CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205395Orig1s000

ENVIRONMENTAL ASSESSMENT

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science

Memorandum

Date: December 17, 2014

From: James P. Laurenson, OPS/ONDQA

To: Fuqiang Liu, OPS/ONDQA/DNDQAII
Stephen Miller, OPS/ONDQA/DNDQAII
Althea Cuff, OPS/ONDQA

Subject: NDA 205-395, Combined Review of Environmental Assessment (EA) and Claim for Categorical Exclusion for Darunavir and Cobicistat, 800/100 mg Tablet

Applicant: Janssen Products, LP
1125 Trenton-Harbourton Road
Titusville, NJ 08560

A. Summary

Janssen Products, LP (Janssen) filed NDA 205-395 for a fixed combination of two active pharmaceutical ingredients (APIs)—darunavir and cobicistat (DRV and COBI)—for treatment of HIV infection in adults. This use is expected to result in increases in the release of each of the two APIs into the environment. For the first API—DRV—the applicant has submitted an EA by cross-reference to a previous DRV EA, which was reviewed by FDA. For the second API—COBI—the applicant submitted a claim for a categorical exclusion from the EA. The main goals of this review were to (1) determine whether the claim for categorical exclusion is acceptable; (2) determine whether the EA contains sufficient information to enable the Agency to determine whether the proposed action may significantly affect the quality of the human environment; and (3) determine whether the proposed action will significantly affect the environment.

Regarding the EA for DRV, the cross-referenced EA was examined and found to be identical to the current EA. FDA concluded that a full re-review of the EA was not required to determine the environmental impact due to approval of this previous EA and application. Furthermore, more recent data, including a European Medicines Agency (EMA) review of an application for DRV, were examined and found to contain corroborating data. Therefore, the previous FDA conclusion of no significant adverse environmental impacts was maintained for this action.

Regarding the claim for categorical exclusion for COBI, the expected introduction concentrations (EICs) calculations appear to be correct. Regarding the claim of no extraordinary circumstances, the Agency found no data to establish that, at the expected level of exposure, there is the potential for serious harm to the environment from this action (21 CFR 25.21(a)).

FDA concludes that the EA and categorical exclusion request are adequate for approval of the NDA. The EA contains sufficient information to enable the agency to determine whether the proposed action may significantly affect the quality of the human environment. No significant adverse environmental impacts are expected from the approval of this NDA. Based on the information available to date, a finding of no significant impact (FONSI) is recommended.

B. Background

Janssen has filed NDA 205-395 for a fixed combination of two active pharmaceutical ingredients (APIs)—darunavir and cobicistat (DRV and COBI)—for treatment of HIV infection in adults. This use is expected to result in increases in the release of each of the two APIs into the environment. For the first API—DRV—the applicant has submitted an EA by cross-reference to a previous DRV EA, which was reviewed by FDA. For the second API—COBI—the applicant submitted a claim for a categorical exclusion from the EA.

For DRV, the applicant submitted an EA that cross-references and is essentially identical to a DRV EA (dated September 7, 2007) submitted for NDA 021-976 (PREZISTA®) by Tibotec, Inc., in accordance with Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications (EA Guidance; USFDA 1998). The EA for NDA 021-976 had been reviewed by FDA (dated February 12, 2008), which found that no significant adverse environmental impacts are expected from the introduction of darunavir residues into the environment due to the use of PREZISTA® tablets. A FONSI subsequently was entered into the record.

For COBI, the applicant submitted a claim for categorical exclusion under 21 CFR 25.31(b), which is for actions that increase the use of the active moiety, but where the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb or µg/L). A calculation accompanied this claim. Also, the required statement regarding “extraordinary circumstances” was provided.

The main goals of this review are to determine whether (1) the EA contains sufficient information to enable the Agency to determine whether the proposed action may significantly affect the quality of the human environment; (2) the proposed action will significantly affect the environment; and (1) the claim for categorical exclusion is acceptable.

