Panel Discussion

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Dr. Sippel: In regard to biologics, I, like many other veterinarians, have thought that since all these products have met the government standards and they have been passed and tested, they must be alright. They have tested them for potency, purity and safety and, therefore, why worry about them? They are all approved so they are all going to be alright but if you look back in history you will find out that this has not been true, starting out with hog cholera serum and virus which was probably the reason for the establishment of biologic inspection. We had frank thievery and dishonesty in those days, wherein people watered the serum to be able to sell more of the stuff that had been passed and, of course, these people were caught and punished. In the late 30's there was a fiasco with the encephalomyelitis vaccine that was being used in some of the epidemics that took place in New Jersey and the east coast at that time. All of us probably remember the virus problem that took place in the 60's with hog cholera and in my own experience in veterinary diagnostic laboratories I can recall just recently having a problem with a biological product for a bacterial disease in which a certain product was having a number of failures in a community in our area. Upon questioning about this I was told by the manufacturer that the product that was failing was a price product; it is a cheaper product put out to meet competition and it just does not have the immunizing capacity that the other does. Well, this upsets you a little bit because here is a product that is approved by the government and has met their standards. So, with that background, I want to introduce our first panel member, Dr. Green, one from whom you have not heard, to give him the opportunity to say what he wants on this subject of biologics. Dr. Green.

Dr. Green: I do not know how to approach this except to say that anyone who is not confused by this stage is a liar! I do not intend to be controversial either, but I hope to be factual. I had probably one concern as I listened to the three papers given today and this dates back to my graduation in 1953. We had a little situation called "red nose" in Colorado, and if "necessity is the mother of invention," they proved it there! I doubt if you could develop "red nose" vaccine today with the expediency needed and get it on the market and save the cattle that were saved in 1955-56. I also know from clinical experience that the vaccines that we have available today are not doing the job that they did in the 1950's with one disease, notably IBR. In 1962 I was younger than today and full of vigor and lots of ideas and some of them were right and some were wrong! I came upon the brainstorm that we ought to test these products in our lots. One night when I could not sleep, I decided that it was going to be very simple to do. Each month I was going to chain X percent of the livestock coming into my lot and take a serum sample which would eventually be a paired sample, and, upon slaughter, by taking another sample from this animal we would get a paired serum sample reading, and I would hope to test two things. I was going to test what the animals had on arrival which would be nice to know, and then test what they developed immunity to—whether it was for natural infection or man-made with a needle during their stay at our particular lot. The more I thought about this, the more this seemed a good idea. I proceeded to approach three of the major manufacturers of vaccines and was turned down 100% and I have still been turned down. From that day on, I discovered that all vaccines are not alike. We do not know all that we pretend to know both clinically and whether you are a manufacturer or in regulatory work. I have one concern, however. I am on the panel but I have one question for the manufacturing industry. Why would a request like that be turned down because I think would be valid?

The other concern I have here today is criteria. The criteria that you are presented and the criteria that they manufacture are only bare minimum. I do not think there is anything wrong with this. I think that if we strive for too much government regulatory function we will hamstring an industry and I do not think that we have that many problems. I think the big danger is to reach out for dear old Uncle Sam and he is going to save you! Well, he will save you but it won't be in the direction you want to go. I think that any industry can solve its problems. I have spent the last year struggling with the Food and Drug Administration and that is also an experience! You people, as livestock consultants, are just beginning with the Food and Drug Administration. Likewise, the commercial feedlots because they too are going to have to register with the Food and Drug Administration. You are going to spend more time studying regulations than you are veterinary medicine books in order to keep them in business. This may or may not be alright, but I think I would caution against expecting to call up some agency and say, "How does this vaccine rate?" I

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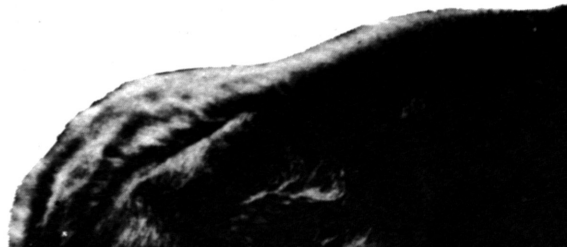

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think we are still back to people and these people make up companies and their integrity. I will state my own criteria. I do not judge a company by its sales policy. I think that perhaps we have been lulled into that too long. We were even taught that while I was in school in the early 1950's and that does not necessarily mean that this company is better or worse than another company. I judge a company by its willingness and ability to back me up when I have problems. It is like a livestock man says, "The only way not to lose cattle is not to have any!" If you are out there dealing with livestock problems and you are looked upon for advice, sooner or later you are going to have a wreck and you will get bigger because of it. You are going to learn from it, but sooner or later you are going to have a wreck in the best laid plans. I can quote a few examples on that too, but that is basically all I would like to toss out and the fact that I think that somewhere along the line we have to judge these things by immunological response. Someone will have to do some work similar to what I had proposed in the 1960's and which was turned down.

