

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
103928Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 2, 2004
From: Dale Slavin, Ph.D. OTRR/DARP
Subject: NeutroSpec - PMCs
To: BLA STN 103928/0 Palatin Technologies

I called Dr. Kaushik Dave and told there were a few last minor changes to the PI these were all format changes except for the addition of the word antibody in line 13 and the removal the discussion of the multicenter trial to be the clinical trial (see Clinical Studies). I sent him a redlined copy of the PI and Palatin accepted all the changes in a subsequent e-mail. I also requested that Palatin propose a date for the submission of their protocol for PMC 5. Dr. Dave proposed the date of October 31, 2005.

7 Page(s) of Draft Labeling have been Withheld in Full as b4
(CCI/TS) immediately following this page

LICENSING ACTION RECOMMENDATION

Applicant: Palatin Technologies, Inc. STN: 103928/0

Product:

Fanolesomab, Technetium (99m Tc) Fanolesomab

Indication / manufacturer's change:

Technetium (99m Tc) Fanolesomab is indicated for scintigraphic imaging of patients with equivocal signs of appendicitis who are five years of age or older.

- Approval:
- Summary Basis For Approval (SBA) included
- Memo of SBA equivalent reviews included
- Refusal to File: Memo included
- Denial of application / supplement: Memo included

RECOMMENDATION BASIS

- Review of Documents listed on Licensed Action Recommendation Report
Inspection of establishment
BiMo inspections completed
Review of protocols for lot no.(s)
Test Results for lot no.(s)
Review of Environmental Assessment
Review of labeling
FONSI included
Categorical Exclusion
None needed

CLEARANCE - PRODUCT RELEASE BRANCH

- CBER Lot release not required
Lot no.(s) in support - not for release
Lot no.(s) for release
Director, Product Release Branch

CLEARANCE - REVIEW

Review Committee Chairperson: [Signature] Date: 7/2/04

Product Office's Responsible Division Director(s)*: [Signature] Date: 7/2/04

[Signature] Date: July 1, 2004

DMPQ Division Director*: [Signature] Date: June 29, 2004

* If Product Office or DMPQ Review is conducted

CLEARANCE - APPLICATION DIVISION

- Compliance status checked
- Acceptable
- Hold
- Cleared from Hold
Date: 7-1-04

Compliance status check Not Required
Regulatory Project Manager (RPM): [Signature] Date: 7-1-04

Responsible Division Director (where product is submitted, e.g., application division or DMPQ): [Signature] Date: 5-6-05

Swider, Marlene (CBER)

From: Hoyt, Colleen
Sent: Wednesday, June 30, 2004 2:02 PM
To: Swider, Marlene (CBER)
Cc: Buhay, Nicholas; Renshaw, Carolyn; Slavin, Dale; Cruz, Concepcion; Rivera Martinez, Edwin; Montemurro, Ann M
Subject: Compliance Checks for DSM Biologics and Palatin Technologies, Inc.
Importance: High

The Investigations and Preapproval Compliance Branch has completed the review of the compliance check request below. There are no pending or ongoing compliance actions that would prevent approval of STN 103928/0 at this time. The preapproval inspections of DSM Biologics, The Netherlands, and Palatin Technologies, Inc., Cranbury, NJ, conducted on 1/26-2/4/04 and 3/10-12/04, respectively, have been classified VAI and approval has been recommended. Corrective actions to the 483 observations found during these inspections will be verified upon future GMP inspections conducted by Team Biologics.

Colleen F. Hoyt
Investigations and Preapproval Compliance Branch
Office of Compliance, CDER
(301) 827-8980

-----Original Message-----

From: Swider, Marlene (CBER)
Sent: Tuesday, June 29, 2004 2:59 PM
To: Hoyt, Colleen
Cc: Buhay, Nicholas; Renshaw, Carolyn; Slavin, Dale
Subject: Compliance Checks for DSM Biologics and Palatin Technologies, Inc.

Please provide us with compliance check for the following firms:

DSM Biologics
Zuiderweg 72/2
P.O. Box 454
9700 AL Groningen
The Netherlands

FEI 3002608687 (EIR completed and received last week along with signatures)

and,

Palatin Technologies, Inc.
4-C Cedar Brook Drive
Cedar Brook Corporate Center
Cranbury, New Jersey 08512

FEI 3001642225 (EIR still in draft. Planned to be delivered tomorrow.)

Both firms above are under STN No. 103928/0.5003 for Class 2 response to 9-25-00 complete response letter and their product is LeuTech (RB5 IgM).

Thanks,

Marlene Swider



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: June 30, 2004
From: Dale Slavin, Ph.D. OTRR/DARP
Subject: NeutroSpec - PMCs
To: BLA STN 103928/0 Palatin Technologies

FDA
Kassa Ayalew
Louis Marzella
Lydia Martynec
Dale Slavin

We spoke to Dr. Kaushik Dave and representatives of Palatin and discussed some changes to the PMCs that had been faxed on June 25, 2004. Dr. Martynec explained that she wanted the pediatric dosimetry study to be done in pediatric patients and that the patients should be stratified in 3 year age groups. She stated that Palatin had a protocol in place with Dr. Kipper, but she was aware Dr. Kipper had left the clinical site. She and told Palatin the study could be done in 12-18 pediatric patients (4-6 per group). Palatin agreed and felt that the study was acceptable and that it could be done. I stated that I would e-mail the postmarketing commitments and that Palatin could look these over and schedule a telecon if they needed to discuss these PMCs or agree to them if they felt these were acceptable. We also went over some other very minor formatting a word changes to the PI (Palatin agreed to make all the changes). I subsequently e-mailed him the PMCs with the caveat that we may make some minor wording changes but the overall meaning would remain. Follow-up – Palatin agreed to the PMCs as written.

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

1. To conduct an open-label single center pediatric dosimetry study to assess the safety, pharmacokinetics and pharmacodynamics of Technetium (99m Tc) Fanolesomab in 12 to 18 pediatric patients, 5 to 16 years of age with equivocal signs and symptoms of appendicitis. Pediatric patients will be segregated into 3 year age groups (5 to 8, 9 to 12, and 13 to 16 years of age) and each age group will include four to six patients. Whole body images will be used to assess organ uptake and excretion of radioactivity. Pharmacokinetics of Technetium (99m Tc) Fanolesomab including blood pool clearance and clearance half-lives will be determined by drawing patient blood samples. The final study protocol will be submitted by September 15, 2004. Patient enrollment will be initiated by February 1, 2005, the last patient will be enrolled and the study will be completed by January 20, 2006, and the final study report will be submitted by June 25, 2006.
2. To conduct an open-label multicenter study to assess the safety and efficacy of Technetium (99m Tc) Fanolesomab in approximately 100 patients with equivocal signs and symptoms of appendicitis and who have polymorphonuclear leukocyte (PMN) counts at or below the lower limit of normal (neutropenia $n \geq 45$) or at low normal levels ($< 3,000/\text{mm}^3$) at the time of enrollment in the study. The final study protocol will be submitted by September 15, 2004. Patient enrollment will be initiated by February 1, 2005, the last patient will be enrolled and the study will be completed by January 15, 2006, and the final study report will be submitted by June 15, 2006.
3. To conduct an assay validation study with patient samples, and provide the data supporting a validated quantitative immunogenicity assay for the detection of a patient immune response (anti-drug binding antibodies) to Technetium (99m Tc) Fanolesomab by January 31, 2006.
4. To conduct a study on the immunogenicity of Technetium (99m Tc) Fanolesomab in patients using a validated assay (PMC #3). The method of storage of archived patient serum samples from completed clinical studies will be assessed to determine the suitability of using these samples in the validated quantitative immunogenicity assay. If these samples are unsuitable for immunogenicity testing purposes, then serum samples will be collected from ongoing and/or additional clinical studies. The sample size of the study will be sufficient to exclude an incidence of anti-drug antibody development $> 10\%$. The study will be initiated January 31, 2006, and will be completed December 31, 2006. The final study report will be submitted June 30, 2007.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: June 25, 2004
From: Dale Slavin, Ph.D. OTRR/DARP
Subject: NeutroSpec - PI and CMC requests for info
To: BLA STN 103928/0 Palatin Technologies

Kay Schneider faxed Dr. Kaushik Dave the initial PMCs (clinical and manufacturing) on June 25, 2003

TELECON MEMO

Date: June 22, 2004
From: Chana Fuchs, Ph.D. DMA/OPB
Subject: June 22, 2004 telecon with Palatin Technologies
To: STN 103928/0.5003
Participants: FDA/OBP/DMA: Chana Fuchs,
Palatin: Kaushik Dave



I called Palatin about:

1. Drug product endotoxin specification. The current specification palatin has put in place is (b) (4) EU/ug. Although this has as validated by the rabbit pyrogen test, from a cGMP perspective this does not reflect their experience with the highest levels at (b) (4) EU/ug for the first couple of lots followed by all lots at (b) (4) EU/ug. Palatin agreed to lower the specification to (b) (4) EU/ug, and will re-assess this level as part of the PMCs. (b) (4)

2. stability

a. I confirmed that Palatin is requesting stability dating of :

DS - (b) (4)
IDP (b) (4)
DP - 24 mon @ 2-8
NeutroSpec kit - (b) (4)

Dr. Dave confirmed that Cenolate has a shelf life of (b) (4) from Abbot, and that for the kit they will use cenolate that has (b) (4) expiration dating left over.

b. I had noticed from stability report SSR 005.01 that the stability results for (b) (4) (b) (4) for all three lots showed a consistent decrease in pH of 0.3, although still within specifications at the (b) (4) time point. Therefore, if Palatin should release a lot at within 0.2 pH units from the lower pH range specified, that lot would fail the stability. Since I had seen that effects on the product (aggregation and fragmentation) occur at much higher and lower pH ranges, I suggested that for stability studies Palatin lower their specifications for pH to prevent lot failure.

3. It was unclear from the validation report if shipping validation from Ben Venue to distributor was done on vials or on kits. Additionally, I noted that the validation study to show that a temperature of 2-8°C can be maintained during shipping was done when outside temperatures ranged from 10-20°F. this is colder than the 2-8°C they were trying to maintain and the deviation occurred on the bottom end of the temperature range. What they did not do is show that they can maintain the upper temperature limit to below 8°C when they are shipping at the high temperatures of summer. Dr. Dave confirmed that shipping validation was done on vials and not on kits, which he maintains is a worst case scenario. As for the temperature range, they had to conduct the shipping validation in the winter and he agrees it doesn't show that they can maintain the product at the appropriate cold temperatures during hot weather.

