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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

AND

PLASMA PROTEIN THERAPEUTICS ASSOCIATION

COMPARABILITY STUDIES FOR HUMAN PLASMA-DERIVED THERAPEUTICS

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C O N T E N T S

P R O C E E D I N G S

Opening Remarks

DR. MENDELSOHN: I would like to welcome everybody back today. My name is Craig Mendelsohn, from PPTA. Again, thank you to everyone from FDA; thank you, gentlemen, from industry who have been here both participating as speakers, as well as working on these topics. Today should also continue with a real interesting dialogue. At the end of the morning session we have a panel discussion again so we will be having index cards for you to send the questions up, or you can come up to the mike again.

I just want to make a couple of administrative announcements. For those who want to FedEx home your books, there will be forms at the table during the break and the business center can send the books home, if you want to, but the forms will be out there. Also, we ask you to please send in your evaluations before you leave. It is the yellow form in your notebook, and there will be a basket out on the table where you can drop off the evaluation.

I would like to turn it over now to this morning's moderators, to Barbee Whitaker, from PPTA, and to John Finlayson, from FDA. Thank you.

DR. WHITAKER: Good morning. Our first speaker is Dr. Don Baker. Don is with Baxter BioScience and he is vice president of post-market quality management.

Comparing Fractionation Intermediates

Industry Perspective

DR. BAKER: Good morning. I tend to be chronically challenged in looking at agendas and I didn't realize until this morning that my talk was in front of Dr. Finlayson's. That is like giving the opening act for God--

[Laughter]

--I should add, not the nice, warm and fuzzy, New Testament God but the old--

[Laughter]

Anyway, industry perspective--I don't know if any of you have ever thought about how strange this industry is, the manufacture of plasma derivatives. But could you imagine pitching this as a business concept? Here is my vision, we are going to go out across the U.S. and set up hundreds of centers, and to these hundreds of centers we

are going to bring normal, healthy people and subject them to intrusive, awful questions about their behaviors and an uncomfortable procedure for a couple of hours to collect their plasma. We are going to take all that plasma and put it in big buckets, and separate it into products, and these products, at one end, will compete against saline and other cheap products. The other end will have real niche market products that have barely touched the orphan status in terms of number of patients. If you tried to sell that concept de novo to your management committee, I can guaranty you your next task would be polishing your resume and pursuing other career objectives. It is a crazy business. Nonetheless, here we are.

Another strange thing about this business is the business model. In most cases, most normal businesses, the demand drives your supply. You make what you can sell. In this business the supply constrains demand. There is a patient out there for every vial that you can manage to make, and that is actually quite a strange concept. It drives a number of unusual things in business and in terms of the way you model the business.

By the way, this all does have something to do with comparing fractionation intermediates and I am going to get to that. So, the consequence of that is that when you are running your manufacturing plant any glitch, anything that happens, any upset in the manufacturing routine means you deviate from your plan which you gave your bosses about how much you were going to make and that, of course, has consequences that aren't usually very nice.

In addition, your raw material, your plasma that you use for the manufacture of these very important pharmaceuticals isn't very expensive. In terms of a normal business, a normal pharmaceutical business your raw materials are typically a very small percentage of your total cost of manufacture. This is quite different with plasma derivatives. Typically, the cost of plasma represents the single largest cost for a manufacturer, or near to it, and what is more, it is becoming more expensive, which reflects the scarcity of plasma. Plasma, in recent times, as you can see, has increased, at least for our company and I presume it is pretty typical for most of us, at roughly twice the cost of inflation.

So, when you are making these materials as you are trying to get everything out the door that you can, and you find that cost of your inventory, your work in process can be very substantive. In fact, when you close the books at the end of the year, you can find that, despite the fact that you sold everything you can make, you have actually lost money because you haven't managed to manage your inventory appropriately and you have all your money tied up in this very expensive inventory.

Another unique feature of this business is balance. Again, you are trying to distribute your products globally and what you find is, of course, your manufacturing capacity, certainly on a global basis, is not uniformly distributed and you don't have your manufacturing capacity exactly the way you want it all the time to sell material. The product demand is not uniformly distributed because you may not have licenses in some areas, or you may not be competitive in various areas.

Finally, and this is the trickiest thing, is to balance the input and output of a given plant. You want to keep your plant optimally running and use all the components of your plant, as we say, all the slots. You

want to keep your tear-down slot occupied, your fractionation slot, your filtration, your filling slots, all of these areas in your plant you would like to keep optimally running. But given that you have your plasma which has a defined yield that you can get from it, keeping all of those components of your plant optimally running and occupied all the time or not over-producing and producing more of this valuable intermediate that you can't take to the next step, that is a very, very difficult activity.

I told you all that to tell you this, that is one of the major drivers in terms of why you want to have comparability of plasma derivatives. For a manufacturer, the ability to either sell or buy intermediates from another entity or from another plant in your own organization tremendously simplifies your operation. It gives you another tool to make you more efficient, more product out the door, and to manage the economics within your plant.

Anyway, that is the sort of constellation of business reasons for why manufacturers are very interested in comparing fraction intermediates so that you can use fractionation intermediates from other sources.

Let's talk about an algorithm for providing an approach for comparing fractionation intermediates which will, of course, make our plants more efficient and improve the availability of plasma derivatives. In terms of the components of the algorithm, I have a particular fondness for alliteration and I would like to focus on the three Ps, provenance, process and parameters.

In an earlier workshop, earlier this year, in talking with Andrew Change there was this question of, you know, the FDA gave its perspective on comparability in 1996 and Andrew challenged me to look at the things, what has changed since 1996; what is different; what might the FDA wish to consider as new information in terms of rethinking comparability.

In terms of the prominence, I think this industry has a lot of new things to offer. There have been tremendous changes in this industry since 1996. The donor screening, for example, the introduction and adoption of PCR, or screening for viral markers, that has really taken off since 1996 and been essentially universally adopted. Plasma collection, certainly the 60,000 donor limit is new since '96. The inventory hold through the industry is also

new. All of these represent significant advances in the safety of plasma.

So, if you were looking at comparing intermediates, one of the key issues is going to be to make sure that the intermediate that you are comparing to that you are using in your plant currently should have a comparable provenance. It should have comparable donor screening; comparable plasma collection practices. Obviously, you already have a qualification program for an entity that you would get a donor from. Short of a short change of custody, you don't want to be taking an intermediate that had been shopped around through various other entities. There should be a certification of GMP compliance. Anybody you are buying it from should be willing to certify their compliance status and, of course, validated shipping and storage conditions and, finally at the end of the day, that intermediate should have a signed quality assurance certificate of analysis. So, I think those are the kinds of elements that you want to put in an algorithm that is used in comparability.

The next part is process. Again, I think this is an area where there has been substantive change in industry

since 1996. Our company, and I know my colleagues in other companies, have spent hundreds of millions of dollars in validating our processes. Relative to '96, we can speak with much more authority about what is required in terms of inputs and outputs in our process steps. We can speak with much more confidence in our control parameters and, of course, we have much better documentation of process validation. So, again, I think this is an area where we have made tremendous progress since 1996. Again, I would expect if you were comparing intermediates that the entity that produced the intermediate ought to have a strong validation package which you can evaluate.

Finally, there are the parameters. Obviously, you must understand those parameters that are important in an intermediate, what you need for your process, and be able to evaluate the candidate intermediate that you want to bring in terms of its match to the parameters required for your process.

You have to understand what you need going out of the process. In other words, you have to be able to test and evaluate the output of your process with this new

intermediate and demonstrate that you do get comparable output.

So, I think those are the key elements of the algorithm. With that, my final slide--and most of you are saying thank goodness--is the devil in the details. I have no illusion about the complexity of comparing intermediates. When we start with this orange, very heterogeneous lump of plasma there are tremendous details in terms of doing simple things, like sampling an intermediate--that is a shot of the centrifuge bowl--and just selecting how you are going to sample an intermediate for evaluation, how you are going to generate a comparable sample. Then, of course, all of the issues surrounding the process itself. Fortunately, most of those are relatively well understood, much more understood I think than often these other two.

Thank you for your attention and I will turn it over to the next speaker.

DR. WHITAKER: Our next speaker is Dr. John Finlayson, the Center for Biologics Evaluation and Research at FDA. Dr. Finlayson is the Associate Director for Science of the Office of Blood Research and Review. He is

going to give us a presentation on the FDA perspective for comparing fractionation intermediates and I anticipate hearing a lot about the history of this interesting subject.

FDA Historical Perspective

DR. FINLAYSON: At the end of the session yesterday Mike Gross said can't you be more passionate? So, I will try my best. And, I should thank by thanking Dr. Baker for that very theological presentation. We start with God and we end up with the devil.

[Laughter]

That slide is just to remind you that you are still in the right session so don't go away. When I was 11 years old somebody gave me a little figure to put on my writing desk. It was called a worry bird. Maybe some of you are old enough to have seen one of these in a novelty shop. It is a little thing that stands about four or five inches high, and the body is made out of a pine cone that has been colored by being dipped in some bright colored paint, and it has a couple of little wooden dowels to make legs and some ridiculously large feet so that it doesn't tip over. Then it has a head which, in those days, was

made of plaster of paris, with a big beak. But the most fascinating thing about this worry bird for me was that it had a little tag attached to it. You see, I was into labeling at a very early age--

[Laughter]

--and this tag described all the characteristics of the worry bird. The first, of course, was that it was supposed to do all your worrying for you, but it went down and it described a whole raft of other things. About two-thirds of the way down this list it said the worry bird always flies backwards because, whether or not it knows where it is going, it always wants to know where it has been.

