

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022454Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 22-454

SUPPL #

HFD # 160

Trade Name DaTscan

Generic Name Ioflupane I-123

Applicant Name GEHealthcare

Approval Date, If Known January 13, 2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

Investigation #2

!

!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====
Name of person completing form: James Moore
Title: Regulatory Project Manager
Date: January 11, 2011

Name of Office/Division Director signing form: Charles Ganley
Title: Office Director, Office of Drug Evaluation IV

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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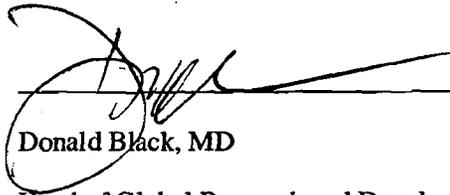
/s/

JAMES W MOORE
01/12/2011

CHARLES J GANLEY
01/12/2011

1.3.3 Debarment Certification

GE Healthcare hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Donald Black, MD

Head of Global Research and Development

Medical Diagnostics

15. December 2008.

Date

January 4, 2011

Regarding your resubmitted application, NDA 22-454, for DaTscan, specifically the submitted labeling, the Division has the following requests.

- 1) Submit revised vial (container) and shield (carton) labels that relocate the NDC number to the first third of the principle display panel in accordance with 21 CFR 207.35(b)(3)(i).
- 2) Submit a revised package insert that changes the following section as displayed below (deletion is strike-through/addition underlined):

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Ioflupane I 123 Injection is a Schedule II controlled substance under the Controlled Substances Act. A DEA license is required for handling or administering this controlled substance.

(b) (4)

Submit marked up and clean copies as soon as possible (within 24 hrs) to me electronically at the following address James.Moore@fda.hhs.gov, cc Dr. Rafel Rieves at Rafel.Rieves@fda.hhs.gov, cc Dr. Libero Marzella at Libero.Marzella@fda.hhs.gov, cc Dr. Phillip Davis at Phillip.Davis@fda.hhs.gov and cc Dr. Ravindra Kasliwal at Ravindra.Kasliwal@fda.hhs.gov Follow up your email response with a submission to your NDA file.

If you have questions, contact me at (301) 796-2050.

James Moore, PharmD., M.A.
Regulatory Project Manager, DMIP

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/s/

JAMES W MOORE
01/04/2011

December 30, 2010

Regarding your commitment to conduct a clinical study to compare the rates of agreement between clinical diagnoses and visual assessment of DaTscan images in non-Caucasian and Caucasian patients with Parkinson's Disease or Essential Tremor, please acknowledge that the following timeline is accurate (this is based upon your email of 12/29/10):

- final clinical protocol submission date: December 31, 2011
- clinical trial completion date: April 30, 2013
- final trial report submission date: July 31, 2013"

You should respond to this email request for clarification to me at James.Moore@fda.hhs.gov by COB, Monday, January 3, 2011. You should cc Dr. Rafel Rieves at Rafel.Rieves@fda.hhs.gov, cc Dr. Libero Marzella at Libero.Marzella@fda.hhs.gov, cc Dr. Phillip Davis at Phillip.Davis@fda.hhs.gov, cc Dr Ira Krefting at Ira.Krefting@fda.hhs.gov and cc Ms. Renee Tyson at Renee.Tyson@fda.hhs.gov.

If you have questions contact me at (301) 796-2050.

James Moore, PharmD., M.A.
Regulatory Project Manager, DMIP

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/s/

JAMES W MOORE
12/30/2010

December 27, 2010

Regarding your pending new drug application for DaTscan, NDA 22-454, the clinical team has the following request.

1. Submit a timeline for completion of your post approval commitment to conduct a clinical trial that assesses agreement between DaTscan image results and diagnostic outcomes among non-Caucasian and Caucasian patients.

You should respond to this request by COB, Thursday, December 30, 2010. Send your response to me via email at James.Moore@fda.hhs.gov, cc Dr. Phillip Davis Phillip.Davis@fda.hhs.gov, cc Dr. Young Moon Choi at Young.Moon.Choi@fda.hhs.gov and cc Dr. Christy John at Christy.John@fda.hhs.gov. Follow up your email response with a response to your pending NDA file.

If you have questions, contact me at (301) 796-2050.

James Moore, PharmD., M.A.
Regulatory Project manager, DMIP

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/s/

JAMES W MOORE
12/31/2010



NDA 22-454

ACKNOWLEDGE CLASS 1 RESPONSE

GE Healthcare
Attention: Marisa Coyle
Manager, Regulatory Affairs
101 Carnegie Center
Princeton, New Jersey 08540-6231

Dear Ms. Coyle:

We acknowledge receipt on November 17, 2010, of your November 16, 2010, resubmission to your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DaTscan™ (Ioflupane I-123) Injection.

We consider this a complete, class 1 response to our December 23, 2009, action letter. Therefore, the user fee goal date is January 14, 2011.

If you have any questions, call me at (301) 796-2010.

Sincerely,

{See appended electronic signature page}

James Moore, PharmD., M.A.
Regulatory Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

JAMES W MOORE
12/09/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (<i>Division/Office</i>): Kim Ritenour-Miller – Consumer Safety Technician James Moore, PharmD, M.A. – Regulatory Project Manager Phillip Davis, MD – Medical Officer Division of Medical Imaging Products (DMIP)		FROM(<i>Division/Office</i>): Carrie Newcomer, PharmD Division of Drug Marketing, Advertising, and Communications (DDMAC) 301-796-1233		
DATE: May 21, 2010	IND NO.	NDA NO. 022454	TYPE OF DOCUMENT: Patient Brochure	DATE OF DOCUMENTS: May 18, 2010
NAME OF DRUG DaTscan (loflupane I 123 Injection) for Intravenous Use	PRIORITY CONSIDERATION Yes	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE: June 21, 2010	
NAME OF FIRM: GE Healthcare				
REASON FOR REQUEST				
I. GENERAL				
NEW PROTOCOL <input type="checkbox"/>	PRE--NDA MEETING <input type="checkbox"/>	RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/>		
PROGRESS REPORT <input type="checkbox"/>	END OF PHASE II MEETING <input type="checkbox"/>	FINAL PRINTED LABELING <input type="checkbox"/>		
NEW CORRESPONDENCE <input type="checkbox"/>	RESUBMISSION <input type="checkbox"/>	LABELING REVISION <input type="checkbox"/>		
<input checked="" type="checkbox"/> DRUG ADVERTISING	SAFETY <input type="checkbox"/>	ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/>		
ADVERSE REACTION REPORT	PAPER NDA <input type="checkbox"/>	FORMULATIVE REVIEW <input type="checkbox"/>		
MANUFACTURING CHANGE/ADDITION <input type="checkbox"/>	CONTROL SUPPLEMENT <input type="checkbox"/>	<input type="checkbox"/> OTHER (<i>SPECIFY BELOW</i>):		
MEETING PLANNED BY <input type="checkbox"/>				
COMMENTS/SPECIAL INSTRUCTIONS: DDMAC is reviewing a proposed patient brochure for the anticipated launch of DaTscan. (We acknowledge the ^{(b) (5)} lack of action date for the drug at this time.) Please see our specific questions below, and please feel free to comment on any other concerns with the proposed patient brochure. Please let me know if there is any additional information you need to assist you during your review. If you have any questions, please call me at 301-796-1233. This consult request, the proposed patient brochure, and draft PI will be placed into DARRTS. Thank you in advance for your time.				
Thank you, Carrie				
SIGNATURE OF REQUESTER Carrie Newcomer, PharmD		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL (DARRTS) <input type="checkbox"/> FACSIMILE		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Kim Ritenour-Miller – Consumer Safety Technician James Moore, PharmD, M.A. – Regulatory Project Manager Phillip Davis, MD – Medical Officer Division of Medical Imaging Products (DMIP)		FROM(Division/Office): Michelle Safarik, PA-C – Regulatory Review Officer Division of Drug Marketing, Advertising, and Communications (DDMAC)		
DATE: May 13, 2010	IND NO.	NDA NO. 022454	TYPE OF DOCUMENT:	DATE OF DOCUMENTS:
NAME OF DRUG: DaTscan (loflupane I 123 Injection) for Intravenous Use	PRIORITY CONSIDERATION: Yes	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE: June 11, 2010	
NAME OF FIRM: GE Healthcare				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER				
<input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> FINAL PRINTED LABELING				
<input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> LABELING REVISION				
<input checked="" type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> SAFETY <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE				
<input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> PAPER NDA <input type="checkbox"/> FORMULATIVE REVIEW				
<input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> OTHER (SPECIFY BELOW):				
<input type="checkbox"/> MEETING PLANNED BY				
COMMENTS/SPECIAL INSTRUCTIONS:				
DDMAC is reviewing a proposed sales aid and proposed journal ad for the anticipated launch of DaTscan. (We acknowledge the ^{(b) (4)} lack of action date for the drug at this time.) Please see our specific questions below, and please feel free to comment on any other concerns with these proposed promotional materials.				
This consult request, the proposed promotional materials, and draft PI will be placed into DARRTS, and the references will be sent electronically via zip file.				
Thank you, Michelle Safarik, 6-0620				
SIGNATURE OF REQUESTER Michelle Safarik, PA-C		METHOD OF DELIVERY (Check one) <input type="checkbox"/> DARRTS and zip file		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		



NDA 22-454

INFORMATION REQUEST

GE Healthcare
Attention: Allison Mueller
Director, Global Regulatory Affairs
101 Carnegie Center
Princeton, NJ 08540-6231

Dear Ms. Mueller:

Please refer to your new drug application (NDA) dated March 6, 2009, received March 9, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DaTscan (Ioflupane I 123 Injection) for Intravenous Use, and to the Agency's Complete Response letter issued 12/23/2009 for this application.

We appreciate your responses and comments for the questions listed below. Your NDA is not currently under review and you are not obliged to respond. However, we believe your insight is useful to help us consider the potential clinical use of DaTscan and its handling as a controlled substance. If you choose to respond, supply your response as a general information amendment to your NDA, preferably within the next week. Your response will be handled as proprietary information and archived within your NDA.

1. Confirm the amounts (and range, if possible) of non-radioactive ioflupane present in the final DaTscan product.
2. What are the health consequences (if known) associated with a large oral or intravenous administration of a radioactive gamma emitting product such as Ioflupane I 123? Is it associated with any specific organ toxicity? Please comment on what could potentially happen to an individual after taking multiple vials of DaTscan (by any route of administration).
3. Will the radioactivity of DaTscan prevent consumption of large doses of the product? Explain.
4. Is the handling and distribution of DaTscan limited to radiopharmacies (what type) or specialized facilities?
5. What are the degradation products of DaTscan? Organic as well as inorganic?

6. According to the NDA material, DaTscan will be prepared upon demand. Who will be ordering DaTscan and how will it be dispensed? Are there special order forms to purchase radiopharmaceuticals?
7. DaTscan is available in 32 countries. Is DaTscan or ioflupane (non-radioactive form) controlled in any of the countries where it is registered/marketed? If so, by what countries and under what regulations? Is there evidence of abuse from any countries where DaTscan is registered/marketed?
8. Please describe what will be done with manufactured DaTscan drug product which is not distributed to radiopharmacies and/or end users.

If you have any questions, please call James Moore, Regulatory Project Manager, at (301) 796- 2050.