An additional point regarding the shipping validation was that validation from Ben Venue was to (b) (4) Venu to (b) (4), but the mode of transportation will be the same. Palatin is writing a protocol to capture the 1st 3 shipment in order to come up w/ data for the final kit, pallet configuration etc., and shipping will always contain templates.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: June 22, 2004
From: Dale Slavin, Ph.D. OTRR/DARP *DS*
Subject: NeutroSpec - PI and CMC requests for info
To: BLA STN 103928/0 Palatin Technologies

I spoke to Dr. Kaushik Dave and requested that he supply information regarding the assembly of the NeutroSpec kit and the manufacture of other products with the same space used to manufacture fanolesomab. He stated that the assembly of the kits is done at Ben Venue and is on page 4-95 of volume 1.4 of the original BLA. He stated that Ben Venue would probably be in contact with us regarding the manufacture of other products within their facility. He stated that he had comments regarding our revisions to the PI.

These included that the NeutroSpec name is trademarked not registered. I stated that he could change. He stated that Palatin for consistency will use single-use vial versus single dose. I stated this is fine. He stated that he would supply all the comments in an e-mail. I asked him about the shelf life of Cenolate and he stated it had a shelf life of (b) (4) if stored at (b) (4).

I asked if the expiry would then be based on the fanolesomab and he confirmed.

He asked about the PMCs and I stated that these are still under discussion but I hoped to have them by Tuesday of next week.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: June 18, 2004
From: Dale Slavin, Ph.D. OTRR/DARP
Subject: NeutroSpec - PI
To: BLA STN 103928/0 Palatin Technologies

I spoke to Dr. Kaushik Dave and told him that I would e-mail him the changes to the package insert. I subsequently e-mailed him and Jerry Orehostky a clean copy of the PI and a document compare copy in order that they could compare the PI that Palatin sent in January of 2004 to the copy we were returning. I did inform him that the revisions were extensive. I have attached the document compare PI.

28 Page(s) of Draft Labeling have been Withheld in Full as
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: June 15, 2004
From: Dale Slavin, Ph.D. OTRR/DARP 
Subject: NeutroSpec - PI o
To: BLA STN 103928/0 Palatin Technologies

I spoke to Dr. Kaushik Dave who questioned our request to

(b) (4)

(b) (4)

I also explained that I thought the PI should be back to him on Friday June 18, 2004. He asked about the PMCs and I explained that I had seen a few proposed but that I did not know what these were going to be and how many would be requested.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 28, 2004
From: Dale Slavin, Ph.D. OTRR/DARP *DS*
Subject: DSM facility 483 storage issues
To: BLA STN 103928/0 Palatin Technologies

Kaushik Dave called me to ask to [REDACTED]

(b) (4)

[REDACTED] . I
asked about putting the barcode on separately or in a different space. I asked about reducing
the size of the tradename. I asked them the size of the vial [REDACTED] We ended the call with
Kaushik Dave would see what Palatin could do.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
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Memorandum

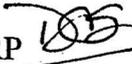
Date: May 18, 2004
From: Dale Slavin, Ph.D. OTRR/DARP 
Subject: DSM facility 483 storage issues
To: BLA STN 103928/0 Palatin Technologies

I spoke to Kaushik Dave regarding their responses to the lack of storage space issue cited in the DSM 483. I asked him to send in Palatin's response to those issues as a hard copy to the file and I would move those through to the TFRB group. He explained that their plans were to add a 400 m² module and at a later date expand. He said he would send me their intention letter. He also informed me that Abbott labs had change their name to Hospira and that this would affect the Cenolate label as the name would no longer be Abbott but Hospira and the NDC # would also change. He stated he would send in the amendment. I stated that this would be fine.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 11, 2004
From: Dale Slavin, Ph.D. OTRR/DARP 
Subject:  (b) (4) tradename unacceptable
To: BLA STN 103928/0 Palatin Technologies

I spoke to Kaushik Dave and explained that the  (b) (4)

 I explained that DMETS and DDMAC were beginning their review of NeutroSpec.

TELECON MEMO

Date: April 27, 2004
From: Chana Fuchs, Ph.D. DMA/OPB
Subject : April 27, 2004 telecon with Palatin Technologies
To: STN 103928/0.5003
Participants: FDA/OBP/DMA: Chana Fuchs,
Palatin: Kaushik Dave



Dr. Dave called wanting to know how the review is going.

I requested clarification on the information he submitted. In the 3/25/04 e-mail about hold time for the (b) (4), Palatin confirmed revising the hold time from (b) (4) in the 4/16/03 e-mail for the differences in production parameters from the original BLA, the table still indicates (b) (4). Dr. Dave explained that the table reflected the method for the 3 conformance lots. The change to (b) (4) was made after these were produced in response to our comments so is not included.

For the method to be licensed, this will change. additionally, in process bioburden specifications will be changed for the license to reflect our agreements.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 27, 2004
From: Dale Slavin, Ph.D. OTRR/DARP 
Subject: Review deadlines o
To: BLA STN 103928/0 Palatin Technologies

I spoke to Dr. Carl Spana CEO and Steve Wills they wanted my assurance that there were no show-stoppers for moving forward towards an approval. I told them that at this time I did not foresee any problems. I explained that everything was under review. They were concerned about product issues and I told them that as far as I knew product was reviewing the data. They asked when they could expect to see the PI. I stated that I was unsure when would finish our revisions but that I had seen comments to the PI and I was working on the second round of the vial, carton and diluent packages and I would try to get those out to them.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 26, 2004
From: Dale Slavin, Ph.D. OTRR/DARR 
Subject: Review deadlines o
To: BLA STN 103928/0 Palatin Technologies

Kaushik Dave called me in regard to requesting a meeting with Carl Spana and Steve Wills and to find out where FDA was in the review process. He wanted to know what they could say to the public. I said he could set up the call but that at the present time everything was under review and I would contact them as soon as I had something concrete to tell them.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 13, 2004
From: Dale Slavin, Ph.D. OTRR/DARP 
Subject: LeuTech Packaging and alt tradenames
To: BLA STN 103928/0 Palatin Technologies

Kaushik Dave called to request clarification on the packaging of fanolesomab kits.

(b) (4)

 They asked me if there was a way in which they could link the old LeuTech name with the yet proposed new tradename. I stated that this was a question for Marci Kiester and suggested that they talk to her. I also agreed to contact her in their behalf.

FDA
Dale Slavin

Palatin
Jerry Orehostky Palatin
Kaushik Dave
Jim Brodack



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 9, 2004
From: Dale Slavin, Ph.D. OTRR/DARP *DS*
Subject: LeuTech Tradename unacceptable
To: BLA STN 103928/0 Palatin Technologies

FDA had a telecon with representatives of Palatin, Mallinckrodt Tyco and an independent Nuclear Medicine physician. (b) (4)

[REDACTED]

Palatin understood FDA's reasoning and accepted that they would need to submit an alternative tradename. They asked if they could submit two names and FDA agreed to review two with an expedited review turnaround. This concluded the call.

FDA
Felicia Duffy
Earl Dye
Carol Holquist
George Mills
Dale Slavin
Marc Walton

Palatin
Carl Spana Palatin
Jerry Orehostky Palatin
Elaine Haines Tyco
Alicia Napoli Tyco
[REDACTED] (b) (4) Med Consult



Our STN: BL 103928/0

APR 08 2004

Palatin Technologies, Incorporated
Attention: Kaushik Dave, Ph.D., R.Ph.
Vice President of Product Development
4-C Cedar Brook Drive
Cedar Brook Corporate Center
Cranbury, NJ 08512

Dear Dr. Dave:

We have reviewed the January 5, 2004, amendment to your biologics license application submitted under section 351 of the Public Health Service Act for Technetium Tc 99m Fanolesomab, and we have the following comment:

We have considered your proposed proprietary name for Technetium Tc 99m Fanolesomab in consultation with CDER's Office of Drug Safety, Division of Medical Errors and Technical Support, and conclude that the proprietary name "LeuTech™" is unacceptable. The proprietary name LeuTech is unacceptable for the following reasons:

LeuTech has the potential to

(b) (4)

(b) (4)

[Large redacted area]

[Redacted] (b) (4)

[Redacted] (b) (4)

[Redacted] (b) (4)

Please submit an alternative proprietary name for our review.

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see <http://www.fda.gov/cder/biologics/default.htm>. Until further notice, however, all correspondence should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

If you have any questions, please contact the Regulatory Project Manager, Dale Slavin, Ph.D., at (301) 827-5101.

Sincerely,



Earl S. Dye, Ph.D.
Director
Division of Review Management and Policy
Office of Drug Evaluation VI
Office of New Drugs
Center for Drug Evaluation and Research

CONCURRENCE PAGE

Letter Type: Other (OT)

Summary Text: Proprietary Name Review Letter

SS Data Check:

- **Communication**

RIS Data Check:

cc: HFM-585/DRMP-BLA Files
HFM-588/K. Schneider
HFM-588/E. Dye
HFM-585/D. Slavin
HFM-558/D. Frucht
HFM-555/C. Fuchs
HFM-588/L. Epps
HFM-573/L. Martynec
HFD-328/M. Swider
HFD-328/C. Renshaw
HFM-579/M. Green
HFM-582/K. Ayalew
HFM-582/L. Marzella
HFM-650/L. Johnson
HFM-219/S. Misra
HFD-420/C. Holquist
HFD-420/A. Mahmud
HFD-420/F. Duffy
HFD-40/A. Haffer
HFD-420/S. Beam



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 6, 2004
From: Dale Slavin, Ph.D. OTRR/DARP 
Subject: LeuTech - Tradename requesting more reasons for uacceptability o
To: BLA STN 103928/0 Palatin Technologies

I spoke to Dr. Kaushik Dave and he mentioned that they felt the tradename was acceptable. He mentioned that he had spoken to Dr. George Mills of FDA. Palatin felt that because this drug was handled in a radiopharmacy that this would enough oversight and would negate any medication errors that could occur because of sound alike look alike names. Dr. Dave also asked about the PI and PMCs. I told him these were under review. They requested to have the Cenolate label reviewed sooner as they wanted to launch the manufacture of the diluent (Cenolate). I stated that we were reviewing these items, and I would try to get them back to them quickly but other items may take precedence based on review deadlines.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 2, 2004
From: Dale Slavin, Ph.D. OTRR/DARP 
Subject: LeuTech - Tradename unacceptable
To: BLA STN 103928/0 Palatin Technologies

I spoke to Dr. Kaushik Dave and he stated that Palatin would e-mail me a position paper arguing their case for keeping the LeuTech name.

