DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration

TRANSMITTED BY FACSIMILE **February 16, 2006**

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

Re: BLA 103928
NeutroSpec™ [Kit for the Preparation of Technetium (99m Tc) fanolesomab]
MACMIS 13720

Dear Dr. Spana:

This letter notifies Palatin Technologies, Inc. (Palatin) and, by copy, Mallinckrodt Inc. (Mallinckrodt), which markets NeutroSpec on behalf of Palatin, that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed four professional digital billboard exhibit panels, one multi-product exhibit panel, and one product-specific exhibit panel for NeutroSpec™ [Kit for the Preparation of Technetium (99m Tc) fanolesomab], all displayed at the American Pharmaceutical Association's 2005 Meeting in Orlando, Florida, submitted by Palatin under cover of Form FDA-2253. Additionally, DDMAC has reviewed a product video for NeutroSpec found on a website administered by Mallinckrodt, (URL: http://www.imaging.mallinckrodt.com/_attachments/videoclips/NeutroSpec_video.html), which was posted on the website until at least October 2005.

We note that NeutroSpec is not being marketed at this time due to safety concerns. If NeutroSpec is marketed in the future, please evaluate all future proposed promotional materials in light of the violations outlined below. FDA has determined that the above promotional pieces are misleading because they fail to communicate the most serious and frequently occurring risks associated with NeutroSpec, overstate the efficacy of the drug, and broaden the indication for NeutroSpec. The panels and video, therefore, misbrand NeutroSpec in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. §§ 352(a) & (n); 321(n), and FDA implementing regulations. Cf. 21 CFR §§ 202.1(e)(5)(i); (iii); & (e)(6)(i). Furthermore, the website, including the product video, was not submitted to FDA under cover of Form FDA-2253 as required by 21 CFR § 314.81(b)(3)(i). These promotional pieces are extremely concerning from a public health perspective because they minimize the risks of NeutroSpec, while overstating the benefits of the drug.

Background

According to the Description section of the approved product labeling (PI), "NeutroSpec™ [Technetium (99m Tc) fanolesomab] is an *in vivo* diagnostic radiopharmaceutical that can be visualized by nuclear medicine instrumentation." The Indications and Usage section of the PI states: "NeutroSpec™ [Technetium (99m Tc) fanolesomab] is indicated for scintigraphic imaging of patients with equivocal signs and symptoms of appendicitis who are five years of age or older."

NeutroSpec is associated with several important contraindications, warnings, and precautions. For example, the PI for NeutroSpec states (in pertinent part):

> **CONTRAINDICATIONS:** NeutroSpec™ should not be administered to patients who are hypersensitive to any murine proteins or other component of the product.
>
> **WARNINGS:**
> **Hypersensitivity Reactions** – Allergic reactions, including anaphylaxis, can occur in patients who receive murine antibodies such as fanolesomab. Cenolate™ Ascorbic Acid, USP injection (diluent) contains sodium hydrosulfite, a sulfite that may cause allergic reactions, including anaphylaxis. Serious hypersensitivity reactions were not observed in the 523 patients who received NeutroSpec™ in the clinical studies. Emergency resuscitation personnel and equipment for the treatment of hypersensitivity reactions should be immediately available during administration of this agent.
>
> **PRECAUTIONS:**
> **Repeat Administration** – NeutroSpec™ has not been studied in repeat administration to patients. Murine monoclonal antibodies are frequently immunogenic. The development of human antimouse antibodies (HAMA) can alter the pharmacokinetics, biodistribution, safety, and imaging performance properties of the administered agent.
> **Use in Patient with Neutropenia** – The biodistribution and imaging performance of NeutroSpec™ in neutropenic patients have not been studied. NeutroSpec™ induces transient neutropenia and a downward shift in white blood cell counts.... The safety and effectiveness of NeutroSpec™ in patients with neutropenia have not been established.
> **General Use and Handling** – NeutroSpec™ [Technetium (99m Tc) fanolesomab], like other radioactive medical products, must be handled with care and appropriate safety measures should be used to minimize radiation exposure to clinical personnel. Care should also be taken to minimize radiation exposure to the patient consistent with proper patient management.

