INTERVIEW WITH

Dr. JESSE GOODMAN

H1N1 ORAL HISTORY PROJECT

Interviewed By Sheena Morrison

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Interview with Dr. Jesse Goodman
Interviewed at Dr. Goodman's Office.
Silver Spring, MD, U.S.A.
Interviewed on December 2nd, 2009
H1N1 Oral History Project
Interviewed by Sheena Morrison

Dr. Jesse Goodman: JG
Sheena Morrison: SM

SM: The following interview was conducted with Dr. Jesse Goodman, Acting Chief Scientist and Deputy Commissioner for Science and Public Health within the Food and Drug Administration. It was conducted on behalf of the National Library of Medicine for the Making History: H1N1 Oral History Project. It took place on December 2nd in Dr. Goodman's office in Silver Spring, MD. The interviewer is Sheena Morrison.

Okay. During the last interview the discussion focused more on your past life as director for the Center for Biologics, Evaluation and Research. Acknowledging that many of their responsibilities overlap, I'd like to talk about your current role in the response efforts. So can you begin with the brief overview of the FDA's role in the continuum

of vaccine preparedness? And when I say continuum I am referring to the development, production and immunization process that takes place even in the absence of a pandemic.

JG: Sure. And just for...One question I would have for you is, as we talk about this pandemic response, are you focusing just on vaccine or on the other things too? 'Cause there are a bunch of other activities that have gone on in FDA: antivirals, diagnostics-

SM: Everything.

JG: OK. So the influenza vaccine process, both for the pandemic and then for seasonal vaccine, is actually quite exceptional in terms of the fact that FDA, the U.S. and global public health community have a very hands on involvement every year in producing vaccine, which we don't normally have for the typical product regulated by FDA. That, I think, both creates a lot of familiarity with influenza vaccine and what needs to be done to get it going. It also creates this global and U.S. network of people engaged in that. It also creates a lot of interactions with manufacturers so that when we come to needing a vaccine for pandemic, there's a lot of shared

knowledge and history and understanding of everybody's roles that plays into that.

Now that said, it is a challenge essentially each year even when using the similar licensed methods and the same manufacturers and the same kinds of approaches to essentially change the vaccine to fit new strains each year. So, typically, every year with seasonal vaccine, typically one or two strains might be changed, rarely none, or rarely all three. So it's a three strain vaccine. And what happened with H1N1 was to accelerate, compress, try to get all the normal things done in the normal high quality way, but as quickly as everyone could. So, there, it really is a global effort. Both a U.S. and a global effort.

There are a number of collaborations that take place through WHO as a focal point. Both CDC and FDA have slightly different roles, but are what are called WHO Collaborating Centers. In the case of CDC, they have a particularly large role, as I'm sure you'll encounter, in surveillance, trying to identify new strains, and each year help provide information that lets FDA and WHO decide on what strains to include in the vaccine. CDC and other

surveillance labs also get the actual virus isolates typically that then can be engineered into strains for vaccines.

FDA is a WHO Collaborating Center as well, and one of what I believe are called a Network of Essential Regulatory Laboratories. And every year FDA, multiple laboratories throughout the world, including FDA and CDC, and in some cases companies, participate in a multi-step process.

Step (1) is selecting what strain should the vaccine be directed against. We do that by bringing data from surveillance to meetings of both WHO and FDA's vaccine advisory committees to choose the strains, and CDC is very involved in that. In the case of H1N1 (in some ways that was a simpler process) it still involved, well, which of the different isolates from different places should be used to start making a vaccine. You want it to be as representative as possible. So let's say there were lots of genetic differences among viruses being isolated, you would - what frequently happens with seasonal vaccine - you would try to choose the one that would provide the most protection against what is likely to circulate. In this case the viruses all looked genetically very similar, so

that was a lot easier. And issues more became about how the virus grows and performs in manufacturing. But, anyhow, step (1) every year is to choose good strains from clinical isolates from patients for the vaccine, and then go through a process of converting those strains that are suitable for manufacturing, because most manufacturing processes can't use just the wild type virus out of patients to make vaccine. They have to use it where it is manipulated to be safe for manufacturing and also to grow well in eggs, which is the normal way that most of the vaccines are currently made, which is obviously one of the challenges.

So once a strain is selected to make vaccine, then FDA's Biologics Center, a number of academic, international laboratories and CDC take those viruses and make candidate strains that have been engineered to be suitable for vaccine production. And so what was exceptional here is that the strain was isolated very quickly by CDC, shared within several days with all the laboratories who began doing this work, and a number of candidates strains were quickly available. I think the first one did come out of the CDC. They had the virus first, and ultimately one of

those were selected, as soon as it was available sent to manufacturers.