C. Review of EA for DRV

The applicant estimated an EIC of (b) (4) ppb for DRV based on the highest five-year use projection of (b) (4) kg and assuming no metabolism and the worst-case scenario of all drug API entering the aquatic environment, as recommended in the EA Guidance. This EIC therefore exceeds the categorical exclusion EIC of 1 ppb noted in 21 CFR 25.31(b), and thus pursuant to 21 CFR 25.15(a), the applicant provided an EA. The EA cross-references and is essentially a duplicate of the previous 2007 EA for DRV noted above. The previous EIC was (b) (4) ppb, slightly higher than the current EIC of (b) (4).

Given the similarities of the current and previous EAs and the FDA review of the previous EA, FDA concluded that a full re-review of the EA was not required to determine the environmental impact. Three issues were identified in this EA, however. First, as noted in Module 2.2, Introduction, of this application's Common Technical Document (CTD), this product is intended to be used in the same adult population for which current DRV (plus ritonavir) is recommended, which could be considered no increased use of DRV. This in turn would negate the need for an EA (21 CFR 25.31(a)). Module 2.2 also notes, however, that this product offers an opportunity to simplify DRV-containing antiretroviral regimens by reducing pill burden, potentially resulting in improved regimen adherence. This improved adherence could result in increased use.

Second, it initially was unclear whether the current EIC reflected the DRV use for only NDA 205-395 and not all of this applicant's products. As noted in the EA Guidance, the quantity should include the quantity used in an applicant's related applications, including those for other dosage forms using the same active moiety and for products using different forms of the active moiety (e.g., level of hydration, salt, free acid/base). Therefore, all recent uses of DRV were examined to better understand the estimate used in the EA. For 2012 and 2013, approximately (b) (4) kg and (b) (4) kg, respectively (IMS 2013, 2014), were used in the U.S., or slightly more than half of the projected amount for this application. It seems unlikely that more than an almost (b) (4) increase would result from an improved adherence to regimen due to use of this product in the same adult population for which current DRV (plus ritonavir) is recommended. Furthermore, in the EA, the wording used, e.g., "the <u>total</u> fifth-year production estimate [emphasis added]" implies that the estimate used did include all of this applicant's products.

Third, more recent aquatic toxicity data not included in the EA exists in a 2012 European Medicines Agency (EMA) assessment report (EMA 2012). These additional data include the following:

Study type	Test protocol	Endpoint	Value	Unit	Remarks
(b) (4)					

The EA used only acute values within the tiered testing approached described in the EA Guidance, concluding that no further testing was required, that the compound is not expected to be toxic to aquatic organisms at the EIC, and thus that these additional tests were not

needed. Nevertheless, given the existence of these tests, it is useful to compare their results to EICs in order to corroborate the results of the tiered testing. Therefore, comparing the lowest NOEC above, (b) (4) mg/L, with the EIC, (b) (4) ppb, or (b) (4) mg/L, results in close to an (b) (4)-fold difference, thus further indicating that DRV is not expected to be toxic to aquatic organisms at the EIC. Therefore, no significant adverse environmental impacts are expected from this action.

D. Review of Claims for Categorical Exclusion

The applicant requested a claim for categorical exclusions for COBI on the basis that the EIC at the point of entry into the aquatic environment will be less than 1 ppb. The calculated EIC is (b) (4) ppb based on the applicant's highest total quantity of COBI expected to be produced for use in the U.S. in any of the next five years, (b) (4) kg/year. The EIC calculation is correct, based on the use amounts provided by the applicant and the assumptions recommended in the EA Guidance. Regarding the claim of no extraordinary circumstances, there is little available data to establish that, at the expected level of exposure, there is the potential for serious harm to the environment from this action (21 CFR 25.21(a)).

E. Conclusions

The EA and categorical exclusion request are adequate for approval of the NDA. The EA contains sufficient information to enable the agency to determine whether the proposed action may significantly affect the quality of the human environment, and the claim for a categorical exclusion is valid. Based on an evaluation of the information provided in the EA and additional reports, of the scientific validity of the "no significant effects" conclusions of the EA, and of the validity of the claim for a categorical exclusion, no significant adverse environmental impacts are expected from the approval of this NDA.