Dr. Sippel: Thank you, Dr. Green. At this time I would like to give each one of the panel members about five minutes to say anything in addition to what has already been said by the other speakers. We will start in reverse order.

Dr. Meredith: One of the things that we have learned about IBR within the last two years really is how to determine to a greater precision whether an animal is susceptible or not. This serum neutralization test, which has been applied to IBR in the evaluation of animals, has been a pretty crude kind of test really and actually gotten down to where you were trying to evaluate it on a 1:2 dilution or one part of the convalescent serum or one part of the serum from the animal plus one part of virus and the virus would contain a certain amount within certain limits, say 100 to 300 tissue culture infectious doses of the virus and then what you are actually looking for (this is a CPE virus) is whether or not the cytopathogenic effect of these bovine cells occurred or not. What happens is that you are down to such a level here that you could not really determine whether or not the animal was susceptible. Mytoviruses are notoriously poor immunogenic agents and the fact that we get any kind of response is something we associated with animal health ought to be tickled about. Nevertheless, the persistence of the immunological response is measured by serum neutralization and is detected by the capability that we have as being crude. This is one of the things that some firms got into when they were working on this seedlot principle test for IBR and that actually they used some animals which were not sensitive—they were not susceptible to IBR to initiate the test and, as we went along, we learned something. That is not uncommon but we did, and a sensitive kind of test can be developed using plaque reduction techniques or a different means of diluting virus serum mixtures to make the analysis. One of the problems that I postulate the firms in the 1960's were dodging with you is that the predictability of response with IBR on individual animals has not always been too good, and this is one of the things that we come to grips with in the seedlot principle tests that in fact we changed the whole level of evaluation of products. We normally released products on the basis of an 80% satisfactory response, and this test was to evaluate them on 1/10 the recommended virus which was to be given to the animal. This was given to 20 susceptible cattle and 19 out of these 20 had to response serologically. In addition to this, they had to withstand challenge with virulent material. Let us put it on an entirely different basis. You evaluated this product on the basis of 1/10 of the virus titer and we have not brought this out here very much. The reason this is not very often brought out is that practitioners, being the kind of businessmen they sometimes are, get this information and then think they can dilute the product ten times! It has happened before—the truth is that ten times is needed in there to take care of the kind of individual variations that we see. This is just in part.

Dr. Phillips: There are a couple of points that I would like to bring out here. We have talked about seed virus concepts, etc. Now, these requirements are listed in my paper. These are all available if you want to get them to see what the requirements are. These are the minimum requirements for the things that I have mentioned. Please keep in mind, of course, that we still depend upon the integrity of the company. We can make all the regulations and rules in the world but we can not look over the shoulder of each company, of each workman and know that they are following all the rules as set forth. With regard to requirements for primary cells, the requirements for cell lines, we are assuming that they are doing an excellent job here although we have been working on BVD contamination for the past three or four years and we are going to have a second round of it after we have done some more intensive research. We are still dependent upon the integrity of the company. We have not taken their responsibility away from them by any means. The way we operate in this so-called concurrent testing (we cannot test 100% of the product but do get about 12,000 to 13,000 a year) is to do confirmed testing, i.e., we test across the board for some factors and presumably all factors. This we call concurrent testing. If we test 10%, this could be a fair number. It might be 20 in some cases and then we find the company gets two or three sales that we turned down. Then we do what we call

simultaneous testing. This is where they have to test at the same time as we do and if this does not work out and they still cannot produce that product according to our standards, then we do confirmary testing. In other words, they have to test every serial before we touch this and then we test it and confirm that it is good. This takes much more time, maybe three or four months, so this is the way we operate here. One other thing that I want to mention is that when these new products come on the market, we do not have the facilities or the personnel to test them to the extent that we would like. We do some work: 25, 30, 40, 50 cattle to the extent that we can test. Now, when the decision is made that this product has merit and could have a place in the market, we give a temporary license (a one-year license) and that product is allowed to be marketed for a year's time and it is all written down that the firm has to report any complaints and trouble cases and give an annual report on the product before getting a regular license. Actually, for example, the case of bronchitis in poultry has been on a temporary license for years.

