

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203971Orig1s000

CHEMISTRY REVIEW(S)



Memorandum

Date: May 13, 2013
From: Martin Haber, Ph.D., Review Chemist
Subject: OC Recommendation for NDA 203971

The overall Office of Compliance (OC) recommendation is Acceptable for NDA 203971, Radium Ra 223 Dichloride, as reported by the EES system. The chemistry, manufacturing and controls recommendation for this NDA is Approval. There are no pending CMC issues.

R/D Init by: Dr. Ali Al-Hakim, Branch Chief

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/s/

MARTIN T HABER
05/13/2013

ALI H AL HAKIM
05/13/2013

ONDQA Division Director's Memo
NDA 203971, Xofigo (radium Ra 223 dichloride) Injection
Sponsor: Bayer Healthcare Pharmaceuticals

Date: 11-April-2013

Introduction

Xofigo Injection is a new molecular entity indicated for the treatment of prostate cancer patients with bone metastases. The drug product is a ready to use sterile solution for intravenous injection. This radioactive alpha particle-emitting pharmaceutical (classified by the US Nuclear Regulatory Commission as "unsealed nuclear byproduct material") should be received, used and administered only by authorized persons.

As a radiopharmaceutical, the strength (radioactivity) decreases with time due to decay of the nuclide, radium-223, which has a physical half-life of 11.4 days. On the manufacturing date, [REDACTED] (b) (4)

[REDACTED] The recommended dose is 50 kBq per kg body weight.

ONDQA recommends approval action for this NDA; there are no outstanding CMC issues. However, the overall recommendation is still pending from the Office of Compliance for cGMP inspections. The CMC recommendation does not include cGMP findings.

Summary

Chemical Name: Radium-223 chloride
Molecular Formula: $^{223}\text{RaCl}_2$
CAS-name and number: Radium-223 chloride ($^{223}\text{RaCl}_2$), 444811-40-9

Molecular Weight: Relative molecular weight for $^{223}\text{RaCl}_2 = 293.9$
Atomic weight for $^{223}\text{Ra}^{2+} = 223.0$

The active moiety of the radium-223 chloride drug substance is the divalent cation, $^{223}\text{Ra}^{2+}$. Anions present in solution are chloride (Cl^{-}) and citrate $^{3-}$.

The **drug substance** is manufactured at the Institute for Energy Technology (IFE), Norway, [REDACTED] (b) (4)

[REDACTED] Drug substance solution tests are appearance, radionuclidic identity (gamma spectroscopy), pH, osmolality, assay for citrate, radionuclidic purity [REDACTED] (b) (4) determined by gamma spectroscopy, residual solvent [REDACTED] (b) (4), and assay for

radium-223 radioactivity (dose calibrator). The drug substance solution is stored in place at IFE [REDACTED] (b) (4)

The **drug product** is a sterile, aqueous solution for injection containing 1000 kBq/mL of radium Ra-223 dichloride and is indicated for treatment of prostate cancer patients with bone metastases. The excipients are 6.3 mg/mL of sodium chloride, 7.2 mg/mL of sodium citrate buffer, a small amount of hydrochloric acid (for pH adjustment) [REDACTED] (b) (4)

[REDACTED] Drug product tests are appearance, radionuclidic identity (gamma spectroscopy with a high purity germanium detector), particulate matter (visible), pH, osmolality, assay for citrate (enzyme assay using NADH), assay for chloride (ion chromatography), total heavy metals (ICP-MS), assay (radium-223 radioactivity measured with a dose calibrator), bacterial endotoxins and sterility. Data for three production scale and 295 development/pilot scale batches was provided. A shelf life of 28 days is supported by stability data for the drug product.

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/s/

ALI H AL HAKIM

04/11/2013

Ali Al-Hakim for Sarah Pope

NDA 203-971

Xofigo (radium Ra 223 dichloride) Injection

Bayer Healthcare Pharmaceuticals

Martin Haber, Ph.D.