But you had a situation where within a very few days and then few weeks there was the virus available, and it was manipulated by various methods into strains that could meet the basic requirements for manufacture: be safe, and be on a genetic background that typically can grow in eggs. And currently two different methodologies are used to produce these, what are called, reassortant strains - strains where you have the protein of interest or gene of influenza, the hemagglutinin, inserted into a backbone of other segments of the RNA of influenza that make this almost chimeric virus. The vaccine strain used every year, with the hemagglutinin of whatever the virus is, is switched into that.

SM: Okay.

JG: Okay. So then, those were provided to manufacturers very quickly, and then the manufacturers - and then again, this is exactly what we do every year, but it was done faster - the manufacturers... Ultimately, several of these candidates were available and shared with anyone who wanted

them, from CDC, from us, from the United Kingdom where there is also a National Institute for Biological Standards, which is another very capable international reference lab.

So the two methods these were made by: one is called just traditional reassortants, where you sort of mix the new virus together with the manufacturing backbone, the strain typically used, and you let them recombine naturally in eggs. And then you select out naturally the ones that have the backbone of the virus we use every year that grows well in eggs, and have the hemagglutin inserted into that, and you identify those. So, that's letting the egg do the work.

The other technique which is, obviously, a little more controlled, is you isolate the gene of interest, the hemagglutinin, and you use genetic methods to splice that into the other, with the other genes, to create a virus that packages that with the other genes of the virus. Actually, you don't have to splice them together, they're a package. There's 8 chromosomes, one of which is the hemagglutinin that the virus has.

So candidate strains were made with both these methods. Sometimes what's called reverse genetics, or the genetic engineering method, can sometimes get you the strain faster. I think in this case that was what was initially done. And then academic scientists, Dr. Bucherat at New York Medical College produced traditional reassortants where the egg produces it.

So then what FDA did, and does immediately, is starts trying to make materials that are ultimately used to calibrate the potency or strength of virus. The manufacturers take these strains and they begin trying to, in a way, coax them to grow well or better in their system. It's very typical that there's a lot of variation every year in how the three strains grow, and typically, the manufacturers spend a matter of days to weeks kind of coaxing and improving how they grow in their particular system. And one of the challenges here is that it soon became apparent that these H1N1 strains were not gonna grow as wonderfully as the best seasonal ones, and more were gonna grow at the bottom end of that scale. That had been in the original planning assumptions of HHS in terms of thinking about vaccine availability, but obviously it turned out to be a real challenge.

But at least, initially, the strains were gotten very quickly, but also initially it was clear that they were gonna grow more like strains each year that don't grow well than the strains that do grow well. So the manufacturers meanwhile start out thinking and hoping 'cause they typically are able to get them to grow better. So, now, at the same time FDA, CBER, and other of these essentially regulatory labs around the world start working to make these potency re-agents. And I wont go into the whole process, but it's also a complex process where you have to take the strain you're trying to check the potency of and make antibody in sheep, and do all that, and that takes several weeks. And then, the manufacturers are going to depend on the supply of the actual antigen from the vaccine to have a set of antigen and antibody that allows them to calibrate and measure for their vaccine how much they're putting in every vial. So all that was going on. Again, it was done quickly, but these are methodologies that still rely on technology that's many, many years old.

And so another activity that CBER has been interested in working on for a few years - after receiving some additional support in congressional appropriations for work

on improving pandemic preparedness - has been to try to develop methods that can speed up the production of potency re-agents. And, in fact, a good thing this year is that those were used at the same time and were available as a backup had problems developed. And ultimately, for the potency reagents, the antigen that was being prepared - actually in large scale by contract to one of the U.S. manufacturers - did not turn out to be right away as good as we would have liked for these assays. And we actually worked with our United Kingdom colleagues and recommended, initially, use of that antigen.

So, again, it's an example of why typically we have three or four irons in the fire, because we see typically every year at least one challenge with vaccine manufacturing. Either one company doesn't grow as well as we thought, or there's an issue with one of the reagents or...So, everybody was prepared for this and there was some redundancy built into the system. But still. Then when these potency reagents became available it was clear that not only had the virus grown slowly, like the manufacturers felt, but the amount of vaccine antigen that it was producing (so how does the virus grow, and then you have, as it grows, how much material is it producing that you can

use for the vaccine), and that was lower than normal. So, this is part of what led to the people feeling they were likely to have more vaccine than they did. Both their hope that they could improve the growth, which ultimately many were, and for some, like for example, for the live vaccine produced by Metamune, it grew fine in their system, but where you had to purify out the antigen, it performed differently for different manufacturers. So there was less when these potency reagents were available to truly measure how much was there. There was less than people thought might be there. Again, problems such as this are not unexpected.