Dr. Macheak: We occasionally get reports about shortages of a particular biological product on the market. We never go into a testing program to create shortages of biological products. You can not always control this that well. There may be a shortage of one particular item with one commercial company, but if you are willing to buy from nine or ten other commercial laboratories, there may not be a shortage from those particular laboratories. I think you should try this first but if that fails, please call us. What we have done in the past and what we will do in the future, would be to give you a list of the particular serials that have been released by our group and the companies involved. We will give you serial numbers and companies involved and we will give you enough serial numbers and companies so you should be able to get this particular biological product and maybe it will be a little more difficult at one time than another but you still should be able to get it. Over the years there is no question the quality of biological products has improved. Some more than others. I do not have any stock in any of the commercial laboratories; in fact, we cannot recommend or endorse a particular biological produced by a commercial company but I do want to mention this. You do have to have great respect for what they are doing. These products are not easy to produce and the more components you get in there, the more difficult it gets. I think from this respect they need a good word too.

Dr. Sippel: I would also like to remind practitioners that if you appear to be having a vaccine failure or some other problem with the vaccine, that the Biologics Division would like to be notified about this so that they can look into it and add your complaint to that of any other that they may receive and thus be able to pinpoint a problem that would not come to their attention if people in the field did not let them know about it. This applies to pharmaceuticals also. The FDA is quite interested in this aspect.

Dr. Vernon Tharp, Ohio: Did Dr. Phillips state that 30% of all bovine kidneys that he has worked with are contaminated with BVD virus?

Dr. Phillips: That was a very rough estimate although it is quite a high percentage. Remember that these were fetuses that were obtained from packing houses, etc. I said 30% but I could be a long way off. In fetal calf kidneys and in fetal calf serum I think it has been about 20% of fetal calf serum. I might comment further that I referred to cell lines and it takes at least six months to get a cell line approved—possibly longer.

Dr. Black, Idaho: How do these same rules apply to such a variety of products?

Dr. Phillips: We received the virus of calf diarrhea last week. We got the information about two weeks ago on this virus and we have already had one conference on it and that was last week and that was pretty early for us. Usually we have to look at it for three weeks so it is under way. It is the old story of course, this CVD approach is entirely different to anything that is available on the market so we are going to take a look at it because we have to. I think I mentioned yesterday in one of my comments that in a regulatory agency, particularly in the area of licensing and approval, you are damned if you do and damned if you don't so most likely this will happen too! We are always criticized if we don't get a license in a hurry and if we make a mistake, we are criticized also. It is under way.

Dr. Black: Would you comment on the clostridial problem also?

Mr. Macheak: I really do not know what you are referring to here. You mean *C. perfringens* C and D? Generally, efficacy has been supported by work done mostly in England in the past. There is no real question in our minds about the efficacy. There is a question in our minds about the duration of immunity which has not been done and this is where we would hope for an increase in potency of *C. perfringens* proficiency C & D products and that this in turn would increase the duration of immunity. This may not happen. This increase in potency may in no way change the duration of immunity. I do not know but it is something we have not been able to test yet and sometimes you have to do some things on a gut feeling that it is going to accomplish what you hope it will accomplsih. It has been documented in the literature that type C does cause enterotoxemia in calves but there is no real good evidence of type D causing enterotoxemia in calves or adult cattle.

Dr. Rinker: What about the potency

standards for mixed bacterins and their efficacy?

Dr. Macheak: Until you get a potency assay that you can depend upon, we really do not know if these products are efficacious or worthless or some degree in between, but I think from our standpoint, we cannot prejudge. In other words, right now all we can say is we do not know how efficacious they are and that is why there is such a high priority to develop these potency tests. Now, if the potency tests cannot be developed, some of these bacterial antigens may come off the market. I am firmly convinced in my own mind that probably even though our work shows that protective response is quite weak, this antigen does people out there some good. I do not know how much good but without knowing more about it, I would hate to see this removed from the various combined clostridial products.