Division of New Drug Quality Assessment III

For

Division of Oncology Products I

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	6
I. Recommendations.....	6
A. Recommendation and Conclusion on Approvability.....	6
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	6
II. Summary of Chemistry Assessments.....	6
A. Description of the Drug Product(s) and Drug Substance(s)	6
B. Description of How the Drug Product is Intended to be Used.....	7
C. Basis for Approvability or Not-Approval Recommendation.....	7
III. Administrative.....	8
A. Reviewer's Signature.....	8
B. Endorsement Block.....	8
C. CC Block	8
Chemistry Assessment	9
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	9
S DRUG SUBSTANCE [Radium Ra 223 dichloride, Institute for Energy Technology (IFE)]	9
P DRUG PRODUCT [Xofigo, Injection]	42
A APPENDICES	60
R REGIONAL INFORMATION	60
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	60
A. Labeling & Package Insert	61
B. Environmental Assessment Or Claim Of Categorical Exclusion	63
III. List Of Deficiencies To Be Communicated.....	65

Chemistry Review Data Sheet

1. NDA 203-971
2. REVIEW #1
3. REVIEW DATE: April 1, 2013
4. REVIEWER: Martin Haber, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original

12/14/2012

Amendment (response to IR)

1/12/2013

Amendment (response to IR)

2/22/2013

Amendment (response to IR)

3/04/2013

Amendment

3/27/2013

7. NAME & ADDRESS OF APPLICANT:

Name: Bayer Healthcare Pharmaceuticals Inc.

Address: P.O. Box 1000, Montville, NJ 07045

Representative: Deepika Jalota, Pharm. D.

Telephone: 973-487-2782

8. DRUG PRODUCT NAME/CODE/TYPE:

Executive Summary Section

- a) Proprietary Name: Xofigo
- b) Non-Proprietary Name (USAN): radium Ra 223 dichloride
- c) Code Name/# (ONDC only): BAY 88-8223
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1 (NME)
 - Submission Priority: P (Expedited)

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Radioactive therapeutic drug

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 1000 kBq/mL (0.027 mCi/mL) at reference date

13. ROUTE OF ADMINISTRATION: Intravenous Injection

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Radium-223 chloride, radium Ra 223 dichloride (USAN), ²²³RaCl₂, 293.9 g/mole

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV	(b) (4)	(b) (4)	4	Adequate		
	IV			4	Adequate		

Executive Summary Section

(b) (4)	IV	(b) (4)	(b) (4)	4	Adequate		
	IV			4	Adequate		

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	67,521	Clinical trials (Algeta ASA)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending		
Pharm/Tox	Adequate	3/22/2013	Dr. Wei Chen
Biopharm	NA (injection product)		
Methods Validation	Exception (MV not possible for radioactive product)		
OPDRA/DMEPA	Pending		
EA	Exclusion requested and acceptable	1/7/2013	M. Haber
Microbiology	Approval	3/26/2013	D. Miller

The Chemistry Review for NDA 203-971

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC review perspective, the NDA is recommended for approval. There are no pending CMC deficiencies to resolve.

The overall recommendation is still pending from the Office of Compliance for cGMP inspections. The CMC recommendation does not include cGMP findings.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product is a sterile, aqueous solution for injection containing 1000 kBq/mL of radium Ra-223 dichloride at the reference date (arbitrarily set to the middle of the shelf life which is 28 days). The excipients are 6.3 mg/mL of sodium chloride, 7.2 mg/mL of sodium citrate buffer, a small amount of hydrochloric acid (for pH adjustment) (b) (4)

The drug product vial contains 6 mL of solution. The mass of radium dichloride present is in the nanogram range.

The drug product is manufactured at the Institute for Energy Technology (IFE), Norway, (b) (4)

Drug product tests are appearance, radionuclidic identity (gamma spectroscopy with a high purity germanium detector), particulate matter (visible), pH, osmolality, assay for citrate (enzyme assay using NADH), assay for chloride (ion chromatography), total heavy metals (ICP-MS), assay (radium-223 radioactivity measured with a dose calibrator), bacterial endotoxins and sterility. Data for three production scale and 295 development/pilot scale batches was provided.

(b) (4) the radioactive decay during the 28 day shelf life leading to (b) (4). The drug product container/closure system is a 10 mL colorless glass vial with a grey (b) (4) rubber stopper fixed with an aluminum shell.