Sincerely,

{See appended electronic signature page}

Frank Lutterodt, M.S.
Regulatory Project Manager
Division of Medical Imaging and Hematology
Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22454	GI-1	GE HEALTHCARE INC	DA TSCAN
NDA-22454	ORIG-1	GE HEALTHCARE INC	DA TSCAN

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/s/

FRANK A LUTTERODT
05/04/2010
Signing for James Moore

Telephone Conference between the Division of Medical Imaging and Hematology Products, Controlled Substance Staff and GE HealthCare, Monday, December 7, 2009, 8AM-9AM, Conference Room 1311, White Oak Campus, 10903 New Hampshire Avenue, Silver Spring Maryland 20903

Subject: Pending NDA 22-454 DaTscan (I-123 Ioflupane)

GE Healthcare Attendees:

Allison Mueller, Director, Global Regulatory Affairs
PK Narang, Head, Regulatory Affairs
Gill Farrar, Project Director
Paul Sherwin, Clinical Project Leader
Paul Jones, Senior Scientist
Stephen Lightfoot, Business Leader
Rob Sgroi, Marketing Brand Manager

FDA Attendees:

Rafel Rieves, M.D., Director, DMIHP
Libero Marzella, M.D., Ph.D., Clinical Team Leader, DMIHP
Michael Klein, Ph.D., Director, Controlled Substance Staff
Silvia Calderon, Ph.D., Pharmacology Team Leader, Controlled Substance Staff
Sandra Saltz, Project Manager, Controlled Substance Staff
Chad Reissig, Ph.D., Pharmacologist, Controlled Substance Staff
Young Moon Choi, Ph.D., Clinical Pharmacology Team Leader, OCP
Richard Fejka, M.S., Radiopharmacist, OODP
James Moore, PharmD., M.A., Project Manager, DMIHP

Background

This meeting was scheduled by the DMIHP to discuss with GE the progress of the review of the DaTscan application by the Controlled Substance Staff, update GE on the review of the labeling of the product and discuss the proposal by GE Healthcare to address the post marketing commitments in the Complete Response (CR) letter of September 8, 2009. After introductions, the meeting began.

Discussion

FDA's Controlled Substance Staff (CSS) began the discussion. The current status of the review of DaTscan, as well as FDA's preliminary assessment of the product, for regulation under the Controlled Substances Act were conveyed to GE Healthcare. FDA acknowledged that part of the review had been completed and according to the regulations, the precursor (b) (4) of the active ingredient in the product automatically placed the product in the category of a Schedule II controlled substance (narcotic). FDA stated, however, that an additional assessment would be made by the Controlled

Substance Staff

(b) (5)

GE HealthCare asked about their options with regard to expressing their position that the product should not be placed under the Controlled Substance Act. GE stated that designating DaTscan as a controlled substance would create an undue logistical burden on GE for distribution of the product and seriously limit patients' access to DaTscan. CSS attempted to clarify that by law their product was already a controlled substance because it is a derivative of (b) (4)/cocaine.

FDA responded that the GE assessment that the product should not be scheduled appeared to have merit, but stated that based on the regulations, and the chemistry of its precursor the product is automatically placed under the Controlled Substances Act as a Schedule II drug.

FDA recommended to GE Healthcare that they contact DEA directly and present their position on the product and see if it was possible to request an exemption for the product based on its pharmacology, manufacture, and any other issue that DEA should consider, including patient access. FDA recommended that GE contact DEA immediately to discuss their concerns about the scheduling of DaTscan as a controlled substance. GE said they would do so and would provide the justification for not scheduling the product. GE asked at what level of the DEA should contact be made and FDA recommended the Office of Diversion Control, Drug and Chemical Evaluation, Dr. Christine Sannerud (Chief).

GE asked how much time FDA required to complete their assessment of the DaTscan product. FDA responded that the final review by the Controlled Substance Staff should be completed by the end of January or mid-February.

(b) (5)

FDA also conveyed to GE Healthcare that the Division had requested a CSS review of the label for DaTscan and the CSS was working on providing the language that should be incorporated in the label designating DaTscan as a Schedule II controlled substance.

FDA stated that after review of the labeling was completed, FDA would provide the label to GE and GE could then decide if they chose to accept the labeling or not. FDA stated, since the product would be scheduled, if GE did not accept the labeling as proposed by FDA, the product could not be approved and a CR letter would be issued.

The postmarketing commitments cited in the September 8, 2009 Complete Response (CR) letter were also discussed. GE proposed to conduct a retrospective study to satisfy the postmarketing commitments from the September 8, 2009 letter. GE proposed revising [REDACTED] (b) (4)

FDA asked GE Healthcare for more details about the study. GE provided the following information. GE stated that there were (b) (4) images from South America, and (b) (4) from London. GE asked if FDA agreed to this new plan to satisfy the commitments. FDA said that GE had not provided enough information for FDA to make a definitive decision on the adequacy of the proposed design. FDA said that acceptance of the proposal was dependent on (1) the quality of the data (2) the centers where the trials were conducted, and (3) the quality of the images acquired. FDA requested that GE provide more detail in a submission to the NDA and FDA would then determine if what GE proposed was acceptable.

Summary

FDA provided an update to GE on the status of the review of DaTscan as a controlled substance under the Controlled Substances Act. FDA stated, according to the Code of Federal Regulations (21 CFR part 1300 to end) governing recommendations for the placement of substances under the Controlled Substances Act, any product containing cocaine [REDACTED] (b) (4) or one of its derivatives is automatically controlled under the Controlled Substances Act in a similar manner as cocaine [REDACTED] (b) (4), that is, as a Schedule II narcotic. Products designated as controlled substances under the CSA can be removed from the schedules if decontrolled by DEA, based upon a scientific/medical evaluation and recommendation by HHS, and possibly by exemption by the DEA, if they deem appropriate. FDA advised GE Healthcare to seek input from the DEA as soon as possible regarding these possibilities and the regulations that need to be applied to their product.

GE Healthcare will provide a revised proposal for addressing the post marketing commitments from the September 8, 2009 action letter in a submission to the NDA for the Division's review.

The minutes were prepared by James Moore, Project Manager.

James Moore, PharmD., M.A.
Project Manager, DMIHP

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22454

ORIG-1

GE HEALTHCARE
INC

DA TSCAN

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/s/

JAMES W MOORE

12/24/2009



NDA 22-454

ACKNOWLEDGE CLASS 1 RESPONSE

GE Healthcare
Attention: Allison Mueller
Senior manager, Regulatory Affairs
101 Carnegie Center
Princeton, New Jersey 08540-6231

Dear Ms. Mueller:

We acknowledge receipt on October 27, 2009 of your October 26, 2009 resubmission to your new drug application for DaTSCAN, (Ioflupane I-123) Injection 2mCi/mL at calibration time.

We consider this a complete, class 1 response to our September 8, 2009 action letter. Therefore, the user fee goal date is December 24, 2009.

If you have any questions, call me at (301) 796-2050.

Sincerely,

{See appended electronic signature page}

James Moore, PharmD, M.A.
Project Manager
Division of Medical Imaging and
Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22454

ORIG-1

GE HEALTHCARE
INC

DA TSCAN

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/s/

JAMES W MOORE

11/20/2009

Record of telephone Conversation

Today's date: November 13, 2009

Speakers: Dwaine Rieves for FDA and Fred Longnecker for GE Healthcare

Re: NDA 22-454

Mr. Longnecker called me this afternoon and said he'd tried to call Dr. Moore and couldn't reach him so they called me. He asked about the CSS status and I said, best I could recall, that we have recently received a note that seemed to indicate CSS was classifying the product as class II and that the company was supposed to request exemption from DEA. I stated that I didn't have these details clear yet and that the review team was trying to decipher what this meant. I mentioned that the review team would try to get back in touch with them as soon as possible.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22454	GI-1	GE HEALTHCARE INC	DA TSCAN

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/s/

RAFEL D RIEVES
11/13/2009

REQUEST FOR CONSULTATION

TO (Office/Division): **Controlled Substances Staff**

FROM (Name, Office/Division, and Phone Number of Requestor): **James Moore, RPM (301) 796-1986 Phillip Davis, Clinical Reviewer 796-4252**

DATE
October 5 30, 2009

IND NO.
101,106

NDA NO.
22-454

TYPE OF DOCUMENT
Consult

DATE OF DOCUMENT
March 6, 2009

NAME OF DRUG
DaTSCAN

PRIORITY CONSIDERATION
Very High

CLASSIFICATION OF DRUG
1P

DESIRED COMPLETION DATE
November 5, 2009

NAME OF FIRM: **GE HealthCare**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: This product is a radiopharmaceutical that will be used to evaluate loss of nigrostriatal dopaminergic neurons in the brain. It is a cocaine analog. The DMIHP is requesting that you evaluate the product that is the subject of the NDA for its abuse potential and/or whether it should be considered for placement under the Controlled Substances Act. This is an electronic submission and the application may be found in the electronic document room under NDA 22-454 (DaTSCAN). The Applicant's evaluation of the abuse potential of the product is located in the m1 folder and the file name is controlled-substance.pdf. The product was the subject of an advisory committee meeting on August 11, 2009. A Compete Response Letter was issued for the product on September 9, 2009. Included with this consult is additional information regarding this product.

September 30, 2009

Division of Medical Imaging and Hematology Products

Consultation Comments/Special Instructions Continued

NDA: 22454 (Datscan)
Submission Date: 3/06/2009
Investigational agent: ioflupane I-123
Sponsor: GE Healthcare
Proposed Use: Diagnostic Brain Imaging
Clinical Reviewer: Phillip Davis, MD

Background and Considerations for Evaluation of Datscan for Scheduling under the CSA: Datscan is a diagnostic radiopharmaceutical containing tracer amounts (sub microgram) of Iodine-123 labeled ioflupane, which is derived from cocaine. Datscan is used to image the dopamine transporter protein in the brain in patients with Parkinsonian Syndromes using nuclear medicine cameras. The drug product is supplied in solution form in a single use vial (5 millicurie radioactive dose) containing a maximum of 0.33 micrograms of ioflupane. Datscan is manufactured (b) (4)

Datscan has a physical half life of 13 hours (b) (4)

It is administered in a nuclear medicine department as a single dose injection prior to imaging.

Datscan binds reversibly to the dopamine transporter protein found in the axon terminals (located in the striatum) of pre-synaptic nigrostriatal neurons, and is used as an indirect method to detect the loss of nigrostriatal neurons. Pharmacological effects are not observed in humans following the intravenous administration of the proposed dose of ≤ 0.325 micrograms. Estimates from phase 2 studies indicate that Datscan occupies less than 1% of DaT proteins in the brain, with no expected pharmacological effect at this level of occupancy.

Phase 1 studies of Datscan revealed approximately 96% clearance from the blood at 15 minutes post injection, decreasing to 1% of the injected dose at 48 hours. Brain uptake was 7% of the injected Datscan dose, with 30% of brain uptake located in the striatum. Datscan is primarily excreted in the urine, with approximately 60% of injected dose voided by 48 hours.

In justification of why Datscan can not be subject to abuse, the sponsor estimates that to achieve a pharmacological effect, approximately 6000 vials of Datscan would have to be administered to a patient. This quantity of drug product would not be available at any point in time. Additionally, the sponsor estimates that extracting enough ioflupane from Datscan vials to produce a pharmacologically-active dose would require thousands of vials and would be impossible given the manufacturing limitations. Furthermore, retro-synthesis of cocaine from Datscan would similarly require large quantities of Datscan vials, which would not be available to anyone.

