efficiently and effectively deliver on a mission. That means our organization has to be top-notch in every single department. We need to keep up with the pace of change – both scientific and social – and continuously improve and evolve.

That is the broad objective. Under that, there have been many, many initiatives and changes over the years.

Parts of that mission were encapsulated in the 21st Century Cures Act (Cures) in 2016. How has the work of the agency evolved post-Cures?

Cures was an act passed by Congress, but we have been changing and evolving for many decades. We work with Congress so most of the provisions in Cures are things that we have been working on already and that Congress wants us to put into statute and direct us to go further on. Key topics include patient-focused drug development, biomarker qualifications, and related qualification efforts – that was a big theme that has been going on for quite some time, but they tweaked the program and made it an official part of our mission.

Congress also gave us some appropriations to help move those things along in areas such as rare diseases. Rare diseases have been rising as a target of pharmaceutical development. Last year around 41 percent of approvals were novel approvals for rare diseases. Part of that is because of targeted therapies that make more rare diseases, and part of it is because rare diseases themselves are being targeted for development. That is a big change from two decades ago when most development was in common diseases, antimicrobials, cardiovascular diseases and so forth.

What are the changes within science, technology and society that strike you the most and which are the ones that you feel have the most impact on the work you and your team provide?

In science, the most dramatic change has been the genomic revolution, it has really taken over drug development so to speak. We get a lot of genetically targeted therapies now, we can diagnose disease better because of genomics and so forth. The cancer drug revolution is driven by understanding the somatic mutations that underlie cancer and maybe targeting those.

In technology, it is really the information revolution and informatics. We are late because formerly we didn’t have the resources to really take advantage of that. But now we do, partially due to Cures, and we have put together a very ambitious plan to really take advantage of all of the technology, knowledge management, automation and machine learning and incorporate it. That will be an effort over several years. Better late than never.

On the social side, one of the really big issues is drug prices in the USA. That is affecting us in many ways; I knew this was coming years ago and it has finally come. Obviously, there is a lot of interest in us improving competition in the USA. Our generics program, our biosimilars program

and what we can do, and then the proposal by the administration to import drugs from Canada. All of these things on the social side will continue to be tremendous pressures, as the FDA is caught in between. We do not set drug prices, but we are approving these drugs, and some of them end up with outrageous prices.

The FDA does not have a “pricing mandate” but approves drugs that then go to market with extremely high prices. In such a fragmented system, where does the responsibility for these high prices fall?

Naturally, people ask us why we approved these expensive drugs. They tell us that they are too expensive and that they do not want miracle drugs if they are going to cost so much. But we are not setting the price. It is going to be a source of tension in the USA for a long time.

There is nothing that the FDA can do apart from ensuring that the drugs are safe and effective. Nevertheless, it doesn’t stop people from looking at us. Articles are being written saying that we are approving too many drugs. Why did we approve a drug for spinal muscular atrophy, a terrible disease which paralyses children? The answer is because it improves their life and probably saves some of them. However, it costs a large amount of money, as gene therapies do.

Some regulators have instituted accelerated approvals, not only to answer unmet needs but also as a means to build expertise in some specific therapeutic areas. How would you describe the way in which the US looks at accelerated approvals?

Accelerated approval is a full approval by the FDA, but with a commitment to do more studies. Some geographies will give automatic approval to certain drugs; for example, a drug for people with metastatic disease who have exhausted all other treatments, that shrinks their tumours and they remain shrunk for six months.

At the FDA, we would probably look to give the drug an accelerated approval, because we regard that as an intermediate endpoint, not a final endpoint. We want more data on how good this drug really is afterwards. That is what accelerated approval is really about.

Some rare diseases such as Fabry Disease, for example, have very slow evolution. But we know the genetic defect, and we know the enzyme that needs to be replaced. Replacing the enzyme has some effect on certain biomarkers. So, we give it an accelerated approval and then wait for more

confirmation that it provides clinical benefits.

So, the FDA sees it as the responsibility of the companies to bring more evidence at a later date?

