FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

THYMOSIN ALPHA-1-RELATED BULK DRUG SUBSTANCES

(THYMOSIN ALPHA-1 ACETATE AND THYMOSIN ALPHA-1 FREE BASE)

Afternoon Session

Topic 3

Wednesday, December 4, 2024

1:00 p.m. to 3:35 p.m.

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C O N T E N T S

P R O C E E D I N G S

(1:00 p.m.)

Call to Order

Introduction of Committee

DR. REBELLO: Welcome. My name is Elizabeth Rebello, and I'm serving as acting chair for this meeting. Before we begin, I'd like to remind everyone to silence their cell phones and devices, and we'll begin with the thymosin alpha-1-related bulk drug substances topic session. Panel members who will be in this topic will introduce themselves by stating their names and affiliation, and we'll begin by those that are here in person, followed by virtual participants.

Dr. Clark?

DR. CLARK: Nina Clark, Loyola University of Chicago. I'm an adult infectious disease doctor.

DR. REBELLO: Dr. Czaja?

DR. CZAJA: Mark Czaja, Emory University School of Medicine.

Dr. Ghany?

DR. GHANY: Marc Ghany, NIH, Bethesda,

Maryland.

DR. REBELLO: Dr. Kris?

DR. KRIS: Mark Kris, thoracic medical oncology from Memorial Sloan Kettering.

DR. REBELLO: Dr. Pau?

DR. PAU: Alice Paul, NIAID, NIH.

DR. REBELLO: Dr. Siberry?

DR. SIBERRY: George Siberry, pediatric infectious diseases and Chief Medical Officer at Office of HIV/AIDS, USAID.

DR. REBELLO: And for those that are joining virtually, Dr. Brian Lee?

DR. B. LEE: Brian Lee, hepatologist at University of Southern California.

DR. REBELLO: Dr. Janet Lee?

DR. J. LEE: Janet Lee, Washington University St. Louis, pulmonary critical care medicine.

DR. REBELLO: Dr. Corbett?

DR. CORBETT: Hi. Amanda Corbett, a pharmacist at the University of North Carolina, Eshelman Schulman School of Pharmacy.

DR. REBELLO: Dr. Gans?

DR. GANS: Hi. Dr. Hayley Gans, pediatric infectious disease at Stanford.

DR. REBELLO: Dr. Monge? I must have missed you; apologies.

DR. MONGE: Cecilia Monge, medical oncology, National Cancer Institute, NIH.

DR. REBELLO: Thank you.

We will now proceed with the FDA presentation on thymosin alpha-1-related bulk drug substances from Drs. Elizabeth Hankla and Jing Li.

FDA Topic 3 Presentation

Elizabeth Hankla

DR. HANKLA: Good afternoon. My name is Elizabeth Hankla. I'm a clinical analyst with the Pharmacy Compounding Review Team in the Office of New Drugs, and I will be presenting thymosin alpha-1 or Ta1-related bulk drug substances with my colleague, Jing Li, from OPQ. I would like to recognize the evaluation team, as well as the contribution of many other FDA colleagues. We would like to give a special thanks to the seven

review divisions that we worked with across the Office of New Drugs and in the Center for Biologics and Research.

Ta1-related bulk drug substances were nominated for inclusion on the 503A Bulks List; however, the nomination was subsequently withdrawn. FDA is evaluating the substances at its discretion. The product proposed in the nomination is a 3-mg per mL injection for subcutaneous administration. Ta1 free base and Ta1 acetate were evaluated for the 12 uses listed in this slide. The criteria we consider in our evaluation for the 503A Bulks List are physical and chemical characterization, historical use in compounding, safety, and available evidence of effectiveness or lack of effectiveness.

I'll now turn the presentation over to my colleague, Jing Li.

FDA Topic 3 Presentation

Jing Li

DR. LI: Thank you, Beth.

Due to conflicting information about the

different Ta1 BDSs in the nomination package, it's unclear which Ta1-related BDS was nominated; therefore, first we summarize the basic information on two BDSs, including Ta1 free base and Ta1 acetate in this table to show some differences between them. From the table, you can see the UNII code, CAS number, molecule formula, and the molecule weight are different between these two substances, but they have the same active moiety, which is Ta1 free base.

This table shows detailed information submitted by the nominator, as well as relevant information identified by FDA. As you can see, the nominated BDS is referring to Ta1 free base, and the UNII code matches Ta1 free base, but the CoA provided is for Ta1 acetate; however, the basic information in the CoA, including UNII code, CAS number, molecule formula, molecule weight, and the chemical name are all referring to Ta1 free base. Because Ta1 free base and Ta1 acetate are two distinct BDSs, their different physical and chemical properties can impact patient safety and

product efficacy. We evaluated both Ta1 free base and Ta1 acetate, and we'll present them in the following slides.

Let's first talk about the Ta1 free base. Ta1 free base is an N-terminal acetylated 28 amino acid peptide. In 1977, isolation and the purification of Ta1 free base from thymosin fraction-5 of calf thymus was reported. Later, chemically synthesized Ta1 free base, named thymalfasin, has been produced. Ta1 free base is a white to off-white lyophilized powder. It's soluble in water up to 2 milligrams per mL. There is no USP drug substance monograph for Ta1 free base.

In terms of storage and stability, manufacturer recommends storing Ta1 free base below minus 18 degrees Celsius. Upon reconstitution, Ta1 free base in solution is stable between 2 to 7 days at 4 degrees Celsius, and for future use, the solution should be stored below minus 18 degrees Celsius.

Like other peptides mentioned in the

morning, Ta1 free base is also sensitive to the product formulation process and the environment conditions, which may lead to aggregation and degradation. In addition, there may be some peptide-related and peptide synthesis process-related impurities presented in Ta1 free base such as starting materials, residual solvents, coupling reagents, et cetera.

Because there is no CoA provided in the nomination, FDA also could not find information from public domain regarding potential impurities and the peptide-related aggregates that may be presented in Ta1 free base; therefore, it's difficult to rule out the potential for immunogenicity associated with peptide-related impurities and aggregates, especially when formulated in the injectable dose form for subQ administration.

In conclusion, Ta1 free base is not well characterized because of lack of certain critical characterization data including impurities, aggregates, bioburden, and bacterial endotoxins.

In addition, there's a potential for immunogenicity, especially when formulated in injectable dosage form for subQ administration due to potential for aggregation, as well as peptide-related impurities in the BDS. Also, no information was provided regarding how to formulate proposed injectable dosage form at the concentration of 3 milligram per mL using water as a solvent due to limited water solubility of Ta1 free base.

Ta1 acetate is an acetate salt form of Ta1 free base. As shown in this slide, the physical and chemical properties, including stability and the potential impurities for Ta1 acetate, are similar to those for Ta1 free base. The CoA provided only includes identification assay, water content, and acetate content; however, no critical characterization data for impurities, aggregates, bioburden, and bacterial endotoxins. In addition, the water solubility of Ta1 acetate is 1 milligram per mL. Due to the same issues as mentioned in previous

slides for Ta1 free base, in conclusion, Ta1 acetate is not well characterized.

That concludes my presentation. Now I hand it over to Beth.

FDA Topic 3 Presentation

Elizabeth Hankla

DR. HANKLA: Thank you, Jing.

Here's what we found on historical use in compounding. As mentioned previously, Ta1 was first isolated from calf thymus in 1977; however, the earliest and extent of Ta1 free base or Ta1 acetate use in compounding is unknown. We found no evidence of compounded drug products containing Ta1 free base or Ta1 acetate in the published literature or in outsourcing facility reports. Compounded drug products containing Ta1 have been marketed online and in the U.S. as an injectable and nasal spray for use in numerous conditions as those listed in the slide.

According to a 2014 annual report from SciClone Pharmaceuticals, which is a pharmaceutical company previously associated with the development

of Zadaxin or Ta1 free base, Ta1 is approved for use in countries in the Asia Pacific region, Latin America, Eastern Europe, and the Middle East. According to the annual report, approvals are primarily for the treatment of hepatitis B and as a vaccine adjuvant, with additional approvals in certain countries for the treatment of hepatitis C or as a chemotherapy adjuvant.

FDA is unable to independently verify these claims of approval in the specified countries. Ta1 is not approved in the United States, Japan, or in Europe, except for Italy. Additionally, Ta1 is not recognized in the European or Japanese pharmacopoeias.

We will now discuss safety information. This slide presents some of the nonclinical safety information we identified from a Zadaxin product monograph. Of note, the monograph did not provide the underlying data for these safety conclusions. In terms of acute toxicity, a single subQ injection of Ta1 up to 20 mgs per kg generated no drug-related safety signals in mice, rats, and

marmosets. In a repeat-dose toxicity study, treatment of mice, rats, and marmosets with Ta1 subQ doses up to 6 mgs per kg per day for 13 weeks, or 1 mg per kg per day for 26 weeks, generated no drug-related safety signals. According to the monograph, Ta1 did not produce genotoxicity signals in vivo and in vitro.

According to a published review article, SciClone Pharmaceuticals successfully completed a lengthy segment 3 reproductive toxicology study, which is a study conducted in rodents to evaluate drug effects during the last trimester of pregnancy and the period of lactation. FDA did not identify nonclinical carcinogenicity studies with Ta1.

In conclusion, summaries of nonclinical toxicity studies available in a product monograph for Zadaxin that contained Ta1 free base 1.6 mgs per mL appear to suggest that Ta1 free base did not induce safety signals in nonclinical toxicity studies; however, the underlying nonclinical data generated to support the safety of Ta1 are not available for review. At the time of

evaluation, FDA did not identify published nonclinical toxicity studies to inform safety considerations for potential clinical uses of Ta1 acetate.

Here, we present some information on the pharmacology of Ta1. Ta1 has immunomodulatory properties mediated, at least in part, by its interactions with Toll-like receptor 9 on dendritic and lymphoid progenitor cells. Per nonclinical studies, Ta1 suppressed tumor growth, suppressed viral infections, and decreased sepsis in in vivo rodent models. Additionally, as post-treatment, Ta1 increased the antibody titer generated by some vaccines in mice.

We note that most nonclinical studies were conducted with fixed doses that, according to body surface area, translate to human equivalent doses higher than those used in most clinical studies. Finally, it's difficult to determine the minimal Ta1 dose required to induce a pharmacological response due to lack of studies assessing dose-response relationships.

Here, we present some information on the pharmacokinetics of Ta1. In rats that received an IV injection of Ta1, the half-life ranged from 1.9 to 3 minutes. The nonclinical PK profile of Ta1 delivered via the nominated route of administration is unknown at this time. After subQ administration, in healthy men, Ta1 was absorbed rapidly with a Tmax of approximately 2 hours and a serum half-life of approximately 2 hours. There was no evidence of accumulation using daily dosing for 5 days.

In terms of clinical safety, FDA's search of the FAERS database of AEs for Ta1 retrieved one report from a 46-year-old male receiving peginterferon alpha-2a and Ta1 for about 12 weeks as part of a clinical trial. The subject was hospitalized with anxiety, atrial fibrillation, and a transient decrease in his TSH levels. Interpretation of causality in this case is confounded by concurrent use of peginterferon, as all three of the reported AEs are potential AEs described in U.S. labeling.