Slavin, Dale

From: Kaushik Dave [kdave@palatin.com]
Sent: Friday, April 02, 2004 10:58 AM
To: beams@cder.fda.gov; SlavinD@cber.fda.gov
Subject: LeuTech Name

Dear Dr. Dale Slavin and Sammie Beam,

Please find attached Palatin's response to DMETS comments regarding the proprietary name LeuTech. Palatin awaits your rapid and favorable reconsideration of DMETS recommendation advising against the use of the LeuTech name.

Thanking you in advance.

Kaushik J. Dave R.Ph., Ph.D.
Vice President Product Development
Palatin Technologies Inc.
4-C Cedar Brook Drive
Cedar Brook Corporate Center
Cranbury, NJ 08512
Tel: 609-495-2227
Fax: 609-495-2202
[e-mailto:kdave@palatin.com](mailto:kdave@palatin.com)

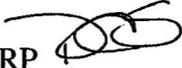
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immediately following this page

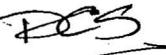


DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 1, 2004
From: Dale Slavin, Ph.D. OTRR/DARP 
Subject: LeuTech - Tradename unacceptable Fax
To: BLA STN 103928/0 Palatin Technologies

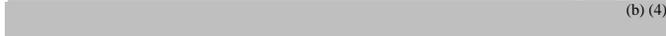
I sent the following fax to Palatin Technologies regarding the unacceptability of the LeuTech tradename.

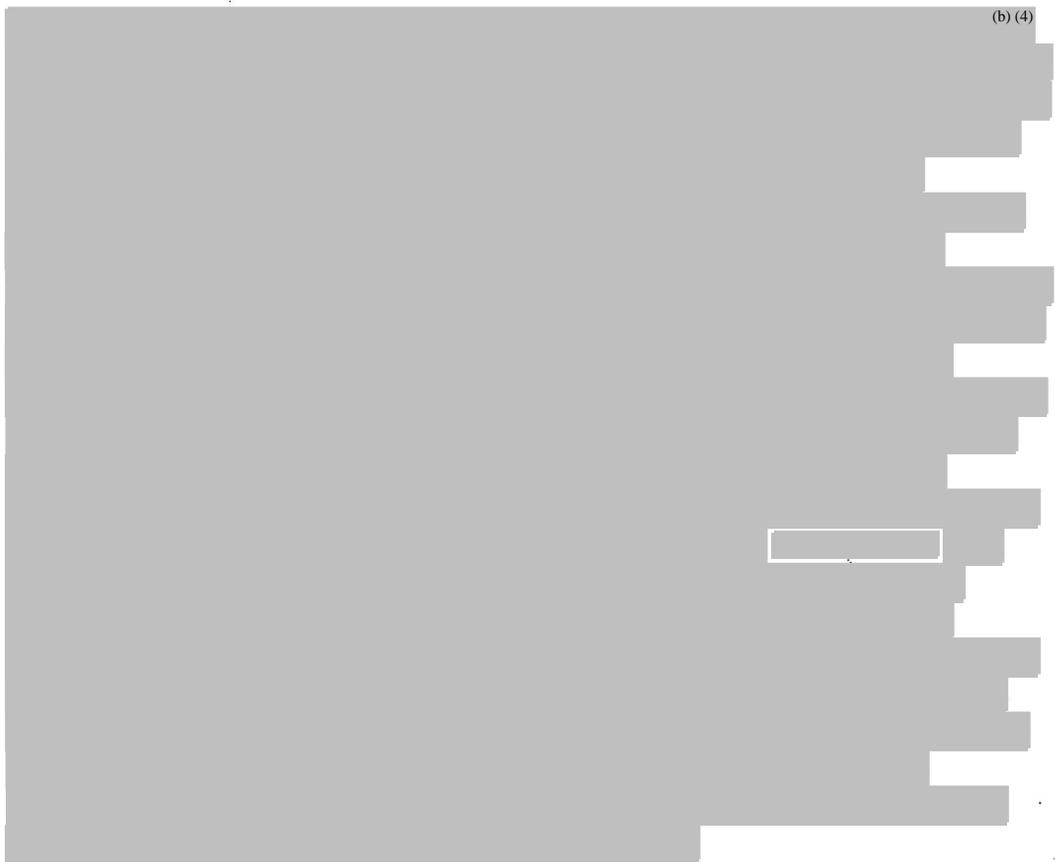
Fax to Palatin 

These are Office of Drug Safety, Division of Medication Errors and Technical Support (ODS/DMETS) comments regarding the proprietary name LeuTech™. A letter regarding the review of your proprietary name LeuTech™ for Technetium Tc 99m Fanolesomab will be forthcoming from FDA.

III. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proprietary name LeuTech because of

 (b) (4)

 (b) (4)

 (b) (4)







DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 1, 2004
From: Dale Slavin, Ph.D. OTRR/DARP *DS*
Subject: LeuTech - Tradename unacceptable
To: BLA STN 103928/0 Palatin Technologies

I spoke to Dr. Kaushik Dave and he stated that Palatin and Tyco wants to talk to Sammie Beam, regarding the LeuTech tradename. I explained that I felt this was inadvisable and that their best course was to move forward with a new tradename. Nevertheless, I stated I would make Sammie aware of their request. Additionally, I did tell them that they could move forward without a tradename and that they could simply use the USAN name until they had tradename approval.

Later in the day I called and left a message that Palatin should send in a rebuttal in writing. I strongly encouraged them to do this quickly. I stated that I would set up an informal telecon to go over their rebuttal.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 31, 2004
From: Dale Slavin, Ph.D. OTRR/DARP 
Subject: LeuTech - Tradename unacceptable
To: BLA STN 103928/0 Palatin Technologies

I spoke to Dr. Kaushik Dave and he stated that Palatin felt that the LeuTech name should be acceptable. Palatin had looked over the risk assessment for the prescribing name and felt LeuTech should be acceptable. I stated that they could talk to Sammie Beam, but that all the FDA offices were in agreement that the LeuTech name presented issues regarding medication errors.

TELECON MEMO

Date: March 31, 2004
From: Chana Fuchs, Ph.D. DMA/OPB
Subject: March 31, 2004 telecon with Palatin Technologies
To: STN 103928/0.5003
Participants: FDA/OBP/DMA: Chana Fuchs,
Palatin: Kaushik Dave,



Dr. Dave called to find out when our review is going to be done, because there is a nuclear med conference on June 19th and Palatin's objective is to hopefully launch the product at that meeting.

I told him that my intent is to get the review of their license application done as quickly as possible, but cannot commit to any deadline other than the PDUFA deadline.

I also requested that Palatin submit a table highlighting the differences between the 1999 and 2004 process for DS, IDP, and DP.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 30, 2004
From: Dale Slavin, Ph.D. OTRR/DARP *DS*
Subject: LeuTech - Tradename unacceptable
To: BLA STN 103928/0 Palatin Technologies

I spoke to Dr. Kaushik Dave and informed him that DMETS had reviewed Palatin's tradename and that it was not acceptable. Dr. Dave and Mr. Steve Wills the CFO called me back to ask whether there was any recourse. I reiterated what DMETS had stated in their review and stated that FDA would want to minimize any type of medication error. They asked if they could speak to the DMETS reviewers and I referred them to Sammie Beam.

Telecon

Sponsor: Palatin
BLA: 103928
Date: 3/30/04
Time: 10:35
Purpose: Information request
Participants:

David M. Frucht

Palatin: Kaushik Dave, Michael Battersby, Tom Yajcaji
FDA: David Frucht, Chana Fuchs

Summary:

David Frucht called Dr. Kaushik Dave yesterday (3/29/04) to clarify whether there was a typographical error in the table LeuTech In-Process Bioburden Specifications (March 25, 2004), as no bioburden rejection limit had been set for formulated drug. When it was determined that this was intentional, a meeting was set up to discuss this issue and other issues regarding in-process bioburden specifications. Palatin agreed to tighten bioburden specifications for R5 IgM virus (b) (4) and propose a reject limit for the formulated drug product. In addition, Dr. Fuchs requested clarification on several issues as follows:

- a. The contrived pool of harvest for mycoplasma and virus testing will be made from bags sampled just before the (b) (4)
- b. During manufacturing of drug product, bioburden is tested (b) (4), and sterility is tested for bulk after the (b) (4) DP lot release sterility testing is done on lyophilized vials.

TELECON MEMO

Date: March 25, 2004
From: Chana Fuchs, Ph.D. DMA/OPB
Subject: March 25, 2004 telecon with Palatin Technologies
To: STN 103928/0.5003
Participants: FDA/OBP/DMA: Chana Fuchs,
Palatin: Kaushik Dave

Dr. Dave called wanting feedback for information which he sent by e-mail. He will also send another e-mail and submit to the BLA a statement re reprocessing, as well as the change in hold times for the (b) (4) at ambient temps that Dave Frucht had requested. He also wanted to know when the CMC review will be complete. I said I cannot tell him that at the moment and it depends on the information provided us.

TELECON MEMO

Date: March 23, 2004
From: Chana Fuchs, Ph.D. DMA/OPB
Subject: March 23, 2004 telecon with Palatin Technologies
To: STN 103928/0.5003
Participants: FDA/OBP/DMA: Chana Fuchs,
Palatin: Kaushik Dave



I called Dr. Dave to request that the in process bioburden limits conversation not be postponed for too long since I will be out of the office for the beginning of April and would like to finalize this topic.

He will be sending us the following open-ended issues tomorrow:

1. Qualification of new HL60 and Raji cell banks knowing that the trigger point has already passed for qualifying a new one. Palatin wanted to find out what they need to address for qualification. I told them that qualification is dependent on how they use the cells. Qualification should include growth parameters, CD15 expression on the membrane, and whatever else is a critical parameter for the assay. Since they are planning to get a new vial of HL-60 cells from (b) (4) it may or may not have the same critical characteristics as their current cells and this is what they will have to assess. The bottom line is that they need to assure that when using the potency assay with the new cells the information they get for potency remains the same as that from the old cells.

