traced back through more than one plasma tree, if you will, or some products, such as a coagulation factor that is stabilized with albumin, can in fact be composed of more than one plasma derivative.

Therefore, the history of any of these products is complex when traced back through the donations from which they were made, and the history of any given donation with respect to the products that it gave rise to is also complex.

[Slide.]

Going back to the scope of the investigation, each lot of each of those products is associated with the voluminous record that documents its production from the source material down to packaging records and final testing.

This is a simple hypothetical example which might reflect the manufacture of an albumin since we have a terminal pasteurization step indicated here. In this case, I would suggest that that step would certainly be one that would be included in a GMP investigation of post-donation information.

However, the manufacturer may have also validated the effectiveness of one or more of the purification steps in reducing the viral burden, and if that is the case, then, those steps would also be included in a GMP investigation.

Finally, although this is rare, it does happen,

some manufacturers perform final container testing on a product for one or more viruses, and if this is performed, the results of that testing and the testing itself, the testing methodology itself would also be included within a GMP investigation.

This entails a record review, and there are several possible outcomes to that review, and these are listed here.

[Slide.]

The most desired outcome is to find that your records for a particular lot are complete and accurate, and the manufacturing process proceeded according to plan with no deviations or discrepancies. In that case, the concern is minimal, because the full assurance of viral safety that has been designed into the production process appears to have been achieved.

The worst case is to find that the records are incomplete or inaccurate or questionable in some way, and in that event, there is no possibility of assuring oneself that those safety measures were implemented as intended. Therefore, the risk factor can't be evaluated and appropriate action, such as withdrawing a product, should be contemplated.

I should add parenthetically if such a deviation or discrepancy in the recordkeeping itself were found, even

absent any other risk factors, because the assurance of viral safety has been compromised, similar precautionary measures should also take place.

Finally, somewhere in the middle, which may represent the most common outcome, is that the record review will reveal some deviation or discrepancy in the manufacturing process that may be relevant to viral safety.

These actually can take on a whole spectrum of characteristics. First of all, the deviation and discrepancy may have been previously identified during routine review of the manufacturing records prior to the release of the product. Those deviations and discrepancies may have been fully investigated and resolved as having no impact on the safety of the product.

In that case, we also have reasonable assurance that the safety measures built into the production process have taken place as intended. However, the GMP investigation itself may reveal deviations and discrepancies that were not recognized at the time of the initial record review.

In that case, an investigation into those deviations must be conducted, and that is a time-consuming process with an uncertain outcome.

[Slide.]

The severity or relevance of the deviations are

also an issue that is germane to the subject. First of all, deviations can occur that have absolutely no bearing on the viral clearance process itself. I think these are not on the table for today's discussion.

There may be, however, a certain category of deviations that are related to the viral clearance procedures, but even there, they can be of greater or lesser import. For example, a deviation may occur that is outside a manufacturer's written instructions, but well within the range that has been validated as being effective, nonetheless.

I will give you an example of this, a simple example relating to a temperature-dependent inactivation process.

[Slide.]

During the course of the scaled-down viral validation study, the manufacturer may have looked at a fairly broad range of temperature, in this case, 18 to 28 degrees. However, because the manufacturing process is capable of controlling that process to a narrower range, and because the manufacturer wishes to afford himself a safety margin, the manufacturing instructions may actually call for controlling that process to within a tighter tolerance, 21 to 25, say.

If an excursion beyond this 21 to 25 degree range

occurs, that is the deviation which gets recorded and documented in the manufacturing records, but if the excursion is still within the validated range, we can say that the viral clearance was still effective, nonetheless.

If, however, the deviation exceeds the validated range, we lose that assurance even though the true failure limits may be outside that range. We don't have any knowledge of that, so we can only rely on what has been validated.

[Slide.]

So, in closing, there are several conditions under which a GMP investigation can be conducted and closed with no further action against products that have been distributed for use, the first of which is when everything occurred perfectly. There were no manufacturing deviations whatsoever.

Another instance is when deviations may have occurred, but they were either irrelevant to the process or were within validated ranges for the viral clearance procedures themselves.

The third instance is where deviations may have occurred, but they were fully investigated, evaluated, and an informed decision to release the product was made. Very often this involves referral to FDA and possibly a licensing action to cover the release of a product. In these cases, a

detailed risk assessment is performed.

Finally, there may be deviations for which a manufacturer has validated and approved procedures for repeating a step or remanufacturing the process in order to correct the deviation and maintain the assurance of viral safety.

I think I will stop there and take any questions if anyone has them.

DR. HOLLINGER: Dr. Boyle.

DR. BOYLE: At the current time, you are doing this review of records to establish GMP for those things that were related to inactivation.

Is that something that involves the review of a database, or is it something that requires the review of physical records?

DR. LYNCH: In most cases, these manufacturing records exist as discrete records, so you would go to an archive and pull out 6 feet worth of documents to review one lot of a product. Six feet may be an exaggeration, but they are rather voluminous.

So, it would be under most recordkeeping practices, would be a record-by-record review.

DR. BOYLE: If manufacturers understood that this was going to be a standard process and that they had 72 hours to comply, and that the records review were limited,

you know, it is focused on the inactivation procedures, the things that you have described as the risk factors for a problem, if that type of material was routinely recorded in an automated database as opposed to having to go and pull out the ledger books, would that type of thing be viewed as a possible way of moving through this type of review, or do you feel that in every case, as opposed to an audit, that it really is important to look at the original entries in a hardcopy or whatever?

DR. LYNCH: You raise a very interesting point. My presentation obviously was focused in the context of a post-hoc investigation. You are suggesting that one can streamline that by organizing the data in a different way.

I see no reason why that would not be a perfectly acceptable way provided that all of the relevant data were captured. Enhanced review up-front may be another alternative to doing it in the crisis mode, if you will, where you are trying to meet a deadline and may have again, not just one record to review, but multiple products off a single pool and perhaps multiple pools captured by the investigation.

DR. TABOR: I think Dr. Lynch also expanded on that at the last BPAC meeting in some more informal comments. The very worst situation is where the records are very bad, where there are many, many donations from the same

donor, and where intermixing of different pools has occurred prior to final manufacture.

As I said earlier, I think the existence of an algorithm of this type and the permission of 72 hours grace would encourage manufacturers to keep even better records. With intermediate qualities of records, I think 72 hours is actually probably quite generous, and I realize I am not speaking from experience, but it would seem to me that if you had a choice of quarantining a large amount of product and putting your entire staff on a rush analysis of your records, that you could put everybody on a 24-hour basis and get it done relatively quickly, even with hardcopy records if you had decent records.

DR. HOLLINGER: I take it the people who use the investigator to go to look at these issues at the manufacturer, there are people who are familiar with all the various inactivation procedures and things like this in general, and I presume that all the material is usually supplied to them very quickly in terms of records and so on, in terms of pressures, and so on, to get the job done.

DR. LYNCH: Yes to both parts of your question, we take some pride in the quality of our investigators now, especially under Team Biologics, and the training of those individuals includes a full orientation, rather exhaustive orientation into viral removal and inactivation techniques

as they currently exist, and what standards one applies when evaluating those on an inspection.

So, that actually is something that we have addressed quite extensively. Also, by the way, they frequently consult with the scientific staff at the center when they are out in the field doing an inspection, and those resources are readily available to them.

Finally, with respect to the cooperation of a manufacturer being inspected with regard to providing records, making information available, in my experience, that has always been good.

DR. HOLLINGER: Thank you, Dr. Lynch.

What we are going to do, we will take a break until 11:15. I have 10:53 now. So, we will take a break until 11:15, we will come back, and open it with the open public hearing. If there are any who wish to speak, let us know this at this time, and then we will go into the open committee discussion.

Thank you.

[Recess.]

Open Public Hearing

DR. HOLLINGER: We have one speaker, Dr. Bablak, from the International Plasma Products Industry Association.

MR. BABLAK: Good morning. My name is Jason Bablak and I am Director of Regulatory Affairs for the

International Plasma Products Industry Association. Our members produce approximately 80 percent of the plasma derivatives for the U.S. market and approximately 60 percent worldwide. I would like to briefly address the subject of inadvertent contamination and respond to the FDA's proposed algorithm.

The subject of inadvertent contamination has been discussed by this committee several times, including during the last two meetings. Last March, the FDA presented a strategy for addressing instances when a fractionation pool contains a unit from a donor with a subsequently discovered risk factor that would have disqualified him as a donor had it been known at the time of donation.

These risk factors are determined from lifestyle or medical information about the donor which may indicate that there is an increased risk of viral exposure. However, it should be noted that all these units are negative by all available serological tests and NAT testing that was done on that unit. We will refer to these units from these donors as unsuitable units.

We raised several concerns with the proposal that was presented last March including its feasibility and our estimate of its significant impact on supply. As we described then, all lots of plasma derivatives would be impacted during their shelf life by some type of PDI report,

and thus require actions including quarantine and/or recall under this proposal.

This committee voted to delay further discussion of this topic and asked FDA and industry to work together to provide more specific information on several issues, including the length of time that a post-donation report would require lookback analysis, whether "significant risk factors" could be defined, the role of NAT testing, and whether quarantining of released plasma derivatives was possible.

Today, we will provide a proposal that we believe addresses the potential safety issues that may be raised by PDI reports with respect to HIV, HCV, and HBV. However, before we address these issues, we would like to focus on several points raised during the last meeting that will shed some light on our proposal.

First is the question raised by Dr. Epstein: Are products any different because you happen to know that you pooled an unsuitable unit? We believe the answer to this question is no, because statistically, we know that unsuitable units, including window period units or PDI units, enter fractionation pools, yet these products continue to be safe.

The second question follows from this: In the case of learning additional information regarding a

particular unit or donor, is it appropriate to take additional steps?

We would like to pose an answer to this question by reiterating another point raised by Dr. Epstein. The most appropriate approach may be to put in place enhancements to existing systems that are feasible and probably ought to be done irrespective of PDI reports.

This point reflects the fact that plasma derivatives made from pools where we do not yet know of the post-donation information are subject to the very same concerns as those made from units where we do know about post-donation information.

Today, we propose an approach to be instituted for all lots of plasma derivatives that we believe will provide an additional layer of safety for these therapies. Because the timing of post-donation information receipt is unpredictable and as can be seen from the earlier presentation of the FDA, the type of information cannot easily be categorized as to risk, our proposal is that we treat all lots the same.

These measures that we are proposing will add to the current procedures already undertaken for every lot and will be performed up-front on an ongoing basis regardless of post-donation information received for any particular lot.

First, all unsuitable units at the collection

center will not be shipped for therapeutic use and all unpooled units held in inventory by the fractionator will not be used for further manufacture into therapeutics.

Second, a maximum potential viral load for the viruses of concern will be established for each pool through the introduction of NAT testing of manufacturing pools and/or minipools through the FDA's IND process.

Third, an assessment of the theoretical risk will be performed for each plasma derivative to ensure that the potential viral burden below the limit of detection by NAT testing could be adequately removed or inactivated by the manufacturing process.

Fourth, an enhanced GMP review of critical viral elimination steps will be performed for each lot as part of the release criteria.

We believe this strategy will allow industry to address the concerns raised by the FDA regarding inadvertent contamination on a proactive, routine manner to help to ensure safety while not affecting product supply.

We would like to briefly expand on each of these points. First, any unsuitable unit in custody will not be used for further manufacture. This includes the initial unit if it is available and all other units held in inventory. As you know, our industry has instituted a minimum 60-day hold for all plasma units, and therefore,

more units from this donor will be able to be removed from the pooling process.