Dr. Horton, Fort Collins: What is the efficacy of multiple antigens given at the same time?

Dr. Macheak: I do not know if I can give you a good answer because I do not think we have that information. We can say that before a combined bacterial viral product is licensed that the commercial laboratory has to produce data to our licensing group showing that, first of all, there is no interference or reduction in the viral titer for instance, by the combination. This data has to be supplied by those commercial companies. How many bacterial or viral combinations can you make? I do not think anyone can give you this answer. Generally speaking, the requirement for potency and efficacy has to come first. If that means that you can put in only one antigen in a product, whether it be bacterial or viral, that has to be the number one consideration. If you can combine two or more and not lose anything by the combination, this is fine, but this is the way the combinations have to be put together, starting with a single component and continuing to work up and prove that those combinations are still as effective as when they are used alone. This is the way the licensing group requires the commercial laboratories to prove their products.

Question: What about antigens from different companies?

Dr. Macheak: Well, I would have to answer your question this way. First of all, any time that you combine two biological products produced by two *different* commercial laboratories, this is a very dangerous procedure because there is no data to prove that, once combined, this product may be worthless. Again, if it is not documented in the literature, you are pretty much on your own. In other words, if you do this without really knowing those various combinations and what they are going to do, I would say that is a very dangerous procedure. I think that is why sometimes the commercial laboratories get trouble reports. I cannot give the answer to your question here. This is something for which you have to really accept the responsibility. You have to balance out the difference in labor costs and stress on the animal with what you hope to get by vaccinating a half dozen different biologics all at the same time. It is dangerous unless you know what this is going to do.

Dr. Green: I do not think there has been any work done on animals—in man there has and they have data to show that a human being, a child, has so many immune responses or is going to react say four times and if you give six, the other two are going to get short changed. They compensate by the fact that first of all they have the temperature of the person before immunization so they can eliminate catching the stress situation, and secondly, they booster my child and yours but I think you can be most aware of the fact that an animal has just so many responses from an immunological challenge.

Question: Can you take human data and use

Dr. Green: Probably not, but I think I would use it as a guide today in my work.

Dr. Sippel: I have been hoping that someone would ask this question but inasmuch as nobody has, the moderator will have to pose it himself. All practitioners are faced with a battery of detail men that come by, each of them representing one of those vaccines that Dr. Phillips portrayed in his first side and almost all of them are different to some degree. Some of them appear to be low passage and, presumably but not necessarily, too pathogenic. Others were very high passage vaccines and presumably but not necessarily non-antigenic. Well, each one of these detail men has been told by the technical people in his company that the vaccine is great and told why it was great so he goes down the road and tells every veterinarian how great this vaccine is! It is better than product A or B and Dr. so and so told him that, and he repeats all that stuff. You are all very familiar with this. Well, obviously, they are not right. All of them are wrong to some degree or another. Now, Dr. Phillips, how is a practitioner who is faced with this, going to make a choice? What route or method would you use if you were a practitioner not having access to the data that you have in your possession?

Dr. Phillips: I knew that question was going to come up! That is extremely difficult because we do not discuss companies. I think I mentioned a few minutes ago that a lot of this depends upon the integrity of the company as well as the government making rules so I think if the salesman may not be telling the truth you may have to go to the company. I was out in California about a month ago and I went to a friend who was having some trouble. He said that he was using this man's vaccine because the salesman said it rated the