Executive Summary Section

The drug substance, radium Ra-223 dichloride, contains the unstable nuclide ^{223}Ra (or radium-223) which has a physical half-life of 11.43 days. Radium-223 decays into a series of daughter isotopes via emission of alpha particles, beta particles and gamma rays. The decay chain is: Radium-223 decays to (b) (4) stable Lead-207 (via beta emission). Stable lead-207 is reached about 45 minutes after the initial decay. The radium-223 and its daughters are in secular equilibrium, reaching roughly stable relative radioactive concentrations about 4.5 hours after isolation of pure radium-223.

Radium is an alkaline earth element and the only stable oxidation state in air and water is the +2 cation. The divalent cation is large, highly basic and not easily complexed. (b) (4)

The drug substance is manufactured at the Institute for Energy Technology (IFE), Norway, (b) (4). Drug substance solution tests are appearance, radionuclidic identity (gamma spectroscopy), pH, osmolality, assay for citrate, radionuclidic purity (b) (4) determined by gamma spectroscopy), residual solvent (b) (4) and assay for radium-223 radioactivity (dose calibrator). The drug substance solution is stored in place at IF (b) (4).

B. Description of How the Drug Product is Intended to be Used

Xofigo Injection is indicated for treatment of prostate cancer patients with bone metastases. The drug product is a ready to use sterile solution for intravenous injection. This radioactive alpha particle-emitting pharmaceutical (classified by the US Nuclear Regulatory Commission as “unsealed nuclear byproduct material”) should be received, used and administered only by authorized persons.

As a radiopharmaceutical, the strength changes with time. On the manufacturing date, (b) (4). The recommended dose is 50 kBq per kg body weight.

C. Basis for Approvability or Not-Approval Recommendation

Executive Summary Section

NA

III. Administrative**A. Reviewer's Signature**

See DFS

B. Endorsement Block

See DFS

C. CC Block

See DFS

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/s/

MARTIN T HABER
04/01/2013

ELDON E LEUTZINGER
04/01/2013

ALI H AL HAKIM
04/01/2013

DATE: [February 6, 2013](#)

Deleted: February 4, 2013

TO: 'Xofigo' Review Team (NDA-203-971)

FROM: Martin Haber, Ph.D., Review Chemist

THROUGH: Eldon Leutzinger, Ph.D., CMC Lead, Medical Imaging, Ali Al Hakim, Ph.D., Branch Chief, Branch II and Sarah Pope Miksinski, Ph.D., Director, Division of New Drug Quality Assessment I

SUBJECT: Product Quality and Manufacturing Memo for NDA 203971

The purpose of this memo is to outline the manufacturing process and control strategy for radium Ra 223 dichloride injection as proposed in the NDA. This memo is not intended to be used as inspectional instructions.

The sponsor, Bayer HealthCare Pharmaceuticals, has proposed Xofigo for the treatment (b) (4). The active ingredient, radium Ra-223 dichloride, contains the isotope Radium-223 which is radioactive with emission of alpha, beta (via daughter isotopes) and gamma radiation and has a half-life of 11.4 days. In addition to the API, the injection vial contains the following excipients: sodium chloride, sodium citrate, and hydrochloric acid. The sterile aqueous drug product (6 mL total volume) is contained in a 10 mL type 1 glass vial, closed with a rubber stopper with a flanged aluminum seal. Each container closure system is wrapped with an adhesive, transparent film supported by a plastic bottom and top cap. The wrapped vial is stored and shipped in a lead container.

The sponsor plans to manufacture the proposed product at their manufacturing site located at the Institute for Energy Technology (IFE), Kjeller, Norway. This site is responsible for manufacturing (production), quality control, batch release and stability.

The manufacturing process involves (b) (4)

[Redacted manufacturing process details]

Details of the manufacturing process are provided in the NDA and discussed in the Initial Quality Assessment. The overall process generally involves [REDACTED] (b) (4)

Note: The Firm did not use a Quality by Design (QbD) approach to develop the proposed drug product manufacturing process.

Reviewer's assessment of risk:

The following are considerations for the team on pre-approval inspection:

- 1. Verify that the purification process for radium-223 is robust. The description in the NDA is unclear. Also, the starting material [REDACTED] (b) (4) specifications do not include an assay test.*
- 2. There is a single site for manufacturing of this product. How will production be maintained in the event of a major issue, such as site/worker contamination, spills, fire/flood, etc.?*
- 3. Data for only a limited number of batches was provided in the NDA and the batch numbers indicate that the batches were non-consecutive. Are there any issues with other batches?*
- 4. The NDA is heavily redacted and contains only minimal information. What are they trying to hide?*

The CMC review team is willing to share their knowledge with the investigator prior to and during the inspection. If you have any questions, please email or call the CMC review team.