Based on the information available to date, a finding of no significant impact (FONSI) and acceptance of the claim for categorical exclusion are recommended for this application.

F. References

EMA. 2012. Assessment report: Prezista/darunavir (EMA/CHMP/304651/2012); Committee for Medicinal Products for Human Use (CHMP).

IMS. 2013. IMS National Sales Perspectives: Retail and Non-Retail, Year 2012. IMS Health, Parsippany, NJ.

IMS. 2014. IMS National Sales Perspectives: Retail and Non-Retail, Year 2013. IMS Health, Parsippany, NJ.

USFDA. 1998. Guidance for Industry: Environmental Assessment of Human Drug and Biologics Application. Page 39 in Center for Biologics Evaluation and Research, editor. US Food and Drug Administration, Rockville, MD.

James P. Laurenson

Digitally signed by James P. Laurenson -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001141777, cn=James P. Laurenson -S
Date: 2014.12.17 14:00:43 -05'00'

Finding of No Significant Impact

NDA 205-395
Darunavir/Cobicistat Tablets, 800/100 mg

Food and Drug Administration
Center for Drug Evaluation and Research

The National Environmental Policy Act of 1969 (NEPA) requires Federal agencies to assess the environmental impact of their actions. The Food and Drug Administration (FDA) is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

Janssen Products, LP (Janssen) requests approval of NDA 205-395 for a fixed combination of two active pharmaceutical ingredients (APIs)—darunavir and cobicistat—for treatment of HIV infection in adults. In support of its application, Janssen prepared an environmental analysis (attached) that includes an environmental assessment (EA) for one of the APIs, darunavir, and a claim for categorical exclusion for the other, cobicistat, in accordance with 21 CFR Part 25, which evaluates the potential environmental impact from the use and disposal of this product. The EA cross references another darunavir EA, dated September 7, 2007 and submitted for NDA 021-976 (PREZISTA®) by Tibotec, Inc.

The FDA Center for Drug Evaluation and Research (CDER) has reviewed the EA and has carefully considered the potential environmental impact due to approval of this application. CDER also has reviewed more recent data, including a European Medicines Agency (EMA) review of an application for darunavir. Based on the CDER review of this information, FDA has determined that approval of the present application for darunavir/cobicistat tablets is not expected to have a significant impact on the human environment. Therefore, FDA is issuing a finding of no significant impact (FONSI), and thus an environmental impact statement will not be prepared.

Attachment: May 2, 2013, Environmental Assessment

Janssen Research & Development, L.L.C.

Environmental Assessment

NDA for Darunavir and Cobicistat

TMC114 (R319064) and JNJ-48763364

Department: Chemistry, Manufacturing & Controls
Document No.: EDMS-ERI-56504598
Report No.: EAUS-CE-TMC114+JNJ-48763364-TAB-NDA-V01

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NDA Categorical Exclusion for Darunavir and Cobicistat

SUMMARY

Potential environmental impacts of darunavir have been evaluated in this environmental assessment according to 21 CFR Part 25.

The calculated Maximum Expected Environmental Concentration (MEEC, Expected Introduction Concentration, or EIC-Aquatic based on use) was more than 1 part per billion (ppb) based on the fifth year projection forecast; therefore fate and acute effects testing results were performed and reported.

In accordance with the Tier 1 Testing Criteria described in the *Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications*{1}, if no rapid, complete depletion mechanisms are known, then a microbial inhibition test should be performed; and if the Log K_{ow} <3.5, then an acute toxicity study should be performed. If the results demonstrate that either the acute EC_{50} (Median Effective Concentration) or the acute LC_{50} (Median Lethal Concentration) divided by the MEEC is $\geq$1,000, then no further testing should be conducted unless sublethal effects are observed at the MEEC.