Our members have also committed to implement NAT testing for HCV and HIV by the end of 1999, and HBV by the end of the year 2000. These tests currently require an IND, and our members are following these requirements to introduce this technology and eventually obtain FDA licensure.

As these new tests are phased in, one critical element of this proposal will be established. A maximum potential viral load for every pool will be established through minipool or manufacturing pool testing.

A risk assessment based on this scenario will be performed to demonstrate an adequate margin of safety for each lot manufactured from non-reactive pools, minipools, or units. Because the maximum viral bioburden will be established prior to release, PDI reports will not affect the original risk assessment, and therefore will not require additional action under this plan.

The second essential element of this proposal is the enhanced GMP review of critical viral elimination steps. Rather than waiting for a PDI report to initiate action, our proposal is to proactively enhance the review already undertaken prior to lot release.

Our intention is to develop a list of critical

viral inactivation and removal steps and identify their key parameters. We will provide specialized, enhanced training to those individuals reviewing each of these steps, and provide them with the tools necessary to ensure proper performance.

We believe this approach addresses the issues raised by instances of inadvertent contamination: what is the potential viral bioburden for the lot in question, and were the viral clearance processes performed as require to assure an adequate margin of safety?

When instituted for all lots, these enhancements reduce the need for a case-by-case algorithm by providing certain information before the lot is ever released. Specifically, the maximum potential viral load of the pool is established through NAT testing results, and the enhanced review of viral inactivation procedures assures adequate GMP compliance for that particular lot. By performing a one-time risk assessment for that particular product, these measures will ensure adequate margins of safety for lots meeting these release criteria.

The benefit of proactively instituting these enhancements is two-fold: first, all plasma derivatives will be subject to the same enhancements regardless of whether or not post-donation information was received; secondly, these actions will be taken up-front, and

therefore will obviate the need for quarantines, withdrawals, or recalls, thus minimizing any supply impact. Most importantly, any potential safety issue will be addressed prior to release of that lot.

As stated earlier, our proposal is to institute these procedures for all plasma derivatives as a proactive method to continue to enhance the margin of safety for these therapies. As with any new technology, it will take a little time to fully develop and implement an ongoing system for its use, and NAT testing is no different.

Our commitment is to institute NAT testing for HCV and HIV before the end of this year, and hepatitis B, by the end of the year 2000. We believe that we will be able to implement the enhanced GMP review somewhat faster, and we are estimating that we can get this done during the fourth quarter of this year.

We would ask that the FDA provide a liaison to our working group on this issue, so that we can expedite the development of the specifics of this proposal.

Thank you for the time to address this important issue. We believe this proposal is both feasible and valuable in terms of enhancing the margin of safety for plasma derivatives, while not affecting supply.

We would ask the committee to endorse this proposal, and we would be happy to report back in December

on the progress we have made in implementing its elements. I would be happy to answer any questions you might have at this time.

DR. HOLLINGER: Are there questions of the committee for Mr. Bablak? Yes, Dr. McCurdy.

DR. McCURDY: What is the coverage of this proposal in the United States, in other words, this is presumably voluntary on the part of the IPPIA? Are there non-members who also distribute plasma derivatives in the United States, and what is the likelihood that they will be covered by it?

MR. BABLAK: That is a point that we have not addressed at this point. This is just for IPPIA members, but certainly if the committee were to endorse this, I am sure we would be able to have discussions with the non-members to bring them up to speed on this issue.

DR. HOLLINGER: Dr. Boyle.

DR. BOYLE: Does your proposal for the enhanced GMP review, which I understand is still ongoing and obviously is not set in stone, but are you saying that in point of fact, that you are going to be collecting and recording or establishing the information in such a way that it is complete for all cases, so that if there is a requirement to look at a case, that that data is there?

MR. BABLAK: That could end up being the result of

this, but really our proposal is to enhance the review that is already done, because as you are aware, through GMP, everybody reviews all of their procedures before a lot is ever released.

What we would do here is make a specific enhancement to part of the release criteria where we would develop a specialized section that would specifically at sections relating to viral inactivation, we would have additional training on these elements, perhaps develop a list for--each manufacturer would have to do this obviously on their own--but develop lists of their critical procedures and the critical parameters, have training that would expand the knowledge of the people performing those, so that they understood if it fell outside of a parameter, what the implications of that might be.

So, really we are talking about a significant enhancement to what is done, not that what is done isn't already adequate. It is just that this is really a way to address up-front the issues that were raised this morning, so that if there is a discovery of something, it is basically found before the lot is ever released.

That is really the critical element here, is that we can do this before a lot is released, and then if there is a problem, it is discovered before the product is out in the field and it can be resolved then rather than trying to

do it within a 72-hour time frame.

If I can just expand on this, one of the other things that was raised, if you looked at even the critical PDI areas that were listed today, we believe that even that is enough, that would really impact every single lot of product that is made.

In the end, what you would end up doing is going through and continually looking at these reports and then going forward and trying to trace those lots down and do your review. Even if it's within 72 hours, it will become a continual process, and we discovered this really as we started to look at this after the last meeting.

It became clear that if you tried to determine what is really "higher" risk than others with regards to post-donation information, even if you tried to limit that list, which is very difficult, it is still going to have an impact on all lots that are released.

So, we decided really what was the best thing to do was to try to put this up-front as release criteria, because that allows us to have a regularized process where we can assure that all products meet this criteria.

DR. HOLLINGER: The manufacturers of these plasma products get this post-donor information almost on a weekly basis. Does someone call in every week that provides some information on this?

MR. BABLAK: What happens is, for instance, even if you look at the list that the FDA set, you may actually get three, four, or five a month, but the way that it follows is you get a report on a particular donor, but that donor has donated many times.

So, the donations from that donor are really what is important when you are looking at how this will implicate products. So, if you have five reports over a month's time, that will reflect to basically affecting all of your product lots.

DR. HOLLINGER: So, an inspection or evaluation or investigation might go on continuously.

MR. BABLAK: It would basically be a continuous process. So, what we have suggested is why don't we don that up-front, if it is going to be a continuous process, let's do it before the product is released, and in that way we have assurances before the product is out the door.

DR. HOLLINGER: And you are going to do that before it is released in what way?

MR. BABLAK: All of these procedures that we are proposing here would be done before release, so as part of the release criteria, an enhanced GMP review would be part of that release criteria, so that if it didn't pass the GMP review, it would never be released.

DR. HOLLINGER: And that would be a review by the

manufacturers.

MR. BABLAK: At this point, it would be a review by the manufacturer. What we have asked is if we can have liaison from the FDA to sit with our working groups, so that we can define what the critical elements are and how that would be accomplished.

DR. HOLLINGER: Dr. Epstein.

DR. EPSTEIN: Thank you, Dr. Hollinger.

I think that there would be general agreement that if all deviations in manufacturing were adequately addressed prior to product release, that we would be in a much better situation regarding post-donation information, and could conceivably waive further investigations and quarantines.

The problem is that we are not there right now, and I think that it needs to be understood that the algorithms that we have been talking about represent the agency's interim strategy. In other words, until the industry gets to the point with regard to GMP controls, where what you are describing is in place, we do have a problem when incidents come to light.

I would say that the same applies to the issue of NAT. Until we have the NAT tests validated and approved and fully in place, we still have a problem when the incidents arise. So, for example, not all manufacturers are routinely testing the pool by NAT, and the NAT sensitivities haven't

all been validated in relation to the viral inactivation and clearance capability of processing.

So, I would accept everything that you have said and endorse it as both correct and highly desirable, but I think that the committee needs to understand that what we are talking about is the current situation, which is we hope an interim situation that will go away someday.

MR. BABLAK: I guess our response to that is we hope to make it go away before the end of this year.

DR. EPSTEIN: Well, that would be nice, but it's the situation we have on our hands now and the one that we have been dealing with for a period of years. We have been doing this. It is just that we have been doing it without having formalized an algorithmic approach, and it has been done ad hoc case by case.

I would say that that problem won't go away overnight and that is why this issue has been in front of us.

DR. HOLLINGER: On this same basis, what do you see as the problem with the algorithm from the industry standpoint, of the algorithm that was given by Dr. Tabor earlier? What is the problem that you see from it, from an industry standpoint?

MR. BABLAK: The problem is it creates a situation where you have to wait for a report to come in. That report

comes in. You have to trace where those units from that particular donor have gone, and then you have to do your GMP review, because I think that is what we are talking about now since NAT testing has not been implemented for all the viruses, so really we are looking at that section.

Our commitment is to do it for all the viruses, but like I said, that won't be really until the end of next year. So, what you are really doing is you are creating the work of looking at when the unit comes in, tracing it, and then finding those particular lots. So, there is an additional amount of work that is done just to do that, when, in reality, we know it is going to affect all of the products at some point.

It may not be that it affects them all at the same time. You may have one that comes in that affects a product lot in one month, and in that case, we can actually take those units out from our inventory hold.

But if you have something that comes in six months later, and some of those units have been pooled and may be in the manufacturing process. If you get a report that comes in a year later, some of the product lot will actually be released, so you are waiting to get that information before you do your report.

What we are proposing is let's do it up-front before it's released, and do it for everything as part of

its release criteria. To respond to Dr. Epstein, I think really, especially when you are talking about the post-donation information reports, what is being done now is you get the information, you may trace where it goes, but there really isn't any additional review that is done, and that is how this has been handled in the past.

What we are saying is we are willing to go a step further and put in this enhanced GMP review. If you look at the algorithm, I think the problem with that is if you are going to have to go back and do a review for every single lot within 72 hours, we are going to spend a lot of time doing this tracing and doing this review, where I think the better us of time is to fully implement this procedure that we have proposed, and then you will handle it for everything going forward.

I guess it's a matter if you are looking at the timing, over the next six months, can we spend the time and develop this proposal and institute it for all product lots, or do you want to continue to address it on a case-by-case basis ad hoc as they come in, because that is really I think what you are going to talk about.

If you are going to spend time reviewing these and tracing them, that is going to take away the time that you can spend instituting this on a regular procedure going forward for all product lots.

MR. JACKMAN: My name is Dennis Jackman with IPPIA. I just want to answer a question and make a clarification here. Somebody alluded to this as being voluntary, I understand that this would be voluntary, and it is a voluntary proposal, but our association members have stated they are committed to implementing this, and would have no opposition to FDA making this mandatory because we would expect to have it in place in any case, so that is a possibility, and we just want to state that.

I mean that is a statement of the obvious in some ways, but we just want to make it clearer that we would have no opposition to that.

DR. HOLLINGER: Thank you.

DR. EPSTEIN: I would look at it from the FDA point of view this way. We think that full resolution of deviations in manufacturing should be resolved before product release now, and that that is an existing GMP provision. In other words, we don't really see it as something novel.

On the other hand, we recognize that the industry is not fully there in terms of compliance with GMP, and so we welcome an initiative to upgrade compliance, but we don't really think that the focus of debate is whether this is something new or something that requires a new policy or new requirement.

Resolution of deviations has always been part of GMP. The problem that we have been faced with is that as we have investigated incidents, we have, unfortunately, found that there weren't full investigations. For instance, we found deviations with respect to viral inactivation temperature that were outside the limits of the validation of the process. That is a serious problem.

Such lots ought never have been distributed under GMP, but they were. So, I think the way I see it is that it is an issue of compliance, it's not really a question of a new standard. We want the industry to embrace the correction, and I think the notion of being able to come into full compliance on resolution of deviations before release of lots does go a long way to mitigating the problem.