Otherwise, vaccine production went smoothly, and I would point out that this involved weekly to daily collaboration between FDA, other international partners - weekly calls with this whole WHO network so that other countries would share their knowledge, 'cause meanwhile much of this is going on in other countries. And then, very intense communication with manufacturers as these different things are done.

So that is very unusual in that essentially every year a new vaccine is produced, and for the pandemic that was done

again, but the challenge was doing it in a more compressed timeframe and the most challenging thing was how the virus grew. On the other hand, one of the challenges which we were all worried about, which was, would it produce a good immune response? It turned out that it behaved just like seasonal, which tells us that there had to be some background immune memory or exposure in the population, because instead of behaving like all of us are infants and our immune systems have never seen anything like this vaccine before, it behaved more like this is something that, although we can't measure antibodies in most people's blood, people have a good immune response to one dose of it. So we ended up with less yield, but not having to use the two doses for anybody but the youngest children, which most people predicted we might have to use two doses. So, you know, this is the big scenario.

The other huge thing that went on, both, and accelerated dramatically as we prepared to potentially have vaccine and immunize people, was to, if you want to get more vaccine out there quickly, one of the remaining steps - so again normally this is extended over time - manufacturers produce the vaccine and do what we call 'fill and finish it', or put it into vials over a several month period. Here you

wanted to get as much out as quickly as possible, and that fill and finishing was also a limiting factor. So the FDA staff worked with BARDA and HHS to identify and bring online as many additional places that could potentially help the manufacturers by filling vaccine into vials. But this involves a lot of quality oversight inspection of new facilities. And so, over the course of these few months a lot of people went out, again worked with manufacturers, but checked on facilities, processes, et cetera, to allow more vaccine to be filled quickly.

And the other area where FDA played a big role is we all had recognized in our planning (and again, in this pandemic started talking early on) that the public expectations and concerns about safely were very high. And that also 'cause we would produce and field a large amount of vaccine quickly, and because of the 1976 history with swine flu and Guillain-Barre syndrome with the vaccine that we wanted to have (even though vaccines are carefully monitored all the time and seasonal flu vaccine we have a lot of experience with, and this was being made the same way), we all decided that it was the right thing to do to try to enhance and put in place enhanced safety monitoring systems. So FDA and CDC kind of have co-led that effort and put together a very

augmented safety monitoring plan and a plan for how they and other government partners collaborate in looking at this information; ultimately created a new external advisory group that they would share the data with to get external feedback as well, et cetera. So I would say those things: getting a vaccine ready, oversight of manufacturing, enhancing ability to fill vaccine, and then the safety monitoring are the key things.

The other piece I actually just completely left out which is huge is that manufacturers produce these vaccines in lots. Every lot they have to both test extensively, provide manufacturing records of, provide samples to the Center for Biologics. Every one of those is reviewed by the Center. Various tests may be performed on various samples, and the center looks at the manufacturing results and testing results for every lot of vaccine and has to individually release every lot. So that's an important quality assurance, but again, wanting to get those lots out as quickly as possible, we're talking well over a hundred lots already. So, a lot of material, a lot of review of records and quality, both by the company and by FDA for those to be released. And again we, our staff, works very hard to make sure that we are doing the appropriate things to maintain

quality, but also kinda working day and night to not hold up any availability of vaccine unnecessarily.

SM: Okay.

JG: So those are the main activities. And the other...Personally, there are a lot of other dimensions, because there's all these other things going on: the antivirals, diagnostics, all these things that were needed that in one way or another had to be ramped up for this, some of which had to be granted emergency use authorizations to be used outside of their normal approved pathways, for example: Oseltamivir or Tamiflu in children under one; new diagnostics that needed to be fielded. And again, these things were done under emergency use authorizations, which was a whole other huge challenge for the agencies to assess the available science and in most cases within days be able to make antivirals available to the public health system; to work with our colleagues to calculate proper dosing for children under one who clearly needed to have access to Tamiflu; to work with CDC to get a diagnostic out to all the advanced laboratories, the states, so that even in the early days one could know, where is H1, who has it, who doesn't.