Furthermore, the Information for Patients section of the PI contains the following special instructions for patients receiving NeutroSpec therapy:

> ...Patients should be informed that the use of this product could affect their future use of other murine based products, and should be advised to discuss prior use of murine antibody based products with their health care provider. To minimize the radiation-

> absorbed dose to the bladder, adequate hydration should be encouraged to permit frequent voiding during the first few hours after injection. To help protect themselves and others in their environment, patients should take the following precautions for 12 hours after injection. Whenever possible, a toilet should be used, rather than a urinal and the toilet should be flushed several times after each use. Spilled urine should be cleaned up completely. After each voiding or fecal elimination, patients should thoroughly was [sic] their hands. If blood, urine, or feces soil clothing, the clothing should be washed separately.

The adverse events most frequently reported during clinical trials included flushing (n=10, 2%) and dyspnea (n=5, 1%).

The Clinical Studies section of the PI presents the performance rates for the determination of appendicitis by the blinded readers and by the clinical investigators of a multicenter, single-arm study evaluating 200 patients with equivocal signs and symptoms of appendicitis (see below). A second supportive study in 56 patients reported similar diagnostic performance rates for NeutroSpec.

Evaluation	Performance Rates (n=200)	
	Blinded Readers Percentages (95% CI)	Study Investigators Percentages (95% CI)
Sensitivity	75 (62, 85)	91 (80, 97)
Specificity	93 (87, 97)	86 (79, 91)
Accuracy	87 (82, 92)	87 (81, 91)
Positive Predictive Value	82 (69, 91)	74 (62, 84)
Negative Predictive Value	90 (84, 94)	96 (90, 99)

The Labeling and Preparation of NeutroSpec™ section of the PI describes a nine step process for the aseptic labeling and preparation of one dose of NeutroSpec. These steps include a 30-minute incubation period. Following preparation, the PI recommends conducting a seven step radiochemical purity test on the prepared NeutroSpec dose. If the prepared dose meets the suggested radioactivity limits, the dose may then be administered to the patient intravenously. Subsequently, patients undergo image collection for up to 90 minutes. The Dosage and Administration section of the PI states:

> Dynamic image acquisition over the lower abdomen should begin at the time of injection and consist of 10 sequential four-minute images. Following dynamic image acquisition, the patient should ambulate for approximately 10 to 15 minutes and void. Static planar images should then be collected, including supine anterior, posterior 10-25 degree RAO and LAO views of the lower abdomen, followed by a standing anterior image of the lower abdomen… it is recommended that a total of one million counts be collected for the anterior supine image. All remaining images should be collected for the same duration of time required for the anterior supine image.

Omission of Risk Information

The digital billboard panels, the exhibit panels, and the product video are misleading because they fail to provide information about the most serious and frequently occurring risks of NeutroSpec. The digital billboard panels and exhibit panels include numerous claims about the effectiveness of the product, such as "Rapid, Safe, and Simple," and "An *in vivo* imaging agent that radiolabels white blood cells and myeloid precursors, and is indicated for equivocal appendicitis in patients 5 years or older." Similarly, the product video includes numerous claims regarding the effectiveness of NeutroSpec. The claims include:

- "NeutroSpec… an *in vivo* imaging agent that radiolabels white blood cells and myeloid precursors."
- "NeutroSpec is a white blood cell antibody directed specifically against the neutrophils, and the neutrophils are the white blood cells that come out of the bone marrow that specifically help fight acute infections."
- "It's targeted imaging."
- "Our surgeons 2 to 1 said, 'I don't need another study to diagnose appendicitis….It's easy to do.' And by the end of the study they would not do a patient without a NeutroSpec study. It was that valuable to them."
- "It doesn't have what we would call a big learning curve."
- "The diagnosis can be made very rapidly and in fact in our experience… you can make the diagnosis about 60% of the time in less than five or six minutes….it doesn't do any good to have a test that doesn't make a difference, and this makes a difference."[1]

Despite these extensive claims, these pieces completely omit the most serious and frequently occurring risks associated with NeutroSpec. This complete omission is exacerbated by the specific, repeated claim of "Safe" without identifying the risks associated with the use of NeutroSpec.