I would agree with that point, but again I think it is a little bit miscast to describe it as something new requiring new policy or new requirement. This is existing GMP thinking.

MR. BABLAK: The only response I would have to that is what we are using to go back and look at those release criteria GMPs is a PDI report, and I guess what we are saying is that is probably not a very valuable way of looking at it because by the time you end up tracing that down, really, what you are talking about is all products and

all lots.

So, I guess what we are saying is we are in agreement, it's just a matter of in that interim period before we develop this enhanced GMP section, is waiting to get a PDI report, which are inevitable and will happen, but also, at the same time, a very random occurrence which really tells us nothing about a lot that would separate it from an additional lot. It that a good criteria to then go through and do this extra work, or is it better to develop going forward how we are going to develop the GMP element of this process.

I think that is really what we are coming down to is in the next five or six months, how is the time better spent.

DR. HOLLINGER: Dr. Fitzpatrick.

DR. FITZPATRICK: I don't understand why the two efforts are exclusive. It seems to me that it makes good common business sense to do what you are proposing, so that if you get a PDI, then, you can immediately respond the FDA and say we have done the enhanced GMP review, and here is our results.

Now, you fit very well into the window, and you can allay them, assure their own compliance, and over time develop a track record to assure the FDA and us that you are now in compliance and eventually, by establishing that track

record, perhaps you can do what you want to do, which is not have to react to the PDIs, but just show compliance on a continual basis.

So, I mean I don't see why the two are exclusive.

MR. BABLAK: I guess the answer to that question is they are not exclusive, it's just the amount of time to trace and go through that extra process of relying on the PDI report takes away time that could be spent going forward.

In reality, the PDI report doesn't give us any additional information one way or the other about that particular lot, because we know that eventually, all lots will be associated with the PDI report, so by using that arbitrary criterion to go through and do this extra work really doesn't accomplish anything.

I think that is what we are trying to show here is going forward it would be better to do this for all lots. If you are going to differentiate based on a PDI report, you are really not accomplishing anything except picking something out of the air perhaps and saying that this is what we are going to use to judge whether or not this lot needs an additional review.

DR. HOLLINGER: Are you saying you wouldn't remove the samples or the units that came from this, that were generated from this PDI report basically?

MR. BABLAK: But we do that already. That is already done, so if a PDI report comes in, any unit that is held is already removed. That is a point we wanted to make sure that everybody understood, that that is something that is being done and will continue to be done.

DR. HOLLINGER: Okay. Dr. Mitchell.

DR. MITCHELL: But in your protocol, you don't say that the units will be destroyed, you say that the units will not be used for further manufacture into therapeutics.

What is your plan to do with the units?

MR. BABLAK: This always raises a question. The reason that that is said is the vast majority are actually destroyed. Some have a value for diagnostics, for instance, units that are in the unit period, that you have a donor who has seroconverted, those units become valuable for diagnostic manufacturers, for test kits, and those types of things. So, those units aren't technically destroyed. They are not just not used for injectable therapeutic products. But to be technically accurate, we have to say that they are not used for that, they are not destroyed, because not every single unit is destroyed.

DR. HOLLINGER: Any other question from the committee? Yes, Dr. Buchholz.

DR. BUCHHOLZ: Just an issue to understand FDA's role versus manufacturers' roles. When an issue like this

comes up at present, is it the current policy that FDA visits the manufacturer and, in fact, documents this record review, or to what extend is the manufacturer allowed to do that and provide the documentation to FDA?

If this, in fact, is affecting every lot, it would seem like there could be a tremendous amount of effort here developed toward doing something, that I think this would seem to obviate much of that effort as proposed by IPPIA.

MR. MASIELLO: Steve Masiello. There really isn't the ability to go out and verify each and every one of these cases on site at the time that it occurs. What we ordinarily do is there is certain communication back and forth on each and every issue. Then, at the time of the inspections, these types of things are reviewed, but not at that moment.

DR. BUCHHOLZ: So, in essence, right now FDA would be relying on the integrity of the manufacturer to, in fact, do that review and provide that information. If that is the case, I begin to see very little difference between what is being proposed and what is currently going on.

There, indeed, may in fact be a small number of problems, but I am not clear as to how this proposal would differ from the current system which basically relies on the integrity of the manufacturer.

MR. MASIELLO: I think the fact of the matter is

we do spend quite a bit of time in the fractionators these days, so there is not a point-by-point verification in all cases, but there is quite a lot of inspectional coverage that is going on.

DR. HOLLINGER: So, lots could be released from quarantine, and so on, just based upon the manufacturer's assessment before an investigation is done, is that correct?

MR. MASIELLO: There probably is a verification via paper. I mean there is a lot of communication that goes on, so that there might be a request for specific documents or copies of specific records to be submitted, so we may not be seeing them on site, but we are probably seeing them via review.

DR. HOLLINGER: Thank you.

MR. BABLAK: If I could just clarify from our perspective, that is not what is done for the PDI reports presently. I think the change would be under the algorithm that there would be some additional element that would have to be satisfied before those lots could either be released from quarantine or released to be sold for use, whereas, the current practice is if a PDI report comes in, the manufacturer looks at that, traces that, understands what happened to that particular unit, and that is where it ends.

So, what we are proposing is an enhanced system, not necessarily based on PDI reports, but based on the

output criteria basically, what will be released.

DR. HOLLINGER: Dr. McCurdy.

DR. McCURDY: It seems to me, and I think this has been stated by at least one other member of the committee, that one of the major results of this, which I think is very salutary, is that the review will go like greased lightning, and if it is already done, then, all you need to do is verify that it is already done, and that ought to be it, and take three hours or whatever. I mean it should go very rapidly.

DR. HOLLINGER: Ms. Knowles.

MS. KNOWLES: I think the concern that I hear from the FDA staff is that if this proposal is adopted by this industry representative and their members, that nothing else will happen in that interim time, and I do think it is important that there still be some controls in place now until they are fully implemented.

DR. HOLLINGER: Even afterwards, I personally would want to see that there is an evaluation done somewhere down the line regardless.

DR. BOYLE: Jason, just for clarity's sake, I want to understand what happens now under the algorithm we have got here. You have got apparently about 8,000 of these post-donation reports per annum.

MR. BABLAK: Let's just stick to the source plasma

side, which is significantly smaller, but will still make the same point.

DR. BOYLE: Fine. Units not yet pooled, and you identify it as being a post-donation problem, what happens right now?

MR. BABLAK: If it is not pooled?

DR. BOYLE: Yes.

MR. BABLAK: The unit and all the units held in inventory from that donor are removed and not used for further manufacturing of therapeutic products.

DR. BOYLE: So, no change then in the first box.

MR. BABLAK: Exactly.

DR. BOYLE: The second box.

MR. BABLAK: It says "destroyed" here.

DR. BOYLE: All right, destroyed versus not used for product.

The second thing is units pooled but not yet processed. What happens now?

MR. BABLAK: If the unit has been pooled, it has basically lost its individuality, and that is the end of the investigation.

DR. BOYLE: So, under current process, it continues through the manufacturing process, and so here the FDA proposal does something new.

MR. BABLAK: Exactly, and that is the same the

rest of the way across.

DR. BOYLE: Okay.

MR. BABLAK: So, everything below that is new. So, I guess the thing is we have been doing that all along. What we are saying is we would like to implement something more, and the question is, over that time of implementation, say, the next five or six months, do we follow what the FDA has proposed, which will require a significant amount of time tracing lots and units based on a PDI report, which is a random event, or do we continue to go forward with a proposal that we can implement across the board for all lots as they are released.

DR. HOLLINGER: So, you want to have some stability.

Dr. Koerper.

DR. KOERPER: Your proposal would mean that you would not need to keep track of what pools individual donations went into because if the GMP were satisfactory, then, it wouldn't matter about getting these post-donation information, because you have already done more than enough to kill any viruses that got in there, and this would then obviate the need to keep track of where the individual donations were going.

MR. BABLAK: Exactly.

DR. HOLLINGER: I see also if you have a

consistency, reproducibility, and so on, and then you really don't have to find out where exactly it goes.

MR. JACKMAN: We do track, it will be tracked going forward. We just got clarification that they will be tracked and they would be tracked, so I want to give the correct answer. I think there was just some confusion there. Thank you.

DR. HOLLINGER: Thank you.

Dr. Tabor.

DR. TABOR: I would like to underline one of the points Dr. Epstein made, and I don't want to detract from what I think is generally an admirable proactive stance that the IPPIA has been taking over the past year or year and half, but at past BPAC meetings, one or two or three of the members of BPAC have raised concerns, and I recall Mr. Corey Dubin raising them, perhaps Dr. Mitchell, perhaps others, related to how well the GMPs are currently being carried out.

When we presented data showing that the currently applied mechanism for removal and inactivation of viruses are more than enough to kill any virus that is present, the question was raised by several BPAC members, yes, but there are so many GMP violations nationwide that we can't rely on that.

So, I would like to ask the question--it doesn't

have to be answered--but at least rhetorically ask the question, your proposal would have to satisfy the critics who are concerned about the adequacy of GMPs, as Dr. Epstein alluded to, and what aspects of your proposal will satisfy those people.

MR. BABLAK: I think if that is a question that is directed to me, basically, what we are proposing is to take the GMP review that has been put into the algorithm and just put that up-front, and I think that is why we asked for an FDA liaison to our working group, so that we can be assured, and assure others, that what we are doing will meet the questions of those people who have raised those questions.

DR. HOLLINGER: Dr. Chamberland.

DR. CHAMBERLAND: I think, first, I would like a little clarification because I may very well have misunderstood this, but when Dr. Boyle just asked you to compare and contrast the proposed algorithm with what you are currently doing in practice, essentially, it started to differ very quickly after units became pooled, but I thought I understood Dr. Epstein to say that actually, this is what is happening currently, we have just never formalized it, and this just happens on an ad hoc basis.

That is my initial starting point is I am a little confused as to what is actually happening in practice. What follows is if there really is a disparity between what is

happening currently and what is being proposed, your comments about this looking back to multiple donations could possibly then really have significant implications for supply.

I think that is an important consideration if this, in fact, isn't currently happening, if it is implemented, are we going to face real significant acute shortages of products because essentially everything being quarantined or at least on an interim basis until it is resolved.

MR. BABLAK: The answer to that is it is a possibility. I don't know in the short term how that would work out with the numbers and things coming downstream. I think our data has showed that over a time period, for a year, every lot would be affected, and so whether that would happen immediately, I can't say. We don't have that data.

MR. MASIELLO: Let me just clarify my earlier statement. Ordinarily, the follow-up that the FDA conducts is associated with releases by a plasma center or a blood bank of a unit that had a testing issue or a window period issue and those are the ones that the FDA is currently focusing on as opposed to these post-donation calls where after a certain period of time, the unit would go into manufacture.

But we do, of course, look at the suppliers to

make sure that those issues are being documented and are being tracked, and looking through our GMPs that the fractionators do receive information and take some steps.

DR. BUCHHOLZ: I have a question with respect to the statement that FDA has made relative to compliance violations and citing examples where there is GMP violations to some extent.

I would presume that that GMP violation would lead to a correlation that there are many examples of disease transmission that have taken place and been documented in recipients that are related to those specific GMP violations.

My impression is that post-plasma derivative infection except in a couple of instances where there is a very good explanation for that, is either nonexistent or exceedingly rare. Could someone clarify that?