Yes, before the accelerated approval happens, we settle on the kind of trial the company is going to do afterwards. For a long time, because we wanted to get HIV drugs out quickly, we would get them out under accelerated approval, when we had the results from 12 weeks of therapy. However, we are concerned that resistance would develop with any anti-infective drug; we want a drug that has a longer period of effectiveness and so we give full approval when that same trial has gone on longer and we can see more evidence.

Are you satisfied with the relationship between the industry sponsors and the FDA in this accelerated approval path? Are you satisfied with the post-approval process or do you wish to see more effort being made?

There are a lot of things written about how the industry is not meeting its commitments. It brings us all a lot of bad press.

However, this is a very complex area. For example, how can you carry out a placebo control trial for a metastatic disease drug that has been shown to shrink tumours and ensure that patients are stable for six months? Who is going to enter the placebo group? Everybody wants the new drug. So, often they have to go back to a less sick group and compare it to some other therapy and do a comparative trial. That might take quite a long time.

With rare diseases, it is even worse. For rare diseases, there are often no other treatments. Therefore, we approve a drug for it and on social media, every single affected parent knows about it. They do not want their child on a placebo control trial when it is available, making it very difficult. The companies have to perhaps do the trials in regions where the drug has not been approved yet.

However, in rare diseases, there are a limited amount of patients and therefore the timeframe may be longer. The rare disease may progress very slowly. Another issue is sponsors; we have seen certain cases where sponsors have not pursued their obligations where they should, although in general, they have. Sometimes the fault lies with the FDA, where we have made unrealistic

requests in terms of timeframes at the last minute and sponsors have been unable to comply.

Last year, the FDA had over 900 applications for regenerative medicines, yet only approved four. What message is the agency sending?

The agency hired me in 1986 because I had expertise in monoclonal antibodies. And so, a few monoclonals were approved over the next couple decades. But monoclonals have only really hit their stride in the last decade. So, what happens is that it takes technology time to settle down once they get into humans – it is not as easy as it seems so to speak. There is a lot for companies to do. It is not a slam dunk now.

Previously, when we were all scared about recombinant technology, we had the Recombinant Advisory Committee. However, nowadays, researchers can raise humanized monoclonals in about a week if they have the antigen and can get a whole portfolio, and they know how to expand those clones.

Things have really changed from way back then when it was all laboratory mumbo jumbo and people didn’t actually know how to do things reliably.

Gene therapy, regenerative medicine and cell therapy are all still in the phase where they need to work on safety and efficacy, which is very important for us.

Data and AI are the current hot topics in the healthcare and life sciences field, with many claiming that they are going to be a total game-changer for the industry. What is your point of view?

I believe that data and AI may be game-changers in the future, but not in the immediate future. We have made a huge amount of effort in this space with the Sentinel initiative, which covers several hundred million lives, in claims data, and we have been told to use real-world evidence (RWE) as part of Cures.

However, the old maxim about data – garbage in, garbage out – still holds. Honestly, the European healthcare systems are in better shape. There is more standardization. US electronic healthcare records are not interoperable. Even within electronic health records, a lot of the terms are not standardized. There is a huge problem of noise in the system.

While, for example, Google can figure out who uses what brand of toothpaste and how often they buy it, health is a different type of thing. Consumer behaviour which is tracked very closely by all these data firms does not tell you whether you are going to get sick or not or what medicine you can take.

So, I think data is somewhat overrated as far as its immediate impact on biology. People do not understand how complicated human biology is.

There seem to be divided views on data, with the industry broadly praising the data revolution and putting a lot of effort into bringing in expertise from the world of technology to reduce the cost of research.

Conducting clinical trials is becoming impossibly expensive. It is the most expensive part of drug development. There is a hope that by using real-world data or evidence, that they can make their trials smaller or substitute data for trials. There is a lot of hope that data can provide a solution to this.

> Conducting clinical trials is becoming impossibly expensive

We are working with companies and we have certainly done approvals based on registry data as a comparator for rare diseases for example. We are funding experiments where you do observational studies in parallel with one of these confirmatory trials, and then, we can see the performance characteristics. What did the observational study find? And then, what did the traditional clinical trial find? And we may learn some things from that, but we are not at a stage where we can make a lot of decisions based on these kinds of data.