Overstatement of Efficacy

The product video overstates the demonstrated efficacy of NeutroSpec to detect appendicitis. Specifically, the product video includes the following claim:

- "We ended up with a 98% sensitivity for NeutroSpec to detect appendicitis, and the specificity was approximately 80%."

This claim is misleading because it suggests that NeutroSpec has demonstrated a 98% sensitivity and an 80% specificity. Table 4 in the PI states the sensitivity of NeutroSpec as reported by blinded readers and study investigators was 75% (CI 62, 85) and 91% (CI 80, 97),

[1] Please note that our comments with respect to the claims in the product video address the content of the product video posted on the website on or about October 2005. We acknowledge that a revised product video containing some risk information and omitting some of the claims cited above was posted on the website on or about December 2005. This letter does not address the content of the more recent December 2005 product video.

respectively. DDMAC is not aware of substantial evidence or substantial clinical experience demonstrating a 98% sensitivity for NeutroSpec or that NeutroSpec can definitively and independently detect appendicitis in patients.

Rapid

The digital billboards and exhibit panels also overstate the efficacy of NeutroSpec through numerous presentations of the claim "Rapid." Similarly, the product video overstates the efficacy by claiming, for example, "The diagnosis can be made very rapidly and in fact in our experience . . . you can make the diagnosis about 60% of the time in less than five or six minutes...." These presentations are misleading because they fail to include both qualifying and quantitative contextual information with respect to the term "rapid."

Specifically, the presentations lack appropriate context to explain the term "rapid." For example, the claims of "rapid" in the billboards and exhibit panels suggest a short duration for the entire process, as well as for each individual component, including preparing a dose of NeutroSpec, administering the product to a patient, conducting the scintigraphic imaging, analyzing the results, and making the final clinical diagnosis.

However, in the context of preparation and administration time, the unqualified claims of "rapid" are misleading. As discussed in the background, the preparation alone of NeutroSpec is an involved and potentially lengthy process. It includes a nine step reconstitution and labeling procedure, requiring a 30 minute incubation period, and a seven step radiochemical purity test of the reconstituted and radiolabeled agent prior to intravenous administration of the product to a patient - assuming successful purity testing. Depending on a pharmacist's familiarity with NeutroSpec's reconstitution and radiolabeling procedures, it is not unrealistic to expect some pharmacists to require over an hour to prepare a single dose.

Moreover, in the context of time to final diagnosis, the claims are misleading because they lack context to convey that once preparation and administration of NeutroSpec are complete, the imaging can take up to 90 minutes. In addition, the ensuing image interpretation cannot be immediately translated into a final clinical diagnosis. Specifically, the results of the NeutroSpec scan must be considered in conjunction with additional diagnostic and/or clinical information. The final clinical diagnosis will be affected by the availability of this additional information, as well as the availability of the radiologist and treating physician. The variability in these concomitant factors can add indeterminate time to assigning the final diagnosis.

The product video contains similar, misleading claims. The claims in the product video misleadingly suggest that NeutroSpec allows clinicians to make a final clinical diagnosis of appendicitis within five to six minutes. However, as indicated in the Imaging Interpretation section of the PI:

> Among those with a blinded diagnosis of appendicitis, 76% displayed uptake of radiotracer activity in the appendix within 30 minutes following injection and 98% did so by 60 minutes following injection. In the trial the acquisition of image collection was

> performed for a 90 minute period. The image finding of a persistent or intensifying uptake in the right lower quadrant (appendix zone) that is seen before the completion of the entire imaging sequence may be considered a positive study, and imaging may be terminated at this time. In the case of a negative image finding at 30 and 60 minutes, collection to 90 minutes is recommended prior to termination of the study.