Well, I gather that that is the role that I have in this session because, you see, after I finish Mary Padgett is going to get up and she is going to give you an absolutely clear, lucid, comprehensive description of the FDA guidance on cooperative manufacturing agreements. What I am supposed to do is, if I understand it correctly, give some explanation of how we got from wherever it was that the worry bird started from up to that point.

As you have had a chance to look at, this says the FDA historical perspective. I can't event guaranty that the FDA has a historical perspective. This is my perspective, but as you kept hearing over and over again yesterday, as far as CBER is concerned I am as historical as it gets. l

This reference is the student's dream. You don't have to write it down; you don't have to look it up; you don't have to read it; you don't have to remember it; and there is not going to be a quiz on it. So, why am I showing it do you? Well, that is a good question, but I really am showing it--maybe it is at our level--for its shock value because maybe by now you have looked at the title and thought why would anybody ever do this? Or, maybe you thought, well, I know that sometimes when you go to the doctor a little sample of blood for certain analyses is drawn into a little tiny tube with heparin in there, but I didn't even know there were units of heparinized blood and, even if there were, why would anybody use this as a starting material for fractionation?

Well, back in 1962 and around that time open heart surgery was very new, and the machines used for

extracorporeal circulation were, to say the least, primitive by today's standards. So, they really tended to beat up the blood, especially they beat up the cells. So, in effect, what one was doing was putting into the priming system more or less continuously some very good tissue thromboplastin. So, you needed to have a very robust anticoagulant in there, and that is why heparin was used.

The problem with heparinized blood is that it had an extremely short shelf life so you would have to bring in the donors and essentially collect all the blood for that surgery the day before. Now, what would happen if that surgery got postponed? Well, most of the time you couldn't just put the blood back into the refrigerator because after 24, 36 hours microclots would start to form and it would not be useful for surgery.

So, Dr. Sgouris and co-workers tried to figure out a way to treat the process so that you could use this material as the starting point for fractionation. Well, if I have done my shock work appropriately--I said shock, not schlock--you are thinking, but that's only a drop in the bucket. I mean, look at the size of the fractionation industry. Why would it be worth anybody's while to do

this? The answer is the plasma supply was so limited that every unit was something that people tried to salvage.

So, what came to the rescue in this situation? We could turn on the William Tell Overture and everybody from PPTA could stand and take a bow? Source plasma! Well, we had source plasma and so then what happened? Well, there was a progression of events. As this material caught on, there was increased collection capacity which made it possible for there to be increased manufacturing capacity, and there was increased fractionation capacity. You are saying, wait a minute, you couldn't have increased manufacturing capacity, meaning ability to start with plasma and get to the final product, if you didn't have increased fractionation capacity. But, as Dr. Baker explained to us, things are not always completely in balance so that the ability to fractionation and the ability to take things all the way to final product were not necessarily completely in sync throughout the industry.

So, let's take a look at these again, increased collection capacity; increased manufacturing capacity; and increased fractionation capacity. What was the result of this progression? Well, once there was enough source

plasma to supply domestic needs, source plasma could be exported. Once there was--I won't say market saturation, but at least an abundance of the final product, final products could be exported.

But if your fractionation capacity had greatly increased, intermediates would accumulate. So, a set of secondary results came about. There was a desire to export these intermediates which immediately had a regulatory impact. There was a need for an export policy and there was a need for a regulatory model on which to base this regulatory export policy. At the risk of sounding like Bill Clinton, I will say there was a need to define intermediates.

Well, the proposed working model, which wasn't necessarily a particularly precise model but was one that existed already, was that of divided manufacturing which was already on the books. Divided manufacturing meant then, and means now, that two manufacturers and, with the usual incisive imagination of the FDA, I will call that manufacturer A and manufacturer B, both of which were licensed for the final product, would get together to produce a final product, one producing some intermediate

and the other taking it to final product. But you see, by virtue of both being licensed for the final product, that meant that both were licensed for the full process.

Typically at that time, divided manufacturing involved downstream material. It might be the final bulk solution. Manufacturer A might go all the way to the final bulk and ship it to manufacturer B. Manufacturer B might do something as simple as just filling it or filling it and packaging it or, on occasion, manufacturer B might do some adjustment of the final conditions but, as you see, this is pretty far downstream.

On the other hand, there was also the popularity of going to the last powder in the Cohn or Cohn-Oncley fractionation scheme. In other words, the fractionation would be taken down to the end of the line. That material would be suspended, subjected to bulk drying and one would be sending to manufacturer B, for example, Fraction II powder to make into immune globulin or immune globulins, or a Fraction V powder to be made into albumin.

But it wasn't too long before people got the idea that they could send to manufacturer B the last paste, in other words, Fraction II paste or Fraction V paste so it

wouldn't have to go through, at manufacturer A, the freeze drying process.

Now, if we could imagine that there was sort of a fusion of the desire to export and do divided manufacturing, this led to the desire to export early intermediates, for example cryoprecipitate or Fraction II plus III paste, which we heard about yesterday. But it wasn't long before there was, for exactly the reasons that Dr. Baker told us, the desire--and I put it in quotations--to export early intermediates to domestic firms. I use the term "export" because I really mean ship around.

There was, of course, a clear difference here because if one was truly exporting material there was the clear understanding, both by the manufacturer and the FDA, that it was a one-way trip; that it was exported and it would never come back into the United States and, secondly, that the labeling on the exported material would say that the final product or products made from this intermediate must not say and must not imply that the final material met U.S. standards. On the other hand, if one was shipping to a domestic manufacturer that was going to take it to final product, the implication was that some or all of it was

going to be distributed in the United States and it would certainly have to meet U.S. standards and, by definition, it was being distributed within the States, or at least it could be distributed within the States.

So, there was a continuing need for a regulatory model. There was, as was already indicated, the need for traceability, in other words, to find the pathway back from manufacturer B to manufacturer A, follow it through both fractionation procedures or both manufacturing procedures, whatever they were, and even all the way back to the plasma and, if need be, even back to the donors. Of course, there was a need for cooperative manufacturing agreements.

So, what models already existed? Well, there was, as we have said, divided manufacturing. There was short supply, and there was contract manufacturing but at that time contract manufacturing was usually limited to very specific operations. It might be the performance of a test that required instrumentation which was not available or was very expensive for the final manufacturer to maintain, or it might be something such as filling.

What was the regulatory result of all of this? Well, here is another reference that you don't have to

write down because it has been superseded, but there is the reference just in case you want it, in 1992, and it had a nice, long bureaucratic title that went right down the column of the Federal Register, but in the middle of it, it said cooperative manufacturing arrangements. Now, it still included divided manufacturing; it still included short supply and it still included contract manufacturing but, in addition, it had shared manufacturing in it. That is to say, no longer did both manufacturers that were participating in this cooperative manufacturing arrangement have to be licensed for the final product, that is, for the whole process starting with plasma and getting to the final product. Manufacturer A could be licensed for that part of the process that manufacturer A chose to carry out.

That is all very fine in the regulatory scene but meanwhile, back at the scientific ranch things were happening. There was an increased knowledge and awareness both on the part of the FDA and the industry, not necessarily being achieved at the same rates. Stability issues, safety issues and, remarkably enough, Dr. Golding yesterday managed to get an example of each in one talk. Of course, we know that all steps of the fractionation

procedure are critical, but some may be more critical than others, and an appreciation of this came about.

Some of these wonderful bad examples that we heard about yesterday indicated that there are hypercritical steps, but the major lesson that came is that despite the fact that we knew all of these things, there was a multitude of things that we didn't know.

So, I have tried to prepare a little bit of a list here about some factors that are known to affect the product, change in starting material; change in a test of the starting material. You realize that is shorthand. The performing of the test per se doesn't necessarily impact the product, but if you make a decision based on the results of that test, such as whether to include that unit in the fractionation pool or to withhold that unit from the fractionation pool it, indeed, can affect the final product. Minor again, in quotation marks, pH change at one step, as we heard; change in duration of one step; introduction of viral inactivation. As we get down the list, we can see that one through four certainly could have an impact on the intermediates.

Five might or might not have an effect on an intermediate depending on the stage of the manufacturing at which viral inactivation was carried out. It might be earlier in stage and, therefore, affect an intermediate. It might be downstream very far and, therefore, one has to consider only the impact on the final product. I won't say for the sake or completeness but lesser incompleteness, I have added to this a change in formulation that could affect the final product, and now we are out of the range of intermediates, and change in physical state, such as going from a liquid product to a dry product or a dry product to a liquid product.

So, I think you see that not only is the devil in the details, but the devil has lots of hiding places. This would be the logical place to end this talk, but no one, certainly not Tom Lynch, has ever accused me of being logical so I am just going to keep going here in order to tell you about what my impression is of a recent development.

Let's look at the conclusions and then look at that development. Because there are all of these possible impacts here, it is reasonable to expect manufacturer B to

demonstrate the ability to make a safe and stable final product, and the ability to make a comparable final product, and the ability to make it consistently.

We can also conclude that the criteria for deciding on safety and stability and comparability are a function of the class of product or products one is talking about, the stage of the intermediate that one is focusing on to get to that final product and, most of all, the status of knowledge because, as we saw, we tend to learn from our mistakes and we hope that we can learn from other people's mistakes.