DR. EPSTEIN: At previous advisory committee meetings where this issue was discussed, Dr. Tabor provided a complete historic review about HIV, HBV, HCV transmissions from plasma derivatives, and the bottom line is that with the exception of the isolated instance of transmission of hepatitis C from one manufacturer's intravenous immune globulin, which dated back to 1994 after the screening policies were changed, since 1987, there have been no reported transmissions of HIV, HBV, HCV by plasma

derivatives, so we do believe on those grounds that the current procedures for manufacturing are adequate to eliminate the risk of transmission of those agents, however, it needs to be understood that the safety of the products is dependent on the manufacturing processes.

We know for a fact that window period units will contaminate fractionation pools. We know it statistically, and we know it from the occasional instances where a documented window period unit was pooled.

We also are operating right now in an environment where there has not been rigorous validation of the inactivating or clearance capability of the processes with regard to the viral loads that might enter the pool. Mainly the problem is that the viral loads in the pools haven't been directly measured.

So, we know the end products have not transmitted. We know that the processes are very robust, and we have reviewed all that data at previous meetings, but we still have this concern at two levels.

One, that we would like to tighten the data set on validation, we would like to really know what tests are in place to ensure upper limits to contamination that may occur, and how many logs overkill or clearance there is in the process. We really need to firm that up, and I think you are calling for that data to be made available and we

applaud that.

The second is that we do know that since the safety directly depends upon the accurate and reliable accomplishment of the inactivation and purification in the course of manufacturing, that deviations are important to investigate, and not all deviations are equal.

There are going to be deviations that raise significant questions, and we gave examples at previous meetings. For example, when there was a report of an HIV antibody-positive plasma pool that was based on pool testing for antibody performed in the UK of products that have been distributed under license by U.S. fractionator, and with the knowledge that an HIV antibody-positive unit must have entered the pool, we then felt that we needed to investigate the adequacy of the HIV viral inactivation and manufacturing, and lo and behold, we found deviations that had not been investigated and resolved, and that the deviations were outside the validation range of the manufacturing process.

We have ancillary data that suggested to us that the processes would be nonetheless robust, but the actual validation data didn't deal with the range of the deviation, and on that basis, there were quarantines of products put into place, particularly for factor IX.

I think the problem is not trivial although I

would agree with you that the safety record of the end products since 1987, with the one exception related to Gamma Gard, is excellent, but what we are trying to do is ensure that, in other words, we want to shift it from retrospective observation to prospective assurance, and that is what this is all about.

I think that in a certain respect, we are getting hung up on the wrong issue. Everyone would endorse the concept that if there is up-front resolution of all deviations if manufacturing based on sound validation data, and before product release, that we can mitigate concerns over investigating specific incidents.

The problem is what do we do today before the doctor comes. I would accept the observation that has been made that what we have described in the algorithm does go somewhat beyond current practice, because current practice has been to do investigations either when there has been pooling of test-positive units or the finding of a test-positive result on a pool, or a reported case of transmission even though none of those has ever been proven. We do get reports.

Those have been the triggers for the investigation, however, as we have discussed the concern over post-donation information and the theoretical possibility of contamination, it has become clear that we

should have as much or greater concern about window period units as about test-positive units. Why? Because the viral titers can be higher.

So, that is why we have broadened the scope of concern to try to define the instances where risk histories ought to worry us about window period, and this committee itself suggested to us that we not create an arbitrary distinction between risk history and window period, those being essentially the same thing.

Now, they are not the same thing in terms of frequency, because most cases of a post-donation information report about risk won't correlate with the donor being in the window, whereas, there is some small subset where we know that the donor was in the window, and the best example of that was a case that we did present as a case study at a previous meeting, where a donor subsequently gave whole blood donation, his units transmitted HIV to red cell and platelet recipients, and the plasma had been fractionated, and that was a test-negative donor.

So, we had absolute proof that the donor was in the window period, and we went ahead and investigated the soundness of the viral inactivation and manufacturing record for the derivatives, and we think that is completely rational.

That is a little bit different than a case where

you have a risk history and you don't know what is true, but again the committee advised us to lump them, so we have lumped them, but that is an extension of what we currently do, in other words, we have currently investigated only, if you will, the better established cases of a risk where we knew it was a donation in the window or where we knew that there was inadvertent pooling of a test-positive unit.

It would be a broadening of our scope of concern to also consider these same procedures simply based on risk history without further information, and that is correct, and that has been highlighted by a number of the committee members, and that is very important, and I think that it leads to where should the debate focus.

The debate should focus on whether the set of triggers, as outlined by Dr. Tabor, are the right ones, and I think what you are hearing the industry say is, look, we can't live with that, it is going to implicate essentially all our products.

That is a legitimate response. I mean that is one of the problems. So, I would rather see the focus shift on discussing the triggers and recognizing that this is an interim policy proposal than debate whether it is in conflict or not with the industry proposal to do up-front resolution of deviations, which I think we should applaud, you know, it is the right answer, and could it in the long

run obviate case-specific investigation, I am prepared to say yes, but only at the point where we are assured that there is full resolution of deviations before products are released, and unfortunately, that has not been the compliance history of the firms to date, and that is where the problem lies.

So, I think we need a strategy in the interim, and I think that it is red herring to pose it as an alternative to up-front investigation, and I think that where we really need to focus our attention is what the triggers for quarantines and investigations ought to be, recognizing industry's point of view that it might be too broad as construed or as proposed.

DR. BUCHHOLZ: Could I ask a question in terms of the issues here, there seem to be potentially two issues with the industry proposal in terms of the six-month or whatever that time period is, five to six months to get fully implemented.

It seems that part of that proposal involves some NAT testing of pooled or final product, and obviously, that isn't something that can necessarily be turned on overnight, but I would wonder if the questions that FDA is concerned about, that is, documentation of good manufacturing practice, aren't, in fact, resolvable in a much shorter period of time, and have the potential to be addressed very

rapidly even though NAT testing of pools may not take place for two, three, four months.

MR. JACKMAN: May I comment because it was addressed as a comment we were going to make. I think some of the issue here is on timing and how quickly this could be implemented, and we are confident that we could work to accelerate our proposal especially with the cooperation and input of the agency on this, and we think that would be beneficial, so we think we could accelerate that from the date we even talked about by the end of this year and make it even sooner, and that might address some of the question of whether or not you need an intermediate step.

The other thing is in discussing the algorithm, the intermediate steps, we have to be aware that if those are implemented, we could be seeing significant amounts of quarantine effect. As it is constructed, we think that most of our products would wind up in quarantine. That is going to take quite a bit of time and have a major impact on supply, so we do favor an up-front check all the time.

This is not new authority, but it is an enhanced method of assuring compliance with GMP on viral inactivation in the most important areas. We can accelerate it, we can have a real impact on this issue here, and with cooperation we think we can get this done. I don't think we really see the need for an intermediate step.

DR. EPSTEIN: I would comment for Mr. Bablak, that I would have put the timing the other way around, because I think that we have created a very significant feature that would expedite investigation and resolution by permitting retesting of the unit or the donor and/or the pool by current licensed tests and NAT as a strategy to avert the need for quarantine and GMP investigation.

Perhaps it is worth showing the algorithm again to point that out, because we do think that that is feasible now, and we do know that the industry has the capability. It is simply a question of showing FDA data on the sensitivity and reproducibility of the NAT tests, and my instinct in the matter is that it will take longer to convince the agency that there is adequate up-front investigation of deviations and resolution before lot release, because the cases that we have dealt with have simply taken many, many months to resolve. I mean some of them are going on years, and they are still not resolved.

So, I have a little bit less confidence that that is going to be in place in five or six months, although I would be very pleased if that were true, but again, the algorithm does provide for an alternate strategy to resolve things rapidly, and I see that as quite feasible today.

DR. HOLLINGER: I just wanted to ask one question. Jay, on the same one, from what Dr. Tabor said initially, we

are talking about HBV, HIV, and HCV, for which there are tests available, and what you are saying I think as an alternative is really if you had the donor there, you actually could obviate all of this if you went back and retested that donor with NAT or with other things, and found them to be negative. Basically, then, you really don't have to move forward for that particular situation.

Is that what I am hearing you say?

DR. EPSTEIN: I think that what is under discussion here, and perhaps Dr. Tabor wants to just highlight it, we are talking about point A in the algorithm where there is concern about the product and you can avert the comprehensive GMP evaluation if you have a validated NAT for HBV, HCV, and HIV on the pool, and the original sample or a fresh sample from the donor.

If you do not have an original sample, such as a segment, and we accept the comment that these units and their segments are traceable, that is, in fact, the norm in the industry, if you don't have the segment, you can retest the donor, but then you should do all the screening tests also to look for seroconversion.

What we are saying is that if you can accomplish that in 72 hours, you don't have to do the quarantine. If you can't accomplish that in 72 hours, you do need to do the quarantine, but you can stili avert the comprehensive GMP

evaluation just by getting negative additional tests.

We think that that is a very important alternative that mitigates the impact of otherwise calling for these investigations, and again, I would agree with the comments that have been made by the panel members, particularly Dr. Fitzpatrick, that this is not in conflict with the parallel strategy to put in place up-front GMP resolution of deviations as a strategy to have the answers in place. I think they are fully compatible.

That is the importance of what was highlighted as Note A.

MR. BABLAK: I think there are two concerns with that strategy. One, very rarely will we have the samples, so then you would have to go back to the donor. If you are able to get a sample from the donor, the time of doing that, running the tests, and getting the results will most likely fall outside of the 72 hours, and therefore you have the quarantine which, from our point of view, is the most difficult part of this whole process is putting products out on the market on quarantine, quarantine products that are in-house, those types of issues.

Obviously, we are all anticipating putting PCR testing in place, and we are in the process of doing that under the procedures that the FDA has asked us to do. Trying to I think circumvent that and go forward with

testing either individual pools or individual donors on an ad hoc basis is not as simple I think as is being proposed, and certainly not as timely.

DR. JACKMAN: May I clarify something? I just want to point out that only one manufacturer has HBV NAT testing at this point, and the other manufacturer for the other viruses, there are INDs that are in place, that are applications, but we are not there yet, so we are not able to do some of the parts that are envisioned in the algorithm.

DR. HOLLINGER: Dr. Verter has been very patient here and has a question and then I think we ought to move into closing the public hearing the get into the questions, so Dr. Verter.

DR. VERTER: Part of the training of a statistician is to be patient. I am confused, so being patient was probably good, but let me see if I can summarize what I think I have heard and then I have a suggestion which can be blown out of the water.

I think what I heard this morning is the following. One, that the risk of transmission of HBV, HCV, and HIV, since 1987, is essentially zero. There have been no known cases in the United States.

DR. TABOR: Transmission by plasma derivatives made in the United States.

DR. VERTER: Correct. Thank you.

This committee in the years that I have been on it has struggled often with the issue of safety versus supply, and almost unanimously, I think, we have come down on safety with maybe one or two small exceptions, but we always worry about supply, and whether that is or isn't an issue I can't speak to because I am not in the business, and I don't know how accurate any of the data or the suppositions made here this morning are, but it is a concern and we can't ignore it.

The other thing is based on Dr. Tabor' algorithm and what we heard this morning, it seems to me that what the industry is proposing to do, if fully implemented, and if all the GMPs are adhered to completely, goes beyond the algorithm. It actually kind of brings A up to the top and says everything will be NAT tested.

DR. TABOR: No, I don't think you understood them correctly. What they said was that by the end of the year 2000, everything would be NAT tested. The entire procedure, A under the algorithm would not be in place until the end of the year 2000. What they are proposing now is to do procedure B on everything regardless of post-donation information.

DR. VERTER: You are right, I forgot about the 2000, but other than that, I agree with that statement.