The sponsor estimates over (b) (4) doses of Datscan have been administered to patients in Europe and the UK, and there have been no reports of any pharmacological effects or abuse potential in the post-marketing or clinical trial data. The maximum dose of ioflupane administered to a patient undergoing medical imaging with DaTSCAN is 0.325 micrograms. Extrapolating from rodent studies, the sponsor estimates the dose required for a human no-effect-dose in a 60-kg man is 288 micrograms. To achieve this, 886 vials of DaTSCAN would have to be administered. To achieve a cocaine-like high (based on human transporter occupancy studies), a 60-kg man would have to receive 1921 micrograms, the contents of 5910 Datscan vials. The sponsor states that in 2008, no single shipment to any end-user institution exceeded (b) (4). Additionally, the sponsor states the no-effect-dose and the effectual-dose would be independently lethal by virtue of the injected volume and the non-ioflupane constituents of DaTSCAN.

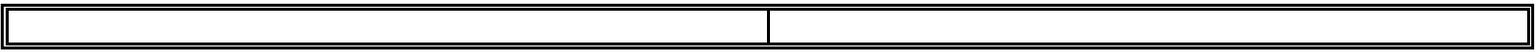
In conclusion, the division agrees that DaTSCAN has no abuse potential and should be considered for exemption from Controlled Substance regulations.

SIGNATURE OF REQUESTOR
James Moore

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER



Appears this way on original

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22454	ORIG-1	GE HEALTHCARE INC	DA TSCAN

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/s/

JAMES W MOORE
10/05/2009

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 2, 2009
TIME: 10:00 – 10:30 AM EST
LOCATION: Teleconference, WO Bldg 22, Room 4322
APPLICATION: NDA 022454
DRUG NAME: Datscan (ioflupane I 123 Injection)
TYPE OF MEETING: Guidance Meeting

MEETING CHAIR: Denise Baugh, Safety Evaluator, DMEPA, OSE

MEETING RECORDER: Catherine Carr, Safety Regulatory Project Manager, OSE
Janet Anderson, Safety Regulatory Project Manager, OSE

FDA ATTENDEES: (Title and Office/Division)

Office of Surveillance and Epidemiology

Carol Holquist, RPh, Director, DMEPA, OSE
Todd Bridges, RPh, Team Leader, DMEPA, OSE
Denise Baugh, Pharm.D., M.B.A., BCPS, Safety Evaluator, DMEPA, OSE
Janet Anderson, Pharm.D., Safety Regulatory Project Manager, OSE
Catherine Carr, M.Sc., Safety Regulatory Project Manager, OSE

Division of Medical Imaging and Hematology

Rafel Dwaine Rieves, M.D., Director, DMIHP, OND
James W. Moore, Pharm.D., Regulatory Health Project Manager, DMIHP, OND

EXTERNAL CONSTITUENT ATTENDEES:

GE Healthcare

Marisa Coyle, Manager Regulatory Affairs
Susan Elliott, Senior Manager Regulatory Affairs
Allison Mueller, Director Global Regulatory Affairs
Prem Narang, Head Global Regulatory Affairs
Robert Sgroi, Senior Brand Manager

BACKGROUND:

Reference is made to RCM # 2009-744 for the tradename review of Datscan.

The sponsor submitted a request for a review of the proposed proprietary name Datscan, which was subject to a pending NDA application (PDUFA date of September 9, 2009). Upon review of the submission, DMEPA concluded that the name “Datscan” was conditionally acceptable provided that the presentation of the name be represented on all labels and labeling as described in the proprietary name “Granted” letter, dated July 14, 2009.

On August 21, 2009, the sponsor submitted a response to DMEPA's comments, which stated that they prefer not to adopt the changes recommended by DMEPA for reasons related to global branding. The sponsor noted that the product was currently approved in Europe.

The Agency requested a teleconference with the sponsor to discuss the presentation of the proposed proprietary name, Datscan.

MEETING OBJECTIVES:

The purpose of this meeting was to discuss the sponsor's submission, dated August 21, 2009, and to reach an agreement regarding the presentation of the proposed proprietary name, Datscan.

DISCUSSION POINTS:

Following introductions, the Agency took the opportunity to provide clarification for their recommendations regarding the presentation of the name Datscan, as cited in their correspondence, dated July 14, 2009. The Agency recognized the sponsor's preference to present the name with a capital "D", small 'a' in red, and capital TSCAN (DaTSCAN). The Agency explained that tall man lettering (i.e., TSCAN) is used to avoid name confusion.

The sponsor expressed appreciation for the explanation, as the Agency's rationale was not initially clear to them. However, the sponsor indicated that they strongly prefer the name presentation as "DaTSCAN" for the purpose of global branding. They asked if the Agency's decision was a mandate or a preference/recommendation.

The Agency further explained that the FDA and the U.S. Pharmacopeia (USP) are trying to standardize the presentation of names to prevent the use of tall man lettering except for the differentiation of names in order to help minimize name confusion and medication errors. When tall man lettering is used out of context, it minimizes effectiveness. Therefore, the Agency stated that they prefer for the name to not use tall man lettering. The Agency confirmed that the recommendation was not to change the name, just the presentation of the name.

The sponsor asked if the Agency would be agreeable to the use of all capital letters in the name. The Agency replied that this was agreeable. The sponsor then referred to "AdreView", which was just approved last year with capital "A" and "V" and asked if they could use the same approach. The sponsor stated that it would be nice to separate the "Dat" from the "scan", which would be consistent with "AdreView" (Adre in red and View in blue).

The Agency pointed out that DaTSCAN stands out for a medical/scientific reason (i.e., visualizing the dopamine transporter and the red lettering implies "hot spot"). The Agency also questioned whether the colors used in the presentation of DaTSCAN would be viewed as promotional.

The sponsor recommended "DaTscan" (DaT in red and scan in blue). The Agency requested that the sponsor submit mock-up labels for their review of the actual presentation of lettering and the colors against a white background. The sponsor stated that they would first email a PDF file to

the OSE Safety Project Managers then follow up with an official submission to the application as an amendment to a pending CMC supplement. The sponsor reiterated that they would model the presentation of the name after “AdreView”.

POST-MEETING NOTES:

On September 3, 2009, the sponsor provided revised labeling via email. Per the DMEPA Safety Evaluator’s email, dated September 3, 2009, the revised labeling was reviewed and looked acceptable per the discussions during the September 2, 2009 teleconference. The sponsor submitted the revised vial and shield labels to the application on September 8, 2009, which incorporated the agreed-upon presentation of the trade name “DaTscan”.

DECISIONS (AGREEMENTS) REACHED:

The OSE Safety Regulatory Project Manager contacted the sponsor via telephone on September 11, 2009 and informed them that the presentation of the trade name “DaTscan” as submitted to the NDA on September 8, 2009, was acceptable to OSE.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22454	ORIG-1	GE HEALTHCARE INC	DA TSCAN

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/s/

CATHERINE A CARR
09/18/2009

RECORD OF TELEPHONE CONVERSATION

Today's date: August 31, 2009

Speakers: Dwaine Rieves for FDA and Fred Longnecker for GE Healthcare

Subject: Labeling for NDA 22454 (Datscan)

I called Mr. Longnecker and told him our draft labeling would be forthcoming and I explained that we had modified the indication from that discussed at the Advisory Committee. I explained that we can talk later if that will be useful.

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/s/

RAFEL D RIEVES
09/02/2009

August 28, 2009

Regarding your pending application for Datscan, (Ioflupane I 123), N22-454, the reviewing chemist has the following comments and requests.

Please revise the labels submitted in the June 25, 2009 amendment as stated below.

1. Revise the statement “Ioflupane I 123 5 mCi (185 MBq) in 2.5 mL solution at calibration” to “ 185 MBq (5 mCi) in 2.5 mL at calibration” on both the carton and container labels.
2. In the quantitative statement revise “ contains 2 mCi (74 MBq) of Ioflupane I 123 at calibration” to “contains 74 MBq (2 mCi) of Ioflupane I 123 at calibration” on both the carton and container labels.

Additionally, your responses to the trademark name and relocation of the NDC number are under review.

If you have questions, contact me at (301) 796-2050.

James Moore, PharmD., M.A.
Project Manager, DMIHP

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/s/

JAMES W MOORE
08/31/2009

August 22, 2009

Attached is the statement from the PeRC granting a full waiver of pediatric studies for pending NDA 22-454, DaTSCAN.

The DaTSCAN (loflupane I-123) full waiver was reviewed by the PeRC PREA Subcommittee on July 08, 2009. The Division recommended a full waiver because studies would be impossible or highly impracticable and because the disease/condition does not exist in children. The PeRC agreed with the Division to grant a full waiver for this product.

The PeRC has requested that the Division modify the pediatric page to reflect the reason for waiver as too few children with disease/condition to study.

James Moore, PharmD., M.A.
Project Manager, DMIHP

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/s/

JAMES W MOORE
08/22/2009

August 14, 2009

Product Quality Microbiology Information Request #2

Regarding your pending NDA for your product DaTSCAN, N22-454, the reviewing microbiologist has the following additional requests.

1. Please provide a summary of the validation studies and results to validate the (b) (4)
[REDACTED]
2. Please provide a summary of the validation studies and results (e.g., media fills) to validate the (b) (4)
[REDACTED]

You should respond to this request by COB, Tuesday, August 18, 2009.

If you have questions, call me at (301) 796-2050.

James Moore, PharmD., M.A.
Project Manager, DMIHP

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/s/

JAMES W MOORE

08/14/2009

August 6, 2009

Regarding your pending NDA 22-454 for DaTSCAN (Ioflupane I-123), the reviewing microbiologist has the following comments and requests.

Product Quality Microbiology Information Request:

The referenced Master File (b) (4) does not contain adequate (b) (4)

Please provide a summary of the validation studies and results to validate the (b) (4)

You should provide this information to the Division by COB Tuesday, August 11, 2009.

If you have questions, contact me at (301) 796-2050.

James Moore, PharmD., M.A
Project Manager, DMIHP

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/s/

JAMES W MOORE
08/06/2009

Attachment

Dear Ms. Mueller,

Please refer to your NDA 22-454 for DaTSCAN™ [Ioflupane I¹²³ Injection]. We have the following questions regarding your NDA in which we need an urgent reply.

According to the US CSR, the original mismatch analysis for Study DP008-003 described in the protocol was not performed, but rather mismatches between DaTSCAN™ results and clinical diagnoses were followed-up with the sites (See quote below). Please explain this process. In particular, was every mismatch followed-up?

If not every mismatch was followed up, how many were followed-up and how was it decided which ones to follow-up?

Did follow-up result in changes to either the DaTSCAN™ results or the clinical diagnoses?

How many follow-ups resulted in a change to the DaTSCAN™ results?

How many follow-ups resulted in a change to the clinical diagnoses?

What blinding procedures were in place for this process?

Please respond to these questions with in 72 hours.

Also, please provide a list of all subjects that were followed-up with the sites. Include the DaTSCAN™ and diagnosis results before and after the follow-up, the reason for the follow-up, and the reason for any revision to the results. Please provide this list within seven days.

“A mismatch analysis was not performed as described in Section 9.5.1.7. It was the intention, according to the protocol, to facilitate the mismatch discussion immediately after the Blinded Read with the same panel. As the logistics of the Blinded Read panel changed from the intended format, it was decided to follow-up each mismatch with the corresponding study site to elicit further data where possible.” Page 52 or 85 US CSR.