All right, what is this recent trend that I wanted to share with you? For want of a better term, I called it matching of intermediates. By that, I meant manufacturer A, rather than making intermediate Y--I thought it would be too sinister to say intermediate X; it sounds like something you would put on a brown bottle somewhere--manufacturer A, instead of making intermediate Y by manufacturer A's usual process, manufacturer B would say I will enter into a contract with you to supply me with intermediate Y but I will reveal to you how we make intermediate Y and I want you, for the purposes of this

contract, to make intermediate Y by our process, manufacturer B's process. I am using matching not in my sense but in Dr. Baker's sense, that would allow matching to the downstream process and would presumably require less tweaking, if any tweaking, to the downstream side of manufacturer B's procedure.

Something that all those people that, in response to Dr. Finkbohner's question, raised their hands when he said how many of you are in regulatory affairs, what you want to know is does this make approval faster or simpler, and the answer is not necessarily. Manufacturer B is still going to have to demonstrate that it can take that intermediate Y and make a final product that is safe and stable, and that it can do it consistently. But manufacturer B may be more comfortable with having this, for want of a better word, pre-matched intermediate.

You thought I gave a talk, didn't you? No, what I did was I gave the longest introduction at this workshop. You see, all of this, as it says over the door of the National Archives, if you have any time to do any sightseeing in Washington, what is past is prologue. So, all that was simply the introduction to Mary Padgett who is

in our Office of Compliance and Biologics Quality, who is going to give the real talk on FDA guidance on cooperative manufacturing arrangements for licensed biologics. Please listen carefully.

FDA Guidance on Cooperative Manufacturing Arrangements for Licensed Biologics

DR. PADGETT: Well, thank you, Dr. Finlayson for that introduction. I hope I manage to present the clear and lucid talk that he advertised.

Good morning. My name is Mary Padgett and I work in CBER's Office of Compliance and Biologics Quality in the Division of Management and Product Quality. I have been asked to talk with you this morning about our draft guidance on cooperative manufacturing arrangements for licensed biologics.

The draft guidance, itself a revision of a previous guidance document that Dr. Finlayson mentioned, published on November 25, 1992, was issued in August of 1999 in response to changes in manufacturing technologies and equipment and consequent changes in actual manufacturing configurations. Limiting issuance of biologics licenses to one company that performed all

manufacturing steps became unproductive. Hence, this guidance, describing avenues to licensure for products with multiple manufacturers and outlining the principles designed to ensure safety, purity and potency of the biological products are not compromised as a result of the flexible manufacturing arrangements.

We have received comments on the guidance and, based on our review of those comments, the guidance will be revised and issued in final form. There are some obvious changes that we will be making, like eliminating references to PLAs and ELAs, and we will make an attempt to translate the guidance into plain language. There may be other revisions that have yet to be decided upon, but what I will do this morning is go through the document as it exists right now.

I intend to follow the draft guidance outline, providing descriptions of four types of arrangements, short supply, divided manufacturing, sharing manufacturing and contract manufacturing. Lastly, I will go through the labeling requirements described in the guidance document.

First two definitions. The May 14, 1996 Federal Register Notice amending the regulations to eliminate the

ELA requirement for specified products also amended 21 CFR 600.3(t) to broaden the definition of the term manufacturer as it is used in Parts 600 through 680. The manufacturer now includes a licensed applicant who may or may not own the facilities engaged in significant manufacturing steps.

The draft guidance is an attempt to address manufacturing arrangements made available by the new definition of manufacturer. Manufacturer, described in 21 CFR 603(u) is defined as all steps in propagation of manufacture and preparation of products. It includes, but is not limited to, filling, testing, labeling, packaging and storage by the manufacturer. There are many examples of a single manufacturer performing all manufacturing steps within facilities owned and operated by that manufacturer. However, as described in the previous version of this guidance, issues in November, '92, various alternative arrangements have been accepted including short supply, divided manufacturing, shared manufacturing and contract manufacturing.

Short supply arrangements are described in section 3 of the draft guidance. Under 21 CFR 601.22, a licensed biologic manufacturer may obtain certain material

that are manufactured at unlicensed facilities under the following conditions: One, manufacturing at the unlicensed facility will be limited to initial and partial manufacturing of a product for shipment solely to the license holder.

Two, the unlicensed manufacturer is registered with FDA in accordance with registration and listing provisions in 21 CFR 207 and 607.

Three, the licensed product is in short supply due to either peculiar growth requirements or scarcity of the source organism required for manufacturing.

Four, the licensed manufacturer can assure that through inspection, testing or other arrangements the product made at the unlicensed facility will be made in full compliance with applicable regulations. Licensed manufacturers may use the short supply provisions to obtain source material only. The source material should have undergone only the limited processing necessary for shipment.

Examples of materials that might be obtained under short supply include certain pollens and insects used in producing allergenic extracts; specific types of human

plasma containing rare antibodies or venoms used in producing antitoxins and antivenims. Short supply agreements can be submitted in annual reports but are usually reviewed on inspection, and source material suppliers are subject to FDA inspection.

Divided manufacturing is discussed in section 4 of the draft guidance. As Dr. Finlayson mentioned in his talk, divided manufacturing is an arrangement in which two or more manufacturers, each registered and licensed to manufacture a biological product in its entirety, participate jointly in the manufacture of the product. Record keeping requirements for each party in a divided manufacturing arrangement are described in 21 CFR 612(e), parts 210 and 211.

Manufacturers entering into a divided manufacturing arrangement should describe the role of each manufacturer in supplements submitted to their respective license applications. FDA will assess conformance to license manufacturing procedures and specifications, equivalence of intermediate products, demonstration of intermediate product stability during shipment,

intermediate and final product labeling, and methods for handling recalls, adverse events and product complaints.

Section 5 of the draft guidance is devoted to shared manufacturing arrangements. Shared manufacturing is an arrangement in which two or more manufacturers are licensed, and responsible for specific different aspects of manufacturing. A participating manufacturer may perform the specified manufacturing steps and/or contract with another entity and assume responsibility for compliance with product and establishment standards. Manufacturers participating in shared manufacturing arrangements must register according to 21 CFR 207 or 607, and each manufacturer should submit a separate BLA describing the manufacturer's facilities and operations applicable to the preparation of that manufacturer's biological substance or product.

The applicant for the final form of the product will have primary responsibility for providing data demonstrating the identity, purity, strength, quality, potency, safety and efficacy of the final product. The applicant for the final product will also be responsible for any post-marketing commitments, complaint handling,

recalls, biological product deviation reports and adverse event reporting.

All license applications that pertain to a particular product to be manufactured under a shared manufacturing arrangement should be submitted concurrently for a complete review. Lack of one or more related applications may be considered a basis for refusal to file. Each licensed manufacturer in a shared manufacturing arrangement must notify CBER regarding proposed changes in manufacturing, testing or specifications in accordance with 21 CFR 601.12, and also notify the other participating licensed manufacturers. All manufacturers participating in a shared manufacturing agreement must also comply with the record keeping requirements four in 21 CFR Parts 210 and 211 and 612(e).

A frequent shared manufacturing arrangement is one in which one manufacturer is responsible for an intermediate product and another for the final product. Applications for intermediate products for further manufacturing use should include criteria used to determine lot to lot acceptability, including sterility or bioburden,

stability, product characterization, potency and purity specifications.

Manufacturers of intermediate products should demonstrate that their product can consistently meet established specifications. FDA intends to accept only those applications for products for further manufacture by the licensed final manufacturer. We will approve only those applications demonstrating the safety and efficacy of the final product.

Similarly, FDA intends to accept only those applications for final products that specify the source of the licensed intermediate. The approval of the final product will be dependent on a demonstration of established specifications for receipt and acceptance of the intermediate.

A participating manufacturer that performs significant product manufacturing is considered eligible for separate licensure. Critical manufacturing steps that may affect the product's safety, purity or potency and that FDA has considered adequate for separate licensure include, but are not limited to, inoculation vessels for animal for production, cell culture production, characterization,

fermentation and harvesting, isolation, purification, physical and chemical modifications.

Manufacturing steps that would not by themselves ordinarily warrant separate licensing, even though important to the purity and integrity of the final product, include chemical and biological testing, formulation, sterile filling, lyophilization and labeling. These steps would generally be viewed as contract manufacturing steps. However, FDA recognizes that companies may be extensively involved in preclinical and clinical development but, for various reasons, may choose to limit their involvement in product manufacturing. Therefore, FDA intends to consider eligible for separate licensure a company that is instrumental in product development and that performs, or is responsible for the performance of several final manufacturing steps, for example, formulation, sterile filling, lyophilization, labeling, packaging and final release testing.

Section 6 of the draft guidance describes contract manufacturing arrangements. Contract manufacturing refers to a situation in which a licensed applicant establishes a contract with another entity or

entities to perform some or all the manufacture of the product as a service to the licensed applicant. The current definition of a manufacturer is any legal person or entity engaged in the manufacture of a product subject to a license under the Act, including any legal person or entity who is an applicant for a license, where the applicant assumes responsibility for compliance with the applicable product and established standards. That is the definition found in 21 CFR Part 600.3(t).

An applicant who does not own all facilities where significant manufacturing is performed may apply for licensure of a biological product either with a single license with the contract manufacturing arrangement or under a shared manufacturing arrangement. Further, a contract facility that is engaged in significant manufacturing is no longer required to be separately licensed.