In clinical trials, Ta1 has been administered in daily doses ranging from about 1 to 16 milligrams usually via subQ administration on a biweekly schedule, for treatment periods ranging from 1 day to 12 months. The most common dose in clinical studies was 1.6 milligrams via subQ administration. The most common AEs reported include local irritation, redness, and injection site discomfort.

On this slide, we note a few potential AEs reported in the medical literature in our review of the studies. These AEs included ALT flares in subjects with chronic hepatitis B; TSH abnormalities in subjects with chronic hepatitis C; nipple pain; fatal immune hemolytic anemia and engraftment failure in hematopoietic stem cell transplant or HSCT recipients.

There are potential safety concerns with administering Ta1 in patients who are undergoing deliberate immunosuppression. For example, in patients who are undergoing HSCT, Ta1 could develop or worsen acute or chronic GVHD and lead to

engraftment failure. Safety data for use of Ta1 when given as a vaccine adjuvant with preventative influenza vaccines are insufficient to evaluate safety or assess the optimal Ta1 dose and regimen and associated risks. Adding an immunomodulatory product such as Ta1 to any vaccine could pose unknown safety concerns that warrant further evaluation.

We searched for products containing Ta1 as an active ingredient licensed and marketed outside of the United States with publicly available labels. We identified two such labels. Information obtained from these two labels include warnings and contraindications when used in children, pregnant and lactating women, patients with autoimmune diseases, and immunosuppressed populations. The label for Indonesia includes information about transient increases in liver enzymes characterized as flares and further Ta1 administration.

As described earlier this morning, immunogenicity is a concern for peptide products.

This immunogenetic response may be enhanced when they are given via the subQ route of administration. The consequences of triggering an immune response may range from antibody responses with no apparent clinical manifestations to life-threatening and catastrophic reactions. Ta1 may pose a significant risk for immunogenicity, potentially amplified by aggregation and peptide-related impurities. Importantly, we are unaware of data in humans to support the proposal for a 3 mgs per mL solution, and it's possible that a more concentrated solution could lead to aggregation, and therefore increased immunogenicity potential.

In conclusion, the use of Ta1-related bulk drug substances in compounding may raise safety concerns. In most clinical studies, Ta1 has not been associated with significant adverse events attributable to Ta1 when administered in doses in the range of 1 to 16 milligrams via the subQ route of administration for up to 12 months. The most common adverse reactions reported included local

irritation, redness, or discomfort at the injection site.

Although Ta1 has not been associated with significant AEs attributable to Ta1 in the literature, there may be concerns about its clinical use in compounding. For example, it's not clear whether the administration of Ta1 in patients undergoing HSCT could lead to the development or worsen GVHD and/or lead to engraftment failure.

In addition, safety data are insufficient to evaluate the risks associated with the use of Ta1 as a vaccine adjuvant with influenza vaccines licensed for use in the United States and, finally, as a peptide with 28 amino acids that is administered through the subQ route, it may pose a significant risk for immunogenicity. Importantly, the highest strength identified to date in clinical studies was 2 mgs per mL, and it's possible a more concentrated solution could lead to aggregation, and therefore increased immunogenicity potential.

Now, I will present information on the effectiveness for each of the 12 uses we evaluated.

Here, we note that studies discussed in the next set of slides for effectiveness administered Ta1 via subQ administration unless otherwise noted. As we need to cover a lot of information in our effectiveness discussion, we will take a brief five-minute break after our discussion of COVID-19.

First, we will discuss hepatitis B. Hepatitis B infection can lead to chronic HBV, which can cause liver damage, cirrhosis, hepatocellular carcinoma, or HCC, and death. In clinical practice, sustained HBV DNA suppression and clearance of HBV surface antigen are associated with improved outcomes and used to assess therapeutic effect.

Per professional guidelines, preferred therapies for chronic HBV include antiviral agents and peginterferon. Oral antivirals or NRTIs, entecavir and tenofovir, are administered long term. Sixty-eight to 90 percent of patients achieve undetectable HBV DNA levels after 48 weeks. They have been shown to reduce the risk of chronic HBV complications. These newer NRTIs are generally

associated with lower rates of resistance. Peginterferon is administered for a finite duration and is associated with lower HBV DNA suppression rates. Of note, Ta1 is not mentioned in the treatment guidelines.

We identified several studies that administered Ta1 as monotherapy compared to placebo, no treatment, or various doses of Ta1. Ta1 was administered at doses up to 1.6 milligrams twice weekly for up to 12 months. The five studies conducted from 1998 to 2005 reported mixed efficacy results. One randomized, double-blind, placebo-controlled trial showed no difference in undetectable HBV DNA rates measured 6 months after treatment.

Other studies with less rigorous design showed undetectable HBV DNA rates of 15 to 30 percent. These studies were generally limited by small study sizes, lack of blinding, HBV DNA assays, with a limit of detection much higher than current standards, i.e., assays used for quantification of HBV DNA were much less sensitive

than current assays, and the interpretation of older studies was complicated by the use of composite endpoints.

We identified several studies that compared Ta1 versus interferon-alpha monotherapy, an older, currently non-preferred treatment for hepatitis B. In these four studies, authors generally observed higher rates of undetectable HBV DNA with the interferon group at the end of treatment versus Ta1 group at the end of follow-up. Surface antigen data were not discussed. These studies had similar limitations to those discussed in the previous slide, as well as the use of an outdated comparator, interferon-alpha.

Of note, peginterferon has replaced the use of standard interferon because it's more effective for serologic and virologic outcomes and is better tolerated with less frequent dosing. Additionally, standard interferon therapies have been discontinued from marketing in the United States.

The next two slides focus on the use of Ta1 in comparison to current preferred therapies.

There were two studies that compared peginterferon monotherapy versus peginterferon in combination with Ta1. In a retrospective analysis from Song et al., the virologic response rates were not different between the two treatment arms. In the open-label study from Kim et al., authors concluded that the addition of Ta1 was not superior to peginterferon alone. These trials had limitations, as listed in the slide.

Finally, we identified one trial where Ta1 was used in combination with entecavir. In this randomized, open-label trial of entecavir monotherapy versus entecavir with Ta1, undetectable HBV DNA rates were similar between groups at 52 and 104 weeks. Surface antigen clearance rates were also similar between groups. Per authors, results show that combination therapy has a similar effect as entecavir monotherapy in mortality, decompensation rate, HCC incidence, virological response rate, and some additional measures.

In conclusion, we have insufficient evidence to determine the effectiveness of Ta1 for HBV,

which can be serious. Available studies are limited by design and the use of outdated assays. While information from available published studies suggests mixed efficacy results of Ta1 monotherapy, we have limited information about its use with or an alternative to current preferred therapies. Available studies of Ta1 with current preferred therapies such as peginterferon or entecavir demonstrated unclear efficacy of Ta1 and have limitations. There are FDA-approved drugs with established efficacy for the treatment of chronic hepatitis B.

Moving to hepatitis C, chronic hepatitis C can lead to chronic infection, which can cause liver disease, cirrhosis, HCC, or death. The treatment goal is virologic cure as evidenced by sustained virological response, or SVR, that is undetectable HCV RNA months after completing treatment. For treatment, currently recommended therapies are oral direct-acting antivirals, which are administered daily for 8 to 12 weeks. With direct-acting antivirals, SVR rates of greater than

90 percent are observed with or without ribavirin. Older, less effective therapies include interferon, peginterferon, and ribavirin.

We identified one study that used Ta1 as monotherapy for chronic hepatitis C. In this early trial, no subject cleared HCV RNA. Ta1 has also been studied in combination with older, non-preferred treatments. Trials of Ta1 in combination with interferon, with and without ribavirin, were limited by study design, small size, older assays, and limited SVR data. In studies that reported SVR, rates ranged from 21 to 40 percent. One randomized, blinded placebo-controlled trial of Ta1 in combination with peginterferon and ribavirin showed an SVR of 12.7 percent with the Ta1 group versus 10.5 percent in the placebo group. Authors stated that the addition of thymosin alpha-1 to the standard of care did not increase the on-treatment HCV viral response.

In conclusion, there are insufficient data to establish effectiveness of Ta1 to treat HCV

infection, which has the potential to be serious and life-threatening. Ta1 was studied as an alternative to or in combination with older therapies with lower SVR than current standard of care, oral direct-acting antivirals for which SVR rates exceed 90 percent in many populations. There are available FDA-approved therapies with established efficacy for the treatment of chronic hepatitis C.

Next, I will discuss HIV. HIV is a virus that attacks the body's immune system. The key component of the immune deficiency associated with HIV is a marked reduction in CD4 positive T cells. Current professional treatment guidelines recommend initiating antiretroviral therapy as soon as possible after diagnosis to reduce HIV-related morbidity and mortality and to reduce transmission risk.

Treatment-induced decreases in viral load have been shown to be highly predictive, a meaningful clinical benefit, and are validated in clinically meaningful surrogate endpoints. Thus,

HIV viral load suppression is often a primary endpoint in HIV treatment trials, while CD4 T cell counts are included as secondary endpoints. Monitoring lymphocyte subsets other than CD4 T cell counts have not proven clinically useful and are not recommended.

FDA identified five published studies using Ta1 in subjects with HIV. These studies are broken up into this slide and the next slide. Schulof et al. evaluated Ta1 as monotherapy, while other studies evaluated Ta1 as part of combination therapy with antiretroviral drugs. None of the four studies on this slide increased CD4 positive T cell counts when Ta1 was added.

The fifth study by Garaci et al. randomized subjects to four treatment groups. In the table, we can see the four treatment groups along with the mean CD4 T cell counts pretreatment and after 12 months. After 12 months of treatment, CD4 counts were significantly increased in group 4 and persisted for up to 18 months; however, small sample sizes, potential bias from the unblinded

study design, and the unknown contribution of Ta1 to the immunomodulatory effect when combined with zidovudine and interferon-alpha limits the interpretability of the data.

In conclusion, there is insufficient evidence to conclude that Ta1 is effective for the treatment of HIV infection. These published studies were not adequately designed. Additionally, CD4 T cell counts and/or laboratory-based immune parameters are not validated surrogate endpoints. None of these studies demonstrated statistically significant effects on clinical endpoints such as prevention of AIDS-defining illness or death, or on the validated surrogate endpoint of HIV viral load. Finally, there are numerous FDA-approved drug products for the treatment of HIV.

Next, I will discuss COVID-19. COVID-19 is the disease caused by SARS-CoV-2. Early in the clinical course, the disease is primarily driven by the replication of SARS-CoV-2. Later in the clinical course, it's driven by a dysregulated

immune/inflammatory response to infection that may lead to further tissue damage and thrombosis. FDA was not able to find literature to discuss the use of Ta1 in children with COVID-19 or adults with COVID-19 in the outpatient setting. Thus, our discussion focuses on the use of Ta1 in adults with acute COVID-19 in the hospital setting.

This table lists the four meta-analyses included in the evaluation. Liu et al. 2022 reported that there was no association between Ta1 treatment and mortality. Shang et al. 2023 reported that Ta1 therapy had no statistically significant effect on mortality. Wang et al. 2023 reported that no differences were found in mortality or length of hospitalization between subjects who did and did not received Ta1. Soeroto et al. 2023 reported that use of Ta1 was associated with a lower mortality rate, but treatment with Ta1 did not reduce the need for mechanical ventilation, nor did it reduce the length of hospital stay. In conclusion, three of the four meta-analyses concluded that there was no

decrease in mortality in subjects treated with Ta1.