Sincerely,

Diane Leaman, SRPM
Division of Medical Imaging and
Hematology Products
Office of Oncology Products
Center for Drug Evaluation and Research

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/s/

Diane V Leaman
7/22/2009 11:55:16 AM
CSO



NDA 22-454

**PROPRIETARY NAME REQUEST
- CONDITIONALLY ACCEPTABLE**

GE Healthcare, Inc.
101 Carnegie Center
Princeton, New Jersey 08540-6231

ATTENTION: Allison Mueller
Director, Regulatory Affairs

Dear Ms. Mueller:

Please refer to your New Drug Application (NDA) dated March 6, 2009, received March 9, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ioflupane I 123 Injection, 2 mCi/mL at calibration time.

We also refer to your April 16, 2009, correspondence, received April 17, 2009, requesting review of your proposed proprietary name, DaTSCAN. We have completed our review of the proposed proprietary name, DaTSCAN and have concluded that it is acceptable on the condition that the last five letters, '-TSCAN' be presented in lower case letters so it reads 'Datscan' on all labels and labeling.

Presenting the '-TSCAN' portion of the name in capital letters is consistent with lettering which is typically reserved for differentiating known look-alike established name pairs or in rare circumstances for proprietary name pairs to help reduce the risk of name confusion resulting in medication error. Since 'DaTSCAN' is not a name that has been involved in name confusion, the capitalization of the letters 'TSCAN' is inappropriately applied.

The proposed proprietary name, Datscan, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your April 16, 2009 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Janet L. Anderson, Pharm.D., Safety Regulatory Project

NDA 22-454

Page 2

Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application, contact James Moore, Pharm.D., Regulatory Project Manager in the Office of Medical Imaging and Hematology Products at (301) 796-2050.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

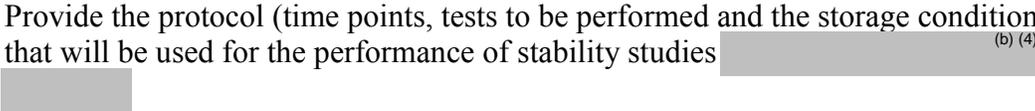
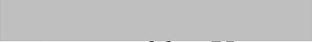
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/s/

Carol Holquist
7/14/2009 07:35:55 PM

June 11, 2009

Regarding your pending NDA 22-454 for DaTSCAN (Ioflupane I-123), the reviewing chemist has the following comments and requests.

1. You have stated that USP grade ethanol is one of the excipients in your product. In the USP, ethanol is not listed as ethanol, it is listed as Alcohol or Dehydrated Alcohol. Clarify which material is used and submit the corrected terminology to the NDA file.
2.  (b) (4)
3. Provide the protocol (time points, tests to be performed and the storage conditions) that will be used for the performance of stability studies  (b) (4)
4. The pH data shows that at  (b) (4)  The proposed acceptance criterion for the pH is therefore not acceptable. You must tighten the pH range limit to 4.2 to 5.2.
5. You have proposed a specific activity range of  (b) (4)  at reference time, while the proposed expiration dating period is 7 hours after the time of reference. The drug product must meet these specifications throughout its shelf-life. Provide acceptance criteria for specific activity that must be met throughout the shelf-life of the product.
6. You indicate that the lower limit of specific activity was chosen so that the maximum level of dopamine transporter occupancy in the human striatum following administration of a whole vial of the product (5 mCi) would not exceed  (b) (4). However, based on the proposed specification the specific activity  (b) (4)  Provide calculations showing the mass needed for  (b) (4) receptor occupancy. Also, provide supporting information to justify that the variation of mass in the proposed specific activity range will not have a significant effect on the efficacy of the drug as provided in the proposed indication.
7. Provide tabular data on clinical lots (individual patient data) to indicate the actual specific activity of the product at the time of administration.
8. Since the  (b) (4)   products could also form under your specified manufacturing conditions, clarify if the TLC method used to determine radiochemical purity has the specificity to distinguish these products from [¹²³I]

ioflupane and other specified impurities. The specificity of the method should be such that potential radiochemical impurities are clearly identified.

You should provide this information to the Division by COB Friday, June 19, 2009.

If you have questions, contact me at (301) 796-2050.

James Moore, PharmD., M.A
Project Manager, DMIHP

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/s/

James Moore
6/11/2009 10:52:46 AM
CSO

REQUEST FOR CONSULTATION

TO (Office/Division): ODS

FROM (Name, Office/Division, and Phone Number of Requestor): James Moore, PM (301) 796-1986 Phillip Davis, Clinical Reviewer (301) 796-4252

DATE
June 10, 2009

IND NO.
101,016

NDA NO.
22-454

TYPE OF DOCUMENT
Consult

DATE OF DOCUMENT
March 6, 2009

NAME OF DRUG
DaTSCAN (Ioflupane I-123)

PRIORITY CONSIDERATION
Very High

CLASSIFICATION OF DRUG
1P

DESIRED COMPLETION DATE
August 10, 2009

NAME OF FIRM: GE HealthCare

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
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| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: This product is a radiopharmaceutical that will be used to evaluate loss of nigrostriatal dopaminergic neurons in the brain. It is a cocaine analog. The DMIHP is requesting that you evaluate the risk management plan submitted in the NDA to determine if the plan as proposed is comprehensive enough to effectively evaluate the safety risks of this product. In addition, please provide any comments on the possible safety risks of the product that you find during this assessment. This is an electronic submission and the application may be found in the electronic document room under NDA 22-454 (DaTSCAN). The risk assessment plan is located in the m1 folder and the file name is risk-mangement-plan.pdf. The product will be the subject of an advisory committee meeting on August 11, 2009. The PDUFA date is September 9, 2009.

SIGNATURE OF REQUESTOR
James Moore

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

James Moore
6/10/2009 11:19:56 AM

REQUEST FOR CONSULTATION

TO (Office/Division): **Controlled Substances Staff**

FROM (Name, Office/Division, and Phone Number of Requestor): **James Moore, RPM (301) 796-1986 Phillip Davis, Clinical Reviewer 796-4252**

DATE
June 9, 2009

IND NO.
101,106

NDA NO.
22-454

TYPE OF DOCUMENT
Consult

DATE OF DOCUMENT
March 6, 2009

NAME OF DRUG
DaTSCAN

PRIORITY CONSIDERATION
Very High

CLASSIFICATION OF DRUG
1P

DESIRED COMPLETION DATE
August 14, 2009

NAME OF FIRM: **GE HealthCare**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: This product is a radiopharmaceutical that will be used to evaluate loss of nigrostriatal dopaminergic neurons in the brain. It is a cocaine analog. The DMIHP is requesting that you evaluate the product that is the subject of the NDA for its abuse potential and/or whether it should be considered for placement under the Controlled Substances Act. This is an electronic submission and the application may be found in the electronic document room under NDA 22-454 (DaTSCAN). The Applicant's evaluation of the abuse potential of the product is located in the m1 folder and the file name is controlled-substance.pdf. The product will be the subject of an advisory committee meeting on August 11, 2009. The PDUFA date is September 9, 2009.

SIGNATURE OF REQUESTOR
James Moore

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

James Moore
6/10/2009 11:52:25 AM



NDA 22-454

**PROPRIETARY NAME REQUEST
ADVICE/ACKNOWLEDGMENT**

GE Healthcare, Inc.
101 Carnegie Center
Princeton, New Jersey 08540-6231

ATTENTION: Allison Mueller
Director, Regulatory Affairs

Dear Ms. Mueller:

Please refer to your New Drug Application (NDA) dated March 6, 2009, received March 9, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ioflupane I 123 sterile solution for intravenous injection, 2 mCi/ml at calibration time.

We also refer to your April 16, 2009, correspondence, received April 17, 2009, requesting a review of your proposed proprietary name, DaTSCAN.

We note that you have also included an alternate proprietary name (b) (4) in your submission. We will not initiate review of this alternate name as part of this review cycle. If the proposed proprietary name DaTSCAN, is denied or withdrawn, you must submit a new complete request for review of the alternate name.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Janet L. Anderson, Pharm.D., Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application, contact James Moore, Pharm.D., Regulatory Project Manager in the Office of Medical Imaging and Hematology Products at (301) 796-2050.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

Carol Holquist
6/1/2009 08:42:35 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-454

GE Healthcare
Attention: Allison Mueller
Senior Manager, Regulatory Affairs
101 Carnegie Center
Princeton, New Jersey 08540

Dear Ms. Mueller:

Please refer to your new drug application (NDA) dated March 9, 2009, received March 10, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for DaTSCAN (Ioflupane I 123) 2mCi/mL.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is September 9, 2009.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by August 26, 2009.

During our filing review of your application, we identified the following potential review issues:

1. As stated in the type C meeting on August 20, 2008, we have concerns regarding the “principal studies to support U.S. approval”. These concerns include the selection of clinical diagnosis as a standard of truth, as well as the lack of pre-specified primary endpoints for determining sensitivity and specificity. We are concerned that the U.S. study reports created from the European clinical development program may not provide the primary basis for determining whether there is substantial evidence to support the

claim of effectiveness of DaTSCAN in detecting loss of functional nigrostriatal dopaminergic neurons, especially as it relates to its association with Parkinson's disease (PD).

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information.

1. For each principal study, please summarize the differences between the original study report and the United States version. The summary should include for both study reports: the primary efficacy population, the primary version of the image read including time point, the primary standard of truth including time point, the primary endpoints, and the primary statistical analysis. You should provide a table summarizing this information.
2. In study PDT408, the standard of truth is the clinical diagnosis at 24 months. Does the clinician responsible for the 24 month diagnosis have access to either (1) the baseline Visit 2 DaTSCAN image or (2) clinical diagnosis or management decisions based on this image?
3. For Study PDT301, the protocol discusses that subjects will be excluded from the efficacy analysis if the DaTSCAN image is inadequate and this is not attributed to the use of DaTSCAN. Please provide the criteria for the decision on whether the inadequate image is attributed to DaTSCAN.
4. For Studies PDT301 and PDT304, the Statistical Reports state that an image classified to the "Other" category will be reclassified by study team into the normal/abnormal categories. Please provide the criteria for the reclassification. Also, was reclassification performed blinded to the standard or truth and clinical information?
5. For Study DP008-003, what blinding procedures were used for the institutional read of the DaTSCAN image? Was the patient identity or clinical information available to the reader?
6. For the Walker Study, what blinding procedures were used for the neuropathological diagnosis? Was the DaTSCAN image or clinical information available for the diagnosis?
7. For the Walker Study, the original study included Parkinson disease patients. However, the longitudinal study does not appear to contain these patients. Is that the case? Also, if they were excluded, at what stage were they excluded and for what reasons?
8. For the Walker Study, in the DaTSCAN reads, the categories "slight reduction" and "significant reduction" were combined. Was this combination prespecified?