The applicant's license application should describe all manufacturing, testing and storage locations, and identify whether they are owned by the applicant or the contract facilities. Contract firms that do not wish to provide all necessary information to the applicant may want

to consider a shared manufacturing arrangement or a master file.

Cross referencing a master file should be limited to circumstances involving proprietary information, such as a list of all products manufactured in a contract facility. In this situation the applicant should be kept informed of the types or categories of all products manufactured in the contract facility and non-compendial test procedures, provided there is assurance of both the applicant and the FDA will be informed of all changes in these procedures. The license application may also refer to master files for information regarding containers and closures.

The license applicant, the manufacturer by definition in 21 CFR 600.3(t), is responsible for the identity, purity, strength, quality, potency, safety and efficacy of the product and for ensuring that the manufacturer of the product complies with the provisions of the license application and the applicable regulations including, but not limited to, 21 CFR 210, 211, 600 through 680 and 820. Since the license applicant is responsible for compliance with applicable product and establishment standards at all owned and contract facilities, applicants

considering contract arrangements are encouraged to verify the inspectional status of contract facilities. The license applicant is responsible for ensuring compliance with both product and establishment standards.

The next few slides list some of the standards and CGMPs including, but not limited to, the following: Adverse event, biological product deviation reporting, product complaint reporting systems, develop and validation of product process, reporting changes to the product process as required by 21 CFR 601.12, quality assurance, oversight and change control for master and batch product records, quality control methodology as it relates to product process, submission of protocols and samples for lot release where applicable, content of the license application, labeling, contracts with the establishments where testing is being performed, validation, maintenance and proper functioning of all equipment and systems, as well as the facility itself, environmental and other required monitoring and training of personnel.

The license applicant should have established procedures for regularly assessing a contract manufacturing facility's compliance and applicable product and

establishment standards. This may include, but is not limited to, review of all batch records, manufacturing deviations and defects and periodic audits.

Because the applicant assumes responsibility for compliance of the contrast site with applicable product and establishment standards, the applicant should have access to floor plans, equipment validation and other product information for the contract site necessary to assure safety, purity and potency of the product. The applicant should be fully informed of all deviations, complaints, adverse events, as well as the results of all tests and investigations regarding or possibly impacting the product.

The applicant's license application and supplements should describe all manufacturing testing and storage locations, and identify whether they are owned by the applicant or a contract facility. The published CMC guidance documents contain information on the content of an application, including descriptions of all contract operations. In addition, for each contract arrangement the applicant should describe the product subject to contract manufacturing, including the product stability and manner of shipping to and from the contract facility,

responsibilities of each participating entity, and a list of all standard operating procedures applicable to the contract arrangement.

Facilities performing contract operations for biological products must register with FDA in accordance with 21 CFR Parts 207, 707 or 807. Because the contract facility is engaged in the manufacture of a drug or device, it is also responsible for compliance with applicable provisions of the Food, Drug and Cosmetic Act and applicable regulations. Contract facilities will be subject to FDA inspection as provided for in Section 351.(c) of the PHS Act and Section 704(a) of the FD&C Act. A contract manufacturer should inform the applicant of all deviations, complaints and adverse events, as well as the results of all tests and investigations regarding or possibly impacting the product, including deviations occurring during operations performed for a different product.

The contract manufacturer should also share with the applicant all important proposed changes to production and facilities, including introduction of new products. Information obtained during the inspection of a contract

facility may also be disclosed to the applicant by the FDA in accordance with 21 CFR 200.10. Compliance actions may be taken against both the licensee and the contract manufacturer for failure of the contract manufacturer to comply with CGMP or otherwise fulfill requirements of the license for which the contract manufacturer is responsible.

Labeling, 21 CFR 610.63 requires that the name, address and license number of each participating licensed manufacturer appear on the package label and on the container if it is capable of bearing a full label. Because of space considerations and the possibility of confusion of multiple names and addresses, FDA will consider package label provisions of 21 CFR 610.63 met by placing the name, address and license number of the manufacturer of the finished dosage form of the biological product on the outer label affixed to the package, and by placing the names, addresses and license number of the preceding intermediate product manufacturers in the description section of the package insert. The labeling for the intermediate product should include a statement that it is intended for further manufacture. Provisions for the labeling of products manufactured under a shared

manufacturing arrangement are consistent with those for the divided manufacturing arrangement.

Labeling for final products prepared under a contractual agreement must conform to the applicable portions of 21 CFR 610.16 through 610.65. The final product container and package label should include the name, address and license number of the licensed applicant. Because the contract facilities are considered to be under the auspices of the license holder, specific identification of the contractor on the product labeling is not required.

The labeling for an intermediate product intended for shipment to or from a contract facility should include a statement that it is intended for further manufacture, and should not bear a license number.

We have just gone through the various types of cooperative manufacturing arrangements as described in our draft guidance, the short supply agreement, divided, shared and contract manufacturing, and I have just described the labeling requirements as stated in our guidance.

I would like to thank my colleagues, Angela Shen and Marlene Swider for providing me with this diagram. We have attempted to show in graphic form the different

cooperative manufacturing arrangements, divided, shared and contract. I would hope this would be an easy guide to use when you want to look up what exactly these types of arrangements entail. Divided, both license holders, licensed for the entire process; for the shared, two license holders, one licensed to manufacture an intermediate and the other intermediate to final; and contract. We have two listed here but it could be more than two entities providing a service to one license holder which, in the end, would result in one manufactured product. Thank you very much.

DR. WHITAKER: We are a little bit ahead of schedule so I would like to introduce Jean Huxsoll, who will come before the break instead of afterwards. Afterwards we will do the panel discussion. Jean is with Bayer Corporation and I am sorry, Jean, I don't know what your current title is, but Jean and I have worked together on industry activities for some years now and it has always been a pleasure so I am looking forward to hearing her case studies for an interesting intermediate situation.

Case Study Presentations from Industry

DR. HUXSOLL: Good morning. Actually, my current title is director of quality assurance operations.

I would like to start out making a few comments before I start. I am a stand-in speaker for one of my colleagues at our Clayton, North Carolina plant, who was not able to make it today. Also, I find being the last speaker, a lot of things in the presentation have been said earlier so there will be a little bit of redundancy.

What I would like to do is share a case study that we have done at Bayer to qualify II plus III paste at our Clayton facility from a new supplier. This is a case study that is currently still in process so it is ongoing.

There are six parts to the presentation, general information about utilizing intermediates, which I think we have probably discussed at great length already; parameters that we feel should be considered before you start trying to qualify a new supplier; some specifics about our case study qualification; some lessons that we have learned that we would like to share; some thoughts for utilization of comparability protocols; and conclusions.

I will skip over some of the information about fractionation intermediates. I think it is important to go

back to what Don said earlier, that at a lot of our facilities we can't totally utilize the fractionation capacity, the purification capacity, filling and finishing, and that it is much more beneficial to be able to share intermediates so that when we increase the capacity and we also utilize the source plasma to its greatest extent and make the best utilization of that so we can supply material to our patients.

Finding a reliable supplier for intermediates is really only the first step in what we consider a lengthy process. The evaluation and validation of intermediates, at least in our experience, can take over a year. Then, if you go through a pre-approval supplement you have another four- to six-month approval process after you complete your own work.

When considering purchasing a fractionation intermediate there are some points that one should look at to make sure that the intermediate will fit in your process. Obviously, the Cohn-based processes are not all identical, and you can have other processes that will have quantifiable differences from the Cohn-based process. I think two important points that have been mentioned are

that you have to have internal validation to be able to compare the intermediates and you want to be purchasing from a supplier who also has validation to ensure that their process is consistent.

As I mentioned, I think you cannot do this, at least from our perspective, if you don't know your own process and don't have your own internal validation. It is important to identify the critical process parameters and establish both the input and output specifications for each operation on the basis of the comparison of the intermediates.

What we have done is divide the fractionation process or subdivide it into unit operations. These unit operations are logical groupings, either by a hold or intermediate storage step. It also would include a sterilization or virus removal step. Then there are critical steps based on our process development, clinical data, adverse events or manufacturing deviations that we think should be considered. Then you would do process and product characterization at each of these unit operations. You would establish your input specifications which would be the specifications of the process that will go into that

particular unit operation, and your output specifications which would be the specifications for the material coming out of that particular unit operation. Your input and output specifications would be established both on prospective and retrospective data, and both bench scale and full scale validation. By examining the input and output specifications at each unit operation, you can indicate the robustness of that particular process step.

When we considered qualifying a new supplier, we started out initially doing some investigation. We took experts from our quality assurance and manufacturing department, visited the vendor site and reviewed their process. We identified any process differences in their process, and we additionally, for this particular activity, verified that they only use source plasma from U.S. licensed centers.

After this initial assessment, then the next step was to assess the paste from the supplier. We received paste samples from ten different lots, and we performed characterization of the II plus III past. We characterized with measurements of conductivity, moisture, cholesterol,

fatty acids, pH, ethanol concentration, triglycerides and protein.

This initial assessment was used to characterize their paste and to determine if it was both statistically characterize similar to our paste, and would it fit into our process. I am going to share with you some of the information that we determined when we were qualifying the paste. The moisture and the alcohol content were higher in the vendor paste. This was not surprising since we separate by centrifugation and the vendor separates by filtration. But it was still within those input specifications that we established for our own II plus III paste. The Biuret protein, the cholesterol, the triglycerides were lower in the vendor paste but, again, still within the Bayer specifications that we had previously established.