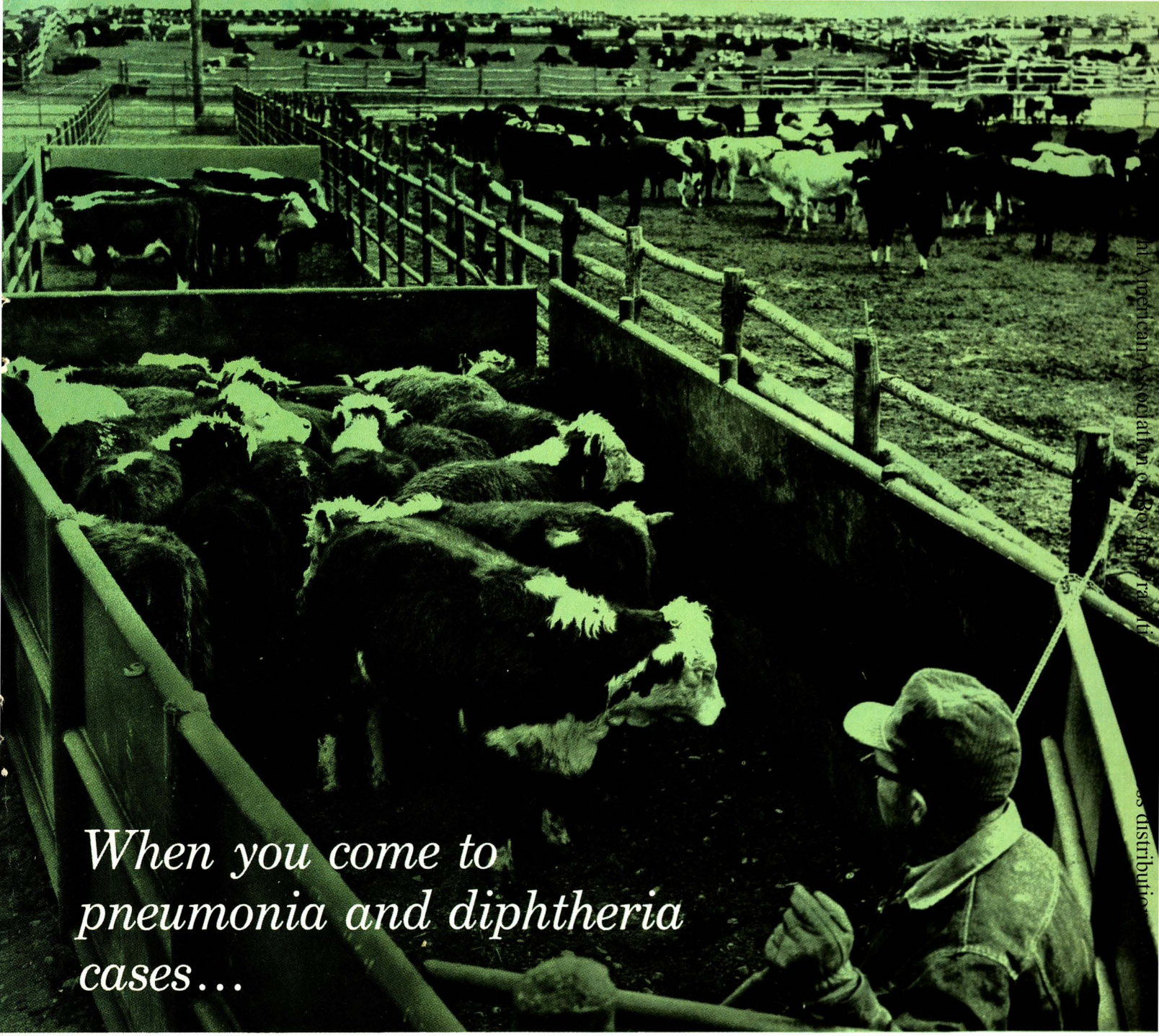
highest. He said 70 is the highest and ours is 70! So actually I think that you have to use your own judgement.

Dr. Green: I think we do ourselves and the government people and the industry people an injustice if we leave here thinking that there is a direct association between the ratings and the testing procedures and immunity response or field immunology *per se.* There is none to date. That is why we have consultants and practitioners in the field and it can change from day to day. What I think the government can do by setting up standards on purity, numbers of cells, etc., is plot out these minimums but from there, it is going to take observation, integrity of the company, and correct me if I am wrong, there is no direct association between cell passages and immunological response.

Dr. Phillips: There is and there isn't! There may be direct association depending on the cell but some of the lesser passages and some lesser cells have produced a good safe product so it is not a rule but it can be that way. I said that in 1958 the first vaccines came on the market. Now, this increase in modification has been an evolution year by year by year over 12 years; they were *all* the same at that time or within a passage or two in bovine kidneys only. Now the seed virus concept has stopped that, so this cannot occur again. Once they stabilize their seed, they cannot change it without doing all this work over again so we hope that never again will this thing gradually increase in modification. Once they have established it, it will remain that way or they get permission to get a new seed and then they go over this whole thing again.

Dr. Sippel: I would like to thank all the members of the panel very much and I am sure that unless you are given one of these papers you do not know what a job it is to get this thing ready. You have to do it at night when you would rather be watching the Monday night football and other things so we do appreciate it and I would like to ask for a hand.

Dr. Rinker: See you all next year.



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