There were three additional references not discussed in the meta-analyses. Tuthill et al. 2023 was a prospective trial in adults with end-stage renal disease. This study has not been completed and results were not reported.

Wang et al. and Wu et al. were retrospective cohort studies in adults hospitalized with COVID-19.

Limitations for the studies include limited sample sizes and deficient study designs, as well as the use of other medications. In addition, most of the studies were conducted early in the pandemic, and it's unclear if the outcomes will be reproducible given the current circulating viral strain and changes in treatment since these studies were completed.

There was heterogeneity between studies in the definition of disease severity and dose and frequency of exposure to Ta1, making it difficult to compare study outcomes. In conclusion, there is insufficient information concerning effectiveness to support the use of Ta1 for the treatment of

COVID-19. IDSA, NIH, and WHO treatment guidelines do not discuss the use of Ta1 for COVID-19, and there are FDA-approved therapies with established efficacy for the treatment of COVID-19.

Thank you. This concludes this portion of our presentation. After a short break, we will return to discuss the available evidence of effectiveness, or lack of effectiveness, for the remaining uses.

(Pause.)

DR. STEVENSON: Hi. This is Takyiah Stevenson, DFO. While we're on this brief break, just a reminder for the panel members to please don't leave your seats or leave the Zoom room. We will resume shortly. Thank you.

(Pause.)

DR. HANKLA: We just wanted to give everyone a couple minutes to digest, and I wanted a taste of water, so I appreciate the short break.

Welcome back. We will now continue our discussion on the effectiveness of Ta1. Next, we will discuss adjuvant to influenza vaccines. FDA

identified five clinical studies evaluating Ta1 as an adjuvant to influenza vaccine in elderly or patients on hemodialysis. Of these, two clinical studies were retrieved in abstract form, and we're not able to identify full-text articles. These five published studies administered Ta1 at different time points in relation to vaccination with monovalent or trivalent influenza vaccines. Interpretation of effectiveness in these studies is limited, as will be discussed in the next slide.

Limitations of the studies for this use are listed. ELISA was used in most studies; however, ELISA is not an accepted methodology used by FDA to evaluate immune responsiveness. Studies had exploratory design without formal hypothesis testing and prespecified immunogenicity or efficacy endpoints.

Importantly, control groups were missing or inadequate, and data quality were difficult to interpret. For example, studies did not use influenza vaccines recommended in the U.S. for use in the populations considered. Overall, the

studies were not properly controlled and did not produce meaningful data on use of Ta1 with influenza vaccines. In conclusion, there's a lack of sufficient evidence to determine any conclusions on the effectiveness of Ta1 as a vaccine adjuvant.

Next, I will discuss malignant melanoma. We identified four published studies using Ta1 in patients with metastatic melanoma, which is a subtype of melanoma. The first study by Maio et al. is described in this slide. This study was an exploratory, multicenter, open-label, randomized study in 488 patients with stage 4 melanoma and unresectable metastases. Patients with previous chemotherapy were not eligible for inclusion in this study. Patients were randomized to 1 of 5 treatment groups as shown in the table on the slide.

Patients received various combinations of dacarbazine, interferon-alpha, and Ta1. The primary endpoint of the study was best overall response rate at 12 months. Overall response rates at study completion are shown in the table. The

study failed to show a significant difference in the overall response rate with any Ta1-containing regimen compared to the control group. Furthermore, in terms of the dose response, the lower response rate of group 3 compared with group 2 suggests that these findings may be due to chance. Importantly, the study was conducted when chemotherapy and either interferon or interleukin were the standard of care.

We identified three additional studies using Ta1 in patients with metastatic melanoma, two single-arm studies where Ta1 was used in combination with interferon-alpha or interleukin-2 and one retrospective review. These studies were limited by their design, and it was not possible to identify the contribution of Ta1 to the observed treatment effect.

In conclusion, the studies investigating the use of Ta1 in melanoma to date are insufficient to demonstrate the effectiveness of Ta1. Published studies used controlled data from inferior, outdated regiments. Statistically significant,

clinically meaningful improvements in Ta1-treated melanoma patients were not demonstrated. The existence of FDA-approved drugs to treat the disease and the lack of rigorous data demonstrating the benefit of Ta1 for use in patients with malignant melanoma weigh against including Ta1 on the list, particularly in light of it being a serious or life-threatening disease.

Next, I will discuss hepatocellular carcinoma or HCC. We identified two studies that used Ta1 with transarterial chemoembolization or TACE. The first study was a single-arm study in 12 patients; however, the study had limitations, including the study design and small sample size. The second study from Gish et al. was a randomized pilot study in 25 patients. Patients were randomized to receive TACE plus Ta1 or TACE alone for 24 weeks. Authors did not find a difference in the response rate or median overall survival between the treatment and control groups. The study was designed primarily as a safety study, and authors recognized the need for a larger phase 3

trial in this setting.

Next, we identified one study that administered Ta1 after hepatectomy and with TACE to reduce recurrence. Cheng et al. 2004 was a randomized-controlled trial in 57 patients, 18 of which received Ta1. Authors did not find a difference in the one-year recurrent rate but did find a difference in the median overall survival. Of note, the overall survival rates in the control arm are much shorter than would be expected based on other published reports, which raises concerns over the reported data. Upon reanalysis of the data from the study, a Cochrane review published in 2011 did not find a statistically significant difference in either the overall survival or disease-free survival.

We identified five additional studies using Ta1 in patients with HCC that are listed on this slide. Four studies evaluated Ta1 post-hepatectomy to reduce recurrence, and one study evaluated Ta1 after liver transplantation to reduce recurrence. These studies were limited by their design, and it

was not possible to identify the contribution of Ta1 to the observed treatment effect.

Limitations of these studies include the retrospective design; small patient numbers; studies were not adequately designed to assess the study endpoints; and in some studies, patients received other therapy in combination with Ta1 and were not designed to demonstrate the contribution of Ta1; and they were mostly single-center studies that were geographically limited. Thus, the results may not be directly applicable to patients in the U.S.

In conclusion, there is insufficient evidence to demonstrate the effectiveness of Ta1 as a treatment option for HCC. In the two randomized-controlled trials identified to date, authors did not find a difference in the one-year recurrent rate or response rate and median overall survival between the treatment and control groups. There are no FDA-approved products for HCC in the adjuvant setting; however, there are FDA-approved products for the treatment of unresectable HCC.

Next, I will discuss non-small cell lung cancer. Two randomized-controlled trials evaluated Ta1 in non-small cell lung cancer. These studies are nearly 40 and 30 years old, respectively. Although there were improvements in both relapse-free survival and overall survival for the Ta1 treated groups when compared with the placebo group in the 1985 study by Schulof et al., we agree with the study authors' conclusions that definitive conclusions regarding the impact of thymosin therapy on survival can only be ascertained in large-scale, multi-institutional trials. Furthermore, these studies are inconsistent with contemporary management of patients with non-small cell lung cancer with placebo controls and without genetic testing.

In the study by Salvati et al., the median overall survival in the ifosfamide chemotherapy arm was 16 weeks, and in the combined chemotherapy, plus Ta1, plus interferon arm was 24 weeks; however, based on the two-arm study design where several drugs were administered, it's not possible

to determine the contribution of Ta1 administration to the overall treatment effect of the regimen.

We identified five additional studies using Ta1 in patients with non-small cell lung cancer that are listed on this slide. These studies were limited by their design, and it was not possible to identify the contribution of Ta1 to the observed treatment effect.

The ability of these studies to establish the effectiveness of Ta1 in patients with non-small cell lung cancer are limited by small sample sizes, advances in staging and genetic characterization since these studies were conducted, and changes regarding U.S. standards of care and available therapies. Furthermore, the controlled therapies received are not consistent with U.S. standards of care for patients with non-small cell lung cancer without actionable genomic alterations. It's unknown whether the addition of Ta1 to contemporary treatment regimens would have resulted in clinical benefit for these patients.

In conclusion, there's insufficient evidence

to demonstrate the effectiveness of Ta1 as a treatment option for non-small cell lung cancer. It is unknown whether the addition of Ta1 to contemporary U.S. standards of care would have resulted in clinical benefit for the patients included in the clinical studies. Non-small cell lung cancer is a serious disease. There are several FDA-approved drug products which have contributed to a sharp decrease in the disease-related mortality.

Next, I will discuss sepsis. We identified four full-text articles in English using Ta1 in subjects with sepsis. This slide describes the first two articles. Wu et al. conducted a single-blind, randomized-controlled study to evaluate the efficacy of Ta1 in 361 patients with severe sepsis. The study showed that in the time-to-event analysis, patients in the Ta1 group survived longer after enrollment than the control group; however, it did not show a significant difference in the overall absolute reduction in mortality, ICU mortality, length of ICU stay, and

duration of ventilation. Authors concluded that larger multicenter studies are needed. Pei et al. conducted a post hoc analysis of the study by Wu et al., however, there were no results for the subpopulation of patients who received Ta1.

The third study was a randomized-controlled trial in septic shock patients who received Ta1 plus blood purification versus control. All subjects received ulinastatin, which is not approved in the United States. Although the Ta1-treated group showed significant improvements in the T lymphocyte subsets, inflammatory cytokines, and myocardial function, it showed no difference in survival.

The fourth study by Wang et al. was a small double-blind pilot study in patients with severe acute pancreatitis that showed a significant reduction in the rate of positive blood and abdominal drainage cultures, and the rate of surgery. The patient population with severe pancreatitis is representative of only a subset of patients with sepsis.

We note several limitations. All clinical studies were conducted in China. Based on the studies reviewed in this section, treatment of sepsis in China may not be reflective of the U.S. medical practice. Due to several limitations, we conclude that there is insufficient information to support the effectiveness of Ta1 for the treatment of sepsis. Published clinical trials show that Ta1 may affect biomarkers of immune function; however, the majority do not provide evidence of meaningful clinical benefit of Ta1 in the treatment of sepsis, reduction in mortality, or need for organ support.

Next, I will discuss infections after hematopoietic stem cell transplantation or HSCT. HSCT can be defined as the transfer of hematopoietic stem cells from one individual to another or the re-administration of previously harvested cells to the same individual. Major causes of early morbidity or mortality for patients who undergo stem cell transplant are disease relapse; acute graft versus host disease; infection; regimen-related toxicity; and graft

failure. Endpoints that can translate to meaningful clinical benefit and survival include decrease in the infection rate and hematopoietic recovery endpoints; for example, time to neutrophil recovery in addition to decrease in infection rate.

We identified two published studies and one abstract using Ta1 in subjects who were stem cell recipients. The first study from Perruccio et al. 2010 was a single-arm study in 14 stem cell recipients who received Ta1 for 16 weeks post-transplant. Authors concluded that Ta1 may favorably affect immune function but recognized that larger number of subjects and longer follow-up are needed to assess its impact on survival.

The second study was published as a meeting abstract. Perruccio et al. 2011 was a study in 30 stem cell recipients who received Ta1 from the day of transplantation for 16 weeks. Authors reported a potential improvement in non-relapse mortality, but the details needed to assess the impact of Ta1 are lacking because it was a meeting abstract.