As discussed above, once imaging interpretation is completed, clinicians should not make a final clinical diagnosis without first assessing the totality of clinical information (e.g., signs, symptoms, laboratory and other imaging results, operative findings or clinical follow up). NeutroSpec should not be used in isolation from such additional clinical information, as it is only one diagnostic modality intended for use in conjunction with additional clinical data to assist in the final diagnosis of patients presenting with equivocal signs and symptoms of appendicitis. Assessing the image and the totality of the clinical information also adds time to the process, further substantiating that the diagnosis is not "rapid."

DDMAC is not aware of substantial evidence or substantial clinical experience to support a claim of rapid time to final clinical diagnosis. For example, in conjunction with the digital billboard and exhibit panel submission to the agency under cover of FDA Form-2253, Palatin submitted two reference articles.[2,3] These publications contain a general discussion of the utility of NeutroSpec, but do not contain clinical data of sufficient quality to be regarded as substantial evidence to support a notion of fast or rapid. Finally, the descriptor "rapid" is not defined in the submitted references, nor is it defined or specifically evaluated in the definitive clinical studies supporting NeutroSpec licensure. If you have data demonstrating this benefit, please submit it to FDA for review.

Simple

Additionally, the digital billboards and exhibit panels overstate the efficacy of NeutroSpec through numerous presentations of the claim "simple." The product video also overstates the efficacy by claiming, for example, "It's easy to do," and "It doesn't have what we would call a big learning curve." These claims are misleading because they suggest that the use of NeutroSpec to assist in the diagnosis of equivocal appendicitis is easy and uncomplicated. As discussed above, the preparation of NeutroSpec is an involved process requiring a nine step reconstitution procedure and a seven step radiochemical purity test on the prepared radiolabeled agent. The prepared dose should only be administered intravenously if the purity test results are judged to be satisfactory. Following intravenous administration, the ensuing imaging scans are extensive and time consuming, requiring up to 90 minutes for image collection.

The administration of NeutroSpec is an involved procedure, not only for the clinicians, but also

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[2] Rypins EB, Kipper SL, Weiland F, et al. ^{99m}Tc Anti-CD 15 Monoclonal Antibody (LeuTech) Imaging Improves Diagnostic Accuracy and Clinical Management in Patients With Equivocal Presentation of Appendicitis. *Ann Surg* 2002 Feb;235(2):232-9.

[3] Rypins EB, Kipper SL. Scintigraphic determination of equivocal appendicitis. *Am Surg* 2000 Sep;66(9):891-5.

for the patients. As stated in the Information for Patients section of the PI, a patient receiving NeutroSpec should comply with the following guidelines with respect to hydration, voiding, fecal elimination and the prevention of contamination from bodily fluids:

> To minimize the radiation-absorbed dose to the bladder, adequate hydration should be encouraged to permit frequent voiding during the first few hours after injection. To help protect themselves and others in their environment, patients should take the following precautions for 12 hours after injection. Whenever possible, a toilet should be used, rather than a urinal and the toilet should be flushed several times after each use. Spilled urine should be cleaned up completely. After each voiding or fecal elimination, patients should thoroughly was [sic] their hands. If blood, urine, or feces soil clothing, the clothing should be washed separately.

Broadening of Indication

The product specific exhibit panel and the product video misleadingly suggest that NeutroSpec is effective in a broader range of patients than has been demonstrated by substantial evidence or substantial clinical experience. While the exhibit panel does acknowledge that NeutroSpec "is indicated for equivocal appendicitis in patients 5 years or older," it fails to communicate that NeutroSpec is not indicated for independent diagnosis of appendicitis. In addition the product video makes NeutroSpec appear appropriate in all cases, and suggests 100% accuracy. The product video claims:

- "Nuclear medicine has not had a good solution to **diagnosing** appendicitis" (emphasis added).
- "We had a number of patients where the surgeon felt definitely this patient had appendicitis. They have a negative NeutroSpec scan, showing no appendicitis. Surgery is cancelled on the spot and that patient ends up not having appendicitis. So here's where NeutroSpec was extremely valuable in avoiding unnecessary surgery."
- "Our surgeons 2 to 1 said, 'I don't need another study to diagnose appendicitis....' And by the end of the study they would not do a patient without a NeutroSpec study. It was that valuable to them."