9. Provide the following for the (b) (4) starting material:
 - The (b) (4) as well as its interpretation to support the structure.
 - Copy of the Certificate of Analysis (COA) of a representative production lot.
 - Copy of representative HPLC and GC chromatograms for this material.
 - Data to support that the HPLC/GC methods are specific and capable of distinguishing (b) (4) from other related impurities.
10. Clarify whether lot 1003A-CYG of (b) (4) was used in the HPLC and TLC studies used to demonstrate the chemical equivalence of [¹²³I]-ioflupane with the (b) (4)
11. Clarify the maximum amount of radioactivity that can be used in a radio-labeling reaction (at the time of radio-labeling) and whether this amount has been validated with respect to the quality of product obtained.
12. Provide a list of parameters that were evaluated for criticality during the manufacture of [¹²³I]-ioflupane and why other parameters such as (b) (4) were not found to be critical.
13. Provide a representative chromatogram of a batch for the HPLC purification of [¹²³I]-ioflupane identifying the peak that is collected and approximate collection points.
14. Clarify whether the recovered (b) (4) procedures, specifications and data to support its use.
15. Clarify if any of the radionuclidic impurities present in (b) (4) solution are (b) (4) emitting radionuclides. You should control such radionuclides as specified impurities as part of the in-process products specifications.
16. Please provide a description of the (b) (4) and a summary of the validation studies for those (b) (4)

You should provide this information by COB Friday, June 12, 2009.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

Please note that this application will be discussed at an Advisory Committee Meeting scheduled for August 11, 2009.

If you have any questions, call James Moore, Regulatory Project Manager, at (301) 796-2050.

Sincerely,

{See appended electronic signature page}

Rafel "Dwayne" Rieves, M.D.
Director
Division of Medical Imaging and
Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Rafel Rieves

5/22/2009 03:45:43 PM

May 18, 2009

Regarding your pending NDA 22-454 for DaTSCAN, the following information is requested for all pivotal studies used to support the efficacy/safety of your pending NDA application:

Study Number, site location (hospital name, clinic name), complete address, telephone number, email address, site/study contact, fax number, Applicant's contact information.

Please provide this information as soon as possible, but no later than COB Wednesday, May 20, 2009.

You may send this information via email or fax initially if you choose and follow-up with a hard-copy submission to the NDA.

If you have questions, please contact me at (301) 796-2050.

James Moore, PharmD., M.A.
Project Manager, DMIHP

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/s/

James Moore
5/18/2009 11:51:43 AM
CSO

Industry Meeting between the Division of Medical Imaging and Hematology Products and GE Healthcare, Friday May 8, 2009, 9AM-11AM, Conference Room 1421, FDA White Oak Campus, 10903 New Hampshire Avenue, Silver Spring, Maryland 20903

Subject: Datscan (Ioflupane I 123) N 22-454

GE Healthcare Attendees:

[REDACTED] (b) (4)

Allison Mueller, Director, Global Regulatory Affairs
Prem Narang, Ph.D., Head Global Regulatory Affairs
Roger Pickett, B.S. Pharmacy, Ph.D., Non-Clinical Scientist
Paul Sherwin, M.D., Ph.D., Clinical Project Leader

FDA Attendees:

Phillip Davis, M.D., Clinical Reviewer, DMIHP
Mark Levenson, Ph.D., Statistical Reviewer, OB
Anthony Murgo, M.D., Deputy Director, OODP
Sunday Awe, Ph.D., MBA, Pharmacology/Toxicology Reviewer, DMIHP
Brenda Ye, M.D., Clinical Reviewer, DMIHP
Qi Feng, M.D., Clinical Reviewer, DMIHP
Liberio Marzella, M.D., Ph.D., Deputy Director, DMIHP
Lucie Yang, M.D., Clinical Reviewer, DMIHP
Yong Moon Choi, PhD., Team Leader, OCP
Eldon Leutzinger, Ph.D., Pharmaceutical Assessment Lead, ONDQA

Background

FDA requested this meeting to provide GE Healthcare an opportunity to present an overview of their product submitted under NDA 22-454. GE's slides from the presentation are attached.

Summary

GE's presentation provided additional insight into the application's contents and provided members of the Division and Office additional knowledge of the product. The meeting concluded at 11:00 AM.

James Moore, PharmD., M.A.
Project Manager, DMIHP

54 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22454	ORIG-1	GE HEALTHCARE INC	DA TSCAN

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/s/

JAMES W MOORE
08/29/2009

KYONG A KANG
09/03/2009



NDA 22-454

GE HealthCare
Attention: Allison Mueller
Director, Regulatory Affairs
101 Carnegie Center
Princeton, New Jersey 08540

Dear Ms. Mueller:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for DaTSCAN® (I-123, Ioflupane) Injection.

We also refer to the telephone conversation between FDA and GE HealthCare on April 17, 2009, in which scheduling of an Applicant Orientation meeting for your pending NDA 22-454 was discussed. This letter confirms the meeting and provides the meeting schedule. The meeting has been scheduled for:

Date: May 8, 2009

Time: 9:30 PM - 11:00 PM

Location: FDA White Oak Campus, Room 1311, Building 22, 10903 New Hampshire Avenue, Silver Spring, Maryland 20903

CDER Participants: Rafel Rieves, M.D., Division Director, DMIHP
Libero Marzella, M.D., Ph.D., Acting Deputy Division Director, DMIHP
Anthony Murgio, M.D., Deputy Office Director, OODP
Phillip Davis, M.D., Clinical Reviewer, DMIHP
Jyoti Zalkikar, Ph.D., Statistical Team Leader, OB
Mark Levenson, Ph.D., Statistical Reviewer, OB
Eldon Leutzinger, Ph.D., Pharmaceutical Assessment Lead, ONDQA
Ravindra Kasliwal, Ph.D., Chemistry Reviewer, ONDQA
Adebayo Lanionu, Ph.D., Pharmacology/Toxicology Team Leader, DMIHP
Sunday Awe, Ph.D., Pharmacology/Toxicology Reviewer, DMIHP
Young Moon Choi, Ph.D., Clinical Pharmacology Team Leader, OCP
Christy John, Ph.D., Clinical Pharmacology Reviewer, OCP
Bryan Riley, Ph.D., Microbiology Reviewer, OPS
Kyong Kang, PharmD., Chief, Project Management Staff
James Moore, PharmD., M.A., Project Manager, DMIHP

If you have any questions, call me at (301) 796-2050.

Sincerely,

{See appended electronic signature page}

James Moore, PharmD., M.A.
Project Manager
Division of Medical Imaging and Hematology
Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

James Moore

4/24/2009 07:58:19 PM

REQUEST FOR CONSULTATION

TO (Office/Division): **Robin Nighswander, CPMS, (301) 796-2250**

FROM (Name, Office/Division, and Phone Number of Requestor): **James Moore, PM (301) 796-1986, Phillip Davis, MD (301) 796-4252**

DATE
April 22, 2009

IND NO.

NDA NO.
22-454

TYPE OF DOCUMENT
NDA

DATE OF DOCUMENT
March 6, 2009

NAME OF DRUG
DaTSCAN

PRIORITY CONSIDERATION
Very High

CLASSIFICATION OF DRUG
1S?, P?

DESIRED COMPLETION DATE
Question 1-April 30, 2009
Question 2a,b-May 14, 2009

NAME OF FIRM: **GE HealthCare**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Question (1) The DMIHP requests evaluation of this application to determine whether it should be reviewed as a priority or standard application based on the following indication. Indication: "DaTSCAN is a radiopharmaceutical containing [123-I] ioflupane, indicated for detecting loss of functional nigrostriatal dopaminergic neurons by single photon emission computed tomography (SPECT) imaging in patients presenting with symptoms or signs suggestive of dopaminergic neurodegeneration." Question (2a) Please address whether and to what extent clinical diagnosis of PS and other disorders (Dementia with Lewy Bodies) at time of imaging or at 18 or 36 months post imaging can be used as a truth standard for SDD". Question (2b) Please provide a general opinion regarding the strength of the clinical and supportive data in the NDA and assist, as feasible, in the preparation for an advisory committee. This is an electronic application, but the link to the application could not be included here. To review the application, please go to the EDR and enter NDA #22-454 (DaTSCAN)

SIGNATURE OF REQUESTOR James Moore	METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

James Moore
4/24/2009 11:14:50 AM

April 10, 2009

Regarding your pending NDA for DaTSCAN, NDA 22-454, the reviewing clinical pharmacologist has the following requests.

- (1) You should provide in depth details on pharmacokinetic parameters such as AUC, T1/2 (elimination) etc.
- (2) You should provide a complete metabolic profile of DaTSCAN.

If this information is in the NDA, please state its location in your response.

Please respond to this request by COB Thursday, April 23, 2009.

If you have questions, contact me at (301) 796-2050.

James Moore, PharmD., M.A.
Project Manager, DMIHP

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/s/

James Moore
4/10/2009 06:48:55 PM
CSO

REQUEST FOR CONSULTATION

TO (Office/Division): **Pediatric and Maternal Health Staff/Maternal Health Team**

FROM (Name, Office/Division, and Phone Number of Requestor): **James Moore, Project Manager, DMIHP (301) 796-1986**

DATE
April 9, 2009

IND NO.

NDA NO.
22-454

TYPE OF DOCUMENT
N000

DATE OF DOCUMENT
March 9, 2009

NAME OF DRUG
DaTSCAN

PRIORITY CONSIDERATION
Moderate

CLASSIFICATION OF DRUG
IS

DESIRED COMPLETION DATE
June 9, 2009

NAME OF FIRM: **GE HealthCare**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
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| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
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| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: This is a New Drug Application. Please review sections of the proposed label as they relate to pregnancy and lactation. This submission can be found under NDA 22-454 (DaTSCAN) in the EDR. The M1 folder contains the labeling.

SIGNATURE OF REQUESTOR
James Moore

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

James Moore

4/9/2009 04:52:16 PM

March 25, 2009

Regarding your pending New Drug Application, NDA 22,454 for DaTSCAN, you must submit an amendment to your pending application requesting a proprietary name review. The request placed in the cover letter is insufficient to initiate the review of your product's proprietary name. You should refer to the "**Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names**" for additional guidance on the contents of the amendment. Your request for review of the product's proprietary name must be prominently displayed in your cover letter.

The review of the proprietary name cannot begin until the submission of this amendment. The amendment must contain all of the elements cited in the Guidance.

If you have questions, please contact me at (301) 796-2050.

James Moore, PharmD., M.A.
Project Manager, DMIHP

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this page is the manifestation of the electronic signature.**

/s/

James Moore
3/25/2009 12:40:15 PM
CSO



NDA 22-454

NDA ACKNOWLEDGMENT

GE Healthcare
Attention: Allison Mueller
Senior Manager, Regulatory Affairs
101 Carnegie Center
Princeton, New Jersey 08540

Dear Ms. Mueller:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: DaTSCAN™ (Ioflupane I-123) Injection

Date of Application: March 6, 2009

Date of Receipt: March 9, 2009

Our Reference Number: NDA 22-454

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 8, 2009 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Medical Imaging and Hematology
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call me at (301) 796-2050.