The albumin levels in the vendor paste were lower but, again, with a plus/minus three standard deviation of the Bayer paste. The normalized IgG levels were identical. The levels of IgA, IgM and IgE were slightly higher and the levels of AAT, CEO and ApoB were slightly lower in the vendor paste.

All of these characterization parameters then were reviewed and standardized to look at in comparison to the Bayer specifications for input and output. We did an initial assessment and we felt that our process was robust enough that it was capable of resolving any minor differences in the paste through our process..

A couple of things before I go on that were identified as risks. We did receive ten lots from the vendor, but these ten lots were during a very short period of time so they may not be representative of the full range of variability from the vendor's process. We also determined, and I think I mentioned this earlier, that the input specifications were similar so we determined at this point that we didn't feel we needed to do bench scale validation but we could go to full lot size validation for this assessment.

Based on that, we went to the next step to validate the past from the vendor on a full lot size assessment. This is a risk or a step that may not be appropriate. The same II plus III paste, if we were to purchase it for another intermediate, we may not reach the same assessment and we may determine that we have to do

bench scale. Obviously, II plus III paste from another vendor may have to go through the bench scale assessment before we go forward.

We then went to full scale process validation. We had three separate paste lots from the vendor and we produced three final container lots. We used the sampling points and the test criteria identical to the Bayer process. We sampled and we compared all test points to the Bayer validation process--one of the reasons why it is important to have your validation data up front before you start so you have parameters on which you can compare. We ran all the same in-process and final container tests on all steps through both the purification and the established specifications.

I forgot to mention earlier the other thing, that when we started we realized that we did not have to change anything. We ran this paste through our process using the set points that are established for the Bayer paste, the BPRs that are established for the Bayer paste, and all of the parameters. So, we ran it through exactly the same process that we would use for our own paste.

Qualification lots were sampled and tested according to the protocol. We placed the lots both on real time and accelerated stability. All of the results were analyzed. Reports were prepared and, as I mentioned, this is in process. The data has recently been submitted to CBER for review.

We feel that the validation studies demonstrated that when this paste is used in the Bayer purification process, the material that is generated is the same as the Bayer final container, and that any comparison with the validation and comparison data from the Bayer paste found only minor differences from the vendor paste which were characterized and resolved by our purification process.

As I mentioned, some of the lessons learned that I think are important for qualifying paste is that you have to have your own internal validation. Without that, you don't have the means of comparison. The protein characterization is an essential component in determining the past comparability, and the scientific evaluations of data must consider some of the risks. Risks that you would want to consider would be whether or not you want to run bench scale studies before you start or start out with full

scale studies, and are the differences in the paste such that your process is not robust enough to accommodate those differences.

One of the things that we did--this was a pre-approval supplement but, obviously, as we have talked about the last day and a half, for the need to utilize paste and get product out it is important that if you had a procedure, as we did, you could prepare a comparability protocol utilizing the parameters in the protocols we had set forth in this example, and then utilize that comparability protocol for outlining and possibly having the methodology to approve intermediates on an ongoing basis. The CBER approval time of the new intermediates could be reduced. Then, intermediates that would not meet the CP specifications would require additional validation work and may not benefit from the comparability protocol, and would require a pre-approval supplement.

The conclusion from our standpoint, as we have mentioned, use of purchased fractionation intermediates to match internal manufacturing capacities and to meet patient needs is a necessary aspect of the fractionation industry, and can help prevent product shortages. The industry needs

a clear path to follow to minimize the amount of time required to evaluate, validate and gain approval for these fractionation intermediates from another source. Thank you.

DR. WHITAKER: Thanks, Jean. We are going to take a half hour break right now, and come back and do the panel discussion, but before you go, could you think of questions that you can write down on the index cards that we have available for you? We will also take questions from the microphone. Thank you.

[Brief recess]

Panel Discussion

DR. LYNCH: If people will start moving towards their seats we can make an attempt to get the last session closed out so people can meet their flights. If the morning speakers would join us on the dais?

I would renew the request that anyone with questions, that they are reluctant to stand up and ask verbally, fill out a 3 X 5 card and send it up front, we will address those questions as they arrive. Initially, I think we would like to focus on the morning's presentations since there hasn't really been an opportunity for the

audience to ask the presenters any specific questions. Then maybe we will open it up to more broad questions or reflections or suggestions from any of the participant speakers on where we have come with this meeting and what we might all be taking home as object lessons from it.

If you want to ask a question and you are sort of in the back rows, we have a pretty short microphone so come forward and ask your question into the microphone. It is important to do that so that the question gets clearly into the transcript. With that, if there are any questions on this morning's session?

DR. GOLDING: I know that Tom is going to keep us here until the end of the session so I am going to ask all kinds of strange questions. I think this question should be directed to John Finlayson but anybody, obviously, can answer it who has information.

My first question is the use of intermediates is interesting and I think can give rise to a lot of theoretical problems but, in actual fact, has any use of intermediates or shared manufacturing been documented in a situation where this is related to adverse events in the

patients so that it has been traced back to the fact that the product was made by use of shared products?

DR. FINLAYSON: Well, the short answer is I don't know, but since it is really not my nature to give short answers let me elaborate. For those of you who have not heard me quote this, I think it was George Bernard Shaw who said I often quote myself. It adds spice to my conversation.

[Laughter]

So, I can quote--I believe the order of authors was Young, Aronson and Finlayson, in 1978, Journal of Biological Standardization, in which we were trying to work out a predictive test for stability. Actually, it was a predictive test for instability of immune globulins. In those days, in the U.S., it was only intramuscular immune globulins. It just happened that in the fairly sizeable array of products that we studied, that is lots representing numerous lots from numerous manufacturers, there were a number that had been prepared by divided manufacturing. So it turned out, as would be predicted now in hindsight from your presentation yesterday, that if you had--and I will have to call it manufacturer C which

sometimes obtained Fraction II for manufacturer A and sometimes from manufacturer B, there was almost a perfect split between which of manufacturer C's immune globulins remained stable virtually throughout their dating period and which began to fragment rather substantially during the dating period.

So, indeed, it turned out that as far as stability is detected by laboratory tests, there was a substantial difference in the quality of the products over their life span as a function of the intermediate and the manufacturer of the intermediate.

Now, we didn't receive, to my knowledge, reports of product failures in the clinic that we could relate back to that finding, but one has to guess that at some points around the extremes of the use in the clinic there, indeed, may have been such events.

DR. GOLDING: Can I ask another question to Don Baker? It has been stated by several of the previous speakers that you should know thy process, and it seems to me that there could be a potential problem with shared manufacturing since when it is shared manufacturing with another manufacturer that holds a license--maybe I am

incorrect, but my understanding is that they do not necessarily, and probably would not, divulge all their manufacturing steps to the manufacturer that gets the intermediate. Doesn't that pose a theoretical problem? Maybe you can tell us, or other people in industry, whether that is actually being associated with real problems. So, if you don't know what they are doing exactly and you don't have any control over what they are doing, I mean, the only control in the process is that the FDA sees their material and it is FDA's responsibility to give them a license. But from your point of view, the manufacturer's point of view, you don't really know their process.

DR. BAKER: Actually, let me respond to both your questions. Baxter buys and sells intermediates and uses other manufacturers' intermediates from other plants and our own plant. As Barbee mentioned, the complaint department does report to me. I have to say that in our experience we have not seen any quality issue in the field associated with the use of another manufacturer's product.

Anyway, coming back to your last question, you know, there is, if you like, a softer side to this issue of sharing of intermediates. One of the issues is that you

have to have a good working relationship in either buying or selling of intermediates. That working relationship requires that there be sufficient trust that, in fact, you can be fairly intrusive in the companies that you are either buying or selling to. For example, we have arrangements with Bayer in terms of intermediates. Bayer does, in fact, audit and has a strong quality supplier program and audits our facility and, as such, they see batch records; they see the process. They are very, very well acquainted with our manufacturing process. If that level of trust in that kind of an arrangement can't be worked out between two manufacturers that are sharing intermediates, I would suggest that that would not be a viable operation.

In addition, even issues such as issues that you might have with donors--I mean, I have discussions and have had discussions with Bayer all the time about donor issues that we have, and the point that I am getting is that there needs to be this very close working relationship and, yes, it is difficult with competitors but it is possible to structure agreements both on paper so that they happen and actually within the working arrangements such that they

happen. So, if you are not comfortable with your partner, don't do it. That is my comment on that.

DR. HUXSOLL: I think I would just add to that that I don't think we would consider purchasing from someone with whom we didn't have the open relationship. It works both ways because if there is an issue that comes back to Bayer, although we haven't had one, we would share it with Baxter if the paste came from Baxter.

DR. FRAZIER: Hi, Doug Frazier, CBER Division of Hematology. Sort of a general question, Bayer has nicely shared their characterization information with us about the tests that they do to compare their fractionation intermediates. Does anyone have any experience with sort of previously unexpected parameters that were troublesome? We know that you can activate PKA if you are adding your albumin. These are well-known--you know, everyone should be looking out for this. Has anyone found sort of unexpected, troublesome variables that popped up in qualifying someone else's fractionation intermediates? I mean, are there any new unknowns that have come to light recently? I guess that is what I am asking.

DR. HUXSOLL: From Bayer's standpoint, I don't know of any.