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/s/

MARTIN T HABER
02/07/2013

ALI H AL HAKIM
02/07/2013

Each 10 mL vial contains:

Composition	Reference to Standard	Function	Amount per vial	Amount per mL
Drug substance				
Radium-223 chloride	In-house	Drug substance	6000 kBq (3.2 ng) ^a at reference date	1000 kBq (0.53 ng) ^a at reference date
Excipients^b				
Sodium chloride	Current Ph. Eur. / USP	Tonicity agent	37.8 mg	6.3 mg
Sodium citrate ^c	Current Ph. Eur. / USP	pH adjuster	43.2 mg	7.2 mg
Hydrochloric acid	Current Ph. Eur. / USP	pH adjuster	1.2 mg ^d	0.2 mg ^d (b) (4)
Water for injection	Current Ph. Eur. / USP			

a Calculated as radium-223

b (b) (4)

c

d

In Section 3.2.P.2.1.01-01, Bayer indicates that the composition of the drug product intended for commercial manufacture (above table) is identical to the drug product formulation used in the pivotal Phase III clinical studies.

1 kBq = 10^3 Bq, but 1 MBq = 10^6 Bq. So, 1000 kBq = 1 MBq, or 0.0207 mCi / mL at reference. The remaining ingredients per mL are as shown in the 5th column. The mass of ^{223}Ra is as follows:

$$m[^{223}\text{Ra}] = [(0.027/1000) \times 2.22 \times 10^{12} \text{ d/min} \times (16459.2 \text{ min}/0.693)] / 6.02 \times 10^{23} \text{ moles} \\ = 2.36 \times 10^{-12} \text{ moles, or } 2.36 \times 10^{-12} \times 223 \times 1000 \times 1000 \times 1000 = 5.27 \times 10^{-10} \text{ g (or } \\ \mathbf{0.53 \text{ ng / mL, the figure they show in the 5}^{\text{th}} \text{ column for mass at reference)}$$

(b) (4)

It is not clear how this should fit into the issue of “what is” the actual chemical form of $^{223}\text{Ra}^{2+}$ that exists in the formulation, i.e., the counter-ion, since ions do not exist in aqueous solution as naked ions, reference to the requirement of electrical neutrality.

One might ask the question: why is $^{223}\text{RaCl}_2$ any more favored than $^{223}\text{Ra}_3\text{Cit}_2$, or some ionic form, e.g., $(^{223}\text{RaCit})^-$ that itself would be associated with an appropriate cation for satisfying the neutrality rule. It seems to have been an arbitrary assignment by either Bayer or the previous owner of the IND. It could be that the larger amount of chloride ions present (over citrate ions) might be interpreted to mean that there would be more of the $^{223}\text{Ra}^{2+}$ associated with Cl^- than associated with citrate. Certainly, it is a lot easier and less messy to settle on $^{223}\text{RaCl}_2$, because the issue then becomes whether it is, e.g., the simple form $[^{223}\text{Ra}_3\text{Cit}_2]$, or whether it is a complex $[(^{223}\text{RaCit})^-]$. Since it is $^{223}\text{RaCl}_2$ that has been adopted by USAN, it obviously sets it up for the established name. If we were to deviate from the USAN, and go for a more accurate assignment of chemical

form, there will need to be a lot of experimental work in establishing the chemical identity in a pool of ions and ionic forms existent in the formulation. This is again discussed under Labeling, since we have to decide on whether it is absolutely necessary to include both chloride and citrate in the naming – that is a labeling issue. Although scientifically, I think there is reason to do this, I am not sure that it actually makes any difference. After all, it is the ion ($^{223}\text{Ra}^{2+}$) that is incorporated into bone. Would the counter-ion affect this, i.e., the efficacy? That is an open question. If it does not, then it does not matter scientifically about the chemical form of the $^{223}\text{Ra}^{2+}$. On the other hand, if it is, the issue of chemical form becomes important, if not critical. The reader is referred to the section in this IQA on labeling.