2. Palatin is still working out bioburden w/ DSM. They are trying to come up w/ a table that encompasses all steps.

3. regarding sterility testing as per 21CFR 610 - at Ben Venu they test for sterility in process (i.e. bulk sterility) and final product. I mentioned that this was not represented on table 1-1.

4. regarding our previous discussions on characterization of (b) (4) Dr. Dave said that it dealt with Ref std qualification and not the comparability protocol. I reminded him that the discussion during inspection about ref. std qualification and analysis (b) (4) also dealt with comparability since this is what they have historically used to compare old to new lots. Palatin had not taken our advice/request and did not run the comparability assays side-by-side, rather they analyzed the lot release data and compared that to the other lots. In such cases, the only side-by-side information we can go on is the new lot compared to the reference standard that is run in the same assay, and therefore, ref. std qualification is relevant for comparability. In future changes, e.g. changes in (b) (4) media components etc. Palatin will have to analyze (b) (4) as part of the comparability. Therefore, the ref. std. (b) (4) profile is most relevant to comparability, and not necessarily to regular lot release.

As to the (b) (4) analysis question I had during the inspection - what are they looking at and how do they assess comparability of this parameter- this is used as an ID test by which they sort 3 peaks - more like a fingerprinting ID tests. The Ref std qualification is not quantitative, its just to make sure that the profile is similar.

According to Dr. Dave, MDS are the experts and they are the ones that told Palatin that the material is comparable. The assay: hydrolyze protein - get sugars - followed by derivitization by fluorescent tag, anion exchange column, gives profile which was compared w/ a previous ref std. They look at major peaks - retention time etc.

I told Kaushik that (b) (4) for us is more than an ID test, since changes in (b) (4) can effect PK, thereby potentially affecting the clinical efficacy and utility which they showed in their clinical trials. Additionally, changes in (b) (4) may impact immunogenicity of a product, which is a safety issue. Palatin will have to work at better characterization of the mAb structure (b) (4) patterns. They will have to also understand what they see in the assay because its not up to MDS to say the material are comparable, but up to Palatin and the FDA. Without knowing what they are looking at, this is not possible.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 22, 2004
From: Dale Slavin, Ph.D. OTRR/DARP 
Subject: Advertising
To: BLA STN 103928/0 Palatin Technologies

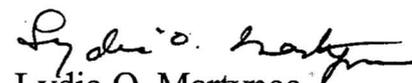
I spoke to Dr. Kaushik Dave and Dr. Dennis Earle of Palatin Technologies. We discussed whether they would need to submit advertising prior to launch. I referred them to Marci Kiester at DDMAC.

I also followed up with Marci and she explained that they would not need to submit prior to launch but they should submit the information at the time of launch, and that they must bear in mind that this is still subject to review. This is stated in the approval letter.

Addendum to File:

The original review was submitted to Dr. William Schwieterman in September 2000 for his review and signature. A signed copy of the review cannot be found in the file.

A significant time has elapsed between the completion of this review and the sponsor's completing the manufacturing changes in order to apply for a licensing the product. The reviewer's copy of the review submitted to Dr. Schwieterman was provided to Dr. Libero Marzella for his signature in order to complete the file.


Lydia O. Martynec

March 20, 2004

Telecon

Sponsor: Palatin
BLA: 103928
Date: 10/28/03
Time: 4:00 p.m.
Purpose: To schedule regular telecons
Participants:

David M. Frucht
3/19/04

FDA: Chana Fuchs, David Frucht
Palatin: Kaushik Dave

Summary:

Chana introduced me as a new reviewer on the team, and listed other product reviewers as well. We discussed tentative dates for facility inspections, in particular the DSM site. We explained that January or February would be best, and that was tentatively acceptable with Dr. Dave, but he would investigate the possibilities. Dr. Fuchs also explained that we would be inspecting Palatin's New Jersey facility, and possibly the Ben Venue in Bedford, Ohio. We also inquired about the timeline for submission of the next amendment regarding the third consistency lot and the comparability study. Dr. Dave thought that very early January 2004 would be the target date. In addition, we discussed having telecons every two weeks starting in December. Several days before the meeting we will communicate the topics to be discussed to maximize efficiency. On 11/25/03 I had further discussions with Dr. Dave to establish the telecon schedule (to start 12/2/03).



MAR 19 2004

Our STN: BL 103928/0

Palatin Technologies, Incorporated
Attention: Kaushik Dave, Ph.D., R.Ph.
Vice President of Product Development
4-C Cedar Brook Drive
Cedar Brook Corporate Center
Cranbury, NJ 08512

Dear Dr. Dave:

Please refer to your biologics license application submitted under section 351 of the Public Health Service Act for Technetium Tc 99m Fanolesomab.

We received your March 1, 2004, amendment to this application on March 3, 2004, and consider it to be a major amendment. Because the receipt date is within three months of the user fee goal date, we are extending the goal date by three months to July 2, 2004, to provide time for a full review of the amendment.

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see <http://www.fda.gov/cder/biologics/default.htm>. Until further notice, however, all correspondence should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

If you have any questions, please contact the Regulatory Project Manager, Dale Slavin, Ph.D., at (301) 827-5101.

Sincerely,

A handwritten signature in cursive script that reads "Earl Dye".

Earl S. Dye, Ph.D.
Director
Division of Review Management and Policy
Office of Drug Evaluation VI
Office of New Drugs
Center for Drug Evaluation and Research

CONCURRENCE PAGE

Letter Type: Major Amendment Acknowledgement Letter (MAA)

SS Data & RIS Data Check:

- **Communication**
- **Milestone: Major Amendment Close Date & Receipt Date In Ltr Should Match**

RIS Data Check:

- **Milestone: Confirm New Action Due Date (2 or 3 Month Extension)**

cc: HFM-585/DRMP-BLA Files
HFM-588/K. Schneider
HFM-588/E. Dye
HFM-585/D. Slavin
HFM-558/D. Frucht
HFM-555/C. Fuchs
HFM-588/L. Epps
HFM-573/L. Martynec
HFD-328/M. Swider
HFD-328/C. Renshaw
HFM-579/M. Green
HFM-582/K. Ayalew
HFM-582/L. Marzella
HFm-650/L. Johnson
HFM-219/S. Misra

Telecon

David M. Frucht

Sponsor: Palatin
BLA: 103928
Date: 3/18/04
Time: 10:30 a.m.
Purpose: Information request
Participants:

Palatin: Kaushik Dave, Michael Battersby, Tom Yajcaji
FDA: David Frucht, Chana Fuchs

Summary:

The discussions during this meeting focused on bioburden testing. Palatin confirmed that the bioburden testing shown in Table 1-1 referred to testing that followed the process step indicated in the left column. They agreed to tighten alert/action/rejection limits following the (b) (4)

(b) (4) will be added to the protocol and Palatin plans to maintain the acceptance criteria of NMT (b) (4) for that step. In addition, Palatin claimed that they do sterility testing of bulk product (b) (4). They will send us an update on this. We also requested that "response level 1 and 2" be updated to denote action, alert and rejection limits. After discussing these issues with DSM, they will discuss their proposal with FDA during the week of March 22, 2004.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 24, 2004
From: Dale Slavin, Ph.D. OTRR/DARP
Subject: February 24, 2004 - Internal meeting to discuss Palatin Package Insert for Technetium Tc 99m Fanolesomab that is "*indicated in scintigraphic imaging for the diagnosis of appendicitis in patients (five years and above) who have equivocal signs and symptoms.*" This is still under discussion?
To: BLA STN 103928/0 Palatin Technologies
Attachment of other Agenda items briefly touched upon at the end of the meeting.

FDA BLA Review Committee

Kassa Ayalew, M.D.
Leon Epps, Ph.D.
David Frucht, M.D.
Chana Fuchs, Ph.D.
Lydia Martynec, M.D.
Louis Marzella, M.D.
Satish Misra, Ph.D.
Dale Slavin, Ph.D.
Marc Walton, M.D., Ph.D.
Karen Weiss, M.D.

Regarding the proprietary name, the name can be used for the kit or for all the components mixed together to create the product.

Regarding the possibility of Aluminum toxicity Dave green will discuss with Palatin the justification for their wording.

Palatin will need to have in the precautions Neutropenia and Hypersensitivity and loss of imaging performance if drug is administered more than once. Will need to understand if there will be any repeat administrations.

Must have an immunogenicity sections.

Regarding clinical PMCs

BLA 103928/0 Tc 99m Fanolesomab Internal Labeling MTG 1-13-04

1. Perform dosimetry studies in (b) (4)
2. Neutropenia study
3. Long term follow-up on patients (lab work)

Telecon

David M. Frucht

Sponsor: Palatin
BLA: 103928
Date: 2/12/04
Time: 8:45 a.m.
Purpose: Information request
Participants:

Palatin: Kaushik Dave
FDA: David Frucht

Summary:

Dr. Dave informed me that he would call me later to confirm a date for our receiving the requested process validation.

Telecon



Sponsor: Palatin
BLA: 103928
Date: 2/12/04
Time: 2:00 p.m.
Purpose: Information request
Participants:

Palatin: Kaushik Dave
FDA: David Frucht

Summary:

Dr. Dave telephoned me to commit to FDA having possession of validation report by March 1, 2004. I read the following comment (and emailed it to him):

Palatin will be expected to submit to the FDA (with a copy sent directly to Dr. Fuchs) a comprehensive validation report for the manufacture of Leutech. This report should include the rationale for the small- and large-scale pre-validation/specification setting studies that were used to develop the specifications for the process parameters of the current production process that is being validated, along with the details of the pre-validation models. The parameters studied and the results of these pre-validation studies should be summarized and conclusions provided. The rationale for the final validation study protocol should be provided, along with the results and conclusions of this study. There should be a clear linkage for each step in the process between pre-validation studies, the final validation study and the manufacturing controls for the final manufacturing process.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 12, 2004
From: Dale Slavin, Ph.D. OTRR/DARP-185
Subject: Integrated Safety Summary, LeuTech Kit and name
To: BLA STN 103928/0 Palatin Technologies

I spoke to Dr. Kaushik Dave and Dr. Dennis Earle of Palatin Technologies. We discussed the submission of the new patient safety data on approximately 84 patients. They had not broken out the data set and had not analyzed it separately. I explained that they would need to do this. They agreed to supply this information in an additional amendment.