DR. GOLDING: It is probably a biased sample though to ask a question like that because, given how expensive it is to qualify an intermediate from another manufacturer, you wouldn't go ahead with the process unless you were pretty sure it was going to work. So, it is not, let's say, a statistically normalized sample as to whether or not you could have problems.

DR. GEODEREN: I think this question is for Mrs. Padgett. Although the 1999 draft guidance is a draft guidance, we all proceed on the assumption that this is actually the way CBER likes to see things. Is that correct?

DR. PADGETT: Right now that is probably a safe assumption, yes.

DR. GEODEREN: Thank you.

DR. LEWIS: Richard Lewis, FDA. John, in the example that you just gave, and I think implied in your presentation this morning, Jean, final product lots are made solely from a single intermediate. Is there additional validation that you would do, Jean, if you were

mixing intermediates of your own or from multiple other manufacturers that you have purchased those intermediates from?

DR. HUXSOLL: I can partially answer that question. Like I mentioned, I am out of the Berkeley facility and not the Clayton. The validation was such that the input parameters were all measured and they all met the same criteria. So, as long as the paste met those input parameters, no matter the source--and I can think of one exception--from a Berkeley standpoint we would mix and match if we happened to have recovered plasma where the number of donors is higher then we, at least at the Berkeley site, might tend, only for that reason, not to mix and match because of the 60,000 donor limit. But that would be the only reason. Otherwise, if the paste wasn't acceptable, then we wouldn't be utilizing it.

DR. BAKER: Just to comment on that, the point that Jean made about the 60,000 donors, sort of one of the unintended consequences of us limiting the number in the donor pool which, obviously, was a post-1996 consideration, is the fact that the control of the intermediate processes is such that we don't tend to mix and match from a variety

of different sources because you would bump up into the 60,000 limit pretty quickly.

DR. LYNCH: I guess this question is for John and Don and Jean. Over the past day and a half we have heard some object lessons where very subtle and seemingly innocuous changes have had some significant consequences. On the other hand, we have also heard examples where measurable differences have been shown not to make a difference. So, on the one hand plasma fractionation downstream processing, like any other pharmaceutical operation, has its points of fragility but obviously also a certain degree of robustness, an ability to accommodate changes and variations whether they be lot to lot of between manufacturers.

It seems to me that that balance is important. If you focus only on the disasters and not the successes, you end up with an extremely conservative sampling. If you ignore the lessons of the past, you are likely to experience them. So, maybe John, you could philosophize on that balance and where it should lie.

DR. FINLAYSON: Oh, I think you have just made the worst mistake of your life--

[Laughter]

DR. LYNCH: I am not that old yet!

DR. FINLAYSON: Certainly it is true, I mean there is a large tendency when one is charged with following up disasters, learning from disasters and hoping to prevent future disasters, that one sort of falls, or could fall into the syndrome of where the policeman or the policewoman goes out into the street and immediately assumes everybody is a criminal. The truant officer assumes that no child ever goes to class. That is a fairly easy syndrome to fall into.

On the other hand, for all of those things that I have listed in my little list, one can sort of turn it around and say these are places where the product has been improved by doing this. In other words, if you got a better starting material you could make a better product. You made a minor change and you got not only a better yield but you got a more stable product. You changed the formulation and, remarkably, you had many fewer adverse reactions.

So, certainly my focus here has been on trying to help people stay out of trouble, but it is rather built

into the situation that you presumably wouldn't make these changes in the first place if you didn't believe there was some benefit to be gained. Certainly, one must not only acknowledge but applaud the fact that sometimes there has been a rather substantial gain either quantitatively or qualitatively. So, yes, absolutely, both of these things happen. So, you know, we should learn from our successes as well as from our failures. I don't know what Francis would have said about that.

DR. LYNCH: I would like to open it up for more general comments that people may have on the meeting as a whole or any particular aspect of it. Obviously, we still have a pretty good quorum among the participants so it is an opportunity, having had the benefit of a day and a half of consideration of comparability issues, to try to take a step back and perhaps evaluate where we have come.

DR. ZEID: Thank you. Bob Zeid, TLI Development. First off, this symposium is outstanding, but I want to return to the foundation of all of our comparability assessments which is analytical data. When a sponsor brings a package to you, they are going to have a mix of internal analytical data from their own methods which are

in the approved application and, most likely, characterization profile testing which may be done in-house, may be done by academic centers, may be done by novel, cutting-edge methods some which you are familiar with and some not. One of the level playing fields is that they are going to compare their product to other similar products in the field.

I would just urge that you keep an open mind that the validity of the data, when compared side by side even by methods which may have incomplete validations or certain other analytical nuances that have yet to be worked out, that this foundation of analytical comparability is key to keep an open mind about, that when these comparability changes come to your desk and you see this plethora of data in front of you, that they do make an outstanding case for where this product sits in comparison to other competitors and other components despite the fact that they were made by other methods, other processes and released by other test procedures.

Would you care to comment? Is the FDA amenable to expanding on that in their comparability protocol

assessments, or are we comfortable with where still stand on all this?

DR. FINLAYSON: Well, I will first ask if any of my colleagues from FDA would like to respond to that. Andrew?

DR. CHANG: Actually, Crhis Joneckis would be the person to address that question but, unfortunately, he couldn't come today. The guidance document is from 1996, and the one thing that I can say is that we do have some activities internally to look at how successful, or whether or not there is room for improvement on the comparability concept and policy. Whether the agency will expand the use of comparability, stay tuned. I cannot say anything here.

DR. FINLAYSON: Any other FDA people? Maybe I will continue. One of the things which I have been absolutely delighted not to hear, and I am following up on your point about some of the measurements are cutting edge or maybe made by academic laboratories and are rather out of the ordinary for what you have been used to measuring as part of either your characterization or your lot release testing, sometimes I have gone to meetings like this and

sooner or later, it followed as the night the day, someone would get up and say that is nice to know but you don't need to know. It is always very dismissive, this "nice to know" type of analytical data. Well, I haven't heard anybody say that here.

So, perhaps I can be so naive as to believe that the message has penetrated that yesterday's "nice to know" is tomorrow's absolutely without fail thing that you had better do and find out. So, I think that on a scientific level certainly we are always interested in anything that you learn, and we are certainly, I think, as a scientific organization aware of the fact that there is not always equal quality control on data. But that is part of life in science. Except in the most carefully and rigorously prepared handbooks, you find "authoritative" data that is heterogeneous in its quality. Dr. Lee will testify that a few days ago, in following up the example that he gave, I said, well, there was a switch from a TRIS buffer to a citrate buffer. So, in order to compute the ionic strength we need the third PKA prime of citrate. He carefully pulled off his shelf, turned to the page and said, ah, here they are, right in the handbook. You know what I said?

Therapy are wrong. So, I think we are well aware of this and I think we are receptive to data of that sort.

DR. STRANGE: I am Charlie Strange, representing Alpha 1 Foundation. One of the discourses I haven't heard in this risk-benefit analysis here are the shortages from the patients' side and how they interplay with the scrutiny from the FDA and from industry, recognizing that there are probably more patients that have died from shortages of a product, be they immunoglobulin or alpha 1, than anything that has happened from a regulatory oversight perspective.

I guess my impression here is that as this pendulum swings, shortages on the patient side might push the FDA to be more lenient in some of its actions, and as the shortages then disappear, it is time to tighten up and go further down the path of scrutiny. And, I would like some discourse on the subject. Thanks.

DR. GOLDING: In terms of shortages causing deaths, that is an extreme situation that obviously all of us here probably would want to avoid. But following the IGIV shortage that occurred a few years ago, and some people would say is still going on, the IDF, the Immune Deficiency Foundation, followed that very carefully, and so

did we, and we had many discussions with them. I am not aware of any patient that died or even data to show that primary immune deficiency patients suffered an increased incidence of serious infections. If anybody here has data to show that shortage situations regarding the products that you mentioned were associated with death or serious health problems, I would like to know about it but I am not aware of it.

DR. FINLAYSON: Mark, do you have any comment in response to shortages?

DR. WEINSTEIN: Generally the activities that we do when there is a shortage, of course, is to try to expedite our procedures as much as we possibly can. In some instances we have taken action to, for example, look at a product by the fast track authority. If there is a severe shortage, if there is, say, a single manufacturer that is making material and other people are coming on board or would like to have product reviewed by us in an IND phase, say, we will do everything that we can to speed our review of the submissions.

It is not a matter of having a lesser standard of review; it is a matter of shifting our resources which are,

of course, very limited, to assuring that we do everything that we possibly can to review these things as quickly as possible. In doing so, we may find other areas where we simply don't have the manpower to expedite, say, the reviews of Factor VIII at the same time as there is a severe alpha 1 shortage or immune globulin shortage. So, there is sort of a balancing act that we have to do. But I want to assure you that we are not skimping on our review process here in the face of a shortage.

DR. FINLAYSON: Yes, I was thinking yesterday that back in the days when I used to participate in inspections, sometimes somewhere toward the end of the packaging line at some manufacturers there used to be a large sign on the wall--I assume it was for the benefit of the employees and not the benefit of the FDA inspectors--that said "the next inspector will be the customer."

I think to emphasize what Mark said, shifting our resources to respond, because you saw one of the things that he showed you at the beginning of our workshop yesterday, was availability of product as well as purity, potency, safety and effectiveness, we are not skimping because sort of in our mind is the next preclinical

experiment will be conducted on the patient. So, I think we, who live in the FDA, never forget that.