The third study by Ding et al. was a case series of 8 stem cell recipients that received Ta1 or standard of care for 4 weeks. The infection rate did not decrease in the small study, and it appears that the infection rates were increased in the Ta1-treated group.

Limitations of the studies include heterogeneous populations; small sample sizes; limited duration of follow-up; lack of clinically meaningful endpoints; and unclear clinical relevance of the measured markers, among others. In conclusion, these studies do not provide evidence that Ta1 reduces infection and/or infection-related mortality after HSCT.

Next, I will discuss COPD. We identified two published studies using Ta1 in patients with COPD exacerbations. The first was a double-blind, randomized trial in patients with acute exacerbation of COPD who received unspecified routine complex treatment and either Ta1 or placebo for 4 weeks. Authors state that pulmonary function and blood gas indicators improved in both groups

but were more pronounced in the experimental group; however, no details of the results were provided.

The second study was a study in elderly patients with an acute attack of COPD with respiratory failure who received theophylline sustained release or theophylline sustained release and Ta1 IV for 4 weeks. Authors state that both groups improved after treatment with better effects observed in the study group in terms of pulmonary function, blood gas indicators, and exercise ability. Authors noted that further trials are required prior to application in clinical practice.

Both studies had limitations, including small sample sizes with short durations; lack of sufficient details about statistical methodology and other study design elements; lack of meaningful clinical endpoints; and a lack of details on other COPD medications. In conclusion, there is a lack of evidence to support the effectiveness of Ta1 for the treatment of COPD. While authors claim that study suggests there are better effects observed in those who received Ta1 compared to the control

group, the available information has limitations, as shown in the list above.

Finally, I will touch on myalgic encephalomyelitis and chronic fatigue syndrome or ME/CFS. FDA did not identify any data to support the effectiveness of Ta1 in the treatment of ME/CFS.

Considering all of the effectiveness information, we conclude there's a lack of evidence to support the effectiveness of subQ administered Ta1 free base and Ta1 acetate for the evaluated uses. None of the clinical practice guidelines for U.S. health professionals recommend Ta1 free base or Ta1 acetate. Studies on the serious and life-threatening conditions considered in the evaluation of effectiveness of Ta1 were inconclusive and limited by small sample sizes and study design deficiencies. There are multiple FDA-approved drug products indicated for use in treatment of many of the conditions evaluated.

On balance, the physiochemical characterization, information on historical use,

lack of evidence of effectiveness, and safety information identified for both Ta1 free base and Ta1 acetate weigh against them being added to the 503A Bulks List. In particular, FDA's proposal regarding these substances is based on the fact that Ta1 free base and Ta1 acetate are not well characterized from a physiochemical perspective, and it's unclear how it will be possible to formulate the proposed injectable form as an aqueous solution with a concentration of 3 mgs per mL.

There is insufficient safety information on the use of the substances and a lack of information about immunogenicity risks. There's also a lack of evidence of effectiveness of these substances for use in the conditions evaluated and the existence of FDA-approved drugs to treat most of these conditions, particularly in light of them being serious and/or life-threatening conditions. After considering the information currently available, a balancing of the four evaluation criteria weighs against Ta1 free base and Ta1 acetate being added

to the 503A Bulks List. Thank you very much. This concludes our presentation.

Clarifying Questions from the Committee

DR. REBELLO: Thank you, Drs. Hankla and Li.

We will now take clarifying questions to the presenters. When acknowledged, please remember to state your name for the record before you speak and direct your question to the specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and the end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

Are there any clarifying questions for the presenters?

Dr. Gura?

DR. GURA: Yes. Hi. Thank you for a great overview. I'm kind of confused because there is a product known as Zadaxin. Where does that fit in the whole scenario? That is FDA approved, and this

does have orphan status; correct? So I'm just wondering how these all fit together. Thank you.

DR. HANKLA: Zadaxin or thymosin alpha-1, any products containing thymosin alpha-1 are not approved in the United States by FDA. There are foreign marketed products, as mentioned in the historical use section, as Zadaxin is approved in other countries. In terms of orphan drug designation, there are four orphan drug designations for thymosin alpha-1, but just to note here that designation as an orphan drug qualifies sponsors for certain incentives, but it's a separate process from FDA approval. So the drugs for rare diseases must still go through the same rigorous scientific review process as any other drug for approval or licensing.

Does that help?

DR. GURA: Well, like I said, I was just looking online, and I see a lot of conflicting information. That's why I'm trying to double-check what the real deal is. Right now, I'm seeing so many citations saying it is FDA approved, and I

haven't had a chance to go into my Lexicomp database. But I'm just curious because I am confused.

DR. HANKLA: Elizabeth Hankla again. It is not FDA approved.

DR. GURA: Thank you.

DR. STAAS: If I may, this is Donnette Staas from Jazz. If you go to the drugs at FDA website, there's a really nice database where you can actually look at drugs that are actually approved by the FDA.

DR. REBELLO: Thank you.

Dr. Gans online has a question.

Dr. Gans?

DR. GANS: Thank you so much. I just really do want to applaud that amazing review of the literature that is out there, so thank you for that. I did have one quick question maybe just broadly for the FDA. I was unaware of why the submission to the FDA was actually withdrawn, and I just wondered if we could have any additional information on that to think about what we're

voting on today.

MS. BORMEL: This is Gail Bormel. The agency doesn't generally comment publicly on litigation, so I'm not really able to talk much about that, but it is important that even though the nominations were withdrawn, we can elect to review the information and bring it to the PCAC.

DR. REBELLO: We have another question online from Dr. Corbett.

Dr. Corbett?

DR. CORBETT: Hi. It's Amanda Corbett. Along those lines, just checking, since the nominator withdrew this application, assuming if it were not allowed to be on the bulk list now, is it a possibility that any of this product could have a nomination in the future? Is there anything to preclude that from happening in the future?

MS. BORMEL: This is Gail Bormel. We are bringing the bulk drug substances to the committee for their recommendation, so the process after that would be to conduct rulemaking. So those bulk drug substances that were addressed would either be

proposed or not proposed for the rule. There's nothing in the future that would preclude an entity or someone from asking us to address it again. I'm not sure it will be a nomination. It might be a nomination or another type of vehicle like a citizen petition.

DR. CORBETT: Okay. Thank you.

DR. REBELLO: Dr. Ghany, did you have a question?

DR. GHANY: I did, yes. Marc Ghany. My question is to Dr. Hankla. In the application, did they outline how they would expect to use this? What was the regimen, in particular, the dosing frequency and the duration; and would it be different for different diseases?

DR. HANKLA: Elizabeth Hankla. No. Unfortunately, we don't have that information in the nominations that we get. We usually don't get dosing information, how long it'll be given post-dosage and that sort of information.

MR. WESDYK: If I could just add to that, one of the things that came in the nomination that

caught our attention was that they were proposing a strength that was twice what we've seen in any of the previous clinical studies and all the history. Almost everything up there was 1.6 mgs per mL, if I recall. What was proposed was 3 mgs per mL, and that's as much as we know.

DR. REBELLO: Dr. Gulur online has a question.

Dr. Gulur?

DR. GULUR: Thank you. If I could just get a clarifying answer to this; once a substance is placed on the bulks list, is there a regulation, or is there any indication or direction on what dose can be used, et cetera, or is it just that it allows people to compound, and the clinical regimens are left to the prescriber?

MS. BORMEL: This is Gail Bormel. Once a bulk drug substance is placed on the 503A Bulks List, it will be left up to the prescriber for the route of administration and the dosage.

DR. GULUR: Thank you.

DR. REBELLO: Dr. Clark?

DR. CLARK: Yes. I have two questions. One was on Dr. Hankla's presentation, slide 63. The improvements in immune function, were those in vitro responses, do you know, or what led them to conclude that Ta1 was helpful for immune function?

DR. HANKLA: Elizabeth Hankla. Can you bring up slide 63?

DR. CLARK: Sorry. This was Perruccio 2010.

DR. HANKLA: Apologies. Can you repeat your question again?

DR. CLARK: Yes. The author's conclusion was that it may favorably affect immune function, and there wasn't data in the background information about this either. I was just wondering what assays were used or if you knew what they were referring to there, if it was just in vitro assessments or how they were measuring that.

DR. HANKLA: Elizabeth Hankla. I believe they were in vitro like T cell responses to specific viruses. I would have to look up specifically what it was.

DR. CLARK: Okay.

I have one other unrelated question. On the CoAs that we've been talking about, for the drugs that have made it to the bulk drug substances list, are those CoAs significantly different than what we've seen today in terms of detail, a list of the impurities? How do nominators know what to include there?

MR. WESDYK: Excuse me. Russ Wesdyk, FDA. It will vary from drug substance to drug substance. I'm going to go back to my old example. For something like aspirin, it's extraordinarily well known, we're less concerned with certain aspects of it. For a large peptide where there are immunogenicity concerns and impurities can have such a dramatic impact, we're looking for more information on impurities in order to ensure patient safety. So it will vary from product to product.

DR. CLARK: Can the FDA require exactly what's put on those so that the nominators know what you're looking for?

MR. WESDYK: Gail, I'm not sure. That's more of a legal question. I'm not sure --

MS. BORMEL: If we can impose certain CoA requirements; is that what you're asking?

DR. CLARK: Yes. I guess, even on the suppliers, to know what the pharmacies are getting is pure.

MS. BORMEL: Yes. I think what's in the statute now just generally talks about a valid certificate of analysis. We haven't further defined that. Is it possible that there could be in the future a definition of that? Yes, but again, part of the issue is going to be standardizing different elements, different substances for one standard. So that may not be as clear as when there is, for example -- we're not in this realm, but when you're talking about a USP monograph, which it's a public standard. Just to answer your question simply, it's possible that there could be a further definition, guidance, about what a valid CoA is.

DR. CLARK: Thank you. That's it.

DR. REBELLO: Just a friendly reminder to state your name before you ask the question. We actually have a queue, so the next person is actually Dr. Gans online, followed by Dr. Kris, followed by Thomas Lupton, but I'll call on each of you.

Dr. Gans?

DR. GANS: Thank you.

DR. REBELLO: State your name.

DR. GANS: Hayley Gans, Stanford. I had a general question again, and it goes along the lines of I think what we're slightly grappling with -- with that amazing literature review, which we now have have to use that as opposed to some kind of nomination -- is that it's been used in many different ways, and doses, and all that sort of stuff.

So I guess my general question is -- and I'm assuming the answer to this is no -- what we decide here today really does not inhibit people further studying the use of Ta1? I think in certain populations, given in certain ways, typically it's

been used later than we would have liked, and that there actually may be some benefit. But that's a very specific study question, and I guess my question is, there's nothing that we do today to discourage people from continuing to look at ways in which it might be helpful to certain disease states. For instance, primary immunodeficiency wasn't evaluated, but there are some suggestions that it might be helpful in people who are deficient in Ta1.

MS. BORMEL: This is Gail Bormel, if I can respond. No. The decisions today are separate from whether a study could continue to occur, but there are parameters for studies. They involve informed consent and a protocol, et cetera. We talked a little bit about the IND process and expanded access, et cetera.

What this process today is, is about whether to place thymosin alpha-1 and the substances on the 503A Bulk Drug List. And what that means is if it's placed on the list, then pharmacies can use that as a substance in compounding, pursuant to a

valid patient specific prescription, but there's no study that would need to occur, formally, and no other parameters on that.