I asked them to please define whether the kit would be LeuTech or the monoclonal.

(b) (4)

I also explained that if they were submitting large amounts of data within three months of the final action date that they might be looking at the possibility of a major amendment submission. They assured me that none of their submissions in their view rose to that level. They stated that the other portion of the ISS would be in early the week of February 23, 2004.

Telecon

A handwritten signature in cursive script, appearing to read "David Frucht", is written in black ink and slanted upwards from left to right.

Sponsor: Palatin
BLA: 103928
Date: 2/11/04
Time: 4:30 p.m.
Purpose: Information request
Participants:

Palatin: Kaushik Dave, Mike Battersby
FDA: David Frucht, Steve Kozlowski, Patrick Swann, Chana Fuchs, Joe Kutza

Summary:

We discussed the timeline for the submission of process validation. Palatin reiterated that they plan to send FDA the data for consistency lot #3 on Monday. We informed Palatin that we would need a completed validation report as soon as possible (not just a table summarizing in-process data and certificates of analysis). This would not only include the 3rd consistency lot data, but a consolidated validation report discussing small and large scale pre-validation studies examining critical process parameters, the results of these studies, along with the resulting validation protocol with results and conclusions. Dr. Dave said that he would call me (DF) tomorrow with a date that we could expect this report.

Telecon

Sponsor: Palatin
BLA: 103928
Date: 2/10/04
Time: 4:00 p.m. (approximate)
Purpose: Information request
Participants:
 Palatin: Dr. Dave, Dr. Battersby
 FDA: David Frucht



Summary:

I called to get more information regarding submission dates. Dr. Dave provided me with the following timetable:

2/11/04 (first by email): responses to several CR points including immunogenicity assay.

2/16/04 or 2/17/04 (with separate FedEx to me): lot release information for 3rd consistency lot with Table I updated, leachable report for container comparability, lyophilization validation, shipping validation

They also informed me that the "formal" validation report regarding the production of drug substance and intermediate reduced drug substance would be available from DSM in mid-March. DSM was not presently planning to send any more prevalidation data other than what was sent in mid-January ("Process Validation Overview").



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 23, 2004
From: Dale Slavin, Ph.D. OTRR/DARP 
Subject: Integrated Safety Summary, Clinical data info request
To: BLA STN 103928/0 Palatin Technologies

Drs. Marzella, Ayalew and Slavin called Dr. Kaushik Dave of Palatin and discussed the additional patient safety data. We requested that the additional 88 patients (Palatin's estimate of patient data) be submitted as dataset that is both analyzed independent of the original dataset and as an integrated piece of the dataset. The clinical review will need to look at the new data independent of the previous data to ensure there are no aberrancies in the data. If the data is appropriate then it can be included in the larger set. Palatin was asked to file this piece of information electronically.

Additionally FDA is interested in the final patient outcome after study completion. PreImaging and PostImaging. FDA wants to know what was the true patient management outcome for both P-2 and P-3 studies. 97003 and 97004 appear to be the two studies.

Palatin was asked whether LeuTech proprietary name was the name used for fanolesomab or for the kit. Palatin responded that it was the kit name.

Telecon

Sponsor: Palatin

BLA: 103928

Date: 1/14/04

Time: 2:00 p.m. (approximate)

Purpose: Palatin initiated call to discuss submission timetables

Participants:

Palatin: Kaushik Dave, Michael Battersby

FDA: Chana Fuchs, David Frucht

A handwritten signature in black ink, appearing to read "David Frucht", is written diagonally across the upper right portion of the page.

Summary:

Palatin agreed to send FDA pre-validation data summaries describing critical process parameters to be tested during the validation studies on Monday January 19. Palatin also agreed to send FDA a comprehensive chart chronologically listing lot number assignments for the conformance lots during production. In addition, FDA requested that Palatin also provide in advance a detailed list of any manufacturing changes made since the time of the original BLA submission. Palatin informed FDA that the only changes that have been made were described in the 26 June 03 amendment.

Telecon

Sponsor: Palatin
BLA: 103928
Date: 1/15/04
Time: 1:30 p.m.
Purpose: Information request
Participants:



Palatin: Kaushik Dave, Michael Battersby, Tom Yajcaji
FDA: David Frucht

Summary:

I emailed Dr. Kaushik who called me back at 1:30 pm. I asked for clarification for bioburden data from pages 06/160, 06/165, 06/167, and 06/169. Specifically, I inquired at which steps samples were retained for bioburden testing. I was informed that pages 06/165, 06/167, and 06/169 likely represented bioburden levels in the

[Redacted text block]

(b) (4)
(b) (4)

Palatin committed to providing FDA with as much data as available regarding bioburden testing during these steps, including the actual number of cfu determined by higher dilutions, if available. Palatin also agreed to provide data regarding bioburden levels of other conformance lots at these steps as soon as possible.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 13, 2004; 3-5pm WOC 2 Conf Rm H 6th Fl

From: Dale Slavin, Ph.D. OTRR/DARP

Subject: **Internal Meeting Agenda** regarding FDA/BLA 103928/0 (Palatin, Technetium Tc 99m Fanolesomab) Labeling to discuss Package Insert

To: **FDA BLA Review Committee**
Kassa Ayalew, M.D.
Leon Epps, Ph.D.
David Frucht, M.D.
Chana Fuchs, Ph.D.
M. David Green, M.D., Ph.D.
J. Lloyd Johnson, Pharm.D.
Glen Jones, Ph.D.
Steven Kozlowski, M.D.
Kathy Lee, M.S.
Lydia Martynec, M.D.
Louis Marzella, M.D.
George Mills, M.D.
Satish Misra, Ph.D.
Carolyn Renshaw
Kay Schneider, M.S.
Dale Slavin, Ph.D.
Marlene Swider
Marc Walton, M.D., Ph.D.
Karen Weiss, M.D.
Hong Zhao, Ph.D.
Boguang Zhen, Ph.D.

Purpose: **To discuss the newly submitted (January 6, 2004) package insert and other pressing issues regarding this Class 2 resubmission.**

Final Action Due - April 2, 2004

BLA 103928/0 Tc 99m Fanolesomab Internal Labeling MTG 1-13-04

APPEARS THIS WAY ON ORIGINAL



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 13, 2004

From: Dale Slavin, Ph.D. OTRR/DARP 

Subject: January 13, 2004 - Internal meeting to discuss Palatin Package Insert for Technetium Tc 99m Fanolesomab that is "*indicated in scintigraphic imaging for the diagnosis of appendicitis in patients (five years and above) who have equivocal signs and symptoms.*" This is still under discussion?

To: BLA STN 103928/0 Palatin Technologies
Attachment of other Agenda items briefly touched upon at the end of the meeting.

FDA BLA Review Committee

Wendy Aaronson, M.S.
Kassa Ayalew, M.D.
Leon Epps, Ph.D.
David Frucht, M.D.
Chana Fuchs, Ph.D.
Kathy Lee, M.S.
Lydia Martynec, M.D.
Louis Marzella, M.D.
Satish Misra, Ph.D.
Anne Pilaro, Ph.D.
Dale Slavin, Ph.D.
Marc Walton, M.D., Ph.D.
Karen Weiss, M.D.
Boguang Zhen, Ph.D.

Regarding the Description section of the PI:

- Remove the  (b) (4) and add "to reconstitute and to radiolabel."
- Remove the sentence  (b) (4)



BLA 103928/0 Tc 99m Fanolesomab Internal Labeling MTG 1-13-04

- Two sentences (ll. 34-37 & 42-43) were suggested to be moved to the clin/pharm section and reworked.
- Line 62 regarding the pyrogen free statement this will need to be verified as the LAL has not been validated against ???.
- As discussed there is a CDER Guidance on imaging products
“www.fda.gov/cder/guidance/3646dft.pdf - 08-18-2003 - Text Version”

External Radiation Section

- Change (b) (4) to nano in line 75
- Line 79 change (b) (4) to 0.25 cm

Clinical Pharmacology Section

- Discussion centered on what are the target cell types that have surface expression of CD15.
- Polymorphonuclear neutrophils (PMNs), eosinophils and monocytes were all considered to have CD15 surface expression.
- Lines 135-140 – “clinical diagnostic images....” suggested that these sentences be rewritten and possibly moved?
- (b) (4) and we noted that we should check on all the references and make sure they have been reviewed.
- Change (b) (4) to ‘patient’

Pharmacokinetics Section

- Regarding cross-reactivity of Fanolesomab – there was discussion regarding inserting a table to explain cross-reactivity versus a paragraph. The question was raised as to whether Fanolesomab organ cross-reactivity was associated with resident macrophages and leukocytes.
- Free Tc 99m goes to the thyroid
- Discussed that PKs view the distribution of Technetium but not free MAb without Tc 99m. The PK of the MAb was not evaluated.

Metabolism section (agreed to remove)

Drug-Drug Interaction Section

- Discussed whether it was needed. If there were specific pharmacology studies it could be necessary.

Clinical Studies Section

- The study design was discussed in regard to whether it was designed to assess diagnostic performance of the agent or the clinical utility of the diagnostic performance of the agent.
- Lines 160-162. Regarding the blinded readers this needed to be clarified that the readers were blinded to the clinical information when they were assessing the images.
- Blinded reads were presented as an aggregate of 2 out of 3 reader agreement; it is not truly a mean readout. The sensitivity of the read varied between the readers and using of the data as “intent to treat” was employed because this provided the best-case scenario for Palatin.
- Because the blinded readers are less biased we should use their assessments.
- Lines 163-166. This sentence was changed around to read, “The study investigators had access to other diagnostic tests including CT scan, ultrasound and other modalities, and they were instructed not to rely on the imaging data.
- Lines 171-173. We discussed that confidence intervals (CI) should be included and that possibly this should be a table.
- Lines 180-182. Satish cautioned that these statements maybe a bit of a misrepresentation of the data.
- Lines 184-187. This was to be changed to possibly read “A supportive single arm ...fanolesomab..gave similar results and 50% of the patients had a final diagnosis of appendicitis.”
- PMC a postmarketing commitment to follow-up with randomized trials to assess Fanolesomab with new therapies and possibly how, if at all, would that change the management of the patient.