Although the FDA's mandate is for the USA, you are the gold standard for regulatory science globally. Is there a danger that the greater uptake of data stands to leave other, less-developed, regulators behind?

We at the FDA were the drivers behind trying to get the International Council for Harmonisation (ICH) reconstituted; inviting in regulators from other countries as well as the innovative and generics industries. It was FDA and Theresa Mullin, director of the FDA's Office of Strategic Programs in CDER, that really made that happen.

We want to develop clear, harmonised technical standards for everybody, that everybody can follow. Then, we would like to see more regulatory convergence and as many alliances as possible. We do not have to rely on each other for approval decisions, but there is a whole lot of duplication in pharmacovigilance for example. My favourite is, of course, manufacturing quality standards. I do not understand why they would have to be different – why can't we have one standard for each dosage form around the world? That would help the less developed countries a great deal because there will be something really reliable that everyone has agreed on.

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With data, we are not yet in a state where we can leave anybody behind. We are just trying to figure it out ourselves. Honestly, I think Europe is in a better shape. Because each country at least has a nationalised health system, with a full population capture. They have more or less standardised ways of how to enter the information about the people, and if you go from one city to another, you don't lose your health records. Whereas here if you go from one health plan to another, then we lose all identification of you.

The FDA does not direct the type of research that might be done in the USA, but are there opportunities in terms of research collaboration with your neighbours at the National Institutes of Health (NIH)?

The NIH is huge. Congress gives them a lot of line items and directions because all the disease groups lobby congress and they have all the different institutes. However, the NIH does not fund drug development science at all. Their mantra is that they have to understand basic human biology and disease, and it has to be innovative. They have specific study sections and their procedures preclude a lot of funding.

We collaborate with them a lot but not on deciding what research to do. Our tobacco centre has money for research, and they have given a lot to NIH to fund basic research on tobacco, for example. But we do not get research dollars. The FDA has received some modest funding in two areas. One is for generic drugs. We got that not through appropriations but through user fees. We have done some really good research on barriers to getting generic drugs. For example, you have to do clinical trials, right now, for many topicals because you cannot use blood levels for

bioequivalence. Inhalation drugs with complex delivery systems have been very difficult. We have done a lot of research on these matters to try to devise programs that would then allow topicals to be approved without a clinical trial. That we can determine they are bioequivalent without doing a clinical trial.

The other field for which we have received funding has been manufacturing. We have been pushing advanced manufacturing for almost 20 years. It is very frustrating, but it is starting to pay off. We have approved a bunch of advanced manufacturing of products that are made by advanced manufacturers.

Most traditional manufacturing today is done outside of the USA, but in 2020 with tax breaks and the 'Made in America' campaign, might we see more advanced manufacturing in the USA?

Traditional manufacturing has a lot of environmental liabilities. It also requires a large workforce and physical footprint. Advanced manufacturing deals with those liabilities, so it is much more feasible to do advanced manufacturing than it is to do traditional manufacturing in the USA. Because we have been pushing this, we have received money from Congress to give out grants to universities. We need a workforce schooled in advanced manufacturing. Of course, we have worked with Novartis and MIT in their successful collaboration to institute a continuous manufacturing set up.

We appreciate the funding from Congress, and we are going to keep pushing. There are a number of benefits to producing ourselves. For example, if China has to shut its borders due to the coronavirus outbreak, much of the world is going to lose its source of APIs.

It may sharpen the interest in having more regional manufacturing. I am not really one to say that "it shouldn't be made in China", it is more a need to move away from single sources and long supply chains. They are both dangerous. Having regional sources of manufacturing is much safer for all people worldwide.

Issues such as chronic diseases and antimicrobial resistance (AMR) may not be where the industry has put their hearts and minds, but are increasingly important. What are the views of the agency regarding these issues? Do you have any concerns about the lack of investment or lack of interest in them?

Yes, I have certainly testified on this. We were able to push Congress to get the limited population use designation which allows us to approve a drug based on a very small data set. The concern in the past would be: “okay, it was approved for this resistant organism, but people just use it for everything”. Actually, that concern has been abbreviated to a great extent because of the cost of these medicines. Nobody is going to use them for a common cold.