The Drug Substance

This is produced and held in bulk as drug substance solution, prior to its use to manufacture the final drug product. It is packaged in (b) (4)

The Drug Substance is indicated by Bayer to be $^{223}\text{RaCl}_2$, Bayer's claim. It is significant to note that (b) (4) (see above, under drug product). Historically, there has been an issue for what is the counter-ion associated with $^{223}\text{Ra}^{2+}$, e.g., whether it should be considered as $^{223}\text{RaCl}_2$ (as Bayer claims), or the citrate. This will be discussed at further length later in the IQA, under Labeling. ^{223}Ra is the last element in Group 2/IIa (Alkaline Earths), with electron configuration $[\text{Rn}]7s^2$, occupying a position between Fr, $[\text{Rn}]7s^1$ (Group 1, Alkali Earths), and Ac, $[\text{Rn}]6d7s^2$ (Actinium series).

Compounds in Group 2 vary systematically with increasing atomic and ionic size, Ra (last element in the Group) having the largest atomic and ionic size, and greatest electropositive character. The principle oxidation state of the alkaline earths, including ^{223}Ra is 2+, i.e., $^{223}\text{Ra}^{2+}$. There are other physicochemical properties of Ra^{2+} that play important roles in its chemistry, but not all of these are discussed here, nor are all of these pertinent to the NDA. The one I will mention is that as the ionic size of the Group 2 elements increases, the tendency is for stabilization of some large anions. This is another factor that may play some role in determination of the chemical form of $^{223}\text{Ra}^{2+}$ in a formation with both chloride and citrate. The elements in Group 2 tend toward greater hydration with increasing ionic size. Yet, it is also known that the ionic size of the hydrated ions decrease as one goes down the Group 2 elements. (b) (4)

The chemistry gets complicated after this, especially when we speculate on similar behavior for association with citrate. I will leave it at this point, since any further consideration needs to be undertaken within the primary review of the NDA.

There are 13 isotopes of Ra, all of which are radioactive. ^{223}Ra has a physical half-life of 11.43 days. It possesses the following emissions:

α -emissions: (b) (4)

Gamma emissions: [REDACTED] (b) (4)

Rn X-ray
 β^- particle emissions: [REDACTED] (b) (4)

Daughter radiations: will be discussed later in the IQA.

A. Critical Issues for Review

DRUG SUBSTANCE:

²²³Ra is manufactured in accordance to the following flow diagram (3.2.S.2.2):

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Drug Product Stability:

I will spend little time on stability, except to point out that the holding time for drug substance solution is (b) (4) (3.2. 7.1.01-01), and that the storage conditions will be in accordance to ICH guidelines; pilot and production scale batches are indicated to be comparable. Data is provided for 4 pilot scale batches and 3 production scale batches at 25⁰C / 60% RH and accelerated conditions (40⁰C / 75% RH), storage for 4 weeks (intended self-life). One of the pilot batches were stored in the commercial 10 mL glass vial; the other 3 pilot batches were stored in a 20 mL glass vial (used for clinical samples); on brief consideration I am have not identified anything that is particularly concerning. A post-approval stability commitment is provided.

Stability for drug product (3.2.P.8.1.02-01) follows similarly, with 3 pilot batches and 3 production batches, and data provided; based on a very cursory examination, I did not find anything of immediate concern. These sections will need to be examined carefully in a full review. As I have not identified any critical issues, I am leaving this to the primary reviewer.

Labeling:

There is provided in the NDA, separate section from 3.2, a proposed label, and this label is shown as follow:



There are obviously some issues with this label, but I am leaving the bulk of it to the primary reviewer.