- Lines 200-201. Delete
- Louis and Kassa mad several tables and put these up for discussion insofar as the presentation of clinical management and disposition of data. Questions and thoughts regarding the tables on pages 9 and 10 were the following:
 - Without reconciling true outcome with the hypothetical outcome should any of the hypothetical be included – the answer was No.
 - Table 64 pool of both studies. This type of work-up a hypothetical disposition of what happened to each patient was done by Jay Siegel, and at the Advisory Committee there was a consensus that presentation of the data in this manner could be useful to the physician. As clarification the physicians did not have to act on the disposition. We do know the outcome but we do not know the management decision.
 - Regarding Table 43. A textual description may be better.
 - Among 30 patients with other infections 13 were read positive for appendicitis by imaging.
 - Regarding Table 44. This is an essential part of the clinical performance – should be in the clinical studies section?
- Lines 443-445. Rewrite to read “...scintigraphic imaging for the diagnosis of appendicitis in patients 5 years of age and older with equivocal signs of appendicitis.” (b) (4)



- PMC, possible postmarketing commitment to perform a pediatric study.
- We discussed whether the MAb should be single use or multiple use. No HAMA has been observed after one administration.
 - The HAMA assay controls are poor. Ab formation is a primary source of concern. Upon a second administration of MAb 5 of 30 patients developed HAMA.

BLA 103928/0 Tc 99m Fanolesomab Internal Labeling MTG 1-13-04

Regarding product information Chana clarified that the 3rd consecutive lot of study drug and all its validation data would come in within the review cycle and that we had agreed to review the data in this manner.

The meeting concluded with discussion of lines 242-244 on page 2-11, and how to better compose this section.

**BLA/NDA/PMA
Review Committee Assignment Memorandum**

IN: 103928/0

| |
|---|
| <input type="checkbox"/> Initial Assignment <input checked="" type="checkbox"/> X Change |
|---|

Applicant: Palatin Technologies, Inc.
 Product: Fanolesomab (Technetium Tc-99m Anti-CD15 Antibody)

Addition of committee members

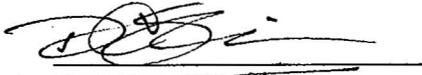
| Name | Reviewer Type* | Job Type | Assigned by | Date |
|------------------|------------------|------------------|----------------|----------|
| Dale Slavin | Reg. Coordinator | Admin/Regulatory | Kay Schneider | 10-2-03 |
| | Reviewer | Admin/Regulatory | | |
| Chana Fuchs | Reviewer | Product | Keith Webber | 10-2-03 |
| | Reviewer | Product | | |
| David Frucht | Reviewer | Product | Keith Webber | 10-22-03 |
| Kassa Ayalew | Chairperson | Clinical | Louis Marzella | 10-2-03 |
| | | Clinical | | |
| | | | | |
| | | | | |
| J. Lloyd Johnson | Reviewer | BiMo | Khin U. | 10-9-03 |
| | | Epidemiology | | |
| Marlene Swider | Reviewer | Facility | Carol Rehkopf | 10-6-03 |
| Felicia Duffy | Reviewer | Labeling | Alina Mahmud | 1-5-04 |
| | | Inspector | | |
| | | Labeling | | |
| | | Other | | |
| | | | | |
| | | | | |

Deletion of Committee Member

| Name | Reviewer Type* | Job Type | Changed by | Date |
|-----------------|----------------|----------|---------------|----------|
| Deborah Trout | Reviewer | Facility | Carol Rehkopf | 10-6-03 |
| Craig Doty | | | Kay Schneider | 10-2-03 |
| Mary Andrich | Reviewer | BiMo | Mary Andrich | 10-3-03 |
| Robert Lindblad | Reviewer | Clinical | | 10-3-03 |
| Carolyn Renshaw | Reviewer | Facility | | 10-22-03 |
| | | | | |
| | | | | |

*reviewer types: chairperson, consultant reviewer, regulatory coordinator, reviewer, and reg. project mgr (RPM)

Submitted by RPM:

Dale Slavin  1-5-04
 Name Printed _____ Signature _____ Date _____

Memo entered in RMS by: PH Date: 6/29/04 QC by: CJU Date: 6/30/04



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

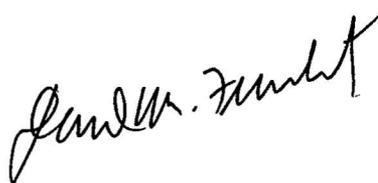
Date: December 29, 2003
From: Dale Slavin, Ph.D. OTRR/DARPA 
Subject: Electronic copy of PI; Integrated Safety Summary
To: BLA STN 103928/0 Palatin Technologies

Dr. Kaushik Dave of Palatin Technologies called me to tell me that the ISS has been completed but that it was done such that all the new patient data was incorporated and this data was not shown also as a separate analysis. I explained that per Drs. Marzella and Ayalew the data should be both incorporated and analyzed separately to determine if problems existed in the new patient safety data set. Dr. Dave stated that they would supply the information. He stated that he would send the updated PI with updated clinical safety data. He also stated that he would send the vial and carton labels, and that concluded our discussion.

Fascimile

Sponsor: Palatin
Date: 12/29/03
BLA: 103928

Kaushik J. Dave R.Ph., Ph.D.
Vice President Product Development
Palatin Technologies Inc.
4-C Cedar Brook Drive
Cedar Brook Corporate Center
Cranbury, NJ 08512



Dear Dr. Dave,

In addition to our previous information requests, FDA requests the following information from you regarding your responses to the CR letter:

- (1) Please address the following additional points regarding your immunogenicity assay:
 - a. Accuracy of the assay in the presence of human sera has not been addressed. Although an affinity purified anti-mouse IgM preparation positive control does not exactly mimic HAMA, it can be spiked at different concentrations into several negative patient sera and the assay results compared to those from the positive control diluted in buffer.
 - b. Repeatability (intra-assay variability) has not been appropriately assessed, as it appears to have been combined with inter-assay assessment. Data needs to be provided on the variability of estimates for samples repeatedly tested in the same assay. It is most important to test sera spiked with low levels of positive control.
 - c. Robustness, the capacity of a method to remain unaffected by small experimental variations in method parameters (e.g., timing, wash steps, temperature, reagent concentration), has not been correctly addressed. Only timing has been assessed. Please provide data regarding assessment of other parameters, including the use of different lots of reagents.
 - d. The testing scheme reports a positive result if the post-treatment sample reading is twice the pre-dose reading. Please provide data that this threshold is statistically justified and based on the variability of the assay.
 - e. Please address why goat anti-mouse Ig is used as the positive control and not anti-mouse IgM. Due to the pentameric nature of IgM, it is essential to assess the performance of an affinity purified anti-mouse IgM preparation in the assay.
- (2) Please provide the complete validation report supporting your Western Blotting assay for detection of host cell proteins. This report should include validation of the limit of detection for host cell proteins spiked into your product samples to be tested.

(3) Please list every production step where you allow re-processing to occur, along with validation reports for these re-processing steps.

Thank you for your attention to this matter.
Sincerely,

David Frucht, M.D.

Telecon



Sponsor: Palatin
BLA: 103928
Date: 12/17/03
Time: 2:00 p.m.
Purpose: Information request
Participants:

Palatin: Kaushik Dave, Tom Yajcaji, Michael Battersby, Alicia Napoli (Tyco-Mallinrodt)
FDA: David Frucht, Chana Fuchs

Summary:

The topic of this telecon was Palatin's responses to CR points #11, #23, and #29. The following points were made by FDA:s

Point #11: FDA commented that Palatin has not provided pre-validation data supporting the development of the new specifications for critical process parameters during this process step [REDACTED] ^{(b) (4)} to support the validation protocol.

FDA has found the lack of pre-validation data to be an overall deficiency in the information submitted to date. FDA requested a list of critical process parameters for each process step and a summary of pre-validation data that support Palatin's choice of ranges for each of these parameters. Based on previous discussions, Palatin had agreed to submit data from the third consistency lot and final validation report in January. FDA requests that Palatin submit the validation protocol as soon as possible so that it can be reviewed in advance.

Palatin responded that they will submit data supporting identification of critical process parameters and a summary of pre-validation data that support their choice of ranges for these parameters. These data will be submitted in advance of the inspection.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

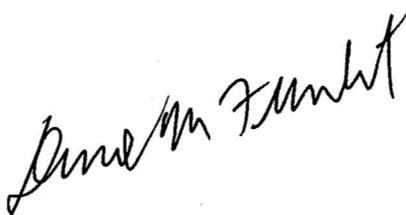
Memorandum

Date: December 11, 2003
From: Dale Slavin, Ph.D. OTRR/DARP 
Subject: Request for electronic copy of PI
To: BLA STN 103928/0 Palatin Technologies

I called Dr. Kaushik Dave of Palatin Technologies and requested an updated electronic version of the PI both annotated and clean. He stated that he would send these with updated clinical safety data. He also stated that he would send the vial and carton labels, and that concluded our discussion.

Telecon

Sponsor: Palatin
BLA: 103928
Date: 12/9/03
Time: 2:00 p.m.
Purpose: Information request
Participants:



Palatin: Kaushik Dave, Michael Battersby, Tom Yajcaji, Alicia Napoli
(Tyco-Mallindrodt)
FDA: David Frucht

Summary:

The topic of this telecon was FDA questions regarding Palatin's response to point #30 dealing with Palatin's immunogenicity assay. The points/questions discussed were as follows:

The Sponsor has addressed some concerns regarding prozone effects and the ruggedness of their immunogenicity assay, however they have not adequately addressed concerns related to the possibility of divalent binding, a factor that could affect assay sensitivity. The parameter most important for determining divalent binding is the concentration of RB5 IgM on the (b) (4) used for the assay. The Sponsor has not provided data validating the optimal concentration of RB5 IgM incubated with the (b) (4) (b) (4). Once this is determined, specifications should be established for the concentration of the RB5 IgM used during this incubation. The Sponsor should also set specifications for the iodination level of the labeled RB5 IgM used for detection in the assay. Also, the Sponsor needs to assess the stability of the RB5 IgM- (b) (4) to establish specifications for the lifetime of each labeled batch (b) (4). Furthermore, they report that their assays shows linearity in the range of 10-500 ng/ml, but they do not provide information in their protocol for processing samples that have HAMA concentrations that exceed this range.