Then, we heard some presentations by the FDA about which post-donation issues, or at least some distribution of the reasons for post-donation notification of problems.

So, we are trying to balance risk and supply, safety and supply. Why not investigate which of those factors resulted in the--well, kind of the hierarchical analysis, which of the factors resulted in the most recalls or taking product off the market.

Maybe only three or four of those actually resulted in having to take product off, so quarantine everything based on any PDI, you know, probably doesn't seem practical or realistic, well, maybe it shouldn't even be considered.

So, my suggestion is to go back and look at all those factors and see if you can narrow it down in the interim, number one. Number two, I would strongly suggest that the FDA and the industry and whoever else can get involved do whatever they can to implement these testing procedures earlier.

DR. TABOR: Well, first of all the procedure B, which was discussed also in March, that is, the comprehensive GMP evaluation, was an attempt to allow the industry not to have to quarantine product.

Secondly, I think the process to get NAT testing on the market is moving forward at such breakneck speed that

it could not possibly, even with special resources, it could not possibly be going faster than it is in this country and elsewhere.

Parenthetically, HBV is being done last because it is expected to have the smallest benefit in terms of this short a window period compare to the other viruses.

There is a question for the committee, as you know, related to this, and before reading that, let me just say that I think it is important for you to follow up on Dr. Epstein's comment. If you do approve the algorithm, you need to--perhaps without going one by one through all the items in footnote i--at least decide whether that list is going to impose an undue burden on the industry in the supply.

I would like to also emphasize what Dr. Epstein said, and that is that NAT testing, when it is in place and licensed, will change the whole algorithm and that this is an interim measure.

DR. HOLLINGER: Before we go on here, is there any other further comment from the public regarding this? If not, I am going to close the public hearing.

MR. BABLAK: Could I make one last statement summarizing?

DR. HOLLINGER: Yes, please.

MR. BABLAK: I think Dr. Epstein has sort of

focused you on what he thinks are important. I would like to at least give my two cents on that.

First of all, I think while the number of PDI reports, there are a lot of them, and they end up affecting all product lots, the actual number of window period units, which is really what we are concerned about, is exceedingly small, so you are using, if I can, the shotgun approach to try and determine whether or not you can look for a particular lot that is released going backwards instead of forwards.

I think that has been done in the past has been for PDI reports, they haven't been seen to be of a significant risk that we would have to go in and do something once the unit has been pooled, and we are saying for the interim, for the next several months, until we get this GMP review, we can continue on that path based on the safety record that we have had with these products since 1987, and then going forward we will enhance what is already being done to add an additional margin of safety to these products which are already very safe.

I think I would like to just leave you with that statement.

DR. HOLLINGER: Thank you, Mr. Bablak, appreciate that.

We are going to close the open public hearing.

Go ahead, Dr. Buchholz.

DR. BUCHHOLZ: As I listen to this conversation, i am getting more and more confused here. It seems to me there are two separate issues that are being discussed. One relates to NAT testing, which is in the process, but not yet there, and the second relates to documentation of validation of good manufacturing practices, and it seems to me we are blurring NAT testing and documentation of good manufacturing processes into this six-month window.

FDA, I have heard it said a couple of times this morning that the current manufacturing processes are safe and, in fact, are very robust, have excess capacity to inactivate, so I think it is important for us to understand whether we are talking about validation of GMP at the manufacturer level or if we are talking about implementation of NAT.

My presumption is that one of these, the validation of good manufacturing process could proceed as a significantly more rapid pace than implementation of NAT testing. If, in fact, there is general agreement that the current manufacturing processes, if followed, are more than adequate to inactivate the viruses of concern, it would seen to me that the industry proposal might be a very valid one and especially enhance the safety in that all lots, not just one that happens to come up for examination, are questioned.

Committee Discussion

DR. HOLLINGER: Thank you.

Any other comments? Maybe we should put up the question what you want us to deal with here, and then we can ask some more questions at that point, at least maybe see the question.

DR. TABOR: The question is very straightforward. It really just asks you whether the algorithm is okay. It is actually the same as Question No. 2 from the March meeting. I would actually like to ask Dr. Hollinger if he could officially designate post-donation information as the wording of choice in place of inadvertent contamination in the question.

For post-donation information regarding plasma in which the contaminating unit was found to have come from a donor who, despite having answered in the negative all questions about risk factors for infectious disease and to have had negative assays for HBV, HCV, and HIV at the time of the donations, was later found to have answered the donor questionnaire incorrectly or otherwise to be at risk, does the committee agree that the algorithm provides suitable responses for FDA to take?

DR. HOLLINGER: There have been some very good comments here, I think, about what is at stake in this. On the one hand, where there should be at last an evaluation by

the FDA of what is going on or whether there should be GMP in place in the first place as validation, I think the key issue is what has been mentioned. We do have a safe product. We should not ignore that issue.

The question is to make sure that there is no breaks, I guess, in GMP down the line because if the product is prepared in the proper way, then, we shouldn't have to worry about it. I mean there is nothing to worry about.

The issue is clearly, as I think Dr. Epstein has mentioned, is whether or not one can be certain under these circumstances that you don't have some breakdown which would allow a unit to be contaminated and transmit.

Dr. Nelson.

DR. NELSON: We have been told by the FDA that there have been breaks in GMP. The issue that I am interested in is that there is a lot of donor screening, and there is a huge list of possible markers for the window period. Most of them vary, still quite unlikely that the person is in the window period. So, I don't think the system has been really put to a good test.

I don't have a good sense as to what have been the breaks in good manufacturing process and how risky have they been, and how frequently does a really high risk break occur. If some really high risk problems have occurred in retrospect, that were only identified because of a problem

donor, then, you know, there is still a theoretical problem.

What I am getting at is I don't think the fact that we haven't had transmissions, although probably when the huge pools, there probably have been donors in the window period, yet, I am not thoroughly convinced that the system has really been highly tested, you know, that we would have detected transmissions for sure.

But if they are all minor breaks, I mean GMP is very complicated. It is a summation of a complex series of procedures. I don't understand what the level of problems with GMP have been that have been discovered so far.

DR. HOLLINGER: Maybe on that same issue about the risk, and so on, of the blood, maybe we should just discuss just for a minute the risk factors that they pointed out here. I think Dr. Tabor wanted you to look at that list under I, Section I, to see if these are the ones that should be used in terms of those which place the product at greatest risk, and if anyone has any comments about those.

Dr. Boyle.

DR. BOYLE: I just have a point of clarification because part of what has been discussed here is timing, that the industry says NAT will be in effect by the year 2000 or sometime in the year 2000. What I am not clear on is if we go ahead and vote in favor of this today, the FDA would still have to go through a Notice of Proposed Rulemaking or

Advanced Notice of Proposed Rulemaking, and my question is if we today said this is a great idea, go for it, how long would it take before this was actually implemented?

DR. HOLLINGER: Dr. Tabor.

DR. TABOR: If you approve this today, we will begin doing it today. It is essentially a codification of what--it is not that far from what we are doing anyway. We do not propose to issue a Notice of Availability, and so forth, initially. We are going to wait until the NAT tests are approved because the algorithm will have to be changed completely at that time.

The same goes for the algorithm that you approved at the last meeting. So, these will be for FDA use. Whether they can be made available stamped Draft or not, I don't know, but so far they have generally not been.

DR. KAGAN: Is there an issue of whether or not we are considering whether an algorithm is needed before we discuss the contents of such an algorithm, or is there an algorithm in place already, and it's just a question of do we want to modify that algorithm? I am unclear on that.

DR. HOLLINGER: It is my impression they are asking about the algorithm that was presented here under the risk factor plasma primarily, and then I think probably they could ask about what are some of the issues within the algorithm.

DR. KAGAN: So, there is currently no such algorithm in place, is that correct?

DR. EPSTEIN: Well, FDA has been involved with this set of evaluations since the 1980s. We have done most of the investigations or mandated them ad hoc. We have developed in the past some matrices that were used as guidance for reviewers, and those were presented at previous meetings of the BPAC.

There was a sense that we needed to move from that ill-defined position to codifying our current thinking on the subject, and that is what led to the development of algorithms which have been vetted publicly because one of the complaints of the industry has been that there was lack of clarity what FDA's expectations were for further investigation or mitigating circumstances or the triggers, et cetera.

So, it is not that there has been no effort to codify internally what we are doing. It is just that we have moved from some internal exercise to having a public discussion about what should be the expectation, what should be the trigger, and what should be the mechanism of resolution.

So, I would say that again we have presented in the past, and perhaps you weren't on the committee at the time, the current state of play as it existed within the

agency, and what has changed is that we have elevated it to the level of public debate and advice from the committee, and that is why you are looking at algorithms.

DR. HOLLINGER: Dr. Verter.

DR. VERTER: I know I am not going to get the data today, but at some point it would seem to me that--well, that is not being facetious, I just know that it hasn't been done probably--but Ms. O'Callaghan's report I think to me is one of the more important things in my reasoning, and that is, in Fiscal Year '98, you reported 3,200 and some-odd PDIs.

Of those 3,200, I just kind of looked at the distribution pretty quickly, and 60 percent are due to three things: the needle category, I.V. drug use, and who is a sex partner. What I don't know from here is of those 3,200 or those 60 percent, how many resulted in destruction of units or recall of units or sending it out to a user and saying, "Quick, get to your doctor, there is a big problem," was it zero, was it 10 percent, was it 100 percent?

The answer to that question to me personally would sway how I vote on something like this. In light of not having that, you know, i am pretty sure I know how I am going to vote, but that is a key element it seems to me.

DR. EPSTEIN: Historically, there have been no plasma derivative withdrawals on the basis of these risk

factors. That is what Mr. Masiello was stating a little bit earlier.

One of the questions here is whether there should be. With respect to individual unit recalls, however, there have been many, but that is not really the point of contention here. I mean no one is arguing that we shouldn't retrieve and destroy unpooled units, whether for further manufacturing or for transfusion.

So, really, the issue does focus on implications for plasma derivatives.

DR. VERTER: Maybe I didn't state it right, Dr. Epstein. What I am trying to get at is--and I think I know the answer based on the data you and others have provided--whether anything got out there because of this, from the FDA perspective, I guess, lack of a complete algorithm that affected any individual adversely.

DR. EPSTEIN: Well, none that we know, but you get into the question of how adequate is surveillance. I think that we can state on statistical grounds that there must have been derivatives distributed that contained units that were fractionated, that were obtained from persons who get post-donation information on risk history.

That must be true, and it has been true for years. There are no validated reports of transmission of hepatitis B or C or HIV from any plasma derivative with the exception

of the Gamma Gard incident, which had unrelated causes.

So, I think it is fair to say that there are no validated reports of transmission in the face of the fact that such unsuitable units must have been fractionated over the years.

DR. HOLLINGER: Also, Jay, in addition to the fact that there hasn't been any more GMP validation requirements up to this point other than what is being currently done.

DR. EPSTEIN: The GMP requirements have not changed, but the agency has become aware of breaches of GMP which do lie in the domain of either validation of the purification or viral clearance and inactivation steps or in the adequacy of investigation of deviations in manufacturing, and it is those observations that have driven this concern, and I would be inclined to agree with Mr. Bablak, that if we were all assured that there was complete and adequate resolution of manufacturing deviations against a background of full validation of the processes, that this problem would go away. It is just that it is my contention that we are not there yet.

DR. HOLLINGER: Dr. Khabbaz.