So that was a huge effort, and to make sure that happened very quickly we actually totally changed how we did things in that we set up an incident command system where all this was being coordinated and tracked, and there was collaboration. So we didn't just have the vaccine people over here, the drug people over there, but we had a unified communication structure with the senior science experts in each area getting together, at first twice daily, to discuss what was going on, and ultimately daily. And as things got well mobilized, we still had that meeting weekly so everybody is aware of everything. And that allowed us to identify problems like shortages more quickly, needs for additional products, et cetera, and have people working on it.

SM: You mentioned two things.

JG: The other thing that I think is important that I'm sure you heard about from HHS and others is that we are part of a very, what has been a…extremely communicative and collaborative response among the different agencies. So virtually daily, actually daily, I mean you've been at some of these meetings, you know that.

So, I'm the lead for the FDA response. There is a senior group of science and public health leadership from FDC, CDC, NIH, HHS that meets at least once daily to discuss what's going on. And then we'll have substantive discussions so that a variety of policy decisions starting with "Do we produce vaccine?" through "Do we use it?", et cetera, were all considered carefully at appropriate times. But other issues like the need for intravenous antivirals, a lot of issues about the public health response, you know, how vaccine would be distributed; there were both throughout all this regular staff level meetings that occurred across all the agencies, and then senior science meetings. So, I think for something that has been extremely complex and involved, hundreds of people here and thousands across the government, there was a need a for all this collaboration. And there were bumps at times, but I think no major disconnect.

SM: Well, I mean that's apparent. You can see that from the news, the progress that's being made. Right now we're at an entirely different phase of the campaign than we were when I spoke with you last.

JG: Right. Right. Right. So there was certainly heat, and I think one of the biggest public perception issues was the initial projections of vaccine availability versus how it became available. And how our culture and our government deal with that have been a real challenge. Of course, now, there's substantial vaccine, and, you know, that's good. And the challenge is gonna be to continue to have people interested in being immunized so that if this comes back in the spring, next fall, et cetera, there's as much immunity in the population as possible, which will protect everyone.

SM: Right. Well, to weigh in on that, many of the successes of the campaign are due in part to, as you said, ongoing communication at multiple levels as well as between the scientific and public health leadership in the agencies. Can you give me some examples where scientifically driven decisions made in terms of safety and regulatory issues were politically contraindicated, or conversely, where politically driven decisions were scientifically contraindicated, and how they were resolved?

JG: Yeah. I think we have been able to stick to the science, and in essence provide the Secretary and the Secretary's office with the best advice of the scientists that has generally been a consensus across the agencies, and that has been adopted. So there hasn't been a situation where I think, for example, a decision - I mean some of the big decisions have been "Do we produce a vaccine? Does the government buy vaccine? How many doses do you need? Do you need a non-approved vaccine? Do you use adjuvants?" Most of those decisions have either been discussed both within the agencies and then by their senior scientist representatives across the agencies to develop policy at the appropriate times, or in the case of something like adjuvants, revisited frequently. And I'm not aware of a situation where anybody in the Secretary's office has said to us, you do something different than what you're recommending. I think part of this is people working together to come up with these recommendations.

I think certainly there are things where we've recognized all along could be improved. We'd like to be able to have reagents more quickly, as everybody knows. We'd like to have systems where we'd like to have more vaccine supplied domestically. We'd like to have more options in terms of

how vaccine is produced cell cultured. I think the adjuvant issue has been particularly challenging given that Europe approved adjuvanted vaccines which allows use of less antigen. Both had one previously approved for the elderly for seasonal vaccine, and then approved two vaccines for pandemic vaccine. That approach was carefully considered here; there was less data available. Two issues are there.

First of all, there's much less experience with those vaccines, which do exert a different response in the people, kind of more sore arms, fevers, things like that. but there's just much less experience with using them year after year in large populations. And also, the vaccines that would have been available to the U.S. were not exactly the same ones that would have been available that were available in the European Union. So there was even much less information about that exact product. And sometimes we see differences between the products. It's sort of not just like one thing; it's the same as everything else. But I think that decision has been revisited frequently and what we were trying to balance was being ready if there was a bad immune response, or there were catastrophic inability

to produce enough vaccine, to have adjuvants and adjuvanted vaccine potentially available.