DR. GANS: Great. That's what I thought. Thank you.

DR. REBELLO: Next, we have Dr. Kris.

DR. KRIS: Mark Kris. Are there any INDs in existence now, for this?

MS. BORMEL: This is Gail Bormel. I don't believe we can comment on that right now.

DR. KRIS: Okay.

DR. REBELLO: Next, Dr. Lupton.

DR. LUPTON: Thomas Lupton; a quick comment regarding the CoA process. We have the number of CoAs in the packets, and I appreciate that, but the CoAs reflect the suppliers QC testing of their product. That does not mean that that item is sufficient for the compounding formulation that that pharmacy is completing. So it's up to that pharmacy to demonstrate that that CoA meets their internal requirements based off their formulation and data.

DR. REBELLO: A question online from Dr. Corbett.

Dr. Corbett?

DR. CORBETT: One of my questions was answered about the IND can't be addressed, it sounds like. But in addition to that, are you able to answer if an NDA was ever submitted as a pharmaceutical agent to the FDA at any time? And I assume not approved, but I'm just curious if that had been done since it's approved at least in other countries, and if it was ever presented to the FDA as a pharmaceutical agent.

DR. SHETTY: Daiva Shetty, FDA. We may have had several communications with different proposals for Ta1 in development, but we are not aware of any NDA that was submitted and approved or not approved. We don't have approval for Ta1 for any condition.

DR. CORBETT: Okay. Thank you.

DR. REBELLO: Next, we have Dr. Gura.

MR. WESDYK: Sorry. If I could just add to that?

DR. REBELLO: Oh, sure. Go ahead.

MR. WESDYK: Russ Wesdyk, FDA. The only thing I would add -- because this is definitely the land of Daiva -- is SciClone's press releases have made clear -- so this is public information -- that they were initiating a phase 3 trial in the U.S. There's been no communication since from SciClone.

DR. GURA: Kathy Gura, Boston Children's. If we decide as a group that this does not make the list, would clinicians still have access to this product under expanded access, or could they import using Zadaxin, for example, now that I've been educated that it's not available in the U.S., but they can import it using expanded access, or an EIND route, or something like that? So patients who need it might benefit as a last-ditch effort; they'd still have access to it?

DR. SHETTY: This is Daiva Shetty, FDA. Yes, there is always availability through expanded access or the IND route.

DR. REBELLO: Next, Dr. Pau.

DR. PAU: Kind of similar to your question,

Dr. Gura -- this is Alice Pau from NIH -- is my ignorance that early on in one of the presentations was you can get online injectable or nasal spray. My question is, whether the online products are from another country, therefore one can get online, or whether those are companies that are making them in the U.S. without having any kind of approval, bulk compounding, or any other approval. This is my ignorance. I just didn't know how that happens.

MS. BORMEL: This is Gail Bormel. With the internet, there are always products that are available that are sometimes counterfeit, sometimes illegal, and a lot of different products that would fall into that category. Sometimes they're from foreign manufacturers, manufacturers abroad or a foreign entity. So there are a lot of things on the internet that may not be legal.

That's a separate aside from what we're talking about now, which is the legitimate practice of pharmacy compounding, which falls within Section 503A. So to the extent that pharmacies are compounding in compliance with the applicable

federal provision, as well as their state laws, that would be legal. There are a lot of things online that are available through websites that may very well be not legitimate.

DR. REBELLO: Dr. Janet Lee online.

DR. J. LEE: Thank you. Washington University in St. Louis. I had a question in reference to one of the statements that was previously made, that one aspect was the concentration that was proposed for the injectable product is greater than what had been shown or in the literature review. Am I to understand that none of the studies -- and it was a very comprehensive review, so thank you very much -- the clinical studies, had ever used that concentration subQ? Thank you.

DR. HANKLA: Hi. Elizabeth Hankla. In terms of the clinical studies, the highest concentration we saw used was 2 mgs per mL.

DR. J. LEE: Thank you.

DR. REBELLO: Are there any other questions either from our in-person group or online?

Brian Lee?

DR. B. LEE: Hi. Brian Lee from University of Southern California. Just to clarify, placing a drug on the 503 list, that makes it legal for pharmacies to compound that drug. If a drug is not on that list, does that make it illegal for pharmacies to compound that drug with enforcement?

MS. BORMEL: Hi. This is Gail Bormel. If a bulk drug substance is placed on the 503A Bulks List, that is one of the conditions of the Act that allows you to be exempt from certain provisions like getting a new drug application or having adequate directions for use, or in the case of compounders, pharmacy compounders from complying with current good manufacturing practices. So it makes it, essentially, yes, a legal practice, if all the other parameters of that provision are met.

If the bulk drug substance is not placed on the 503A Bulks List and a pharmacy would compound with it, it means they would no longer be exempt from certain provisions of the Act. They'd have to get a new drug application, they'd have to have

adequate directions for use, and they would have to comply with cGMPs. So it's a little bit of a twist on what you said.

And remember, after the committee makes its recommendation, we go through a rulemaking process, so there's a proposed rule for which the public can provide comments before there is a final rule to actually finalize the list. I just wanted to point that out as well.

DR. B. LEE: Thank you.

DR. REBELLO: Are there any other comments or questions from the group?

Yes?

DR. HANKLA: Hi. Elizabeth Hankla. I just want to loop back.

Dr. Clark, I looked at that article. They measured T cell counts and functional pathogens, specific T cells responses by a limiting dilution assay. Thanks.

DR. REBELLO: Thank you for that additional information.

Any other questions or comments?

(No response.)

DR. REBELLO: Online, any questions or comments?

(No response.)

DR. REBELLO: I want to thank everyone for their questions, comments, and FDA for their responses.

We'll now take a 10-minute break, so we'll reconvene at 2:32 to continue the thymosin alpha-1-related bulk drug substance topic. Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or any member of the audience, and we'll see you all at 2:32. Thank you.

(Whereupon, at 2:22 p.m., a recess was taken, and meeting resumed at 2:32 p.m.)

DR. REBELLO: Before we resume, FDA has a comment. Go ahead.

MS. BORMEL: Thank you. This is Gail Bormel. I was just taking a look at the final rules and the proposed rules for the 503A bulk substances, and I have noticed that for many of the

bulk drug substances that were -- well, some that were finalized and many that were proposed, we have limited it for route of administration, and in some cases, there are percentages that have also shown up as proposed limits.

So if that's, in part, what was evaluated at the time by the agency and then brought to the PCAC, they made it into the proposal. I didn't want to leave with the impression that it couldn't be limited at all, the bulk drug substance, because many of them in the proposed rule, and in the final rule, are at least limited by route of administration.

DR. REBELLO: Thank you. Thank you for providing that information.

MS. BORMEL: Two of them that I see in the proposed rulemaking are also limited in concentration.

Open Public Hearing

DR. REBELLO: Great. Thank you.

We will now begin the open public hearing session.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the product, and if known, its direct competitors. For example, this financial information may include the payment by a bulk drug supplier or compounding pharmacy of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not

preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect.

For those presenting virtually, please remember to unmute yourself and turn on your camera when your OPH number is called. For those presenting in person, please step up to the podium when your OPH number is called. As a reminder, please speak only when recognized by the chairperson. Thank you.

We'll begin with speaker number 1. Please state your name and any organization that you represent for the record. You will have three

minutes.

MR. D. DeNEUI: Good afternoon. My name is Dan DeNeui. I am the Chief Executive Officer of Evexias Health Solutions, which is a national network of over 10,000 medical providers, all representing many different disciplines of medicine. To clarify to our panel, if Ta1 is not on the list, patients and practitioners will lose access, and that's what leads to patients seeking out online fake pharmacies.

The real-world results of the FDA's recent decision around Ta1 is that thousands of these patients have turned to the black market to obtain peptides. The black market includes fake online, completely unregulated pharmacies, as well as other pharmacies advertising that they are a research facility, many of whom provide little or no direction on how a patient should be using the compound.

Strangely enough, the agency became extremely active in policing thymosin alpha-1 compounding when a group of physicians reported

high rates of success in addressing COVID-19, and this was far earlier than any of the studies that were cited earlier in the presentation. The agency even put out a special notification that expressly prohibited compounders from making this extremely beneficial peptide, demonstrating again and again the willingness of the agency to overreach and interfere with the medical providers' freedom to practice medicine, which is truly a travesty; and there seems to be a massive disconnect between medical practitioners and the FDA.

To quote our soon to be HHS commissioner, RFK, Jr., "The FDA's war on public health is about to end. This includes its aggressive suppression of psychedelics; peptides; stem cells; raw milk; hyperbaric therapies; chelating compounds; ivermectin; hydroxychloroquine; vitamins; clean foods; sunshine; exercise; nutraceuticals; and anything else that advances human health that can't be patented by big pharma."

I represent thousands of medical providers who are burned out on writing band-aided

prescription after band-aided prescription for patients, only to see their health and well-being continue to decline. Our practitioners want to help their patients. Our citizens long to live happier and healthier lives, to create a world that is positive and is uplifting to the human spirit.

Ladies and gentlemen, we can do, and must do, better because it is our moral and ethical duty to do so. Anything less is unacceptable. Thank you for your time.

DR. REBELLO: Thank you.

Speaker number 2, please state your name and any organization that you're representing for the record. You have three minutes.

MR. LaVALLE: Yes. Jim LaValle, International Peptide Society and American Academy of Anti-Aging Medicine. I'm not even going to go off of these slides. I've got to address a few things here. I taught 18 years at the College of Pharmacy and Medicine, University of Cincinnati, and currently adjunct professor at the George Washington School Medicine and Health Sciences,

Department of Integrated Medicine.

At the International Peptide Society, we're trying to do the right thing. We're trying to help providers help people feel that they have a chance for a healthier life when they are in chronic illnesses and conditions. I'd have to say the review of your information on thymosin alpha-1 was incredible and thorough, and I can tell you that the majority of doctors that are in integrative medicine, or you want to call wellness space, are not using it to treat hepatitis A and are not using it to treat hepatitis B.

What they're looking for is how can we help people not move down the path of metabolic inflammation, or as you well know from the literature since 2008, metaflammation leads to inflamm-ageing. And the key process in that is the disruption of the immune system, the loss of homeostasis of the immune system, and the loss of immunomodulation of the immune system, where Ta1 offers a potential benefit, and where at least 300,000 prescriptions have gone out. Physicians

have responsibly wanted to write prescriptions to pharmacies that want to comply, that can be inspected, that they can then see a result with their patient, and that is what's being taken away.

I'm not in disagreement with you what the assessment was for the more acute condition, but where peptides provide value, what we have seen with our thousand physicians in IPS, our 15,000 physicians at the American Academy of Anti-Aging Medicine, is they're using these type of compounds in order to be supportive as part of a structured program that helps people to reduce that risk of moving towards acute conditions.

I could give you a bunch of slides and information. We know it's immunomodulatory. It doesn't seem like there's immunogenicity, at least it wasn't shown to be that way. Just as, I would say, a quasi academic -- I can't claim full time as an academic -- I've directed a fair amount of my life towards it, as well as writing databases for Lexicomp, and it was mentioned earlier. We have a chasm between acute care, disease care, and how

we're going to keep people well, and that's where these compounds, I think, sit squarely in that gray area.