These claims suggest NeutroSpec may be used in the absence of additional clinical data or diagnostic modalities to assign a definitive diagnosis of appendicitis. On the contrary, as discussed above, NeutroSpec should be considered only one of several diagnostic tools available to assist in diagnosing appendicitis, and the sensitivity of the test is increased when clinical data other than the NeutroSpec test are utilized. A final clinical diagnosis of appendicitis is not synonymous with a positive scintigraphic image following image interpretation. Clinicians need to assess other clinical information, such as lab work, physical exam, vital signs and potentially other diagnostic modalities, to arrive at a final determination of clinical status, be it positive or negative for appendicitis. We are not aware of substantial evidence or substantial clinical experience demonstrating that NeutroSpec can be used successfully in isolation as a diagnostic test for appendicitis. If you have data demonstrating this use, please submit it to FDA for review.

Moreover, the second and third claims not only misleadingly suggest that NeutroSpec can be used as a stand-alone test to diagnose appendicitis with a high degree of accuracy, but also misleadingly suggest that NeutroSpec is useful in a broader range of patients than has been demonstrated by substantial evidence or substantial clinical experience. In particular, these claims suggest that NeutroSpec is appropriate for all patients presenting with **any** signs or symptoms of appendicitis. However, according to the PI, NeutroSpec has only been studied in patients presenting with **equivocal** symptoms of appendicitis. Specifically, the Clinical Studies section states, "A multicenter, single-arm study evaluated 200 patients (5 to 86 years of age) with equivocal signs and symptoms of appendicitis defined as absence of one or more of the following: periumbilical pain migrating to right lower quadrant (RLQ), gradual onset of pain, increasing intensity of pain over time, pain aggravated by movement and coughing, McBurney's point tenderness, referred tenderness to RLQ with palpation in other quadrants, abdominal muscular spasm with RLQ tenderness, temperature > 101°F, white blood cell count > 10,500/mm^3." In the clinical trials, NeutroSpec was not used as a "confirmatory" test for a positive appendicitis diagnosis. We are not aware of any substantial evidence or substantial clinical experience to support such a broadened indication. Furthermore, claims such as these pose a serious concern in that NeutroSpec is not associated with a zero false negative rate. A clinical decision to cancel surgery following a false negative NeutroSpec scan can result in serious sequelae, such as peritonitis, hospitalization or death.

Failure to Submit Under Form FDA-2253

FDA regulations require you to submit specimens of mailing pieces and any other labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs and Biologics for Human Use) and is required to include a copy of the product's current professional labeling. You did not submit the website referred to in this letter to FDA, including the product video referred to in this letter, under cover of Form FDA-2253 as required by 21 CFR § 314.81(b)(3)(i).

Conclusion and Requested Actions

Your promotional pieces omit important risk information associated with the use of NeutroSpec, overstate the efficacy of NeutroSpec, and broaden the indication for NeutroSpec. Therefore, these materials misbrand your drug in violation of the Act (21 U.S.C. §§ 352(a) & (n); 321(n)) and FDA implementing regulations. Cf. 21 CFR §§ 202.1(e)(5)(i); (iii) & (e)(6)(i). Furthermore, the website, including the product video, was not submitted to FDA under cover of Form FDA-2253, as required by 21 CFR § 314.81(b)(3)(i).

Should Palatin resume marketing of NeutroSpec, please evaluate all future promotional materials in light of the violations discussed above. If you choose to respond to this letter, please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale

Road, Beltsville, MD 20705-1266, facsimile at (301) 796-9878. In all future correspondence regarding this particular matter, please refer to MACMIS #13720 in addition to the BLA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for NeutroSpec™ [Kit for the Preparation of Technetium (99m Tc) fanolesomab] comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above in any future promotional materials may result in FDA regulatory action, including seizure or injunction.

Sincerely,

Catherine B. Gray, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

cc: Tyco Healthcare Mallinckrodt Inc.
Steven Hanley
President, Imaging Division