Sincerely,

{See appended electronic signature page}

James Moore, PharmD., M.A.
Project Manager
Division of Medical Imaging and Hematology
Products
Office of Oncology Drugs Products
Center for Drug Evaluation and Research

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/s/

James Moore
3/23/2009 03:27:06 PM

Industry Meeting Minutes for meeting between GE Healthcare and the Division of Medical Imaging and Hematology, Wednesday, August 20, 2008, 12 PM-1:30 PM, 10903 New Hampshire Avenue, Silver Spring Maryland, FDA White Oak Campus, Building 22, Conference Room 1313

Subject: DaTSCAN Pre-IND 101,016

GE Health Care Attendees:

Donald Black, M.D., Head, Research and Development
Giles Campion, M.D., Head, Global Research and Development
Patrick Cella, Manager, Technology
Gill Farrar, PhD, Project Director
Fred Longenecker, Director, Regulatory Affairs
Allison Mueller, Director, Regulatory Affairs
Roger Pickett, PhD, Nonclinical Scientist
Paul Sherwin, MD PhD, Clinical Project Leader

FDA Attendees:

Rafel Reives, M.D., Division Director, DMIHP
Christy John, Ph.D., Clinical Pharmacology Reviewer, OCP
Jyoti Zalkikar, Ph.D., Statistical Team Leader, OB
Anthony Mucci, Ph.D., Statistical Reviewer, OB
Alexander Gorovets, M.D., Clinical Team Leader, DMIHP
Scheldon Kress, M.D., Clinical Reviewer, DMIHP
Alexander Mohab, M.D, Clinical Reviewer, DMIHP
Qi Feng, M.D, Clinical Reviewer, DMIHP
Tushar Kokate, Ph.D., Pharmacology Toxicology Reviewer, DMIHP
Mina Holen, IT, OODP
Richard Fejka, M.S, Radiopharmacist, OODP
James Moore, PharmD, M.A., Project Manager, DMIHP

Background

This meeting was requested by GE Healthcare in a meeting request of May 16, 2008. In response to the meeting package of July 18, 2008 the following responses were provided.

August 19, 2008

We refer to your Pre-IND 101,016 (DaTSCAN) and to your submission, dated July 18, 2008 which contained the Meeting Information Package for the August 20, 2008 meeting. The Division of Medical Imaging and Hematology Products (DMIHP) review team has reviewed the submission and have the following comments (sponsor's questions are in bold italics, followed by our responses):

FDA PRELIMINARY COMMENTS

This material consists of the reviewers' preliminary comments in preparation for the discussion at the August 20, 2008 meeting between GE and the FDA Review Team. The material might not have been fully vetted internally and should not be considered as an official position of the FDA. The comments are shared with the Sponsor solely to promote a collaborative and successful discussion at the meeting. The minutes for the meeting will reflect agreements and discussion at the meeting and might not be consistent with these preliminary comments. These draft comments by FDA to GE are being communicated to Ms. Allison Mueller of GE on August 19, 2008.

Preclinical

Sponsor's Question 1:

Following the FDA's review of the non-clinical summary data included in the December 28, 2007 briefing package for the Type C meeting held on January 31, 2008, the FDA commented that additional toxicology studies may not be needed. In light of GE Healthcare's plan to provide additional non-clinical study data, to that outlined in the December 28, 2007 briefing package, does the FDA find the non-clinical package adequate to support filing an NDA?

FDA's Response 1:

Yes, the nonclinical package is adequate to support filing of an NDA.

Sponsor's Question 2:

Assuming technical comparability of the European DaTSCAN product with that manufactured at GE Healthcare's North Arlington Heights facility in Illinois, does the FDA agree that separate non-clinical toxicology studies are not required?

FDA Response 2:

Additional nonclinical studies may not be needed if the products are technically comparable (e.g. impurity profile). However, this will depend on the CMC review of the product.

Sponsor's Question 3:

As DaTSCAN is a single-dose radiopharmaceutical, GE Healthcare intends to request waivers for a reproductive toxicology, a long-term, repeat-dose toxicity, and a long term rodent carcinogenicity studies in accordance with FDA Guidance for Industry, entitled "Developing Medical Imaging Drug and Biological Products, Part 1: Conducting Safety Assessments (June 2004)". Does the FDA find this approach acceptable?

FDA's Response 3:

Yes, the proposed approach for waiver request is acceptable.

Clinical

Sponsor's Question 4

GE Healthcare is planning to file an NDA for DaTSCAN with existing clinical study data to support an indication of detecting loss of functional nigrostriatal dopaminergic neurons.

- a. ***GE Healthcare has completed a total of eight European clinical studies on DaTSCAN: one phase 1 (CY95.FP.I), two phase 2 (CY96.FP.II and PDT02005), four phase 3 (DP008-003, PDT03004 (aka PDT304), PDT301, PDT03007) and one phase 4 (PDT408). Of these studies, three have been deemed principal to support US registration of DaTSCAN for the proposed indication, namely DP008-003, PDT03004 (aka PDT304) and PDT301, with the addition of data to be provided from an investigator-initiated imaging clinicopathological correlation study (Walker Z et al, 2007), along with a literature summary. Does the FDA agree with this approach to support registration?***

FDA's Response 4a:

No, we do not agree.

We are concerned that that in none of the listed studies, performed by you, have you proposed a measure that has been validated or could be justified as a Standard of Truth (SOT) for the detection of the loss of functional nigrostriatal dopaminergic (FND) neurons. We are also concerned that the study reports you have selected to submit in the NDA as "principal studies to support US registration" do not provide the primary basis

for determining whether there is "substantial evidence" to support the claim of effectiveness of DaTSCAN in "detecting loss of functional nigrostriatal dopaminergic neurons", especially as it relates to its association with Parkinson's disease (PD). The development program in the Dementia with Lewy Bodies (DLB), as described by you to date, appears to be somewhat more robust.

Specifically, you propose to submit two "principal" studies for Parkinson's (#_003 and #_004) and two studies for DLB (#_301 and the still ongoing "Walker study").

The study #_003, conducted in Europe in '97-'98, involves 189 patients with either Parkinson's syndrome (PS) or Essential tremor (ET). The spectrum of PS diagnoses in this study is unclear and it is not clear how many patients with PS have PD and by what criteria each of the diagnoses is established. (PD rather than PS is the subject of your currently proposed claim for US). As the severity of the disease in the enrolled patients has not been clearly stated, it is possible that the conclusions of the study might not be relevant to the population of intended use.

Blinded reads in study #_003 appear to have been performed only for the secondary analyses and been conducted by consensus which could be subject to bias. No clear information on the uninterpretable images and the missing data has been identified in your submission. Please note that the core laboratory has to be available for inspection; the appearance of images and the method of presentation of images to the readers have to be thoroughly described in a reviewable charter-like document; all images have to be available, if requested, for demonstration, review, adjudication and inspection (the comments in reference to the conduct of blinded reads are applicable to all studies you plan to submit for review).

In addition, in reference to study #_003, the validity of a clinical SOT based on European criteria from 10 years ago and its relevance to current clinical practice in the US is unclear. The review of the study design has not identified a pre-specified clinically meaningful primary endpoint, and the results do not appear to show clinical utility or a "value added" for the use of your product. We are doubtful that this study, even upon full review, would be deemed adequate and well controlled for providing the substantial evidence of effectiveness necessary to support your claim.

Study #_004 involves 179 patients with either ET or with "early features of PS" (again, not PD) and was conducted in '99-'03. It might have been more representative of the population of intended use; however no clear pre-specified primary endpoint for measurement of a clinically relevant performance characteristic has been identified. Sensitivity and specificity appear to have been measured as secondary endpoints; validity of evaluation of videotaped clinical exams as the basis for a SOT assessment is not justified or clarified.

In study #_301, for the DLB indication, 326 patients have been studied to address the clinical utility of the proposed imaging methodology in the differential diagnosis of dementia (DLB vs. AD plus vascular), the clinical SOT appears to have been reasonably

selected, and the reads appear to have been adequately blinded. In the “Walker study”, we agree with the use of pathology based diagnosis as the SOT but note that only 23 patients have been studied to date.

As discussed previously, we recommend conducting a new Phase-3 study with a pre-specified clinically meaningful primary endpoint which would evaluate the diagnostic performance of your agent in the patient population of intended use, with the SOT consisting of a clinical diagnosis by a movement disorder specialist, and with DaTSCAN images being evaluated by the properly conducted blinded reads. It would also be preferable to involve a representative number of US sites in such a study.

Sponsor's Question 4b:

Does the FDA agree that the efficacy data from the three principal phase 3 studies (DP008-003, PDT03004 (aka PDT304J) and PDT301) and the Walker study (which demonstrated a correlation between reduced DaTSCAN striatal uptake and the presence of nigral cell loss in DLB cases) are adequate to support the proposed indication?

FDA's Response 4b:

Please see our response to the question 4a. above.

Sponsor's Question 4c:

To support labeling statements in the Clinical Studies Section of the package insert, we have identified one additional study (PDT408) as principal. We would appreciate the Agency's perspective on the strength of PDT408 to support labeling claims.

FDA's Response 4c:

Study#_408, involving 120 patients with an “uncertain“ diagnosis of PS (not PD) aims at assessing an impact of utilizing DaTSCAN on patient management and diagnostic confidence, with the measurements of sensitivity and specificity, obtained by non-blinded reads, serving as exploratory endpoints. It is unclear what labeling claims you plan to support with this study.

Sponsor's Question 5:

Does the FDA agree that the overall safety database for DaTSCAN is adequate for filing?

FDA's Response 5:

The proposed overall safety database appears to be adequate.

Format and Content

Sponsor's Question 6:

Does the FDA agree with the proposed electronic submission of the DaTSCAN NDA in accordance with the Common Technical Document (CTD) guidelines and using CDISC-compliant formats for principal clinical safety and efficacy data?

FDA's Response 6:

Yes. We agree.

Sponsor's Question 7:

In addition to the CTD summaries provided in Module 2 of the DaTSCAN NDA, GE Healthcare intends to provide an Application Summary, an Integrated Summary of Safety (ISS) and an Integrated Summary of Efficacy (ISE). Does the FDA find each of these documents necessary?

FDA's Response 7:

Yes.

Sponsor's Question 8ab:

In support of the safety database described in the ISS, GE Healthcare proposes the following:

- a. Individual study datasets and a pooled safety analysis dataset for all eight completed GE Healthcare-sponsored studies***
- b. Descriptive safety summary of the on-going PDT409 study, up to a data cut-off date (to be specified later), as well as a summary of one phase 1 clinical study from Japan and a summary of the post-marketing safety experience (based on experience in Europe); there were no safety data collected in the Walker study.***

Does the FDA find this approach acceptable?

FDA's Response 8 ab:

Yes. All available safety data, both as individual study data and as pooled data, should be submitted for analysis.

Sponsor's Question 9a:

In support of the ISE, GE Healthcare proposes the following:

Individual study datasets (CDISC-compliant) for the three principal phase 3 studies (DP008-003, PDT03004 (aka PDT304J and PDT301) for registration, an efficacy dataset from the Walker study (in Microsoft EXCEL), and PDT408 (supporting label statements)

FDA's Response 9a:

In general, the approach is acceptable.

Sponsor's Question 9b:

***A pooled efficacy analysis dataset (CDISC-compliant) for sensitivity and specificity values from studies DP008-003, PDT03004 (aka PDT304) and PDT301) to support the proposed indication; the pooled dataset will form the basis of the ISE
Does the FDA find this approach acceptable?***

FDA's Response 9b:

Pooling data will be acceptable as an exploratory analysis. We question the rationale for pooling data across two diagnostic categories and the relation of the pooled data analyses from the studies listed above to the claim sought by you in the indication statement.

Sponsor's Question 10:

GE Healthcare has identified a number of Japanese non-clinical studies on ioflupane (FP-CIT) that are relevant to DaTSCAN. These will be summarized in the NDA (CTD Modules 2.4 and 2.6). In Module 4 (Non-Clinical Study Reports) GE Healthcare intends to provide that original Japanese reports and full English translations for those studies deemed principal in supporting the application. For the remaining Japanese studies, which will be considered supportive, does the FDA agree it is acceptable to provide the original Japanese reports (including tabulated data in English) but with a translation of only the abstract rather than the full report?