Hopefully, we're going to provide guidance from the FDA on what are acceptable excipients, how do we protect a compound, as well as be able to collect real-world evidence through doctors that are using EHRs so that we can provide that information to all of you, so that we can make great decisions forward that help people to improve on their quality of life. Thank you.

DR. REBELLO: Thank you.

Speaker number 3, please be sure to state your name and any organization you're representing for the record. You have three minutes.

MR. WYNN: My name is Tom Wynn. I'm with FarmaKeio Pharmacy. One thing I wanted to comment on is somebody asked before about the C of A and what are the requirements that are on there. There is a USP guidance, 1503 I believe it is, that's for synthetic peptides, and it does go through specifically what tests should be done in that

case. The FDA brought this up before. It is there and available, so there is something to move that along.

The other thing I want to mention, too, is, again, we brought up the immunogenicity several times today, and every time, it's been said it can, it has potential, it might, maybe. There's never been one time we said it will cause immunogenicity, so we're not really getting to the point of the immunogenicity; we're just saying it could. It's a possibility.

Now, I will say one of the products that's currently available, commercially available, semaglutide, has not been brought up at any point. That's not what we're talking about today, but there is a preservative they're using called phenol in there. Phenol has been shown, for sure, to cause protein aggregation, and it's actually in the product that's commercially available.

Now as a compounder, we would move away from that. We'd probably use a different one, maybe benzyl alcohol or something else. We would

purposely stay away from phenol because -- and I know it's in some vaccines, and it's in a lot of different products, but in this case, how do we know that that is not causing some immunogenicity, some aggregation, if you will, from all the different kind of side effects we're having lately on semaglutide, whether it be the GI stuff or they're even getting a different kind of lethargy and different things of that nature that you're hearing about if Google it online?

What I'm getting at is how serious are we about immunogenicity if we're putting something into products that are commercially available that will do that? If you look here -- I'm going through, again -- uncontrolled manufacturing process, something they brought up at a pharmacy.

We do follow USP guidelines for preparations. And as far as USP goes, they have new revisions, 797 for sterile. The FDA was a part of that. They did have somebody there during the committee meetings, maybe not all of them, but I know there was an advisor that was able to help put

in place some of the particular aspects of that particular chapter. I'm not against the chapter. It's fantastic, and we all want to abide by that chapter. But to say that we have uncontrolled processes isn't true because you were there at the point when that chapter was brought, written, and proposed for us to actually use. You weren't a voting member, probably just an advisor, but still you had some play in what was going on there.

Pharmacies do have controls in place as far as temperature controls. We do --

DR. REBELLO: We're at time.

MR. WYNN: Thank you.

DR. REBELLO: Thank you.

Speaker number 4, please state your name and any organization that you're representing for the record.

DR. E. LEE: Can I have slide deck number 6, please? Can you stop the time?

DR. REBELLO: Sure.

DR. E. LEE: My name is Dr. Edwin Lee. Thank you for letting me be here. I'm a board

certified endocrinologist. Fifty years ago, in 1974, the FDA approved an IND for thymosin fraction-5, which is a precursor of thymosin alpha-1, to be used in children with primary immune deficiency. Most of the kids had a dysfunctional thymus gland. They were very sick.

The very first child was Heather, 5 years old, and she was critically ill, slowly dying, multiple infections, and thymosin fraction-5 was life-saving. She was titrated off it and was doing very well. Unfortunately, she died in her early 20s from lymphoma, and she developed cancer from a weak immune system. Dr. Amman, involved in the thymosin fraction trial, told Dr. Allan Goldstein, who discovered thymosin alpha-1, his biggest regret was stopping the medicine.

So fast forward, in 2024, Dr. Elliott Dinetz and myself published an article titled Comprehensive Review of the Safety and Efficacy of Thymosin Alpha 1 in Human Clinical Trials. We've tabulated over 11,000 subjects worldwide that received an average dose of thymosin alpha-1

1.6 milligram subQ, 3 times a week. It was absolutely safe, and most of the studies showed positive results, not 100 percent.

A colleague of mine, Dr. Luis Martinez, did a study in his office, and tested that thymosin alpha-1 can improve the immune function in 10 of his patients; and you can see their age and their conditions there. He used a biomarker CD4/CD8 ratio. A ratio under 1 indicates a weak immune system. A ratio over 1 indicates a normal immune system. Using thymosin alpha-1 1.6 milligrams subQ 3 times a week in 6 months showed 100 percent improvement of the ratio.

I have many patients that have used thymosin alpha-1 over one year. This is one of my patients. She had stage 4 colon cancer in 2021 before treatment of surgery, radiation, and chemo. She started thymosin alpha-1 1.6 milligrams subQ, 3 times a week and, fortunately, she has had no complications, or neuropathy, or even lost her hair. There is a study published showing that thymosin alpha-1 with chemotherapy reduces

neuropathy.

In conclusion, thymosin alpha-1 has been approved in 37 countries. It's naturally made, decreases as we age. It is safe, efficacious. It's life-saving. Thymosin alpha-1 should be used as an adjuvant therapy with chemo or cancer therapy, and the American public deserves thymosin alpha-1. Please save it. Thank you.

DR. REBELLO: Thank you.

Speaker number 5, please come to the podium. State your name and any organization that you're representing for the record. You have three minutes.

DR. T. DeNEUI: My name is Dr. Terri DeNeui. I'm an acute care nurse practitioner and research clinician. I'm going to talk about some real-world data that was collected recently from our internal medicine clinics. This was looking at 38 patients. I'm going to go through this quickly because you can look at it, the demographics of the patients, the age ranges, et cetera, and ethnic breakdown.

These are the primary diagnosis codes used,

and these are the primary diagnosis codes in hundreds of my colleagues that have been through advanced peptide training and use it primarily for an autoimmune disorder in the early stages. Somebody mentioned earlier a lot of these other studies in late-stage disease. Early stage is what we're finding where it has the most benefit.

The concentration that we're using, these 38 patients were 3 mgs per mL, initially BID, so it's 300 micrograms twice a day, and then daily thereafter. No side effects or adverse events were noted. This is just a slide from the VA distinguishing between a side effect and adverse event. They are two completely different things, and, again, none were reported.

I'm going to present a quick case study. This is a very common presentation of patients that we see. A 67-year-old healthy female, she came to our office diagnosed with autoimmune hepatitis. When she was seen by her PCP, she had LFTs way up there, 1400, 970, and couldn't find anything wrong with her, no cancer, everything was negative. All

her serology was negative. After 3 months on oral prednisone, she showed some improvement. They wanted to put her on methotrexate. She researched it, she refused, she wanted other options.

She came to us still with elevated liver enzymes. We started her on Ta1 BID for 12 weeks with nutritional support, tapered off her oral prednisone, and then over the course of 6, 12, and 24 weeks, she normalized on her LFTs. No side effects and no adverse events for 3 years she was on it. She was very afraid to go off and very devastated a year ago when it was taken off. Last I saw her a year ago, she was seeking off-market options, unfortunately.

This is a common clinical picture of patients that have seen massive benefit with thymosin alpha-1 to their immune status and their chronic condition, that had no other treatment or other treatments had failed, and now this has been taken away from them. Thank you.

DR. REBELLO: Thank you.

Speaker number 6, please state your name and

any organization that you're representing for the record.

DR. ROSEBUSH: Sure. My name is Lee Rosebush. I'm a PharmD, Doctor of Pharmacy, and I'm also an attorney in this case, and also here to represent some of the pharmacies associated with this. But this may be even news to some of the FDA folks, that 20 years ago, I actually spent time in the Office of Orphan Products. I was there underneath Marlene Haffner, Diane Centeno-DeShields, and Jeff Rich, and, in fact, they actually wrote my letters of recommendation to get into law school.

I say that because I am here not just as a pharmacist and an attorney. I'm also here as an OOPD patient advocate, and we're going through that in just a second and what that actually means. More importantly, I have a daughter, that many of you know from this perspective, who has a rare disease, is life-threatening, and at Children's Hospital on a weekly basis, so this really does mean something.

To answer some of the questions that were asked earlier, if you put this on the list, it will be taken away. It is illegal to compound from that perspective. Some of you asked about INDs. Many pharmacy compounders are the ones who supply those products. They will be taken away. And if you encourage expanded access of the foreign-based product, that means FDA is actually on record encouraging the importation of a non-FDA approved product from a non-FDA registered site over that product that could be made domestically and inspected today; and instead it's going to be made in a facility that FDA would have no jurisdiction over. That's important to remember.

There are four specific criteria we've gone through multiple times. Is it well characterized? Obviously. This one is approved in 36 countries, including Italy. It is approved in Europe, from that perspective. Has it been used historically in compounding? If we can go to the next slide, you'll see. We actually have over 300,000 prescriptions that have been dispensed by this. It

is a huge historical record associated with this.

Are there safety concerns associated in effectiveness use? I'm going to read directly from FDA's own slide that was just given to you. "On the safety side, in most clinical studies, Ta1 has not been associated with significant adverse events attributable to Ta1 when administered in doses at a range of 1 to 16 milligrams." That's from FDA.

On the efficacy perspective -- this is just one indication, and we'll go through others -- study authors suggest that Ta1 may favorably affect immune functions, period. That's all four criteria. I'm not sure why we're here from that perspective. If this was FDA approved, as was asked about Zadaxin, we wouldn't be here from that side of it because we'd have the ability to compound. If this had a USP monograph, which we have approached USP to make a monograph, we wouldn't be here from that perspective. Unfortunately, USP will not allow us to make a monograph.

On the orphan side and the reason why I

raise that, for those that don't know, in this situation, there is a specific regulation, 21 CFR 316.20, and in it, it says -- this is what's in court in order to get orphan drug status -- quote, "a discussion of the scientific rationale to establish a medically plausible basis for the use of the drug for the rare disease or condition, including all relevant data from in vitro laboratory studies, preclinical efficacy studies conducted in animal mode for the human disease or condition, and clinical experience with the drug in rare disease or condition that's available."

FDA has granted orphan status using that standard, safety and efficacy, four times in the last 15 years to this substance. As somebody who has a kid, a child who's potentially dying from a rare disease, if you say no to this and get it put on the list, it will be removed regardless of what is said.

Practically from that perspective --

DR. REBELLO: We're at time.

DR. ROSEBUSH: -- if this says no, ask yourself what wholesaler would ever carry this product. They won't. So in this case, you'd be asking for an expanded-use product from a non-FDA approved source, from a non-FDA inspected facility, and you're taking away something that could be domestically made here that saves lives for kids that have rare diseases.

And you know why it's not approved? Because there's no money to it. Don't let this get caught up in politics with COVID-19 and peptides that you just heard about from Lilly. That's why the other ones were there.

DR. REBELLO: We're at time.

DR. ROSEBUSH: Don't let this one get taken away because of politics, please.

Clarifying Questions from the Committee (con't)

DR. REBELLO: Thank you.

The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience. We will now take additional questions and comments from those here

and want to open that up at this point.

Are there any clarifying questions?