DR. KHABBAZ: In looking back and forth, I am looking at this algorithm, and I am struck that despite all the complexities, it is quite simple and it really relies on comprehensive GMP evaluation. If you go down A, and you

have a sample and you can test, then, the test is positive. Then, you go to B, and there is a comprehensive GMP evaluation is adequate, then, the pool or the product is released.

So, basically, this algorithm and the proposal are one and the same. What this does is require a fractionator to send reports to FDA of the GMP evaluation for those pools where you have a risk factor. So, it is kind of a first step towards No. 2. I just wanted to comment on that.

DR. EPSTEIN: I think the debate is over the up-front quarantine. What the industry is saying is that if the triggers are as broad as proposed, that a very large number of product lots would become subject to quarantine, and I think that that is a legitimate observation by the industry and very important for the committee to focus on.

DR. KHABBAZ: But if you had a comprehensive GMP evaluation ahead of time, and that was sent to FDA, and it clears a product, and quarantine is really limited. Would you have to quarantine if you can do it within 24 hours?

DR. EPSTEIN: Again, we asked the committee that question at a previous meeting, and I don't remember if it was September or March, whether an adequate GMP status in all manufacturing steps which could impact on product safety could obviate a recall of the product or withdrawal of the product, and FDA's proposed view was yes, it should, and the

committee concurred.

What we are really just debating is when and how that happens

DR. HOLLINGER: Dr. Stroncek.

DR. STRONCEK: I think this protocol is straightforward and clear. I think that it is realistic to expect the FDA to confirm that cGMP was done. There is just no way that they cannot do that. It is like saying a center swears to abide by all the rules and they won't be inspected annually.

Concerning what the industry, about this pooling quarantine issue, they have not been very clear with what they wanted, and I would recommend the committee vote in favor of this protocol and get on with it, and if there is a problem, they can come back to us.

DR. HOLLINGER: Dr. Fitzpatrick.

DR. FITZPATRICK: I just need to ask two points for clarification. On A, when we talk about a validated NAT, does that mean that there is the possibility of using a non-IND-approved NAT?

The other is, is the FDA going to go back through the IND approved NATs now because there is a least one that I know of that prohibits retesting of the pool?

DR. HOLLINGER: Does anybody from FDA want to respond to that? Dr. Tabor.

DR. TABOR: I think we are going to get into an issue of semantics unfortunately, because really, none of the NATs are fully validated yet because they are not licensed.

I think what we are talking about is an NAT for which the information filed in the IND satisfies FDA as to its sensitivity, specificity, and reproducibility.

DR. FITZPATRICK: Wouldn't it be simpler just to say IND approved?

DR. TABOR: I am sorry, i can't hear you.

DR. FITZPATRICK: Wouldn't it be simpler to just say IND approved?

DR. TABOR: Well, IND approved has too much ambiguity. We can take out the word validated if you like and say FDA sanctioned or--I mean the point being that you can't just take a homebrew test that hasn't been seen by FDA and test it. I don't know of a better word, but I agree that there are weaknesses in the word validated.

DR. FITZPATRICK: Are you going to review current?

DR. TABOR: You can't ask a manufacturer to test in conflict with the approved IND.

DR. FITZPATRICK: The FDA staff who reviewed the INDs are very familiar at least with what has been submitted to FDA regarding validation before the clinical trials of the NAT tests begin. So, for us to obtain the answer to the

question is this an adequate NAT test to use for this algorithm is quite easy.

DR. HOLLINGER: So, you could say either an NAT done under IND or a licensed NAT.

DR. TABOR: Well, if there were a licensed NAT, yes. I think that answer to your question is yes.

DR. HOLLINGER: Dr. Chamberland.

DR. CHAMBERLAND: A couple of things. There have been several FDA comments, and I would concur that I think there is a need for some interim strategy or rearticulation of what currently is being done, but I am sort of following along the same path that Dr. Verter is, which is if I have interpreted Ms. O'Callaghan's data correctly, in Fiscal Year '98, there were 618 instances in which post-donation information that is in sync with footnote i were reported, so that we overnight would be going from a situation in which industry is moving from zero to, in a given year, potentially 600 instances in which they have to proceed along this algorithm of which the largest impact seems to be quarantine.

We have heard from industry that in their view at least at this point in time, not a lot of these would be resolvable in 72 hours. I am trying to balance that also with what I view the items in footnote i are again, as has been stated previously, are very insensitive predictors of

window period.

So, I am struggling with is there any sort of compromise along the way in which I think FDA is wanting to move from just acting on test data, as Dr. Epstein explained, the current triggers are really based on test information, you know, a donor testing positive or a pool testing positive to acting on post-donation information reports, which again, as BPAC members have really had some concerns that that is not currently really being done, but I have to say I have a concern of moving so quickly from nothing to a fairly comprehensive albeit insensitive list of triggers and worrying where we might be with respect to product supply and keeping that flowing, because we know for certain products at least we are already in a shortage situation.

I don't know if the committee feels there is any point discussing how this current list of triggers might be modified, if that is even doable.

DR. HOLLINGER: Dr. Mitchell.

DR. MITCHELL: I, in fact, do like the list of triggers that are listed there, but I understand and I agree that there has to be some kind of an implementation period, and I would expect that FDA would come up with some kind of a date. If we are only talking about reassuring that GMP is being followed correctly, it seems to me that that should be

able to be done in less than six months, and I hear industry saying that it might be able to be done in less than six months. However, I think it would be unreasonable to say that by tomorrow that we would expect this to be done.

I think there has to be some kind of implementation period, and I think that it should be up to FDA to sort of judge what that should be.

The only thing that I would change, like I said, in the algorithm, is I would adopt the industry's term of under the first one, instead of destroying units, that the units be removed from use for therapeutics.

DR. HOLLINGER: I think we will go ahead and vote on the question, and then if there is issues that have to do with the algorithm, if that is what is voted, then, we can deal with those, but I think we first ought to find out if everyone on the committee agrees with the question for the committee, which is whether or not the algorithm provides suitable responses for the FDA to take as such.

Dr. Tabor has already read the question. A yes vote would mean that you agree that this algorithm should be adopted, and then we can discuss about the algorithm itself, and a no vote would be no, that you do not agree with that, and people have to go back to the drawing board again.

Dr. Smallwood wants to indicate who is going to be voting.

DR. SMALLWOOD: I would just like to clarify for the voting process that our advisers, Drs. Chamberland and Fitzpatrick, will not be voting. Neither will our non-voting consumer and industry representatives.

DR. HOLLINGER: Dr. Boyle wanted a question. I meant to call on him. I am sorry I didn't. So, this will be the final.

DR. BOYLE: The only issue I have is in some sense, the relationship of the two questions. I want to sort of basically agree with Dr. Chamberland's comments. Number one, we believe that the product is safe only because good manufacturing practices are followed, if they aren't, it is not going to stay a safe product. So, that is very important.

It is not good when people say that the data doesn't exist to be able to verify whether good manufacturing products have been done, and it is appropriate to have as a trigger to investigate that, things that appear to be greater risks.

On the other hand, if there are 600 and some of these cases which may involve half of all the products shipped, that 600, given the absence of NAT, these 600 immediately have to go through these good manufacturing practice investigations. That is an average of two a day across the industry.

So, if we go forward with voting in favor of it, you know, my concern is we are running the risk of basically shutting down availability or dramatically reducing it. On the other hand, I think the basic algorithm is a good idea, and if we went forward with, for instance, the category AIDS related signs or symptoms, of which there were six reported cases last year, or something on that order, then, you have an opportunity to see how well it works before moving to the next step.

If I were, as I am going to be asked to vote, if I were asked to vote on a very limited scale where we were taking one or two of these items and seeing how the process worked, how long it took to do these things, what the burden to the industry was, how many quarantines occurred, and then had that reported at the next session, I could vote in favor of that.

If, on the other hand, we are voting across the board on implementing a process that basically could shut down product availability or dramatically reduce it, then, I would have to vote against it.

So, that is why the order of these two questions becomes of some significance.

DR. HOLLINGER: The order of the algorithm versus?

DR. BOYLE: What is in the algorithm, what the triggers are.

DR. HOLLINGER: I will give an issue, if anybody has any comments about that where they think that is an issue.

Dr. Stroncek.

DR. STRONCEK: It is my opinion it doesn't do any good to have product out there that is not any good. I would be appalled if half the products in the country didn't meet good cGMP. I think that would be a disaster in itself.

DR. HOLLINGER: I am going to call for the question.

All those in favor of the question, agree that the algorithm provides suitable responses for the FDA to take as such, please signify by raising your hand.

[Show of hands.]

DR. HOLLINGER: All those opposed?

[Show of hands.]

DR. HOLLINGER: Abstaining?

[One hand raised.]

DR. SMALLWOOD: According to my count, it doesn't come out right, so I am going to need you to vote again. We are one short.

DR. HOLLINGER: I voted yes. Sorry.

DR. SMALLWOOD: The Chairperson explained to me that he is voting with the yes votes. All right.

The result of voting. There were 7 yes votes, 5

no votes, 1 abstention. There are 13 members here who are eligible to vote.

DR. HOLLINGER: Dr. Buchholz, you were going to comment how you--

DR. BUCHHOLZ: I would vote no.

DR. HOLLINGER: Ms. Knowles?

MS. KNOWLES: I am going to abstain.

DR. HOLLINGER: Are there any questions, then, in regards to the algorithm then or the contents of the algorithm? Yes, Dr. Verter.

DR. VERTER: I will just quickly reiterate what I said before, and also comment again on what Dr. Chamberland said. I think someone needs to go through the items in i and rank them in some order, both in the numerical reports, as well as what happened when they investigated those reports.

I am concerned, as Dr. Boyle indicated, of the balance between risk and supply. I mean this is a good example of where we might have a problem.

DR. HOLLINGER: Dr. Ohene-Frempong.

DR. OHENE-FREMPONG: My concern was also with the list. I imagine that the list was compiled based on some scientific data or maybe the best suppositions that could be made, but I see some inconsistencies in them, and unless there is some full explanations for some of the broad

sweeps, it is hard for me to, for instance, see whether there is a difference between a risk of incarcerated females and female prisoners versus incarcerated men in male prisons, and whether somebody incarcerated for contempt of court in a minimum security prison is different from somebody in the maximum security prison.

I think there are some issues and some brushes have been cast very wide, and maybe there are data to support them.

DR. TABOR: May I answer that question? The way it was compiled was with the data presented by Sharon O'Callaghan. A small committee of us went through that list and tried to eliminate the things on the compliance list that we thought were of minimal significance.

Obviously, we are willing to modify that list further, and we welcome your suggestions. In answer to Dr. Verter's comment, you said to rank them. Do you really mean to rank them or do you mean to reduce the list to a smaller list?

DR. VERTER: I meant to rank them based on data which may not be possible to get. In other words, if you could--I forget how many items--say there were 8 items, and you could start by ranking them in the frequency that they occurred, but more importantly it seems to me, what percentage of those resulted--I mean was the result of every

one of those PDIs that something was brought back and destroyed?

DR. TABOR: I am not the one to answer that, but my question about the ranking is if we rank them, do you want us to drop the ones that are low ranked?

DR. VERTER: My suggestion was that in the ranking and the further investigation, if you could determine that some of those PDIs resulted in no action, that it was not worthwhile doing a recall, that those would be dropped, yes.

DR. HOLLINGER: I think it is important. This is a very close vote here. Obviously, there is a lot of concern about the algorithm and what it might mean both for the industry and otherwise in a product that is fairly safe.

Does anyone want to respond? We know why the yes votes are there, but does anyone want to respond who voted no or abstained, because I think the FDA needs--I think they have heard this anyway under comments, but I think they probably need to find out what the real issues are here with the other major group.