For darunavir, no rapid, complete depletion mechanisms are known. A microbial inhibition test showed darunavir to be relatively non-toxic with an empirically estimated EC_{50} > 1000 mg/L, and the Log K_{ow} <3.5. The calculated assessment factors for algae, daphnids, and zebra fish were each greater than 1,000, according to the calculation described above, and sublethal effects were not seen at the MEEC; therefore additional testing is not required. No potential adverse environmental effects resulting from the manufacture and use of darunavir have been identified.

1. Guidance for industry-environmental assessment of human drugs and biologics applications. US FDA - Food and Drug Administration, Washington, DC, July 1998.

1. DATE

February 2013

2. NAME

Janssen Research & Development, L.L.C.

3. ADDRESS OF APPLICANT

1000 Route 202
Raritan, NJ 08869

4. DESCRIPTION OF THE PROPOSED ACTION

4.1. Requested Approval

Janssen originally submitted NDA 21-976, including an environmental assessment (EA), for darunavir drug substance in 300-mg tablets. The original NDA was approved 23 June 2006.

Janssen is submitting a NDA pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for darunavir drug substance in combination with cobicistat drug substance.

An EA is being submitted pursuant to 21 CFR Part 25 for darunavir drug substance.

A categorical exclusion (21 CFR 25.31(b)) is being submitted for cobicistat drug substance, see CONFIDENTIAL MEEC CALCULATION: Cobicistat. To the best of Janssen's knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment.

4.2. Need for Action

This EA supports a New Drug Application (NDA) for darunavir. Darunavir is an HIV protease inhibitor. It selectively inhibits the cleavage of HIV encoded gag-pol polyproteins in virus-infected cells, thereby preventing the formation of mature and infectious progeny virus particles. Cobicistat inhibits liver enzymes that metabolize darunavir and therefore achieve higher concentrations with lower dosing, to optimize viral suppression but minimize side effects.

4.3. Locations of Use

This combination drug will be used in hospitals and private homes across the US. It will be available by prescription only.

4.4. Disposal Sites

Disposal of prescribed product will be through use, with returned product disposed through high temperature incineration at licensed disposal facilities. U.S. hospitals, pharmacies, or clinics will dispose of empty or partially empty packages according to their internal handling procedures. In the home, disposal will be through community solid waste management systems, which may include landfills or incineration, although minimal quantities of the unused drug could be disposed of in the sewer system. Where available, disposal of unused medicines could also be through take-back programs in local community waste disposal systems or pharmacies.

5. IDENTIFICATION OF SUBSTANCES

5.1. Nomenclature

5.1.1. Established Name (U.S. Adopted Name-USAN)

darunavir

5.1.2. Brand/Proprietary Name/Trade Name

PREZISTA®

5.1.3. Chemical Names

[(1*S,*2*R*)-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3*R,*3a*S,*6a*R*)-hexahydrofuro[2,3-*b*]furan-3-yl ester ethanolate

Carbamic acid, [(1*S,*2*R*)-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-, (3*R,*3a*S,*6a*R*)-hexahydrofuro[2,3-*b*]furan-3-yl ester ethanolate

5.2. Chemical Abstracts Service (CAS) Registration Number

206361-99-1

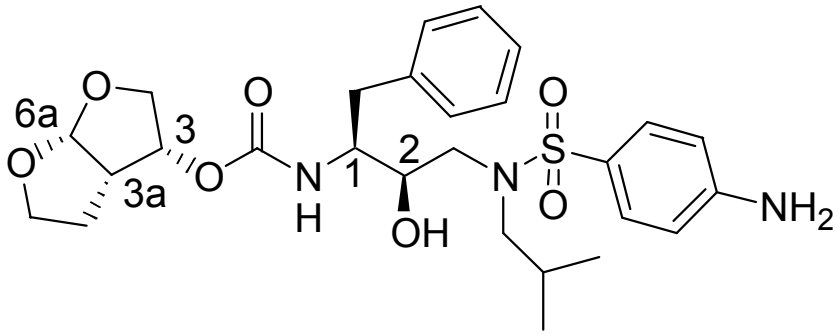
5.3. Molecular Formula

$C_{27}H_{37}N_3O_7S$

5.4. Molecular Weight

547.66

5.5. Structural (Graphic) Formula



6. ENVIRONMENTAL ISSUES

The manufacture and use of darunavir tablets are not expected to result in significant environmental releases of the active ingredient or excipients. No potential adverse environmental effects resulting from the manufacture and use of darunavir have been identified.