MR. WESDYK: Yes. Russ Wesdyk, OPQ, FDA. Dr. Rosebush and many of the speakers raise some really good points. One of the challenges for us in the FDA, and especially from the standpoint of characterizing a bulk drug substance, is, going back to my presentation first thing this morning, there are dramatic differences in quality from bulk drug supplier to bulk drug supplier. You'll see a lot of clinical trials without significant safety signals, potentially, done with material that was manufactured by, in essence, branded companies under tight controls.

For any approved product, there is an approved synthetic pathway. There is an approved set of methods and specifications for the drug substance and an approved set of methods and specifications for the drug product. That's not the case here. Anybody can make it, to any standard, and it can be imported and compounded. And that's part of what we're asked to do in OPQ,

is take a look at what's out there, look at the C of As, and see is it similar to what's been tested and shown to be safe and effective, if it was, or not? And that's our challenge. We don't have information to make that assessment.

I talked this morning about three potential pathways, synthetic pathways for large peptides. You can go through a biochemistry standpoint, you can go from a chemical synthesis, or you can isolate it from natural sources. This can be made all three ways. It will have dramatically different impurity profiles, and out of that, you have dramatic differences in terms of immunogenicity potential. To that point, it's not to say it will happen, but certainly the potential is there. And that's why we come to the conclusion from an OPQ perspective that it's not well characterized. Thank you.

DR. REBELLO: Thank you.

Any other additional comments or questions?

Yes? Please state your name.

DR. BOGNER: Got it.

DR. REBELLO: An affiliation.

DR. BOGNER: Oh, and affiliation. Robin Bogner, University of Connecticut. I have similar concerns about some of the certificates of analyses that I've seen. They may be called valid, but I don't trust a lot of what's there. With this particular compound, drug substance, could a pharmacist in the U.S. source it as the manufactured product from overseas, and compound with the manufactured product that has presumably gone through not FDA but some other agency's regulatory approval and oversight? That's my question because if that's the case, I might look at it differently.

MR. WESDYK: Russ Wesdyk, FDA. I think both Gail and I will likely comment. Could they? Yes, they could. But the important question, to me, is, are they constrained to do that? And the answer is no. They can buy it from anybody, anywhere.

I want to be clear. There's an implied criticism here. It's not so much aimed at the compound industry. It's a bulk drug substance

industry that can make and do whatever they want. Some of the C of As, it's kind of shocking. If you really dug into the materials you have on multiple substances here, this isn't a compound. This is a bulk drug substance manufacturer, and there's a C of A that has a name on it. And then you look at the tests, and you're like, "Wait a minute. They didn't make that from these tests." You know they made something else, in fact. Then you look at the molecular formula, molecular weight, and chemical name, "Wait a minute. It's a third thing entirely."

It's hard for us because I look at it, and I'm like, "Do they even know what they're making? Do they even know what they're testing?" That's not a compounder's problem; that's a bulk drug substance manufacturer's problem. But that's what we're seeing when we look at some of these C of As. So it becomes challenging to say, "Hey, this is well characterized. Could it be? Yeah. Is it?"

MS. BORMEL: This is Gail Bormel. I think the challenge is also that there could be a number

of different manufacturers of an API, and if they register with FDA and they list their product, they can ship it into the U.S. for appropriate uses like compounding research, et cetera.

I think what Russ is saying is it doesn't mean that the supplier that's registered and has listed their product, that every BDS is necessarily identical in its quality. So again, it's a little different scenario than when we have a substance that's in the USP and has a public monograph, and that's what is required to be adhered to. I think that's the difficulty. There could be multiple manufacturers of the same BDS, but it may not really be the same quality.

DR. REBELLO: Yes? Go ahead, Dr. Bogner.

DR. BOGNER: If I can respond --

DR. REBELLO: Yes.

DR. BOGNER: -- I think my point is -- because I agree with you -- for many of the other peptides, I wouldn't know where to go looking for a good bulk drug substance. Yes, you can get bulk drug substance from anywhere, but in this

case, I know there's a product out there that has gone through somebody's regulatory review that I would feel more comfortable with. So while a compounder could go anywhere, maybe a more careful compounder would go to a very specific place that I know exists, a marketed product elsewhere, to be sure; whereas with other peptides, it's not clear where I would go. That's my point, I think, the differentiation here.

DR. REBELLO: So we have Dr. Gupta first, online, and then Donnette Staas.

Dr. Gupta?

DR. GUPTA: Yes. Hi. Thank you. I had a question and perhaps a comment on this. My concern is I see a lot of patients that often come in on a lot of different supplements, some of them including these, and much of the concern I have is where does the consumer go? We're talking about the compounder, we're talking about the individuals that ultimately have side effects that may perhaps be mild to severe, and no one has addressed the consumer and the patient.

When they're having a side effect, and I'm the physician managing it, or any physician in the United States, what are we supposed to do? That is ultimately the question that seems to be going unanswered here. And it's frustrating because many of these individuals have no recourse, there is no solution, and there's no response from the companies that are developing these products, and no one really has an answer. So I would love to hear an answer today from somebody in the room on what we're supposed to do.

MS. BORMEL: Hi. This is Gail Bormel. I think the question -- and correct me if I'm wrong -- is about where to report certain adverse events. Is that the question?

DR. REBELLO: My understanding as a physician, how do you help the consumer? Is that correctly addressing your question, Dr. Gupta?

DR. GUPTA: Yes. I think that's basically it. There are so many side effects that we're seeing to these products, and many times patients will come in with bottles of different -- because

they don't want to take traditional medications; they want to try these substances.

So I think the question I have, again, is where do consumers or patients go for addressing these symptoms or these conditions? Usually, the compounder doesn't because they're not the prescriber. The prescriber doesn't know, which would often be someone that doesn't know how to handle it, and the manufacturer may be foreign. So what what are we supposed to do in that situation? And the evidence is lacking from what I'm understanding, so I'm trying to comprehend here, today, what we're supposed to do in those situations. If anyone can answer that, I would love to hear the answer.

MS. BORMEL: Again, this is Gail Bormel. Let's just go through the process that we know about, which is for drugs, in general, either approved, or for compounded drugs that are not made by outsourcing facilities, if there are complaints about them or certain concerns, usually what happens is there's a recourse to either -- it's

mandatory in our law, but there's a recourse to submit complaints to the State Board of Pharmacy. You can voluntarily report information to FDA through its MedWatch program. So it's a voluntary reporting thing for these drugs that are not FDA approved, either compounded drugs or other drugs they may be obtaining from the the internet.

It is an issue that when people purchase drugs -- and I'm not really sure if you're alluding to people buying things from the internet, or they're buying things from just other sources, or they may be mail ordering things. We still do get complaints through different systems in FDA, even if they're not FDA-approved drugs.

That's just a mechanism of reporting, but I'm not sure if you're trying to figure out a way to advise patients about practices or you're trying to get information out there. The reason we have IND and expanded access programs is it's a way of formally getting drugs to patients with informed consent and looking at the data in a controlled way; and it seems what you're talking about are

patients that are purchasing things on the internet, not even being sure that they're legitimate.

DR. REBELLO: I believe Dr. Donnette Staas had the next question.

DR. STAAS: Hi. Dr. Donnette Staas from Jazz Pharmaceuticals. I actually just wanted to follow up on Dr. Bogner's question about sourcing outside of the U.S., really just directing this to Dr. Wesdyk and Dr. Bormel.

I guess the consideration is that if you were to go and get Zadaxin from outside the U.S., it would already be formulated as a drug product. It wouldn't be the drug substance, so if you were to bring that in, I don't know -- and that's a question I have -- and I'm not sure how you would then compound that. You would have to extract the drug substance from that, and then reformulate it in the way that you would like.

So perhaps maybe the thinking, then, you'd be more targeting the drug substance supplier that that company used to make the product. You would

have to go to that source if you were looking for something that was of high quality, if you will; otherwise, I don't think it really helps you to go after the actual marketed product, but I'm happy to hear what the agency has to say about that. Thank you.

MR. WESDYK: Russ Wesdyk, FDA. I absolutely agree with everything you just said. With respect to my colleague, yes, I don't think a compounder is likely to import a commercial drug product to compound it. It would be much easier to go buy the bulk drug substance from somebody. And the whole reason you're compounding it is, in theory, you want to put something in it. You're concerned with an allergen in it; otherwise you would just frankly dose that product.

DR. REBELLO: Yes? Dr. Bogner?

DR. BOGNER? Actually, a lot of compounding is done from a marketed product, and then compounded to a different dosage form. I work mostly in the large molecule biologics, and bulk drug substance is, partially at least, formulated

so that it can be stored. So I think that you can compound from a drug product.

MR. WESDYK: Russ Wesdyk. I absolutely agree with you, certainly, but in this case, we're talking injectable to injectable. The product on the market is an injectable. What they're proposing to make is an injectable. Why would you re-compound it? It just seems like it would be going through a lot of extra steps. Not saying you couldn't do it, just logically, as a formulator, where you're coming from, why would I do that? But it could be done, absolutely.

MS. BORMEL: This is Gail Bormel. I read it the way that Dr. Staas was reading it; that you would want to import the API from the reliable API manufacturer that was providing the drug, that the product was approved in a foreign country. Once you start importing drugs that are approved in another country but not approved in the United States, there are other laws that take effect. So you can't necessarily bring in drugs that are approved in another country and bring it over to

use in this country, necessarily. So I just wanted to caution if you think that we could just allow that importation of the finished product that's approved in another country.

DR. REBELLO: Any other comments? Questions?

(No response.)

DR. REBELLO: Online?

(No response.)

Committee Discussion and Vote

DR. REBELLO: The committee now will turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We will now proceed with the questions to the committee and panel discussions. I'd like to remind the public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel. After I read each question, we will pause for any questions or comments concerning its wording.

We'll proceed with our third question, which is a voting question with subsections. We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you've entered your vote. Please press the button firmly that corresponds to your vote. If you're unsure of your vote or wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone's completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we'll go around the room, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did, if you want to. We'll continue in the same manner until all questions have been answered or discussed.

For Question 3, Section 503A Bulk Drug Substances List, thymosin alpha-1-related bulk drug

substances. FDA's evaluation addressed two thymosin alpha-1-related bulk drug substances, which include one active moiety, thymosin alpha-1 free base, and two different BDSs. FDA proposes using a single voting question to address them as a group.

Do committee members agree to vote on thymosin alpha-1-related bulk drug substances discussed today, thymosin alpha-1 free base and thymosin alpha-1 acetate, as a group; yes or no? If any member of the committee votes no, FDA will take separate votes on each of these substances. If voting yes, committee members will vote on the substance as a group and will proceed to answer one additional voting question. If voting no, committee members will vote on each of the substances separately and will proceed to answer two voting questions.

Are there any issues or questions from the panel about the wording of the voting question?

(No response.)

DR. REBELLO: If there are no further

questions or comments concerning the wording of the question, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote. You'll have approximately 20 seconds to vote. Please press the button firmly. After you've made your selection, the light may continue to flash. If you're unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

DR. STEVENSON: Takyiah Stevenson, DFO. For the record, there are 20 yeses, 1 no, and 0 abstentions. I will hand it back to the chair.

DR. REBELLO: Since one or more panel member voted no, we will proceed with Questions 3B and 3C. Now that the vote is complete, we'll go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record.

DR. DURHAM: Todd Durham. I voted yes.

DR. VAIDA: Allen Vaida. I voted yes.

DR. BOGNER: Robin Bogner. I voted no.