So we decided early on that both NIH and the manufacturers would be asked to do clinical studies to check on dose, et cetera, and safety, both with the vaccine preparations, with and without adjuvants. But as it's been revisited periodically, the decision has been that given there is much more knowledge about non-adjuvanted vaccines, and given the severity of the pandemic, which was not like in H5 where adjuvants were required to have an effective immune response and where the disease severity was far, far more challenging, those decisions are still revisited. But as of now, there's been unanimity that factors such as less knowledge and experience and therefore less ability to rule out uncommon adverse events that might occur, and the issue of the importance of public confidence, which even for the vaccines we're producing using standard methods we use every year for hundreds of millions of dose of vaccine, there's still such incredibly high consciousness in the public about vaccine safety. So, putting all these factors together - our knowledge about, our level of confidence about safety in products that there's a lot more experience with, and then the importance of that confidence in

preserving the confidence of the public, I'd say we're still in a position where we're collecting more data. And we're ready if we needed to consider that under emergency, use, but again, there was unanimity among the scientists that this was the right way to go.

SM: I guess maybe politically was the wrong word to use. What I'm trying to get at is the way that there is the balancing act between what actually has to be done, transparency, and then the way that, for instance, now we're at the fill finish, the point where we're deciding whether or not to stop production or to let them continue beyond a certain time. Well, perhaps the best thing to do is to stop it, but you can't really stop it without incurring perhaps the displeasure of the public. So, in that sense I mean the political contraindicated.

JG: I think. Yeah. I mean, I think that what has been very challenging, I don't think it's derailed any decision, but its taken up a lot of time and effort, is that as you're doing this, you have very diverse public, political, media, views of everything, you know. So we've got people…and so there's a lot of time spent responding to those views. I think that's not bad, because its not bad

hearing those views and having to take them seriously, because the reason that there's a diversity of views is (1) that people come at things from different perspectives, and (2) that there's been a lot of scientific uncertainty all along: uncertainty about could the pandemic change, uncertainty about vaccine yields, uncertainty about the effect of the vaccine, uncertainty about how to best treat people with antivirals.

So, I think what perhaps shouldn't be surprising, but has been a little surprising, is that a big part of the effective response is taking all these points of view, which one could consider political or opinions rather than science, into account and responding to them. Because if we can't communicate to the public, and if we're not responsible in responding to these different views, we're not doing a good job. Now, I feel like it's been very challenging and difficult for all of us. But I feel like, in general, if I look at, did we make a reasonable scientific decision based on the data available at every time point where we had to make decisions? Or, were those unduly influenced by pressure rather than legitimate views or whatever? I think, again, because of the amount of communication - and also the other thing we did and CDC has

done and HHS has done - there's been pretty frequent use of advisory committees. There's been weekly or bi-weekly media calls. There's been lots of opportunities to get this kind of input and a lot of transparency. So, I think that while everybody, while there's a diversity of views on many decisions, it has to be clear that at least those views have been heard; there have been discussions.

SM: And that's very clear in (I think it was yesterday's meeting) the decision to stop, to not fill finish the remaining bulk from Novartis. Dr. Lurie said, "Well, as we have discussed previously, we have to have all of the agency heads weigh in on this." Everything is brought to the table. So, that's clear that there is a lot of discussion, and that's what I was trying to elicit.

JG: No, I think that's gone on. And, you know, it's not over yet. This is an ongoing process. I mean, clearly, the biggest challenge was the difference between these initial projections and what was then produced. But when I look at the actual things that were about scientific or public health decision making, and also the interactions among multiple parties, the private and public sector, et cetera. Given the intense interest, the complexity and

time frame in which things were done, the multiple partners with diverse interest - the states, the private sector, health systems, FDA, CDC, NIH - you know, I think, partly based on relationships inside and outside the government that many of us worked on from before this event, in general, everybody has kept their eye on the ball, which is, what's the best public health response? Even though we are completely deficient in the science of a lot of areas, knowing what we know, which is substantial also, how do we make, can we make, the best decisions? I've been actually, in general, I feel positive about the quality of both the decision making and the decisions and the outcomes.

Still at this point, despite many, many challenges, I think this country has made available and administered more vaccine than anywhere in the world, and the safety record is looking very good. We're continuing to monitor that. But I think, it clearly tells us, though we've got a long way to go in terms of the reliability and the amount of vaccine we can produce quickly, I think some of the investment in thinking about vaccine safety, in terms of our ability to monitor and respond to questions, has paid off. But that's an area where much can be improved. We're fortunate in that antiviral resistance has been fairly

limited, but again, an important lesson is, we need additional antivirals.

Again, I think, when appropriate data were available, we worked with various partners within and outside government to make intravenous antivirals available. But I think there's a lot of need for work on the products that are needed to respond to these public health emergencies, because you don't have a market generally driving something that is not predictable. So, if you said, well, once every forty or fifty years you need enough influenza vaccine for the whole world, how…you can't just expect that to magically materialize. Or, if you use very little antivirals to treat influenza every season, yet you want a wide variety of antivirals to be available for a pandemic or a bio-terrorism attack, there's a lot of unsolved problems in how you make market driven things work when the market isn't there every year or every minute.