FDA's Response 10:

Yes, in general, the approach is acceptable. It is acceptable to provide a translation of only the abstract and the tabulated data for the studies that you considered supportive as listed in your submission. However, if the agency determines that a full review of a supportive study is essential for a regulatory decision, a full translation of the Japanese report will be requested.

Sponsor's Question 11abcd:

With regard to the Clinical Study Reports (CSRs) for the GE Healthcare studies designated principal for registration (DP008-003, PDT03004 (aka PDT304J and PDT301), and PDT408 (intended to support label statements), GE Healthcare proposes the following:

- a. To prepare US versions of the CSRs, to include updated tables and figures (listings will not be provided) as a result of database conversion to CDISC-compliant format***
- b. For studies PDT03004 (aka PDT304J, PDT301, and PDT408, the US CSR will integrate both the core analysis period and the long follow-up period (the follow-up periods were originally reported separately as an addendum to the CSR)***
- c. Streamlining the analyses in the US CSRs for ease of review; specifically, to summarize in less detail than in the European CSR certain secondary and exploratory analyses that are not felt to add clinical value***
- d. To provide the European versions of the CSRs for reference***

FDA's Response 11abcd:

In general, the approach is acceptable. Please note that in reference to all processes listed above, you will have to show and confirm that the processes implemented by you are fully verifiable and valid.

Sponsor's Question 12:

With regard to the CSRs for the supportive studies (CY95.FP.I, CY96.FP.II, PDT02005, PDT03007) GE Healthcare intends to provide the European CSRs only, with the data tables and figures to be provided in PDF format (SAS datasets will not be provided). Does the FDA find this approach acceptable?

FDA's Response 12:

Yes.

Sponsor's Question 13:

Healthcare is preparing a summary of the extensive clinical experience with DaTSCAN reported in medical literature, to help support the proposed indication. Does the FDA agree that a summary of this kind would be of value?

FDA's Response 13:

Yes.

Sponsor's Question 14:

Radiation dosimetry estimates from study CY95.FP.I were calculated using the

MIROSE 3.1 program, as reflected in the European Summary of Product Characteristics (SPC). GE Healthcare intends to report these same estimates in the US package insert to keep the labels globally harmonized. As GE Healthcare acknowledges the FDA's preference for use of the OLINDA program, we have estimated the absorbed radiation doses of Ioflupane (123I) Injection using this program as well. A comparative analysis of the estimates using both programs has been conducted and it is our conclusion that there are no clinically significant differences. Does the FDA agree with our approach to reporting the MIRDOSE estimates in the labeling?

FDA's Response 14:

FDA prefers that OLINDA software be used for dosimetry calculations. This is the Agency's approved software.

Sponsor's Question 15:

Does the FDA agree with the proposal to provide completed Case Report Forms for all deaths, SAEs and withdrawals due to an AE for all studies?

FDA's Response 15:

Yes.

Sponsor's Question 16:

Does the FDA agree with the proposal to provide patient narratives for all deaths, drug related SAEs and all AEs leading to withdrawal for all studies?

FDA's Response 16:

Yes. •

Labeling

Sponsor's Question 17:

Does the FDA agree that sufficient scientific data and documentation exist to support the following proposed indication?

DaTSCAN is a radiopharmaceutical containing (b) (4) [123-I] ioflupane indicated with single photon emission computed tomography (SPECT) imaging of the brain for detecting loss of functional nigrostriatal dopaminergic neurons, (b) (4)

FDA's Response 17:

The discussion of the wording of the proposed labeling is premature. However, you will have to justify the use of the specific diagnostic entities in this claim which otherwise appears to be a "functional" or a "pathology detection" type of a claim. Please note that in none of the studies you listed have you proposed a measure that has been validated or could be justified as a SOT for the detection of the FND neuronal loss.



(b) (4) Please clarify whether any loss of FND neurons not associated with PD and DLB can also be detected with the use of your imaging product.

Sponsor's Question 18:

Does the FDA have any comments on the draft labeling proposals outlined in the Target Product Profile (TPP)?

FDA's Response 18:

No, we have no comments at this time.

Administrative

Sponsor's Question 19

In compliance with the Pediatric Research Equity Act of 2003, GE Healthcare intends to submit a request for a full waiver of pediatric assessment in the NDA, as DaTSCAN does not address a medical need in pediatric patients but rather is to be indicated in adult patients who present with signs and symptoms of a neurodegenerative disease. Does the FDA find this approach?

FDA's Response 19:

Yes, we regard it as reasonable to request a waiver (please be aware that this response does not mean a waiver has been granted; the final determination will be made following submission of your request).

Sponsor's Question 20:

GE Healthcare proposes the proprietary (trade) name of DaTSCAN for Ioflupane (123-I) Injection and would like the FDA to advise on the appropriate timing of submission of this trade name for FDA review.

FDA's Response 20:

The acceptability of the proposed trade name will be determined during the review process which would take place after your application is filed. We suggest submission of the trade name at the time of NDA submission.

Sponsor's Question 21:

Does the FDA envision an advisory committee?

FDA's Response 21:

Such an approach would be consistent with the review of a new molecular entity. In general, we anticipate the use of advisors and/or an advisory committee to assist in the review of your NDA, if submitted.

Sponsor's Question 22:

Does the FDA envision any post-approval commitments for this NDA?

FDA's Response 22:

We cannot comment on any such commitments at this time.

Discussion

After introductions, the meeting began. FDA asked if GE Healthcare (GE) needed clarification on any of the responses provided and GE replied that the only item they wished to discuss was FDA's item 4 which addressed completed clinical studies and the proposed indication for the product.

GE Healthcare opened the discussion by providing a brief history of the European experience with the product. GE stated that their product has been marketed successfully in Europe for 7 years. GE Healthcare said they planned to seek an anatomic/functional (detection) claim in the U.S. whereas in Europe the product has a diagnostic claim.



FDA emphasized to GE Healthcare the necessity to provide to FDA the clinical utility of the product. FDA also stated that there was no clear standard of truth for assessment of efficacy of the product.

FDA asked GE Healthcare about the ability of DaTSCAN to quantify the number of diseased neurons in the brain and GE responded that the product does not quantify the number of non-functional neurons but simply states whether there are functional neurons with dopaminergic receptors present.

GE Healthcare said that they will provide a revised indication to the Division that provides clearer language and emphasizes the functional/anatomic claim (b) (4)

(b) (4)

FDA queried GE about use of their product and its ability to detect early or late disease. GE responded that by the time symptoms develop over 60% of the dopaminergic neurons have been lost.

FDA requested that GE provide their statistical rationale for all the trials conducted and cite hypotheses used to determine study power.

Summary

GE will provide minutes of the meeting and address the questions of clinical utility and a revised indication statement in a future submission.

The minutes were prepared by James Moore, Project Manager.

James Moore, PharmD., M.A.
Project Manager, DMIHP

Linked Applications

Sponsor Name

Drug Name

IND 101016

GE HEALTHCARE

DaTSCAN (loflupane I-123) Injection

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/s/

JAMES W MOORE

09/19/2008

Industry Meeting between the Division of Medical Imaging and Hematology Products and GE Healthcare, Thursday, January 31, 2008, 2:00PM-3:30PM, Building 22, Conference Room 1419, FDA White Oak Campus, 10903 New Hampshire Avenue, Silver Spring, Maryland

Subject: DaTSCAN PreIND 101,016

GE Healthcare Attendees:

Larry Bell, M.D., Head, Global Regulatory Affairs
Patrick Cella, Manager, Technology
Gill Farrar, Ph.D., Project Director
Fred Longenecker, Director, Regulatory Affairs
Allison Mueller, Senior Manager, Regulatory Affairs
Roger Pickett, Ph.D., Non-Clinical Scientist
Paul Sherwin, M.D., Ph.D., Clinical Project Leader
Thomas Shifflett, Manager, QC Analytical Chemistry

(b) (4)



FDA Attendees:

Rafel Rieves, M.D., Acting Division Director, DMIHP
Liberio Marzella, M.D., Ph.D., Acting Deputy Division Director, DMIHP
Alex Gorovets, M.D., Clinical Team Leader, DMIHP
Robert Yaes, M.D., ScD., Clinical Reviewer, DMIHP
Scheldon Kress, M.D., Clinical Reviewer, DMIHP
Christy John, Ph.D., Clinical Pharmacology Reviewer, OCP
Eldon Leutzinger, Ph.D., Chemistry Pharmaceutical Assessment Lead, ONDQA
Tushar Kokate, Ph.D., Pharmacology/Toxicology Reviewer, DMIHP
Anthony Mucci, Ph.D., Statistical Reviewer, OB
Jyoti Zalkikar, Ph.D., Statistical Team Leader, OB
James McVey, Ph.D., Microbiology Team Leader, OPS
James Moore, PharmD., M.A, Project Manager, DMIHP

Background

Prior to the meeting a fax was sent to GE Healthcare that contained comments on their clinical development program. The questions from the meeting package were not addressed but general comments regarding the meeting package were provided. Here is the copy of the response.

January 29, 2008

PIND 101,016 DaTSCAN GE HEALTHCARE Type C Meeting January 31, 2008

Draft Comments to the Sponsor

Reference is made to PIND 101,016 for DaTSCAN, to the meeting package dated December 28, 2007, and to our upcoming meeting on January 31, 2008. As agreed, the meeting will not address any of your specific questions listed in the package but rather will provide you with an opportunity to give us a presentation on DaTSCAN, with an overview of the product and its development. Nevertheless, upon review of the materials submitted with the package, we wish to communicate certain comments that will help to focus the discussion at the upcoming meeting. Please note that the comments do not represent FDA opinions and are only meant to facilitate the discussion. Any conclusions reached at the meeting will be reflected in the meeting minutes.

GENERAL COMMENTS

1. Our understanding is that you plan to submit an NDA for DaTSCAN with a claim for a “functional indication”. As most of the studies cited in the meeting package appear to be addressing the issues of clinical performance and utility, please clarify what studies you are planning to submit that support the qualification of your product as a measure of “loss of functional nigrostriatal dopaminergic neurons?” Specifically, please identify the clinical studies that will allow FDA to verify that the scan results provide “clinically useful information” (as described in the FDA “Clinical Indications” guidance regarding medical imaging products).

2.  (b) (4)

CMC COMMENTS

1. According to the briefing package, one of the radiochemical impurities found in the [¹²³I]ioflupane drug product is  (b) (4), and the limit for it as listed in the release specifications is NMT  (b) (4)  (b) (4)

(b) (4) What in-process controls do you have in place to assure proper cutting of the peak so that the presence of (b) (4) can be eliminated? If this impurity cannot be eliminated, do you know if it will have any potential adverse effect on biodistribution of [¹²³I] ioflupane or any toxicity?