Yes, Dr. Nelson.

DR. NELSON: The reason I abstained was I was confused. One of the things that I was confused about is that I guess this algorithm for inadvertent contamination or post-donation information has not been used, but there has been used the test result, and I didn't see any data

presented about how the review of GMP practices on the test results has affected the industry and how many units have ended up being quarantined or not used.

Therefore, even though there are a lot of instances, maybe half of the pools, I couldn't really tell whether or not these could, in 90 percent, be resolved within 72 hours with no problem or if two-thirds of them would be quarantined for six months.

Therefore, I didn't have the data to project what would be the impact of this even on the short term. I don't know if there is any answer to that question. I mean since it hasn't been used in this number before, you maybe don't know, but there is some experience with the test results.

Can anybody enlighten me about this?

DR. EPSTEIN: Well, first of all, in terms of frequency, it has only been a handful in any given year, like two or three. Second of all, the resolutions of the GMP concerns have ranged from resolving the matter of hours to days to remain unresolved after years.

So, there has been no consistency. I would say that it is also sorted out differently by product, that most of the time when there has been potentially affected albumin, for example, the validation records on heating in the liquid state have been adequate, and there hasn't been a problem, that with some of the more recently introduced

practices related to solvent detergent processing or column purifications, there has been a wider spectrum as to the adequacy of the validation data as it could bear on interpreting the significance of the deviation, and it has just been much harder.

So, there really has not been a consistent experience. It has simply varied from manufacturer to manufacturer, and product to product. But I would say that the majority of cases have been resolved within weeks. It has been rare to resolve it within the course of a day or two, and there have been some outliers that have been extreme.

MR. BAKER: Don Baker, Baxter Health Care. I would like to give the committee a couple of pieces of information that I think is relevant to some of the numbers that we have heard.

With respect to the inadvertent contamination for source plasma units, roughly two-thirds to 75 percent of the proximal units are interdicted in the 60-day period. So, by that I mean of that 610 that we heard thrown out, roughly two-thirds to three-quarters of them, of the proximal unit to the report, will be caught in our 60-day period. That is our industry experience.

However, I should say of the remainder that aren't caught, and of those ones that are caught, on average, a

source plasma donor gives something in the neighborhood of 10 to 14 units a year. So, of the nonproximal units, there is a significant multiplier. So, the number doesn't come out to 600 in terms of these post-donation information reports, and I think that is what you have to understand. That is what is driving the industry concern.

I also want to point out Baxter Health Care manufactures for the American Red Cross, and I am sorry there was no Red Cross spokesman here, but for those of you that are looking at the numbers, you should, of course, keep in mind that there is a difference in the volume of donation by a source plasma donor versus recovered plasma donor, i.e., it's about a quarter.

So, there are four times as many units roughly in a liter of recovered plasma versus a liter of source plasma. This algorithm will have a disproportionate effect on products manufactured from recovered plasma in terms of the number of PDI reports that are going to have to be reviewed, and you saw that there was, I think 8,000-odd in the recovered plasma side. The American Red Cross accounts for about 50 percent of the plasma collected, so you can say just for the American Red Cross manufactured product, there is going to be some 4,000-odd PDI reports.

So, when you start thinking about the workload, that is what is driving the industry concern.

DR. HOLLINGER: Dr. Tabor.

DR. TABOR: I think it is worth emphasizing we are dealing with a low risk situation here. We are dealing with units that are test-negative, donors who are in risk groups, most of whom are not in the window period, and with products that despite some of these problems that have occurred over the years have not been known to transmit these viruses since 1987.

But we are also dealing with a society that expects zero risk from things made from blood, and I would say that some of what we are doing today is driven by the fear or anxiety that at some point, a window period donation will get into a pool, and due to GMP failures, will infect a large number of people, and then there will be a lot of fur flying.

I think this concern was very vehemently raised at previous BPAC meetings by BPAC members. If all GMPs could be met, it would be a different situation.

DR. HOLLINGER: If there are no other comments, we are behind, but I think it is important that these issues be discussed. We had a lot of important issues this morning.

We are going take an hour break. We are going to come back at 2 o'clock for the session this afternoon.

Thank you.

[Whereupon, at 1:00 p.m., the proceedings were

recessed, to be resumed at 2:00 p.m.]

AFTERNOON PROCEEDINGS

[2:00 p.m.]

DR. HOLLINGER: The first session this afternoon is on strategies for insuring compliance in the plasma fractionation industry.

Mr. Masiello, Director of the Office of Compliance and Biologics Quality is going to talk to us about it.

II. Strategies for Insuring Compliance in the Plasma Fractionation Industry

Steven Masiello

MR. MASIELLO: Thank you.

[Slide.]

We have a little bit of a change of pace from this morning's discussion. The purpose of this particular presentation is really to give you some insights into how we are regulating the fractionation industry in terms of GMPs, and we are going to talk mostly about the injunctions and consent decrees that we have in place and what the elements of are.

There will be a few things before we get there.

[Slide.]

I would like to thank Larry Fenner for, first of all, creating or making up the slides and then for helping me out here today.

We are talking about inspectional frequency is one

of the things that is a manner in which you might provide mechanisms for insuring the compliance with GMPs. Enhanced training of investigators is another thing we will mention. Communications, really talking about communications with the industry, and post-inspectional issues, and that is when we will really talk about the consent decrees.

[Slide.]

In terms of inspectional frequency, right now we are conducting annual inspections. I put down here that there is an exception for pulling back a little bit from the frequency of the inspections if you have certain conditions that exist.

The fact of the matter is we are really not at that position at this time. I think we would be willing to consider doing that, but certain conditions have to exist first, namely, have NAI, which is no action indicated, or VAI, which so voluntary action indicated conditions. The VAI is a broader category, and you may have some flexibility in there.

In terms of "as needed" basis, we certainly do conduct inspections to follow up on complaints, recalls, and to verify corrective actions under certain circumstances.

[Slide.]

In terms of investigator training, Dr. Lynch covered a little bit this morning in terms of the specific

comprehensive training that some of our ORA investigators undergo before they go out to the fractionation industry.

A few words of explanation. The Team Biologics, that is a whole lecture in itself talking about Team Biologics, but the Team Biologics is made up of core team members and the cadre.

The core team are those individuals--and there are about 12 to 15 ORA investigators that receive specific training for each of the product areas that they will be inspecting--fractionation is one of those, IVDs, allergenics, and in October, the vaccines will be going over to the Team Biologics investigators.

So, they receive this training and as Tom mentioned, there are product specialists, which are those CBER personnel that have expertise in the product, in the process, that will either accompany the Team Biologics inspectors, or be available in some other capacity, either by phone or however.

So, that is the core team. The blood cadre are the inspectors, the ORA investigators who do the blood and plasma inspections. At one time I believe there were somewhere in the area of 200-plus individuals who at one point or another during the year or during the cycle might do an inspection of a blood or plasma center.

When Team Biologics was developed, the idea was to

reduce that number, so that we could enhance consistency in terms of inspections. I believe now--I don't know whether there is anyone from ORA here or not--there are approximately 125 FDA investigators that will be doing blood and plasma.

I think that is really all I need to say on the investigator training.

[Slide.]

Communications. I will just mention very briefly that meetings, such as this, provide hopefully opportunities to communicate on key and important issues, public meetings, such as the one noted that dealt with plasma product withdrawals and recalls, and liaison meetings that occur with industry are ways that we can and do communicate current issues.

[Slide.]

In terms of post-inspectional issues, I really want to talk about just two here, and that is warning letters and consent decrees. Just to briefly mention the warning letters, in the next chart we will have a view of the warning letters that have been issued over the last couple of years.

[Slide.]

What I want to be careful here is not to mislead you as data can sometimes do in terms of the slope of this

change. There were, of course, a peak number of warning letters that were issued in '97 following some fairly intensive inspections conducted in '96 and '97, and there are, as you can see, fewer warning letters that have been issued since that time.

This is not meant to imply that the industry is fully complying with GMPs, but I think you can look at this and see that there has been some progress and that we are not in the same situation perhaps that we were in, in Fiscal Year '97.

[Slide.]

In terms of the consent decrees, it is certainly not any secret that there are two primary manufacturers in the fractionation area that are under consent decree at the moment, Centeon and Alpha, and just to mention that Parkdale Pharmaceuticals, which is owned by King Pharmaceuticals, is also under injunction that was initially a Warner Lambert/Parke-Davis facility, that also might in the future make blood products.

[Slide.]

What Larry has done for us here is identified a number of the elements of the consent decrees that would be useful for you to see what kinds of things are being addressed in the consent decrees.

On top on that list, of course, is the reworking,

reprocessing of returned and rejected products, and this is an area that over the years there have been some different interpretations that have taken place, and consistent with current GMP, these are being addressed and identified for follow-up.

We also as part of the consent decree, in all consent decrees, there is an element for expert consultants, and really the purpose here is to assure that manufacturers develop the systems in conjunction with experts in the area that will not therefore be reliant on FDA to find problems. The consultants working with the industry will develop the audit systems, quality assurance programs, what have you, where they will have the ability, the capacity to find and correct problems independently.

Management and personnel controls, these are areas where the agency always stresses the importance of having strong management and control over the various kinds of personnel, how they operate, and the type of people that are in place, whether they are appropriately trained for that position.

Quality assurance and quality control programs. We certainly always insist on a consent decree that the firm develop and have in place quality assurance and quality control programs.

[Slide.]

As I mentioned, training is obviously an important element in all consent decrees, and there is a high degree of emphasis in that area. Internal audits, again, it is important for us to have that level of assurance that the company, as it works through its problems, is also developing sufficient expertise, so that they will be able to identify the problems, and not rely on FDA.

Production and process controls. It is obviously important to have these in place, laboratory controls, and building and facilities have to be adequate, and these areas have to be addressed, and there may be sufficient attention on that, and a fair sum of money that would be spent.

[Slide.]

Equipment, of course, you have to have the appropriate equipment in place, records and reports. I think there is a great deal of emphasis on assuring that the manufacturers have in place adequate records and reports, so that they can make the appropriate decisions.

I think this morning there was some discussion about out of spec findings, inadequate investigations, and I think it is in that area and others that we would expect to see the records complete, so that they can make adequate decisions and that we can verify those.

Recall procedures have to be in place at the manufacturer, so that should there be a need, those can be

implemented, and post-compliance audits and reports. Ordinarily, what we are asking for from firms is periodic reports to the FDA, so that we can measure their progress in certain areas.

[Slide.]

In addition, there are certainly specific procedures in most of the consent decrees that deal with issues where there may have to be a revision or a modification of any reports, so if we get reports and in conjunction with either inspectional information or other reports, find that these are inadequate for us to assure compliance, then, these can be modified in some way to assure that.

At anytime, additional information can be requested and reports requested for submission to the agency, and, of course, if there are findings where it is apparent that a change has been made or changes need to be made or an existing condition is not acceptable, then, you may have to require the submission of supplements to the license.

[Slide.]

In addition, the agency can, and does, often look at the facility and make a determination that there are sufficient problems that manufacturing needs to cease or processing or any aspect of manufacturing may come into

question, and the agency has the power and the authority to require that the manufacturing or any of those areas cease.

That is something that perhaps doesn't come across clearly if you look at a consent decree and you see the titles of management controls and records, and things like that. This is a very important and powerful tool for the agency in terms of bringing firms into compliance.

The agency can also order specific recalls under the consent decree, so if there is evidence that points to problems with a particular lot or lots, the agency can order a recall.