And there's science challenges too. We need new classes of antivirals. We need better vaccine technologies. It's not all just simple like snapping your fingers. So, I think while many have pointed out that if the virus were worse, or if the vaccine production were worse than it were, or if

there where wholesale antiviral resistance, we could be facing a very different picture. We have to realize that, number one, that could have happened. But again, my view is that, well, we were prepared on the adjuvant path wave that did. But in other areas: the strength of our public health system; our ability to deliver vaccine; (I think even though we've done a lot to communicate clearly,) the trust of the public in the government, in the pharmaceutical industry, in the questions raised more generally about vaccine safety; these are all incredibly important things that we need to pay attention to.

SM: One of the things, dealing with new technology, is the new manufacturing site in North Carolina. What role does that play in the overall safety and regulatory process?

JG: That facility which just opened this week,(to begin operating initially, or to begin to get ready for operations), Novartis, that was the result of a very large HHS investment to try to get U.S. based manufacturing capacity, and also to use new technologies. In this case, cell culture based technologies. So, I think that is very important. But, you know, there's more need for that. There's need for more vaccine and antiviral capacity, not

just in influenza, but in other areas of public health. We almost think of that as if the first generation technology is the egg, and it has an advantage of generally working very well and being able to produce huge amounts of vaccine economically. The second generation technology which we're already using for many other vaccines - but its been more challenging for flu - is to grow it in cells, which you don't have to depend on the egg. You could take cells out of the freezer and grow large quantities pretty quickly. But that technology is not gonna - it may create more flexibility in terms of scaling up, it may speed the process somewhat - but there's a whole third and fourth generation of technologies: recombinant protein vaccines, one of which was recently discussed at our advisory committee; DNA and artificial virus particle type technologies that I think, ultimately, we need to see developed in a much more robust and clearly safe effective manner to respond to real public health emergencies.

Those are things that could take us...I think it's a remarkable human achievement to get a vaccine out in 5 or 6 months for a disease that didn't exist before, but a lot of that is 'cause we have a lot of that infrastructure in place, you know. But I think, obviously, both in this case

and in cases where there might be more severe disease - more severe influenza (SARS was one health threat), bio-terrorism, anthrax - there are technologies that could probably get us there in half that time, potentially. But, you can't go thinking you're gong to vaccinate an entire population of the world without some pretty good data about the safety and reliability of those technologies. So I think there's a real chance now to generate more public interest and support to bring those technologies along, get more data so that people can be more confident (both FDA and the public), and that we can be much better ready to respond. But like that, or developing new antivirals and antibiotics, all those things are investments at a time when obviously the country and the world is economically challenged.

SM: Right. And the fact that there were supply and production challenges helped foster the environment for a more–

JG: But let's hope people don't forget about that.

SM: Right.

JG: But, I think, again, there's something of a good background here, which is that the effort of the last few years better prepared us for this. For example, the government had invested, and FDA had helped, for Sanofi to be able to increase its U.S. capacity, and that's helped us. That was a bi-partisan investment in public health preparedness. So hopefully, despite all the normal everyday occurrences of politics, we can have a bi-partisan national approach to - what do we learn, how do we further enhance our ability to respond?

SM: So what are you working on now? What's on your plate right now?

JG: In terms of this issue?

SM: Yes.

JG: So, I think, multiple issues. You know, vaccine production is continuing; lot release is continuing; the safety monitoring is continuing.

There's been this interesting issue of this cluster and potential increased number of cases of anaphylaxis in

Canada with an adjuvanted vaccine, and that continues to be under discussion. That may or may not represent an increase in adverse reactions. It's still under investigation, and our staff are working with international regulatory partners, Canada, EMEA, to be sure we have that data too.

The intravenous antivirals: we're trying to bring along additional ones so that any emergency use authorization was approved for Paramavir. Several hundred people have already received that. FDA is monitoring the safety data from that. Also, concern is that if resistance develops to Olsetamivera or Tamiflu, it's very likely it would be resistant to this intravenous drug Paramavir. So there's an effort, again involving both the manufacturers and HHS and FDA, to bring other antiviral medications along that potentially could be used following resistance. There's an intravenous form of Rolanza or Zanamivir that is, I think, very important to develop. So those kinds of activities are going on.