1. The Sponsor should amend the SOP to address the protocol to be used to assess HAMA in patients with levels >500 ng/ml.
2. The Sponsor should provide data validating the optimal concentration of RB5 IgM used for (b) (4), and set specifications for the concentration of RB5 IgM used in this step, accordingly.
3. The Sponsor should set specifications for the level of iodination of the labeled RB5 IgM with supporting data.
4. The Sponsor should set specifications for the lifetime of the RB5 IgM (b) (4) (b) (4) and provide supporting data for these specifications.
5. FDA assumes that this assay will be available to perform studies in the future to satisfy post-marketing commitments that may be identified.

Palatin responded that they have already amended their SOP to address point #1. They will a send us this information and the other data requested ASAP. I will email Palatin on Friday to give them advanced warning about next week's topic.

Telecon



Sponsor: Palatin

BLA: 103928

Date: 12/2/03

Time: 2:00 p.m.

Purpose: Information request

Participants: Palatin: Mike Battersby, Thomas Yajcaji, Kaushik Dave

FDA: David Frucht and Chana Fuchs

Summary:

This meeting represented the first in a series of weekly telecons, and it involved the following persons: Mike Battersby (Palatin), Thomas Yajcaji (Palatin), Kaushik Dave (Palatin), David Frucht (FDA) and Chana Fuchs (FDA). We focused on points #'s 1 through #8, #16, and #30 in the Palatin response to the BLA CR letter. The following issues were discussed with Palatin:

1. We requested that Palatin provide FDA with a comprehensive table listing the disposition of each production lot generated from a thaw, including those that were failures. This table should include a listing of all relevant lot numbering information, so that it would be possible to trace a lot from the initial thaw through each intermediate step to final drug product. Also, we requested that Palatin submit process validation data pertaining to the manufacturing process of RB5 IgM. Palatin agreed to this request. The process validation data will be submitted in the planned amendment once the third lot is manufactured. We requested all process validation data, including validations done with lots that are not the consecutive conformance lots.
2. FDA requested that Palatin amend (b) (4) bioburden specifications for the (b) (4) drug product from "Report Results" to numerical limits for acceptability. This is a prerequisite for licensure. Palatin agreed to amend these specifications once data from the third conformance lot is generated.
3. FDA requested Palatin to explain why they do not test bioburden levels during the (b) (4). Palatin responded that this step was (b) (4). They believed that this should not be considered a hold step requiring monitoring. FDA requested should bioburden be identified at any time on the following step, monitoring of bioburden on the (b) (4) should be part of the investigation to root cause.
4. FDA requested that Palatin provide more data supporting the development of specifications, specifically IgM concentration in (b) (4) harvests and clarified bulk products. FDA requested data from prior assay validation lots be included to justify these specifications.

5. FDA inquired the status of the Western blotting assay for host cell proteins in the drug substance. Palatin responded that the assay had been developed and validated. Palatin agreed to send us the data supporting this assay. FDA pointed out that a Western blotting assay would be more specific for host cell proteins than would be their silver staining assay, especially since a major HCP band co-migrates with the IgM on SDS-PAGE gels
6. FDA inquired the reason why there was a large decrease in the RB5 IgM measured by ELISA in the stability assays for RB5 IgM concentrate. Palatin believed this was a typographical error that they would correct. Palatin also remarked that their RB5 IgM ELISA had some inherent variability, specifically the precision of the method in the harvest matrix. FDA requested that Palatin justify their acceptance criteria for stability parameters in intermediate process steps, as they do not fulfill the parameters used for stability of drug product. Palatin agreed to provide this information. Palatin also agreed to provide data regarding bioburden in WP-PEI eluates maintained at ambient temperature for 2 days.
7. Palatin agreed to provide FDA with a table listing in a step-by-step manner the alert/action limits on the revised batch record, as well as SOPs detailing specific actions to be taken if these limits are exceeded.
8. Palatin agreed to provide FDA with SOPs for describing the process for immunogenicity testing in patients whose titers exceed the range of the assay.
9. Palatin agreed to provide FDA with an updated list of all reagents derived from animals/humans that are used in the manufacturing process, beginning with the development of the Master Cell Bank.
10. Palatin was informed that their LAL test used for final drug product release needs to be validated against the rabbit pyrogen testing.
11. FDA requested that any changes in analytical methodology made during these past 3 years be submitted to the BLA.
12. FDA made it clear that this discussion does not cover all of our inquiries for the points discussed, and we will revisit these items individually once the additional data requested is submitted.



Our STN: BL 103928/0

NOV 18 2003

Palatin Technologies, Incorporated
Attention: Carl Spana, Ph.D.
President and Chief Executive Officer
4-C Cedar Brook Drive
Cedar Brook Corporate Center
Cranbury, NJ 08512

Dear Dr. Spana:

We have received your September 30, 2003, resubmission to your biologics license application for Technetium Tc-99m Fanolesomab on October 2, 2003.

The resubmission contains additional chemistry manufacturing and controls information that you submitted in response to our September 25, 2000, complete response letter.

We consider this a complete, class 2 response to our action letter. Therefore, the user fee goal date is April 2, 2004.

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see <http://www.fda.gov/cder/biologics/default.htm>. Until further notice, however, all correspondence should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

If you have any questions, please contact the Regulatory Project Manager, Dale Slavin, Ph.D., at (301) 827-4358.

Sincerely,

A handwritten signature in black ink, appearing to read "Earl Dye". The signature is fluid and cursive, with the first name "Earl" being more prominent than the last name "Dye".

Earl S. Dye, Ph.D.
Acting Director
Division of Review Management and Policy
Office of Drug Evaluation VI
Office of New Drugs
Center for Drug Evaluation and Research

CONCURRENCE PAGE

Letter Type: Resubmission Acknowledgment Letter (RAC)
Summary Text: Class 2 Resubmission

SS & RIS Data Check:

- **Communication**
- **Milestone: Receipt Date In Ltr. & Milestone (Response To CR) Should Match**

RIS Data Check:

- **Confirm New Action Due Date**

cc: HFM-585/DRMP-BLA Files
HFM-585/D. Slavin
HFM-558/D. Frucht
HFM-555/C. Fuchs
HFM-588/L. Epps
HFM-573/L. Martynech
HFD-328/M. Swider
HFD-328/C. Renshaw
HFM-579/M. Green
HFM-582/K. Ayalew
HFm-650/L. Johnson
HFM-219/Satish Misra

TELECON MEMO

Date: October 31, 2003
From: Chana Fuchs, Ph.D. DMA/OPB
Subject: October 31, 2003 telecon with Palatin Technologies
To: STN 103928/0.5003
Participants: FDA/OBP/DMA: Chana Fuchs,
Palatin: Kaushik Dave, Mike Battersby



Palatin called re:

1. PAI at DSM - to modify the information relayed previously. DSM is in a holiday shutdown but will be fully operational by the 2nd half of January.
2. The second amendment is planned for submission at the end of January.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 3, 2003
From: Dale Slavin, Ph.D. OTRR/DARP 
Subject: Extra copy request and request for electronic copy of PI
To: BLA STN 103928/0 Palatin Technologies

I called Dr. Kaushik Dave of Palatin Technologies and requested two extra copies of the complete 8 volume amendment 103928/0.5003 and one extra copy of volume one. I also requested an electronic version of the PI both annotated and clean. He stated that he would send these and that concluded our discussion.

Sent To Sponsor
4-18-02

Telecon Announcement

From: NOSKA, MICHAEL

Date: February 12, 2002

Subject: Other BLA

Meeting ID: 2108

Appl Type/Appl No/Supp id Indication
BLA 103928 0 BLA - diagnosis of appendicitis in patients with equivocal signs and symptoms

| TO: | Mail Code | FYI: | Mail Code |
|-----------------------|-----------|-------------------|-----------|
| ELTERMANN JR., JOHN A | HFM-670 | AARONSON, WENDY | HFM-588 |
| EPPS, LEON A | HFM-596 | BISHOP, PHILIPPE | HFM-573 |
| FUCHS, CHANA | HFM-556 | SICKAFUSE, SHARON | HFM-588 |
| TROUT, DEBORAH | HFM-675 | STEIN, KATHRYN E | HFM-555 |
| WEBBER, KEITH O | HFM-556 | | |

This Telecon has been scheduled as follows:

Requestor: Palatin Technologies, Inc.

Product: Tc-99m radiolabeled anti-CD15 IgM Antibody

Purpose: Discuss Palatin's plan to address deficiencies in Sept. 2000 CR letter, process validation & lots, stability, vial/carton labeling

Summary/ Diagnosis of appendicitis

Non-appl
Indication

| | Date / Time | Location | |
|-------------------|---------------------------------------|-----------------|--------------|
| Pre-Mtg: | Friday, March 15, 2002 13:00-14:00 | WOC I, Rm. 376N | 301-827-5383 |
| Requestor: | Friday, March 22, 2002 13:00-14:00 | WOC I, Rm. 400S | 301-827-5910 |

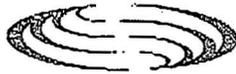
Contact: WILLS, STEPHEN
Contact Phone: 609-520-1911

Please note the date and time on your calendar!

Prepared by: MCFADDEN, EMILY

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PALATIN
TECHNOLOGIES



PALATIN
TECHNOLOGIES, INC.

103 CARNEGIE CENTER
SUITE 200
PRINCETON, NJ 08540

TEL: 609 520 1911
FAX: 609 452 0880

March 21, 2002

Michael Noska, CBER, CSO
Woodmont Office Center 1
Room 380N, FFM 588
140 Rockville Pike
Rockville, MD 20852-1448

Dear Michael:

Please be advised that the list of participants for tomorrow's teleconference is as follows:

Palatin Technologies

- ✓ Carl Spana, Ph.D., Chief Executive Officer
- ✓ Stephen T. Wills, CPA, MST Chief Financial Officer
- ✓ Perry Molinoff, MD, Executive V.P., Research & Development
- ✓ Edward Patten, Director of Quality Operations
- ✓ Michael Battersby, Director of Manufacturing Operations
- ✓ Elizabeth Gordon, Ph.D., Regulatory Affairs Consultant

Tyco/Mallinckrodt

- ✓ Alicia Napoli, Senior Director of Regulator Affairs

Please feel free to contact me with questions or comments.