DR. LYNCH: I never thought you did! Following on the same theme, we talked yesterday a little bit about clinical trial issues both with respect to safety and efficacy and, at a lower level, Dr. Maplethorpe even raised the possibility of pharmacokinetic studies demonstrating comparable behavior. But one of the assumptions was that the design of those trials would necessarily meet the rigorous standards that a new product under clinical development would be required to satisfy. It occurred to me, in response to shortages, that one of the rather creative steps that the FDA took was to reevaluate the design of clinical trials intended to support the PID indication for immune globulin intravenous. Dr. Golding described those accelerated trials, if I can use that term, at BPAC in 2000, I think.

I am going to get back to comparability at one point or another, but I have three questions I think. Has that reevaluation of what is actually necessary to demonstrate been expanded from the PID indication to other

immune modulatory indications that various IGIVs might carry?

Secondly, are there any ongoing efforts to maybe expand the envelope of analytical or preclinical data that may further accelerate the review and approval of these products, facilitate the review and approval of these products?

Third, how does this different paradigm for licensing new products affect a comparability study in the clinic to support a manufacturing change?

DR. GOLDING: Well, your first question was do the proposed studies which were put in place reduce the number of patients required to participate for PID to other indications of IGIV? The answer to that is no, we have not proposed any studies that could use smaller number of recruits. As it stands, just thinking very quickly, the other common indication is immune thrombocytopenic puerpera and the number of patients for those studies is relatively small to start out with. I don't know if we could ever reduce that. The endpoint, which is increasing platelets, is a very objective endpoint. So, you know, I don't think there is any need to change that. But there are many other

potential indication for immune globulin, that I don't think we want to go into and a lot of these are very controversial.

For many of those other conditions I think the situation is very different. For example, in prime immune deficiency the only treatment is immune globulin intravenous. For many other conditions, neurological, hematological, autoimmune, on and on and on, there are many other treatments and immune globulin would be part of it and for many of them there is no dramatic data that says that immune globulin is going to be a life saver and a shortage would impose severe restriction in those conditions. So, I don't think there is a need to really expand it.

In terms of analytical data, what has happened, there were several public and private meetings with IVF to discuss what else could be done to characterize immune globulins. I think that is potentially going to be very productive because we have our own studies, in collaboration with academia, looking at specific antibody titers against certain infectious agent, and we are starting to collect data from the actual products and from

ongoing trials looking at the serum of patients that are receiving products and looking at their titers against specific infectious agents.

We think that that information is going to be very important in helping to characterize immune globulins in the future. The IVF hope was that we would eventually come up with some kind of surrogate markers so that we could avoid clinical trials completely. Well, you know, I think that is a hope that may or may not come into being but for the moment I would say that there are studies in progress which, hopefully, will help to better characterize immune globulins and the measurements will be more relevant to the function of those immune globulins in vivo.

Your third question I have proceeded to forget already.

DR. LYNCH: How does all this fit into support of production of relevant data to evaluate comparability after a manufacturing change for IGIVs?

DR. GOLDING: Well, you know, I think that the type of data that was alluding to analytical data could be part of a comparability protocol. I mean, a lot of work still has to be done. I mean, we are developing the data

but that has to be correlated with clinical data and all the assays have to be validated, on and on an on, but eventually I think those kind of measurements could be potentially very helpful in developing comparability protocols for these products.

DR. LYNCH: Questions?

DR. SEAVER: Sally Seaver, Seaver Associates. I want to address one question that came up yesterday, if I might. That was the complaint or observation that some of the USP methods are antique and required eye of newt and steam baths that we no longer have access to.

In one of my other lives I am chair of the expert committee on gene therapy, cell therapy and tissue engineering, and chair of the whole complex active section at the USP. This is as a volunteer. One of the complex active section expert committee's is Harvey Klein's blood and blood products. Last night I went out to dinner with Roger Dabbah, who is a USP employee, whom most of you probably know very well, Lokesh Bhattacharyya. So, I asked them about this, and the issue is they know that there are certain tests for raw materials or other things that are antique, but when they try to go to the manufacturer and

say would you like to update these tests, the manufacturers will say we have a large supply of eyes of newts and steam baths and we are very happy with this test. And, once they say that, immediately at the USP, given the politics, it gets to be a low priority, which means it doesn't get done.

So, if you want to see a more relevant test in the USP, what you, as a manufacturer, really need to do is actually submit a proposal to USP with the test and the validation and, believe me, there are people there who would be very happy to see it and will jump on it.

One of the things that we are grappling with is that many of these newer assays also involve kits. Some of these kits are approved by CBER or CDRH. Sometimes they are kits just to extract stuff to do PCR. And, one of the things we are dealing with, and would love your opinion on, is getting controls for these kits. How do you know the kit is working on the day you use it?

DR. LYNCH: Go ahead.

DR. FINLAYSON: Yes, I was quite taken by the comments yesterday bout compendial methods because I so seldom hear that term. I am not sure whether it was in a conversation with Francis Bacon or Paracelsus that I last

heard it used! But whereas CDER is, almost by a legalistic sense, bound to the USP, CBER is not. You know, a manufacturer may say we qualified this raw material by using this USP method, but we would look at that and evaluate it. I hesitate to use the words on a case by case basis, but if a manufacturer has an independent method which is supportable, we would certainly look at that as well.

Perhaps I can give you a specific example, and I don't think I am going to be revealing anybody's trade secrets if I mention the actual name of the compound, and it is not recent. Somebody could probably identify it by an FOI request. So, it was in the mid-1980s. I asked to see some of the tests for the raw materials. Since there was a chromatographic absorption step being used in the course of the manufacture of the product, I thought that one of the raw materials worth looking at was TRIS. They very proudly pointed to the USP method which had been duly photocopied and was proudly shown to me. I read quickly through it and I said do you realize that this would give you a positive result for TRIS for any compound that had a hydroxyl group and an amino group in it? I am not sure of

the word for word comment, but it had the general translation of "good grief, you're right."

By the time of the end of the next day's inspection the firm had already worked out--obviously, the validation was not complete, but they had already worked out an infrared method for the identity test of TRIS, and by the time I left the inspection a day later, they had already dispatched a letter to the FDA saying it is our intention to submit a supplement changing our method for this raw material.

So, we are not bound to compendial methods. We are looking for the best method and most reasonable and reliable method that you can find. Harvey Klein is one of my favorite people, and I laud all of his efforts but I don't have to wait until the USP gets revised in order to improve something if I think it needs improvement.

DR. RITTER: Well, having been in the unfortunate soul who use the word "compendial" yesterday, I would like to just add a couple of comments. Thanks, Sally, for bringing it up because this has been an issue that we have been talking to USP about and I applaud their efforts to try to upgrade the methodology that is there. Lokesh is

correct. The energy barrier to getting an antiquated method updated to a more modern method is very high by the manufacturers who, as you said, have copious quantities of these unusual materials around, or still have one person hanging on before retirement who can still do that method just exactly right.

But the question is not just for upgrading the methodology, but what happens to the specs? The example that I can use in a general way is if you have a product where the purity test for the product by the compendial method is something like thin layer chromatography, for example, and the spec is that it needs to be 90 percent or better, well, that spot on the TLC plate is a very forgiving spot. If you would subject the material on that TLC plate to even size exclusion chromatography you might find five peaks. Now, those five peaks might have been there from the very beginning of time, but how do you set a spec of 90 percent or better on those five peaks? Do you then have to go through and determine--and we know what we would normally do for a well characterized molecule, we would go through and determine the identity of those five peaks and their relationship to the product, and are they

impurities; are they constant; are they active? There is a whole paradigm to follow for that. But when faced with that choice of going down that pathway to assess what the spec should be for those peaks, or sticking with the old method using eye of newt, what choice do you have? You stick with the eye of newt until or unless you can no longer buy the reagents and materials anymore.

So, the question is for purposes of release testing, even though CBER products aren't bound to the compendial methods necessarily, there is a strong attachment of manufacturers to use those methods because they can claim they were tested by USP.

On the other side of that though for comparability, as Bob mentioned, when you are dealing with a comparability study wouldn't you want to use the size exclusion method to show that at least on the same day, with two batches of material side by side, you got the same relationship of peaks, quantities of peaks, proportions of peaks? Because now you are getting a more fine look at the detailed differences in that material, whether or not one needs that method for release testing. In addition to the spec issue for replacing a compendial method, there is a

massive amount of validation data that has to go on to make it appropriate for use by the common community.

So, my comment was, you know, hopefully, USP will be able to bring some additional new methodologies but it really will rest upon the backs of manufacturers to make that actually happen.

DR. LYNCH: If there are no more comments--sorry, Andrew, please.

DR. CHANG: I have a question, not a comment. Yesterday we mentioned doing analysis side by side. I have seen some studies where actually it is not side by side but, rather, mixed material made from the old and new processes. I have not seen that for plasma derivatives. I just want to get a sense from industry people in this room for how useful, or whether or not there is utility for these plasma derivatives.

DR. LYNCH: Are you asking that in a validation sense?

DR. CHANG: In a comparability sense. For side by side you need two assays to answer one question. If you mix them together you may need just one assay.

DR. SEAVER: If you do two assays and you have slight shifts if you are doing a very complicated reverse phase, you can always wonder if something is slightly off. If you can mix the two compounds together and compare them to one alone, it is still two assay, but you can really see very small differences.