The limited population designation helps, but we cannot make a law, there have to be additional incentives. Congress has put some into place. But people are tearing their hair out because you cannot have an incentive for getting a single drug through – you need a development program because it turns out it is very hard to develop new antimicrobials. A lot of people have tried and failed. You have to put 100 people in laboratories and sustain them for a long time. What is worse is that companies have been shutting down their programs and going to more lucrative areas such as cancer and rare diseases. I predicted all of this.

So, as far as other chronic diseases go, that is also a concern. More people in the USA have problems with diet, obesity and lack of exercise, so the population has heart disease, hypertension, etc. There is only so much that you can do to treat that with medicine. That is probably not the right approach. But, when you have a population with those problems, as a society it is probably more practical to try other broader approaches.

This state of affairs is somewhat ironic in the only country in the world where Food and Drugs are grouped together in a single agency. What is the significance of this?

We have the Centre for Food Safety and Applied Nutrition, but they have a very small staff and must spend most of their time on food bacterial outbreaks, pesticides and so forth. But clearly lifestyle modifications are what is needed, but when you have a population that is not going to modify their lifestyle, then medicines are the next thing that you reach for.

Especially for a country that pays more for its healthcare than anywhere else on earth. With life expectancy not rising, the outcomes do not seem to match the input.

Life expectancy is going down. There are fees for service in healthcare here in the USA. If you pay more, you get more imaging, X-rays and tests, and they lead to more tests and so forth. It is not all a cost of medicines, but the whole treatment process. We are concerned about chronic diseases, and many of them have treatments, so drug development has to be comparative, and that is more

costly, right? You notice some of the cardiovascular trials may have 25,000 patients in the trials, that is an expensive enterprise.

We are working with groups like PCORnet, and one of the other things that I have been trying to push is that people set up research networks so that you can do lots of studies on the same platform. I am talking a lot about this, and we are starting to see these master protocols, and platform trials and so forth. PCORnet is a network of trials and they can run trials, even cardiovascular trials, more cheaply. They are running one looking at what dose of aspirin people who have had a cardiovascular event should take. The problem with aspirin is that you can get a stroke or cerebral bleed, that is a trade-off, but it prevents heart attacks and strokes. They are asking what dose people should be on because right now it is one baby aspirin a day, but nobody knows the correct dosage.

So, they are able to run a humongous trial to figure that out. Since they have all people in these healthcare systems, they already have captive patients, and they can run their trials much more quickly than a pharmaceutical company which would have to recruit sites and train the sites.

Evidently some sort of incentives will be needed on that front.

Yes. There are lots of people starting master protocols now. I imagine that if we get more candidates through the coronavirus that will be a master protocol. The Ebola trial in Africa was a master protocol.

But pharmaceutical companies are not going to originate this – because they do not think this way, they are thinking about their asset, and how to get it most efficiently to market. So, we work with patient groups and other non-profits that have an interest in the patients, the disease and making the disease better.

There are some master protocols going on in the USA, and there are some that are being started worldwide – and they would test multiple interventions; they have the capacity if you come up with a new intervention they can test it because they have set up the whole infrastructure.

The FDA remains the gold standard in regulatory science. Do you see this position being challenged in the coming years?

I am not sure I am the one to say we want to be the gold standard. I think we have worldwide citizenship obligations. As we did with ICH, we are trying to bring everybody up to a certain level and be fit for purpose. Other agencies sometimes make better decisions than we do, and sometimes we make better decisions. But I think the future is one of regulatory convergence and of working much more closely together. That is really necessary in the drug world. We are no longer islands out here. We used to make drugs here, test the drugs here and take the drugs here. None of that happens anymore. They are used worldwide, made worldwide and tested worldwide. So, the stronger the systems we have worldwide, the better off we are going to be.

We all need to work together. Science really can deliver better health for all the people in the world but only if we work together and have common standards to make sure that these interventions are fit for purpose and work for everyone. We should also be able to know who these interventions are going to work for; that is part of personalized medicine. That is a very important part of worldwide development, that people do differ, and science will be able to figure that out too.

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