2. In the controls for release of the finished drug product, TLC is proposed for determination of both radiochemical identity and radiochemical purity. Because HPLC is generally considered to provide greater separation power compared to TLC in the vast number of chromatographic separations, we are concerned about the use of TLC as a release test for determination of individual radiochemical impurity species and for making decisions whether the amounts detected/determined meet specification limits. Unless you can rigorously demonstrate that your TLC procedure for determination of radiochemical impurities has the accuracy and reliability equivalent to or better than HPLC, the product release test for radiochemical purity and radiochemical impurities should be HPLC.
3. Because identification of the drug molecule is indirectly determined by comparison of the chromatographic mobility with that of a suitable reference standard, as for radiochemical impurities, we are concerned about whether TLC has sufficient specificity to effect an accurate and reliable identification. As for radiochemical purity, unless you can rigorously demonstrate that your TLC procedure for radiochemical identity is equivalent to or better than HPLC, the product release test for radiochemical identity should employ HPLC.

MICROBIOLOGY COMMENTS

1. It is suggested that (b) (4) are evaluated other than (b) (4). It is not clear if these other approaches have been explored.
2. Comments regarding (b) (4) processing of the product:
 - a. Include in future submissions (b) (4). This specification should also be listed as a product specification or test for product release in Section 3.2.P.5.1 since the (b) (4) results are not available at product release.
 - b. Clarify if the (b) (4)
 - c. Provide validation data summaries of all (b) (4). Please refer to the FDA *Guidance for Industry for the Submission Documentation for* (b) (4) for specific information to be submitted in the NDA application.

3. Comments regarding the comparability protocol:
 - a. The proposed manufacturing site must have an acceptable GMP status at the time of the NDA submission.
 - b. The protocol must provide in sufficient detail the validation/qualification plan for all (b) (4). Specific acceptance criteria for each process should be provided in sufficient detail to allow for an evaluation of the plan. Please refer to the Guidance mentioned in 2.c for information to be included in the comparability protocol.
 - c. The protocol should include a timeline for completion of the validation/qualification plan and state when commercial manufacture of the product is expected to begin.

PHARMACOLOGY-TOXICOLOGY COMMENTS

Based on the summary data provided, additional toxicology studies may not be needed. However, a final decision on the adequacy of non-clinical data is dependent on review of complete study reports that are submitted at the time the IND application for DaTSCAN is submitted.

CLINICAL COMMENTS FOR THE PROPOSED PHASE-3 STUDY

Please note that after extensive review of the design of your Phase 3b Study GE-001-010, that you propose to conduct while the NDA review is ongoing, there remains considerable confusion regarding the proposed primary endpoint and the choice of the Comparator. The apparent complexity of your protocol design in part appears to stem from the proposed secondary and other exploratory analyses. Please note that our comments at this time are limited to the assessment of the primary endpoint.

1. You propose to demonstrate that community neurologists will be able to improve the specificity without loss of sensitivity in diagnosing Parkinsonian syndromes when utilizing the results from DaTSCAN SPECT imaging. You propose, as the SOT, the clinical assessment by an expert MDS neurologist, based on an initial examination (b) (4), without benefit of the results from DaTSCAN SPECT imaging. We find these proposals generally acceptable however we recommend a longer observation interval, preferably 1 to 2 years. Alternatively, please justify the choice of (b) (4), as a follow-up interval.

2. You propose that (b) (4)

We find this unreasonable and recommend that the enrollment into the study and the endpoint assessments are performed by different groups of physicians.

3. We propose that you consider the following design outline:
 - a) We suggest that the enrollment into the study of the patients with the suspected Parkinsonian syndrome be conducted through the referral by the community physicians (generalists, internists, neurologists).
 - b) We further suggest that you utilize a pool of study neurologists and randomly choose one of them for every patient, with a given neurologist, once chosen, examining the assigned patient just once, while performing the baseline assessment (Comparator). Such an assessment should be recorded on the Case Report Form (CRF) according to the predefined parameters.
 - c) We recommend that the same neurologist perform the assessment with the DaTSCAN result plus his/her own baseline assessment report (Test). The assessing neurologist should not have access to patient's progress or any other observation of the patient from the time of the baseline evaluation till rendering the Test assessment.
 - d) We recommend that you propose non-inferiority for Sensitivity and superiority for Specificity as the primary endpoint analyses, with the SOT as defined above.
 - e) We suggest that you continue study enrollment until a sufficient number of subjects negative for Parkinsonian syndrome, as assessed by the SOT, are enrolled into the study, so that the performance characteristics of the Test can be adequately evaluated.
 - f) We recommend that you propose other analyses, including Accuracy measurements and ROC-AUC calculations, as secondary and exploratory analyses.
4. We suggest that you plan to provide, in a justifiable and safe manner, a drug treatment-free period prior to the neurological examinations to avoid the confounding of the expert evaluations.
5. We recommend that you clarify how the blind SPECT scan reads will be performed and how the independent readers will arrive at a single imaging diagnosis, normal or abnormal, (for instance, two readers with a third reader serving as an adjudicator; three readers with a majority read, etc.).

Discussion

After introductions the meeting began with a presentation by GE Healthcare (GE). In their presentation GE Healthcare stated that their product is approved in Europe and that there have been more than (b) (4) exposures to their product (DaTSCAN). The product is an analog of cocaine and binds reversibly to the dopamine transport protein in the nigrostriatum. GE Healthcare stated that the product doesn't need to be metabolized to exert its action. According to GE, the principal indication for use of their product in Europe has been for the diagnosis of Parkinsonism, dementia, and dementia with Lewy bodies. GE plans to submit the NDA with the following indication "indicated with single photon emission computed tomography (SPECT) imaging for detecting loss of functional nigrostriatal dopaminergic neurons". GE Healthcare stated that the NDA submitted to FDA would seek a functional claim of binding to dopaminergic sites as a tool in diagnosing the aforementioned disorders. FDA questioned the sponsor's reasoning for making a functional claim given that the pharmacologic activity of DaTSCAN suggests that DaTSCAN provides more anatomic evidence of dopaminergic neuron loss rather than the evidence of a loss of function.

GE Healthcare pointed to the product's ability to diagnose disorders characterized by lack of dopaminergic activity in the brain (Parkinsonism, dementia, dementia with Lewy bodies). GE Healthcare stated that with the use of this agent it is possible to determine whether a patient has Parkinsonism prior to the patient exhibiting symptoms. According to GE Healthcare by the time Parkinsonism is diagnosed about 40 percent of the dopaminergic neurons have already been lost. FDA queried GE Healthcare about the number of dopaminergic neurons that are lost per year in the normal aging process in a 50 yo and GE Health Care replied that there is a normal loss of about 1% per decade. According to GE, the loss with Parkinson's is about 5% per year.

FDA queried GE Healthcare about the number of uninterpretable images seen with the use of DaTSCAN and GE Healthcare stated that the number of uninterpretables seen is about 2%.

FDA queried GE Healthcare about the standard of truth for Parkinson's disease. GE Healthcare stated that an initial diagnosis is made by movement disorder experts and follow-up is made at a given time point after the initial diagnosis. According to GE Healthcare, use of DaTSCAN would vastly improve the diagnosis of Parkinson's in patients with movement disorders.

FDA queried GE Healthcare about lesions seen on scans and asked whether 10% of loss of neurons could be detected visually by a clinician and GE Health replied that some clinicians could.

Summary

GE Healthcare claims that DaTSCAN will greatly enhance the clinician's ability to diagnose disorders associated with the loss of dopaminergic receptors in the brain. According to GE, DaTSCAN through its diagnostic capabilities will reduce the use of inappropriate therapeutic agents through early diagnosis.

GE Healthcare will request a Pre-NDA meeting with the Division to discuss preparation of the NDA, their clinical studies, preclinical, and CMC information for their product. GE Healthcare will also respond to the fax provided by FDA to GE prior to the meeting.

The minutes were prepared by James Moore, Project Manager.

James Moore, PharmD., M.A.
Project Manager, DMIHP

Linked Applications

Sponsor Name

Drug Name

IND 101016

GE HEALTHCARE

DaTSCAN (Ioflupane I-123) Injection

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES W MOORE

02/29/2008

Minutes of Industry Meeting DaTSCAN (I-123) GE PreINDI101016
1-31-08

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 22-454 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: DaTscan Established/Proper Name: Ioflupane I 123 Dosage Form: Injection		Applicant: GE HealthCare Agent for Applicant (if applicable):
RPM: James Moore		Division: HFD-160
<p>NDA's: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDA's and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>January 14, 2011</u> 		<input type="checkbox"/> None CR September 8, 2009, December 23, 2009
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics ²</p> <p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 1</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Communication Plan <input type="checkbox"/> Submitted in response to a Pediatric Written Request <input type="checkbox"/> ETASU <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<p>• Office of Executive Programs (OEP) liaison has been notified of action</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<p>• Press Office notified of action (by OEP)</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<p>• Indicate what types (if any) of information dissemination are anticipated</p>	<p><input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other</p>

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDA only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
CONTENTS OF ACTION PACKAGE	
<p>❖ Copy of this Action Package Checklist³</p>	x
Officer/Employee List	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<input checked="" type="checkbox"/> Included
<p>Documentation of consent/non-consent by officers/employees</p>	<input checked="" type="checkbox"/> Included
Action Letters	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s) X CR September 8, 2009 X CR December 23, 2009 X AP January 14, 2011</p>
Labeling	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	X (See RPM Labeling Review)
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	x
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

³ Fill in blanks with dates of reviews, letters, etc.
Version: 8/25/10

<p>❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</p>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	NA
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	NA
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	NA
<p>❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</p>	
<ul style="list-style-type: none"> • Most-recent draft labeling 	NA
<p>❖ Proprietary Name</p> <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	<p>X June 29, 2009 X December 14, 2009 Acceptability Letter July 14, 2009 Acceptability Review January 5, 2011</p>
<p>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</p>	<input checked="" type="checkbox"/> RPM September 3, 2009, January 12, 2011 <input checked="" type="checkbox"/> DMEPA December 14, 2010, January 4, 2011 <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC May 13, 2010, <input checked="" type="checkbox"/> CSS November 10, 2009, December 14, 2009, September 4, 2009 <input checked="" type="checkbox"/> Other reviews PMHS June 17, 2009
Administrative / Regulatory Documents	
<p>❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</p>	September 3, 2009
<p>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</p>	<input type="checkbox"/> Not a (b)(2)
<p>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</p>	<input type="checkbox"/> Not a (b)(2)
<p>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</p>	<input checked="" type="checkbox"/> Included
<p>❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</p>	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.
Version: 8/25/10

❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>July 8, 2009</u> If PeRC review not necessary, explain: _____ Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	x
❖ Internal memoranda, telecons, etc.	none
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg January 31, 2008
• EOP2 meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	none
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	August 11, 2009
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None September 8, 2009, January 12, 2011
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None September 2, 2009, December 22, 2009, January 5, 2011
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None September 1, 2009, December 17, 2009, January 4, 2011
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	September 3, 2009
• Clinical review(s) (<i>indicate date for each review</i>)	August 31, 2009 December 16, 2009, June 15, 2010, January 3, 2011
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None

⁵ Filing reviews should be filed with the discipline reviews.

❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input type="checkbox"/> Not applicable See Labeling Review
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input type="checkbox"/> None See Labeling Review
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested x
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None August 26, 2010
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None August 26, 2010
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None August 26, 2010
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None August 31, 2009
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None August 31, 2009, January 4, 2011
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None September 4, 2009
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None September 3, 2009
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None September 2, 2009
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None September 3, 2009
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None September 3, 2009
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed August 31, 2009
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	See Chemistry Review
<input checked="" type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	See Chemistry Review
<input checked="" type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	See Chemistry Review
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶)</i>	Date completed: August 25, 2009 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication **AND** a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.