DR. RITTER: Actually, and I don't really look at it myself as two assays. Sometimes it is just replicate injections or duplicate lanes on a gel or multiple injections of a peptide map.

The other point I wanted to make is that in the '96 document I believe the words are that you need to use sensitive and validated assays for comparability. I have had lots of conversations with people about whether they really mean validated or not because if you are dealing with something on a side by side comparison two things today, loaded on the same gel--all of your experimental bias should be in one direction and you should make the best assessment of comparability under those circumstances.

If you are trying to take data that you generated today and compare it to data that you or somebody else generated a week ago, a month ago, five years ago then,

yes, you have to know something about the operating parameters of the assay and the directions in which the variations can go because how can you assess comparability away from the intra-assay variability that you are going to get from day to day and from time to time?

So, the comparability studies that I have done from an analytical perspective with physicochemical methods has almost always been urging to be side by side, one together, in the same assay, preferably with co-mixes because I think you get the most exquisite understanding of two materials in relation to each other.

DR. CHANG: Well, I opened this question to hear exactly the comments that have come from the audience. On the other hand, you can argue that sometimes a company uses the assay variation--which in many cases is true, that the variation you see between the comparability analysis is embedded in the variation of the assay. Now, in my judgment, variation can be reduced when you mix the two samples in a single assay, at least the variation embedded will be the same. Well, I am just opening this for your consideration from a scientific point of view for whether or not there is any utility here.

DR. LYNCH: One more.

DR. ZEID: Well, just as a non-sequitur but basically when it comes to outdated compendial requirements or compendial testing, I can't think of a better candidate to just unilaterally remove than the general safety test. Let me just ask you, how many manufacturers are still doing that? Anybody? The general safety test? Which I think Francis Bacon did contrive!

My question is, one, do we still need to do it and, if so, why? Are there lots that are failing the general safety test but passing all other criteria? My point is that the general safety test is superseded by much more elegant biochemical parameters and that, if anything, PPTA could take from this seminar a request to FDA to unilaterally remove general safety testing requirements for IGIVs and other plasma derivatives or, on a case by case basis, to evaluate that.

DR. LYNCH: Well, the requirement to apply general safety test to the specified biologics was removed sometime ago. The reason why I guess people still do it is not because it is a compendial test but because it is in the CFR and you are required to do it. The question of its

value in light of other alternative analyses, I won't even attempt to address. You know better than I do. Certainly, there are some products for which you obtain very anomalous results when you do a general safety test, and there have been examples where specific products were relieved of that requirement or where the test was modified to accommodate the specific characteristics of a product, but as far as I know the regulation hasn't been revoked. It would be something to consider.

Are there any more questions, comments, critiques, criticisms? I think I would like to maybe move us toward adjournment. It strikes me that there are a couple of themes that have emerged. Not surprisingly, a lot of common things are shared by the industry and the FDA that oversees their activities, I venture to say as well as by the patients whose needs are served by these products and the physicians who are responsible for treating them. The objectives of the programs that we have been talking about for the last two days are threefold I think.

They are to create a mechanism by which manufacturing changes can be made, changes to processes and facilities, in the hope of improving either efficiencies or

the quality attributes of the products. These mechanisms need to be efficient. The term least burdensome or effective have been used by various speakers both from the FDA and industry.

But they also need to assure the continued safety and efficacy of the products from a clinical standpoint, and to get there you need to assure the safety, purity, potency and identity of the product as a product.

In order to accomplish this, you have several hierarchies that have been set up. One is a hierarchy of reporting requirements and the other is a hierarchy of establishing comparability from a scientific and operational standpoint.

What we have been wrestling with is not that framework. That is well recorded in the guidance document and within the regulations. But the rules that govern the application of these principles. I think we struggled in some respects. You know, you can make rules based on the type of manufacturing change that is being made that is very common for establishment changes that John Finkbohner mentioned. You can make rules about hierarchy or reporting on the basis of underlying concerns that have emerged over

the years, historical problems that we tried to learn from. That is much of what John emphasized. You can make rules based on the type of product that is affected by the change. The individual products may have different vulnerabilities or susceptibilities to unforeseen consequences of change.

But the theme that runs through this conference, in my mind, is that if you select rules based on any single criterion that I have mentioned, you either come up with an overly strict rule or a rule that isn't scientifically rational.

Apparently, the system is to consider all aspects of what is being proposed, the change, the product that the change applies to and consequences of concern in order to assign a regulatory comparability status to that change. That gives maximum flexibility and, arguably, the best scientific basis or justification for regulating that change, but at some sacrifice of predictability because the case by case approach is, by its flexibility, something that is hard to understand up front.

One of the important aspects from the manufacturer standpoint I think is to be able to plan

changes and evaluate how long and how difficult it will be to implement. Certainly, this is an area where certainty would benefit the manufacturer as well. So, this may be the one area where further deliberations may be useful from the perspective of both FDA and the industry.

Without saying more, I would like to introduce John Finlayson again who selective provide closing remarks from the FDA's perspective.

Closing Remarks

DR. FINLAYSON: Well, Tom has just given my summary so I may just say thank you. Actually, I do want to say thank you to Tom for his good efforts in moderating the panel discussions that we have had. I think they have been very fruitful and very useful. I want to thank all of the speakers and all of the attendees. Especially, I want to thank the organizers, and there are so many people who contributed to the success of this workshop that if I started names, I am sure that I would leave someone out unintentionally. So, let me just simply say that we are particularly grateful to Craig Mendelsohn for all of his heroic efforts, and I still don't know how, in his busy schedule, he found time to write that violin concerto.

From our side, I would also like to thank Andrew Change who also managed somehow to get his work done and to spend hours and hours getting this show on the road.

Now, for reasons that you will see a little bit later on, I was thinking what could I do here, at this late stage, to be the very most useful to everyone under the rubric of lessons learned, and one of the things Mark Weinstein told me, who actually is supposed to be giving this summary because he wasn't going to be here, and I don't know how he managed this off but he did so I am here and he is there--that is all right, Mark, you can stay--he said be sure to take lots of blank overheads. So, just before the panel discussion I was thinking, you know, maybe the most useful thing I could do would be to take my magic marker and write out the formula for ionic strengths and illustrate how we can utilize it when we do not have exclusively the monovalent salts in the mixture, but I thought better of it and you are spared.

So, let me just go through these overheads which I prepared, which I think maybe are some of the lessons learned. If we take a look at the next one, if this one looks familiar to you it is because I hope it looks

familiar to you. These are some lessons that I hope we have learned independently of this meeting, but if this is your first encounter I certainly hope that you take away this lesson.

More importantly and to the point since this was a workshop on comparability, I think that one of the things that has emerged is that you don't put all the eggs in one basket. You should measure as many aspects of the material, whatever it is, the product, the intermediate, as you reasonably can.

Once you have made those measurements, don't just record the measurements. Think critically about what the measurements mean. We heard yesterday how having a comparability program and a comparability protocol can help you focus that thinking. There may be many tools that can help with this critical thinking. There may be statistical analyses; there may be trend analyses; and maybe other mathematical approaches; there may be more global approaches; or taking the message from Dr. Lee's presentation yesterday, it might be something as simple and straightforward as thinking when the results look too good to be true, they probably are too good to be true. So,

again, I think this is one of the messages that we take away.

Furthermore, don't just make the convenient measurements. By convenient, I don't necessarily mean financially convenient because we heard some presentations yesterday where I was trying to add up the dollars for all the instruments that were being used and it ran into some very big mega bucks. But, once one has instruments set up there is a tendency to use them. Well, that is good. You should do that but one should make every effort, on the basis of experience with the product, to make the right measurements.

Now, there is a strong caveat in this. Once we know that we are supposed to measure something, we can often measure it very well, very sensitively and very precisely. Now, what I am addressing is the fact that when there is a body of experience that says you should make this measurement it is sort of derelict not to make it. But the problem is you don't know that you should be measuring it and that is a problem because, you see, inherent in this statement to make every effort on the

basis of experience with the product to make the right measurements is what the next overhead is.

How do you know you have made the right measurements?

Well, as this one says, you don't always know. The measurements you made may be necessary but they are not necessarily sufficient to tell you everything you need to know. A name that used to be a household word in the biologics world but which, I daresay, hardly anyone in this room has ever heard is that of Roderick Murray. In the days of many nomenclature changes, back when CBER was named the Division of Biologics Standards, Dr. Roderick Murray was not only the first but the only director of the Division of Biologics Standards during its entire lifetime, which ran from 1955 to 1972. What Dr. Murray used to state over and over again is what you would like is an analytical test that has the same specificity and sensitivity as homo sapiens. So, you may not have that test at your disposal.

Well, given this unhappy fact, we can say furthermore what we have learned in these two days is that not all changes are equal. Some are major and some are minor. And, not all minor changes are equal. Okay?

Moreover, we have learned that the body of experience does not stand still. That has sort of a nice ring to it, don't you think? But lest the ring drown out the message I put in the translation. It is that we are always learning new lessons.

Therefore, we are unlikely in the near future, if ever, to have a formula that will allow you in every instance to decide what is comparability but you should know the formula for ionic strength.

[Laughter]

The translation, at least in my opinion, is that judgments will always be needed. Well, so what? So, call up and talk to us. Thank you very much. Have a safe trip home.

[Whereupon, at 11:40 a.m., the proceedings were adjourned.]

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