And I think, the activity to do things like make progress on recombinant vaccine. We had a recent advisory committee meeting on one of those to (as we get data from these

adjuvanted vaccines, both our trials and the European experience with them,) understand what could their role be. Both in an emergency like this, and are there populations for whom if their safety profile turns out to be favorable, who could benefit? For example, some initial data suggests they may be particularly helpful for kids in getting an immune response stronger and quicker, especially for the littlest kids who don't respond that well to unadjuvanted vaccine. Obviously, to do that, you want to be sure there's a very convincing strong safety profile, which whatever you use, but it may be ultimately that those things can really be technologies that are adapted.

Another issue is trying to work with - I mean, if we have challenges in the U.S., we're relatively well prepared with the manufacturing capacity and with public health and financial resources - what about the rest of the world? I mean, clearly, my view is that there should be, not just a global emergency response. We may be comparatively far along in the U.S. and Europe in terms of preparedness for emergencies, but, you know, really this is a global challenge.

SM: Does the FDA have any control over...like, we're committed to donating vaccine and antiviral as well to the global community, does FDA play a role in regulating those?

JG: Well, we really are only the regulatory authority for the United States. So we don't…However, we're also an agency that WHO considers a qualified high level regulatory agency. So we can do what is called prequalify a vaccine for global use through WHO. So WHO can look to us as what's called the National Regulatory Authority of Record for them to recommend a vaccine for use for other countries. So we do that. We participate on lots of senior level advisory committees with WHO about their immunization policies, about quality of vaccines and biologics. So we try to be part of a global scientific community that affects that. So, a real concern and we started working with WHO, Health Canada, EMEA. We actually initiated a meeting with all the global regulators about three years ago to start to be better prepared to...I mean the worst thing would be for countries or WHO to distribute vaccines that didn't meet quality standards and have terrible problems. So to try to help establish what are reasonable global approaches and quality standards.

In general, you bring up and you remind me of one thing I wanted to point out, which is at FDA it's a real and a cultural challenge to get the balance right. So, first and foremost, I see myself as a physician, as a public health person and wanting to have an effective public health response. On the other hand, people look to FDA to be the objective referee in a sense. And so, my view is that we want to help get vaccines and antivirals out and respond effectively to a public health response, but it's extremely important that at the end of the day we behave and are respected as an independent regulatory agency, that we step back and that our scientific staff say, well, is this vaccine ready to be approved, is this anti-viral ready for emergency use, have we…? There's often not one right answer. But are we making judgments with integrity and with the best interest of the public in mind? Because one thing that could really happen is that the pressures you talked about - in the heat of the moment there are lots of different kinds of pressures. It's very important, I think, not just in the U.S. but throughout the world to have independent and strong regulatory agencies that if you see a problem you're attentive to that; that if there are quality concerns those are brought up. But we can't also be just off on our own ignoring the fact that there's this

public health crisis. (Door opens. Someone speaks (indistinct) to Dr. Goodman.)

JG: I guess I probably have to…did we leave any major things?

SM: Well there were some other things-

JG: Let me just see what I have coming up-

SM: But if we can't finish them, I can perhaps get a shorter-

JG: We can do five more minutes.

SM: Okay. Well let's see what is the most exciting question.

JG: Okay.

SM: Let's see. Well let's go back to the supply and production challenge. Right now, the government, we are faced with supply and production challenges. To what degree

was regulatory and safety issues a factor in manufacturer delays?

JG: Um...I...

SM: By that I don't mean in what way did FDA hold it up, but in what way were you overseeing-

JG: Right. I think that there are several things which had to be done that couldn't be made to happen faster. So, for example, the production of reagents to calibrate the potency of vaccines, it was done at the fast end of the scale compared to what would typically be done for seasonal vaccine, but there were challenges in doing that. I don't think things like our lot release, our inspections, that those have slowed anything down. I think the performance has been pretty stellar really. Doing things in a high quality way, yet expeditiously.

I think in the sense that, and again these weren't FDA decisions they were sort of cross agency science decisions, but you know, I went through all the discussion about adjuvanted vaccines. So it's possible if we'd had more data, if we'd had those vaccines approved in the past, that

they could have been available and potentially gotten us more vaccine sooner. But the fact is we did not have the data available for them to meet the standards expected for approval by the FDA as safe and effective. And so, we said, "Let's have these...get as much information as possible so if we do have to use them, it can be a science based decision."

But I'm trying to think of what are...you know, I think a lot of the challenges come from not having enough to drive the needed studies to meet some of the standards for regulatory approval for some things before a pandemic, despite some of the investments of the last few years, in, like I said, antivirals, et cetera. But those are largely issues of, I think, the investment needed by industry and probably the government to get the data we need to have these products ready. So, I think that from the FDA's point of view that's the biggest challenge. I really think those are the issues.