Very truly yours,

Stephen T. Wills, CPA, MST
Chief Financial Officer

RECEIVED
MAR 21 2002

DRAFT

MEMORANDUM

Date: May 4, 2000

To: Palatin BLA 99-1407 File

From: Michael A. Noska, M.S.
Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Teleconference with Sponsor
May 3, 2000, 13:40-14:30

Agency Participants: Lydia Martynec, Robert Lindblad, William Schwieterman, Chana Fuchs, Leon Epps, Mary Andrich, Peter Lachenbruch, Michael Noska

Sponsor Participants: Charles Putnam, Terrye Smith, Elizabeth Gordon, Carol ~~Karen~~ ~~MacHveney~~, Greg Shindledecker, Dawn ~~Mc Elvany~~, Peggy Wingert

This call was initiated by the Agency to seek clarification on problems with the imaging database identified by Dr. Martynec, to discuss the HAMA assays used in the clinical trials and to briefly discuss the July 10, 2000 advisory committee meeting.

Dr. Schwieterman opened the discussion by explaining the problem with the database. He noted that the current PC format does not allow the Agency to verify time-to-positive in the nuclear medicine scans because the time stamp for each image is missing. This was available in the earlier Macintosh format but not in the PC format. Dr. Schwieterman emphasized that this is a critical component of the BLA review.

Mr. Putnam noted that the company is willing to do whatever it takes to correct the problem even though it was not noted during earlier discussions with the Agency. He added that there are limitations to what can be provided. Mainly, it would take a significant amount of time to fix. During transfer of data from the Mac to the PC, it was found that the PC software is not able to read text from the Mac and integrate it with the graphic display.

Mr. Putnam offered that the company could provide a spreadsheet which gives all of the scan times for each image. Dr. Martynec noted that the spreadsheet would need to clearly cross-reference the time data to the image. Mr. Putnam acknowledged this and stated that the spreadsheet would clearly identify each scan. Drs. Martynec and Schwieterman stated that this proposal sounded acceptable but asked the sponsor to submit a proposal for review before the Agency would give final approval.

[HAMA discussion to be filled in by Chana.]

Regarding the upcoming advisory committee meeting, Dr. Schwieterman noted that briefing packages should be prepared by the middle of June. The Agency will share its package with Palatin and it would be best if Palatin forwards a copy of its package before they are sent to the advisory committee. This is only for the purpose of reviewing the documents for factual errors. In addition, the Agency and the Sponsor should compare their presentations to avoid redundancy. This will not influence the interpretations made by the two groups. Dr. Gordon asked whether Palatin should prepare only a summary of the clinical data and whether the Agency's package would be complementary to theirs. Dr. Schwieterman stated that the concern is redundancy in the presentations, not the briefing packages, so each group should prepare complete packages. Dr. Schwieterman also noted that the Agency would be preparing a list of questions it intends to ask of the advisory committee and this may or may not be included in the briefing package. The Agency will try to provide the Sponsor with these questions within the next two weeks.

Dr. Schwieterman closed the teleconference by stating, in regard to the image database, that the reviewers assumed that they would not have to scrutinize every element of the database and that it was understood that all data from the NucMac program would be transferred to the PC platform. The proposed solution seems workable, however, it will require approval from Office management.

The telecon concluded amicably.

Telecon

Date: 4/14/00
BLA: 99-1407
Title: LeuTech
Sponsor: Palatin
Participants: FDA Company
Robert Lindblad, MD Charles Putnam, CEO

- Mr. Putnam was informed that the mid-cycle report for LeuTech went well and was well received.
- He was informed that there were significant issues with the HAMA assay and that follow up would be coming from the product review team.
- I requested that any banked serum be held to retest for HAMA pending discussions as to the assay and the development of a new assay.
- A repeat dosing study has been completed and there were no clinical adverse events though there was a rise in HAMA titer by the current assay in ~15% of patients. This data is in the process of being submitted to the agency.
- He was informed that there was a good chance that this product would be presented to the MIDAC for review and if/when that is finalized that more information would be forthcoming.
- Lastly, a request for the submitted labeling/insert for the product was requested in an electronic version, and that will be supplied.

AGENDA

Mid-Cycle Review
LeuTech™ (Palatin) Biologics License Application
Reference Number 99-1407
April 10, 2000, 3:00-5:00 p.m.

Objective: To update the status of the review of Palatin's BLA for LeuTech™ (Tc-99m-radiolabeled anti-CD15 IgM antibody) and to decide on the future direction of the review process

| <u>Presenter</u> | <u>Topic</u> | <u>Time</u> |
|--|-------------------------------------|-------------|
| Mike Noska | Review of timelines | 10 minutes |
| Chana Fuchs/Leon Epps | Review of product issues | 20 minutes |
| Debra Trout/Patricia Hughes | Review of facilities | 10 minutes |
| Mary Andrich | Update on status of site monitoring | 10 minutes |
| Dave Green | Pharmacology | 5 minutes |
| Bob Lindblad/Lydia Martynec/ Satish Misra | Clinical/Statistical Review | 40 minutes |

Open Discussion/Action Items

Review Committee
LeuTech™ BLA Supplement
Reference Number 99-1407

Chana Fuchs, Chair, Product Reviewer

Leon Epps, Product Reviewer

Robert Lindblad, Clinical Reviewer

Lydia Martynec, Clinical Reviewer

Satish Misra, Biostatistics

Mary Andrich, Biomonitoring

M. David Green, Pharm/Tox

Deborah Trout, Facilities

Patricia Hughes, Facilities

Michael Noska, Regulatory Coordinator

Milestones

Reference Number 99-1407

Standard 10 Month Review Cycle

Application Received on November 22, 1999

| <u>Action</u> | <u>Due Date</u> | <u>Completion Date</u> |
|-------------------------|--------------------|------------------------|
| Committee Assignment | December 6, 1999 | December 9, 1999 |
| First Committee Meeting | December 13, 1999 | December 20, 1999 |
| Filing Meeting | January 6, 2000 | January 12, 2000 |
| Filing Action | January 21, 2000 | January 21, 2000 |
| Mid-Cycle Meeting | | |
| Action Letter Deadline | September 22, 1999 | |

Advisory Committee?

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Our Reference Number 99-1407

JAN 21 2000

Mr. Charles L. Putnam
 Palatin Technologies, Inc.
 214 Carnegie Center, Suite 100
 Princeton, NJ 08540

Dear Mr. Putnam:

This letter is in regard to your biologics license application submitted under Section 351 of the Public Health Service Act.

The Center for Biologics Evaluation and Research has completed an initial review of your application dated November 22, 1999 for Technetium-99m Radiolabeled Anti-CD15 IgM Antibody (LeuTech™) for the diagnosis of appendicitis in patients with equivocal signs and symptoms, to determine its acceptability for filing. In accordance with 21 CFR 601.2(a) the application is considered to be filed effective today's date.

This acknowledgment of filing does not mean that a license has been issued nor does it represent any evaluation of the adequacy of the data submitted. Following a review of the application, we shall advise you in writing as to what action has been taken and request additional information if needed.

As of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 601.27, please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 601.27.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 601.27 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

FILE
 COPY

| OFFICE | SURNAME | DATE | OFFICE | SURNAME | DATE | OFFICE | SURNAME | DATE |
|-----------|----------|---------|--------|---------|---------|--------|---------|------|
| OSTR/DARP | M. Hoche | 1/20/00 | DARP | DIXON | 1/21/00 | | | |
| DARP | Hovav | 1/20/00 | | | | | | |
| DARP | M. Jones | 1-21-00 | | | | | | |

Page 2 – Mr. Putnam

Should you need additional information or have any questions concerning administrative or procedural matters, please contact the Regulatory Project Manager, Mr. Michael Noska, at (301) 827-5101.

Sincerely yours,

Glen D. Jones, Ph.D.
Director
Division of Application
Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

CBER:DARP:M.Noska:1/19/00:Dixon:1/20/00
(S:\Noska\Letters\License\Filing_99-1407.doc)

MILESTONE: FILING LETTER - (FA)

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immediately following this page

Dixon, Julie

From: Noska, Michael
Sent: Thursday, December 09, 1999 11:20 AM
To: Dixon, Julie
Subject: [REDACTED]

Julie,

Below is the pertinent information for the above reference number:

Reference number: 99-1407
Sponsor: Palatin Technologies, Inc.
Product shortname: Tc-99m radiolabeled anti-CD15 IgM antibody
Chairperson: Chana Fuchs, DMA
Other Committee Members: Leon Epps, DMA
M. David Green, DCTDA
Robert Lindblad, DCTDA
Lydia Martynec, DCTDA
Satish Misra, DBE
Janice Brown, DMPQ
Patricia Hughes, DMPQ
Mary Andrich, DIS (BiMo)
Regulatory Project Manager: Michael Noska, DARP

Please let me know if you need any further information.

Mike



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: December 8, 1999

To: BLA File

From: Karen Weiss, M.D., HFM-570 *KW*

Subject: Designation of Priority for BLA Review

Sponsor: Palatin Technologies, Inc.

Product: Tc-99m-radiolabeled anti-CD15 IgM antibody

Indication: Diagnosis of appendicitis in patients with equivocal signs and symptoms

The review status of this Biologics License Application is designated to be:

- Standard (10 mo.)
- Priority (4 mo.)

Best Copy Available

Mr. Charles L. Putnam
Palatin Technologies, Inc.
214 Carnegie Center, Suite 100
Princeton, NJ 08540

December 3, 1999

Dear Mr. Putnam:

REFERENCE NUMBER 99-1407 has been assigned to your recent submission for your biologics license application for Tc-99m Radiolabeled Anti- CD15 IgM Antibody for the diagnosis of appendicitis in patients with equivocal signs and symptoms, received on November 22, 1999.

All future correspondence, supportive data, or labeling relating to this application should be submitted in triplicate and should bear the above REFERENCE NUMBER and be addressed to the Director, Center for Biologics Evaluation and Research, HFM-585, HHS/PHS, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

This acknowledgement does not mean that a license has been issued nor does it represent any evaluation of the adequacy of the data submitted. Following a review of the application, we shall advise you in writing as to what action has been taken and request additional information if needed.

Should you have the need to discuss any technical aspects of the application, you may obtain the name of the chairperson of the licensing review committee by contacting this office, 301-827-5101. Any questions concerning administrative or procedural matters should also be directed to this office.

Sincerely yours,

Glen D. Jones, Ph.D.
Director
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

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bcc: Ref. No. File
Director, Product Release Staff, HFM-235
Red Folder
Mike Noska, HFM-588
Chana Fuchs, HFM-558

OTRR/DARP: J. Dixon:12-03-99
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REF NO. ASSIGNMENT - APPLICATION