DR. SERUMAGA: Brian Serumaga. I voted yes.

DR. REBELLO: Elizabeth Rebello. I voted yes.

DR. GURA: Kathy Gura. I voted yes.

DR. McELHINEY: Linda McElhiney. I voted yes.

DR. FENSKY: Tim Fensky. I voted yes.

DR. PAU: Alice Pau. I voted yes.

DR. GHANY: Marc Ghany. I voted yes.

DR. CZAJA: Mark Czaja. I voted yes.

DR. MONGE: Cecilia Monge. Yes.

DR. SIBERRY: George Siberry, yes because nothing in the presentation or discussion considered either of these differently from the other. Thanks.

DR. CLARK: Nina Clark. I voted yes.

DR. KRIS: Mark Kris. I voted yes.

DR. REBELLO: Dr. Gulur?

DR. GULUR: Padma Gulur. I voted yes.

DR. REBELLO: Dr. Corbett?

DR. CORBETT: Dr. Corbett. I voted yes.

DR. REBELLO: Dr. Gans?

DR. GANS: I voted yes.

DR. REBELLO: Dr. Gupta?

DR. GUPTA: I voted yes.

DR. REBELLO: Dr. Brian Lee?

DR. B. LEE: Brian Lee. I voted yes.

DR. REBELLO: Dr. Janet Lee?

DR. J. LEE: Janet Lee. I voted yes.

DR. REBELLO: Great. Thank you.

Since one or more panel members voted no, we will proceed with Questions 3B and 3C.

Question 3B, Section 503A Bulk Drug Substances List, thymosin alpha-1-related bulk drug substances. FDA is proposing that thymosin alpha-1 free base not be included on the 503A Bulks List. The question asks, should thymosin alpha-1 free base be placed on the list? If voting yes, you're recommending FDA should place thymosin alpha-1 free base on the 503A Bulks List. If voting no, you're recommending the FDA should not place thymosin alpha-1 free base on the 503A Bulks List.

If a substance is not on the list when the

final rule is promulgated, compounders may not use the drug for compounding under Section 503A unless it becomes a subject of an applicable USP, or National Formulary monograph, or a component of an FDA-approved drug.

Are there any issues or questions from the panel about the wording of the voting question?

Actually, Dr. Corbett, has a question.

Dr. Corbett?

DR. CORBETT: I think it's just a clarification from the previous conversations. So just confirming if this is a yes, it should be placed on the list, or no. And then let's hypothetically say it's a yes, we are not voting towards the specificity in the code as far as indication, dosing, any of that; is that true?

MS. BORMEL: This is Gail Bormel. That's true. If you vote yes, you would be recommending placing thymosin alpha-1 free base on the 503A Bulks List, and there are no parameters of route of administration or dosage.

DR. CORBETT: Thank you.

DR. REBELLO: Are there any other questions from the panel about the wording of the voting question?

(No response.)

DR. REBELLO: If there are no further questions or comments concerning the wording of the question, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote. As a reminder, you'll have approximately 20 seconds to vote. Press the button firmly. After you make the selection, the light may continue to flash.

(Voting.)

DR. STEVENSON: Takyiah Stevenson, DFO. For the record, there are 4 yeses, 17 noes, and 0 abstentions. Thank you.

DR. REBELLO: Now that the vote is complete, we'll go around the table, and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record.

DR. DURHAM: Todd Durham. I voted no.

DR. VAIDA: Allen Vaida. I voted no.

DR. BOGNER: Robin Bogner. I voted yes. I struggle all the time with access versus quality, and in this case I fell toward access.

DR. SERUMAGA: Brian Serumaga. I voted no.

DR. REBELLO: Elizabeth Rebello. I voted no.

DR. GURA: Kathy Gura. I voted no.

DR. McELHINEY: Linda McElhiney. I voted yes.

DR. FENSKY: Tim Fensky. I voted yes.

DR. PAU: Alice Pau. I voted no.

DR. GHANY: Marc Ghany. I voted no.

DR. CZAJA: Mark Czaja. I voted no.

DR. MONGE: Cecilia Monge. I voted no because of lack of evidence of efficacy.

DR. SIBERRY: George Siberry. I voted no for the same reason, lack of evidence of efficacy.

DR. CLARK: Nina Clark. I voted no also due to the low-quality efficacy data that I thought was well summarized by the FDA.

DR. KRIS: Mark Kris. I voted no because

curative therapies are now available for some of these conditions, and I would definitely want those curative therapies to be offered first.

DR. REBELLO: Dr. Gulur?

DR. GULUR: Padma Gulur. I voted no for reasons already stated.

DR. REBELLO: Dr. Corbett?

DR. CORBETT: I voted yes, and I, too, very much struggled with this decision. The reason for voting yes, it was an excellent summary on the efficacy of the conditions that were presented. I would not necessarily support them in any of the clinical trials and data that was submitted, but being an integrated health doctor in a supplement world, I do kind of struggle with availability, I think similar to what Dr. Bogner listed around availability and purity, and just decided to trust my colleagues that are prescribers and compounding pharmacists to do the right thing. I realize I would probably be in the minority, but I appreciate this was a really great summary and presentation by the FDA. Thank you.

DR. REBELLO: Dr. Gans?

DR. GANS: Hi. I voted no, but that is not to say that I didn't really appreciate the presentations for those who are in support of this. I didn't see much of a way in which this vote for compounding would actually change since it's already in use, and I think that if there are all those prescriptions already being used, that should be studied in those cases. And given that that's not out in the scientific world, we really need to know more about this.

Case reports are really important, but it looked like when there were larger studies, the efficacy of these -- albeit in the ones that were studied. And I agree that chronic disease and primary immunodeficiency still need to potentially have access to this and other forms, but I want to make sure that people understand its value before just prescribing it, which seems is being done at the moment. So I really support the scientific investigation into important peptides such as Ta1.

DR. REBELLO: For those of you that I'm

calling out, please state your full name, and then your vote.

Dr. Gupta?

DR. GUPTA: Thank you. I voted no. I struggled with this answer. I really deeply am for patients and for access, but I do really believe that the rigor is necessary for patients. They deserve the due diligence for these products to ensure safety and to ensure efficacy of these products at various doses and formulations, given what we heard today. Thank you very much.

DR. REBELLO: Dr. Brian Lee.

DR. B. LEE: Brian Lee. I voted no. I think that the public deserves to have access to drugs that have shown efficacy and that have been shown to be safe, and I think that the data demonstrated today has not met that bar.

DR. REBELLO: Dr. Janet Lee?

DR. J. LEE: Janet Lee. I voted no.

DR. REBELLO: So to summarize, the majority of the votes were yes based on a lack of evidence, and those that voted no cited two issues: one,

access, and two, availability. Sorry. The majority was no. Correct.

Next, we'll proceed with Question 3C. Question 3C, Section 503A Bulk Drug Substances List, thymosin alpha-1-related bulk drug substances. FDA is proposing that thymosin 1 alpha acetate not be included on the 503A bulks list. The question today is should thymosin alpha-1 acetate be placed on the list? If voting yes, you're recommending FDA should place thymosin alpha acetate on the list. If voting no, you're recommending that FDA should not place thymosin alpha-1 acetate on the 503A bulks list.

If the substance is not on the list when the final rule is promulgated, compounders may not use a drug for compounding under Section 503A unless it becomes a subject of an applicable USP, or National Formulary monograph, or component of an FDA-approved drug.

Are there any issues or questions from the panel about the wording of the voting question?

(No response.)

DR. REBELLO: If there are no further questions or comments concerning the wording of the question, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote. As a reminder, if you're unsure of your vote or wish to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

DR. STEVENSON: Takyiah Stevenson, DFO. For the record, there are 4 yeses, 17 noes, and 0 abstentions. Thank you.

DR. REBELLO: Now that the vote is complete, we'll go around the table and have everyone who voted state their name, vote, and if you want to, the reason why you voted as you did into the record.

DR. DURHAM: Todd Durham. I voted no.

DR. VAIDA: Allen Vaida. I voted no.

DR. BOGNER: Robin Bogner. I voted no.

DR. SERUMAGA: Brian Serumaga. I voted no.

DR. REBELLO: Elizabeth Rebello. I voted

no.

DR. GURA: Kathleen Gura. I voted yes.

DR. McELHINEY: Linda McElhiney. I voted yes because I think there are some rare indications where patients need access to this drug.

DR. FENSKY: Tim Fensky. I voted yes.

DR. PAU: Alice Pau. I voted no.

DR. GHANY: Mark Ghany. I voted no.

DR. CZAJA: Mark Czaja. I voted no.

DR. MONGE: Cecilia Monge. I voted no.

DR. SIBERRY: George Siberry. I voted no.

DR. CLARK: Nina Clark. I voted no.

DR. KRIS: Mark Kris. I voted no.

DR. REBELLO: And online, Dr. Gulur?

DR. GULUR: Thank you. Padma Gulur. I voted no, and I would like to take a minute to just go over the decision. As many have stated, it was not an easy decision because access is something we would all like to ensure patients here in the United States have to drugs and compounds that could help them, especially with rare diseases. I want to thank the presenters who advocated strongly

for this and brought broad data; however, the data was not adequate to ensure the safety and efficacy of this drug when compared to the FDA presentation. That said, we do applaud those efforts.

The argument that we should be manufacturing this here and to provide access to our patients is valid, but on the flip side, that is exactly what consumers here -- and I think that's what Dr. Gupta was alluding to. Consumers of the United States who consume products that are available here assume that they are safe. And while the compounders, I'm sure, are making every effort on their part to do so, as the FDA pointed out, this is really a bulk drug substance sourcing, and since most of the sourcing is not in the United States, that is concerning. So for those reasons, I voted no.

I also wanted to take this opportunity to thank Dr. Rebello for stepping in for me at the last minute, so thank you very much.

DR. REBELLO: Thank you.

Dr. Corbett?

DR. CORBETT: Hi. Amanda Corbett. I voted

yes for similar reasons as I've mentioned before. Thank you.

DR. REBELLO: Dr. Gans?

DR. GANS: Dr. Hayley Gans. I voted no again for many of the similar reasons. In addition, because putting on in bulk doesn't in any way help with decisions on how to use it, so we need all of that to be part of an application to the FDA.

DR. REBELLO: Dr. Gupta?

DR. GUPTA: Thank you. Dr. Gupta. I voted no for the same reasons already stated.

DR. REBELLO: Dr. Brian Lee?

DR. B. LEE: Brian Lee. I voted no.

DR. REBELLO: Dr. Janet Lee?

DR. J. LEE: Janet Lee. I voted no for the same reasons eloquently stated by others.

DR. REBELLO: Great. Thank you.

I just want to take the time to thank Dr. Takyiah Stevenson, who's gone above and beyond in making this meeting happen today. I want to thank all of you for being present for the

presenters, both on the FDA side, on both sides. I want to wish you safe travels.

Before we adjourn, are there any last comments from the FDA?

MS. BORMEL: This is Gail Bormel. I wanted to personally thank everybody for coming today and for their expertise, and taking the time out to participate in this very important advisory committee meeting.

Adjournment

DR. REBELLO: Well, with that, we will now adjourn the meeting. Thank you.

(Whereupon, at 3:35 p.m., the topic 3 session was adjourned.)