We always try to stay out of (again, 'cause of our regulatory role,) actual contracting decisions, things like that. Again, to stay independent so we didn't make this decision with this company or that company or do this and

that. No, I think some of this we are limited by the technologies and methodologies. I mentioned the potency reagents. One of our scientists has been working on - and this is the first year we tried it and we had it as a backup - but methods that could get us those reagents faster using recombinant DNA technology. So, maybe if we'd been able to make those investments a few years ago faster, or had placed it as our absolute highest priority, that could have been ready before this. But we're always balancing a million different priorities: the safety of the blood supply, the vaccines for other things.

SM: Do you think we're uniquely poised now? I mean, the campaign is practically, for lack of a better description, over, because it's decreasing in terms of it's presence here, and we are now thinking about putting this H1N1 into next year's seasonal. So are we in a position now to really deal with some of the challenges that FDA has had with this particular pandemic?

JG: Well, I think, first of all, I do think we probably, we're at a point where in some parts of the country where the vaccine supply is meeting the demand, or for some of the high priority groups has met it. So some states are

broadening the eligibility. I think we're gonna see that rapidly shift from a situation of excess demand to a situation of supply, maybe in some parts, be more than demand. But I think because of the, I think it's desirable to not look on this event as over, but maybe the emergency phase is over. But we can have issues where even though the epidemic curve is going down there could be a recrudescence now, next fall, next spring, so I think it's very important, I would view it as more moving into a different phase with H1N1.

But I do think it's critical now to strike while the iron is hot, with the public, with congress, et cetera, and say what could we do to better position us, particularly with respect to needed vaccines drugs, et cetera. Whether its for future pandemics or other future biological events: SARS, natural, unnatural bioterrorism. And I think just like a few years ago in, you know, related H5 coming around and people being concerned about avian flu, related to the anthrax attacks, there was interest in what we can do to improve our preparedness. I think we can see how much more we have to go. And I think at FDA what we need to do is really say how can we play a proactive role in helping

facilitate these products get developed and evaluated so that we have as much information and confidence and as many kinds of arrows in the quiver when something occurs in the future.

So I think it's...if it weren't for the economic challenges and many of the budget challenges that the government faces, I think it would be an incredibly opportune time to have substantial investment here. The other point I would make, getting back to the H1N1 vaccine, I think if we're able to continue to immunize and get substantial amounts of people immunized, we're gonna– (Vicky?)

(Door opens. Someone speaks to Dr. Goodman, "I'll stop by….") So anyhow, I didn't want to lose that. I think um, that–

SM: H1N1.

JG: I think, what I was going to say is that with H1N1, if you think about even the investments, or the billions that will have been spent responding to this pandemic and producing this vaccine, my guess is that the savings from ultimately having much of the population be immune, were, will probably offset some of that or maybe all. I think

though that in thinking about preparedness for potentially more severe pandemics or other events, one of the things that we have to help look at critically and help to educate...I mean you can't be prepared for everything; you can't have a vaccine for everything in the world; you can't spend a billion dollars on every conceivable threat, but I think that investing to improve our infrastructure, particularly for things like vaccines and antivirals, and then on the public health and medical care delivery end, those are things which probably are like insurance policies. They are worthwhile investments for society, and in the long run may be investments where the return on investment is worth it, not just for the humanitarian reasons, but for economic reasons. Alright.

SM: Thank you.

JG: Sure.

End of Interview

Broad Themes

- FDA's role in vaccine preparedness
- Influenza vaccine production process
    - FDA hands-on involvement
    - WHO collaborating center - FDA/CDC
    - Network of Essential Regulatory Laboratories
- Vaccine production – Multi-step process
    - Two methodologies
        - Traditional reassortant strains
        - Genetic splicing/engineering
- Hemagglutinin
- Potency reagents
- Challenges with vaccine manufacturing
- Fill and finish
- Key collaboration
- Lot testing, lot release, quality review
- Incident command system
- Senior science and public health leadership meetings
- Adjuvanted vaccine – European data
- Diverse views: political, media, the public
    - Uncertainty, based on
    - Advisory committees
    - Bi-weekly media calls

- Safety record, safety monitoring
    - Need for anti-retrovirals
- Intravenous anti-retrovirals
    - Emergency Use Authorization
    - Drug resistance
- Science challenges
- Recombinant vaccine
- Global Emergency Response
    - FDA as WHO regulatory agency
    - National Regulatory Authority of Record
- Data – studies needed for FDA approval
- Post epidemic phase of H1N1

Follow Up

Names: None

Documents: None