One issue that was raised during previous communications with Bayer is what chemical form does $^{223}\text{Ra}^{2+}$ exist in the Bayer formulation. The formulation contains both chloride and citrate ions, since the material is formulated in sodium citrate. Arguments have been made that it might exist as citrate, based on the analogy with other chelates. Citrate is probably a weak chelate, and may not complex with radium to enough extent to merit assigning to it as $^{223}\text{Ra}_3(\text{citrate})_2$ any more than as $^{223}\text{RaCl}_2$, since if all the ions actually exist in aqueous solution as salt-like associations, then there is no chemical justification to choose preferentially between the two. We had made preliminary to Bayer's question on chemical identity, and Bayer had responded back to us, providing rationale and a proposal for studies to elucidate the chemical form; this is found in the communication dated 07/06/2012. We responded to Bayer that we agreed with their approach for experiments proposed. The primary reviewer should refer to these communications that are located in DARRTS. There is a complicating factor – that of the assigned USAN to the drug substance, which is $^{223}\text{RaCl}_2$. That may put the clinch on this issue. Still, one needs to think about what is the rationale for choosing $^{223}\text{RaCl}_2$ over the citrate. It is not clear that there is any theoretical justification, based on the known chemistry of radium. This is an issue that will need to be settled here during the review of this NDA (**Critical Issue # 5**).

Manufacturing Facilities:

The manufacturing and testing sites are identified in Sections 3.2.S.2.1.01-01 (drug substance) and 3.2.P.3.1.01-01 (drug product). Rather than listing these, as is, the pertinent sites have already been entered into EES, and they are listed as follows:

Drug Substance manufacturer and Finished Dosage Manufacturer:

Institute for Energy Technology (IFE)

Kjeller, Norway

CFN: 3008160514

Profile: (b) (4) small volume parenteral drug

(b) (4)

Profile: control testing laboratory

Finished Dosage Release Tester:

(b) (4)

Profile: control testing laboratory

Drug Master Files:

DMF	FOR	
(b) (4)	(b) (4)	(b) (4)

Letters of authorization for all DMF's are provided in the NDA (section on references).

INITIAL ASSESSMENT - FILING:

(the final decision for filing will be left to the CMC Review Team)

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Has stability data and analysis been provided to support the requested expiration date?			
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		Section 3.2.P.2.1.01-01
14	Is there a Methods Validation section?	X		
15	Is a separate Microbiological section included?	X		
16	Have all consults been identified and initiated?	X		

CMC Lead: Eldon E. Leutzinger, Ph.D. Date: 12/19/2012
 Division of New Drug Quality Assessment III, Branch VII

Branch Chief: Ali Al Hakim, Ph.D.
 Division of New Drug Quality Assessment III, Branch VII

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/s/

ELDON E LEUTZINGER
12/19/2012

ALI H AL HAKIM
12/20/2012

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Application: NDA 203971/000	Action Goal:
Start Date: 14-DEC-2012	District Goal: 14-APR-2013
Regulatory: 14-AUG-2013	
Applicant: BAYER HLTHCARE 1000 MONTVILLE, NJ 070451000	Brand Name: Xofigo (Radium Ra-223 Dichchoride) Estab. Name: Generic Name: Radium-223 Dichloride
Priority: 1	Product Number; Dosage Form; Ingredient; Strengths
Org. Code: 150	001; INJECTION; RADIUM CHLORIDE RA-223; .027mCi

Application Comment: PLANNED EXPEDITED PRIORITY NDA. RADIOACTIVE PRODUCT. RADIOPHARMACEUTICAL, NON-PET. TARGET OND ACTION DATE IS 5/17/13. (on 04-JAN-2013 by D. MESMER (HFD-800) 3017964023)

THE RADIOTHERAPEUTIC API IS RADIUM CHLORIDE, SPECIFICALLY THE ISOTOPE RADIUM-223, AN ALPHA PARTICLE EMMITTER (+ SOME BETA AND GAMMA PARTICLES) WITH A HALF-LIFE OF 11.4 DAYS. (on 17-DEC-2012 by M. HABER () 3017961675)

FDA Contacts:	M. HABER	Prod Qual Reviewer	3017961675
	D. MILLER	Micro Reviewer (HFD-003)	3017963854
	D. MESMER	Product Quality PM (HFD-800)	3017964023
	E. LEUTZINGER	Team Leader	3017961399

Overall Recommendation:	ACCEPTABLE	on 13-MAY-2013	by R. SAFAAI-JAZI	()	3017964463
	PENDING	on 17-DEC-2012	by EES_PROD		
	PENDING	on 17-DEC-2012	by EES_PROD		
	PENDING	on 17-DEC-2012	by EES_PROD		

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment:

CFN:

(b) (4)

FEI:

(b) (4)

DMF No:

AADA:

Responsibilities:

FINISHED DOSAGE RELEASE TESTER

**Establishment
Comment:**

(b) (4)

Profile:

CONTROL TESTING LABORATORY

OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	17-DEC-2012				HABERM
SUBMITTED TO DO NME AND FIRST INSPECTION	17-DEC-2012	Product Specific			SMITHDE
ASSIGNED INSPECTION TO IB	18-DEC-2012	Product Specific			PHILPYE
DO RECOMMENDATION AFTER DISCUSSION WITH DGMPA, PAI WAIVED - ENOUGH COVERAGE IN 2009 AND 2012 INSPECTIONS	18-JAN-2013			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
OC RECOMMENDATION	18-JAN-2013			ACCEPTABLE DISTRICT RECOMMENDATION	SHARPT

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: FEI: 3008160514
INSTITUTE FOR ENERGY TECHNOLOGY (IFE)
INSTITUTTUN, 18
KJELLER, , NORWAY

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE MANUFACTURER

Establishment Comment: FOR DRUG PRODUCT: MANUFACTURE, QUALITY CONTROL, BATCH RELEASE, STABILITY STORAGE AND TESTING. STORAGE (b) (4)

FOR DRUG PRODUCT: PERFORMS PRODUCTION, QUALITY CONTROL, BATCH RELEASE OF DRUG PRODUCT IN PRIMARY PACKAGING, SECONDARY PACKAGING, STABILITY STORAGE AND TESTING, (b) (4) OF DP. HANDLING OF RADIOACTIVE MATERIALS (on 17-DEC-2012 by D. MESMER (HFD-800) 3017964023)

Profile: (b) (4) **OAI Status:** NONE
(b) (4) NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	17-DEC-2012				HABERM
SUBMITTED TO DO NME	17-DEC-2012	Product Specific			SMITHDE
ASSIGNED INSPECTION TO IB	28-DEC-2012	Product Specific			BRYKMANR
INSPECTION SCHEDULED	(b) (4)		(b) (4)3		IRIVERA
DC AS PER M. FARBMAN, ATL	13-MAY-2013			ACCEPTABLE INSPECTION	PHILPYE
OC RECOMMENDATION	13-MAY-2013			ACCEPTABLE DISTRICT RECOMMENDATION	SAFAAIJAZIR
SUBMITTED TO OC	17-DEC-2012				HABERM
SUBMITTED TO DO NME	17-DEC-2012	Product Specific			SMITHDE
ASSIGNED INSPECTION TO IB	28-DEC-2012	Product Specific			BRYKMANR
INSPECTION SCHEDULED	(b) (4)		(b) (4)		IRIVERA
DO RECOMMENDATION AS PER M. FARBMAN, ATL	13-MAY-2013			ACCEPTABLE INSPECTION	PHILPYE
OC RECOMMENDATION	13-MAY-2013			ACCEPTABLE DISTRICT RECOMMENDATION	SAFAAIJAZIR

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT**

Establishment: CFN: [REDACTED] FEI: [REDACTED] (b) (4)
[REDACTED] (b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE RELEASE TESTER

Establishment Comment: CORRECTION: QUALITY CONTROL TEST FOR DRUG SUBSTANCE [REDACTED] (b) (4)
[REDACTED]
(on 08-FEB-2013 by M. HABER () 3017961675)
FOR DRUG SUBSTANCE: QUALITY CONTROL [REDACTED] (b) (4)
[REDACTED]
FOR DRUG PRODUCT: PERFORMS RELEASE TESTING [REDACTED] (b) (4)
(on 17-DEC-2012 by D. MESMER (HFD-800) 3017964023)
Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	17-DEC-2012				HABERM
SUBMITTED TO DO FIRST INSPECTION AND NME	17-DEC-2012	Product Specific			SMITHDE
ASSIGNED INSPECTION TO IB	28-DEC-2012	Product Specific			BRYKMANR
INSPECTION SCHEDULED	[REDACTED] (b) (4)		[REDACTED] (b) (4)		IRIVERA
DO RECOMMENDATION	13-MAY-2013			ACCEPTABLE INSPECTION	PHILPYE
OC RECOMMENDATION	13-MAY-2013			ACCEPTABLE DISTRICT RECOMMENDATION	SAFAAIJAZIR