Now, of course, all of these issues can be challenged by the firm in court, so if there is a belief that the agency is acting arbitrarily or capriciously, the firm can go to the court and request relief from that, but that has not occurred yet.

Lastly, the agency essentially can take any action, can request or order any other corrective action that is appropriate to the situation.

[Slide.]

Just a listing pretty much of the kinds of things that, in fact, we have done over the last couple of years. You probably are well aware that the agency has ordered manufacturers to cease manufacture and distribution of products based on inspectional findings, based on noted

examples of contamination, and things of that sort.

We have ordered recall of products, requalification of products via inspections, and additional testing, so that if there is a situation where there is a need to essentially enhance our level of assurance that these products are safe, we can ask or require that additional testing be done.

FDA has also requested the submission of data for us to review prior to the release. This, of course, is above and beyond lot release provisions where there is a set protocol for what comes into the agency and what the agency would do. There may be instances where we need to go beyond that.

[Slide.]

We have certainly had issues of validation and requested that firms cease reprocessing until the system that is currently in place has been validated, and a lot of that, as you can imagine, goes back a number of years.

There is the request for third-party reports in terms of lot release issues or lot release requests, so that in addition to the specific testing that was done, these particular circumstances, there was a review conducted by a third party and then that review was submitted to the agency with the lot release.

Again, that goes back to the concept of the firm

developing the procedures and the capability of making these kinds of reports and findings without the FDA having to go out on site and conduct inspections.

There have been requests for submission of things such as environmental reports and requests for increased frequency of media fills.

[Slide.]

I bring this up on insofar as it impacts on the fractionator industry. There are of course, as we mentioned this morning, the suppliers of plasma, source plasma and recovery plasma. Insofar as a fractionator uses material from the American Red Cross or Blood Systems or New York Blood Center, there are things that are done in the consent decrees that exist with these firms that have what we believe is a positive impact.

[Slide.]

There is a similarity here. You can see that in the consent decrees with the blood banks, we have requirements for management control, quality assurance, quality control programs.

A few different items here that are unique to the supply side, or course, are the computer systems and the databases. If there is a problem with deferrals and things of that sort, they are going to usually be associated with the databases.

Records management, part of that, and, of course, making sure that establishments have the systems in place for reporting errors and accidents, adverse reactions, lookback cases, et cetera.

[Slide.]

Also, we have again the need for internal audit systems, employee training and education, donor suitability determinations, and the testing areas. There is a great deal of time that is spent on assuring that these particular establishments have these systems in place and have the capability of auditing their own systems and making sure that they carry through with that.

There are in these particular consent decrees also provisions similar to the ones in the fractionation consent decrees which really allow the government to pursue whatever else really needs to be done if there is a finding of problems in terms of GMPs or testing, what have you.

I believe that is it. If there are any questions, I would be glad to address them.

DR. HOLLINGER: Questions? Yes, Dr. Mitchell.

DR. MITCHELL: You had mentioned OSRs, I believe.

MR. MASIELLO: OSRs. Tell me what I meant by OSRs.

DR. MITCHELL: You said that the groups that were doing the inspections--maybe I had the initials wrong.

MR. MASIELLO: There is the core group--the ORA, sorry about that, the Office of Regional Affairs. These are the field investigators.

DR. MITCHELL: Also, on the orders issued, you had said something about monthly environmental reports and increased frequency of media fills. What does that mean?

MR. MASIELLO: In terms of the manufacturing process, the manufacturers generally have in place procedures for monitoring the environment.

DR. MITCHELL: The outside environment? I don't understand.

MR. MASIELLO: No, the manufacturing environment, I am sorry. Those areas within the manufacturing suite where it makes a difference what the quality of the air is, so that it prevents contamination, and so we may ask for additional monitoring or media fills, which are a way in which a manufacturer essentially tests their aseptic processing abilities to make sure that they can manufacture material in an aseptic way. I am sure Dr. Lynch or others can say that so much better.

DR. HOLLINGER: Dr. Koerper.

DR. KOERPER: What are NAI and VAI?

MR. MASIELLO: The NAI is No Action Indicated and the VAI is the Voluntary Action indicated, so that if a firm has had an inspection that we classified as NAI,

essentially, that is either a no 483 or very minimal 483 that has been issued to them, the list of observations.

The VAI is a little broader. You may have issues that come up during the inspection that a firm can address and fix without a need for the agency to take any action, and that is a voluntary action.

DR. KOERPER: So, if they have two of these consecutive inspections, you then will only go to see them every other year?

MR. MASIELLO: Well, there is under consideration right now a decision that we need to--again, we have 12 to 15 Team Biologics core investigators, and they are doing all of the biologics, fractionator work, IVD work, allergenics, and they will be doing the vaccines.

So, the resources are somewhat limited, and what we will do is insofar as we can do that, we will cut back in areas that have demonstrated ability to be in compliance. We are really not there yet, but hopefully, we are approaching that.

DR. KAGAN: In this particular industry, is there any other monitor of compliance other than FDA? Are there any organizational accrediting bodies, voluntary accrediting bodies, or are you the only level of monitoring for this particular type of industry?

MR. MASIELLO: Well, certainly we are the last

ones. Of course, all the firms that I am aware of have internal procedures, and I think the vast majority, if not all, have outside consultants that conduct audits of their facilities. I would defer to someone in the industry to answer if there are other bodies that are inspecting.

Certainly, there might be states or other government agencies. I am not hearing that there are others out there.

DR. LYNCH: I am not sure that you would consider it relevant, but many of these firms have licenses in other countries and inspectional authorities from Europe, for example, will also be performing similar, but not identical investigations.

DR. HOLLINGER: Do they share information? Let's say they inspected and they found something wrong, do they share it with you?

DR. LYNCH: It may not be routine, but in exceptional circumstances, yes, we communicate with each other.

MS. WAYS: This is Judy Ways from Centeon. Actually, Dr. Lynch said exactly what I was going to say. Many of us have European licenses, and we are inspected by the regulatory authorities of those countries, for example, the Paul Erhlich Institute in Germany, Medicine and Control Agency in the UK.

DR. HOLLINGER: Thank you.

Dr. Mitchell.

DR. MITCHELL: Can you tell me what percentage of the products from the fractionators is currently under consent decree?

MR. MASIELLO: I am sorry, I missed the first part.

DR. MITCHELL: I am trying to figure out what percentage of the fractionators or what percentage of the market is currently under consent decree.

MR. MASIELLO: Domestically, what is generally viewed as the Big 4, I guess there are two, so that would be about 50 percent of the larger facilities.

DR. HOLLINGER: I am sorry, there are four fractionators?

MR. MASIELLO: No, four large, considered generally large.

DR. HOLLINGER: How many fractionators would come under all this--

MR. MASIELLO: There is somewhere in the area of 24.

DR. HOLLINGER: Twenty-four.

MR. MASIELLO: Yes, because I think some have discontinued manufacture, but internationally, 24 or so.

DR. HOLLINGER: Thank you.

There were two individuals who asked to speak on this topic in this session, and I will call on them to do so now under the Open Public Hearing. The first is Jan Hamilton from the Hemophilia Foundation.

Open Public Hearing

MS. HAMILTON: I am Jan Hamilton with the Hemophilia Federation of America. I want to thank you once again for allowing me to address you with some of our concerns regarding consent decrees.

We would like to pose a few questions about them and their effects upon industry, product shortages, and other results.

First of all, it is our understanding, and now we know for sure, that there are a set of standards generally referred to as general manufacturing practices and that each manufacturer has access to these standards.

We would like to know how they are regulated, are they viewed on a regular basis similar to the way hospitals go through JAACO accreditation? I understand that it is annually by the FDA. Is the only monitoring done by the FDA? Somebody else just asked that question. If so, is it on a regular basis or just when a problem occurs?

We appreciate the plethora of information that we have received this morning regarding GMP, but we had a few additional questions, many of which were just answered by

Mr. Masiello, but I will go ahead and review them anyway.

We wanted to know who conducts the GMP review, how long does it take to do an entire facility, and is everything in the facility covered, such as records and procedures and equipment and products, the whole nine yards?

What is the structure of such a review, is it conducted by just one person or a multidisciplinary team or what is the makeup of it, and what are the checks and balances?

Can consumer groups get results of these reviews?

We are now getting supply reports through IPPIA. We would also like to get the GMP reports.

In the same light, if each of the manufacturers have those standards, and they know they must adhere to them or face a consent decree, which must prove to be costly for everyone, then, to use a borrowed phrase, this is a puzzlement.

Why would a manufacturer slip out of compliance? Why wouldn't good working quality improvement, quality assurance practices prevent a situation that would result in a consent decree?

In the last couple of years, as we saw in the chart a few minutes ago, there have been several consent decrees issues. In a couple of situations, the companies voluntarily closed facilities to correct a problem.

We hear about the consent decrees being issued. Perhaps there are others who, like our group, would like to see reports on the correction along with what plans have been made to prevent recurrences of these situations.

Are there levels of severity of consent decrees? What is the cutoff between a consent decree and suspension or removal of licensure? What if the reasons for the issuance of a consent decree are of a repetitive nature, same cause, same company?

If there is a suspension or removal of licensure, then, is there a formula to determine the length of that suspension or removal, and what must be done to accomplish reinstatement?

We have been observing shortages in supply over the last several months, and how much of these shortages result from plants being under consent decrees versus other problems?

We have been pleased to see the increase of information from industry regarding recalls and/or withdrawals through the IPPIA and the establishment and operation of the patient notification system through IPPIA and the National Notification Center.

In addition, we appreciate the efforts of IPPIA as presented this morning by Jason Bablak, but we have some concerns similar to those already stated here today, and

would hope for a solution that would allow forward progress without leaving any gaps in surveillance.

We would like to see similar data to the recall withdrawal information made available surrounding consent decrees and other sanctions.

Those of use who lives depend on obtaining safe, reliable products to keep us healthy, safe, and leading productive lives are concerned about the effects of consent decrees upon the supply of quality products and wonder what are the reasons a company would allow themselves to create a situation that would call for these measures.

Once again, we thank you for the opportunity to express our concerns.

DR. HOLLINGER: Thank you.

I next want to call on David Cavanaugh for the Committee of Ten Thousand.

MR. CAVANAUGH: Thank you, Dr. Hollinger.

We also are very pleased to have this presentation when two of the four producers of the products we consume are under legal sanction for some years, and no further feedback is available on the results of that process, if you will. It is scary and it makes us wonder how the product is doing in terms of becoming improved, algorithm or no algorithm, if you will, if I can borrow from the earlier presentation on a different matter.

There were 16 warning letters in the last half decade, and I don't know if those covered whole blood as well as fractionators alone, but although it is a large and important industry to us and the four fractionators that are the largest make up a huge piece of industry, and the 24 being on there, perhaps another if you do add whole blood, that seems like not so many in terms of warning letters.

Obviously, when you move to legal decrees, your scope vastly increases in terms of the enforceability of various provisions and the kinds of provisions you can impose, but it looks almost like you write a few letters and then you slam the industry under legal control, and then you don't say anything about how it is going with it.

We are confused. We don't know how it is going with obtaining GMP. In Mr. Masiello's comments on the overview and insuring compliance, he talked about frequency of visits and some of it is an ad hoc basis and training. Sometimes the CBER people go along and sometimes they don't in terms of expertise on site.

He talked about communication at BPAC meetings and at special meetings with industry. I would like to add consumers into your thinking, so that there is more--I grant you these meetings are open, but they are for the members of the committee, and general reporting on consequences of legal actions would be appreciated by this regulatory