The physical/chemical characterizations used to evaluate potential adverse effects in the environment are presented in Table 1.

Table 1: Physical/Chemical Characterization

Property	Value	Source
Dissociation Constant pKa	2.02 at 25 °C	DMF 18825{1}
Partition Coefficient n-octanol/water (Log K_{ow} or Log P)	2.47 at 23 °C	DMF 18825{1}
Adsorption Coefficient (K_{oc})	265 to 993 for soils 345 for activated sludge	Report 13844.6106{3}

OECD = Organization for Economic Cooperation and Development

The dissociation constant (pKa) indicates the tendency of an organic chemical to ionize and is related to the adsorption of the chemical into biological membranes. The pKa of darunavir was determined to be 2.02 at 25 °C. At environmentally relevant pH levels, such as those commonly found in rivers and lakes, darunavir shows minimal potential to be readily adsorbed into biological membranes.{1}

The partition coefficient (log K_{ow}) indicates the tendency of an organic chemical to partition into lipids or fats, sorb to particulates such as soils or sediments, sorb to biomass and sludge, and distribute among the various environmental compartments. According to the Tier 1 Testing Criteria described in the *Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications* (July 1998), chemicals with log K_{ow} <3.5 do not have potential to bioaccumulate.{2} The log K_{ow} for darunavir is 2.47,

which is below 3.5, therefore darunavir does not show a potential to bioaccumulate.{1}

The adsorption coefficient (K_{oc}) indicates the tendency of an organic chemical to mobilize in the environment. The K_{oc} for darunavir was evaluated in a study according to OECD Guideline 106. Generally, K_{oc} values below 100 show no binding potential, between 100 and 1000 are considered to have slight to moderate binding potential, and >1000 shows strong binding potential. Based on the results of this study, the K_{oc} ranged from 265 to 993 for soils, and 345 for activated sludge, therefore darunavir shows slight to moderate potential to bind to soils.{3}

Information related to the Maximum Expected Environmental Concentration (MEEC, expected introduction concentration, or EIC-Aquatic, based on use) calculation is confidential and is provided in Confidential Appendices, CONFIDENTIAL MEEC CALCULATION: Darunavir.

6.1. Assessing Toxicity to Environmental Organisms

The following environmental effect studies have been conducted with darunavir drug substance; the results are summarized in Table 2.

A. Microbial growth inhibition (activated sludge respiration inhibition){4}

B. Algae (*Pseudokirchneriella subcapitata)* acute toxicity{5}

C. Daphnids (*Daphnia magna*) acute toxicity{6}

D. Zebra fish (*Brachydanio rerio*) acute toxicity{7}

Table 2: Toxicity Testing of Darunavir Drug Substance with Representative Environmental Organisms

Test Organism	Conditions	Results	Source
Microbial Inocula	Microbial growth inhibition	EC_{50} > 1000 mg/L	Report 13844.6103{4}
Algae (*Pseudokirchneriella subcapitata)*	Acute toxicity	NOEC = 43 mg/L EC_{50} > 43 mg/L (72 h)	Report 13844.6107{5}
Daphnids *(Daphnia magna)*	Acute toxicity	NOEC = 2.6 mg/L EC_{50} > 43 mg (48 h)	Report 13844.6108{6}
Rainbow Trout (*Oncorhynchus mykiss*)	Acute toxicity	NOEC = 38 mg/L LC_{50} > 38 mg/L (96 h)	Report 13844.6109{7}

EC_{50} = Median effective concentration
NOEC = No observed effect concentration
LC_{50} = Median lethal concentration

6.1.1. Microbial Inhibition Test

The influence of darunavir drug substance on microorganisms was determined by measuring the respiration rate under defined conditions in a 3-hour activated sludge respiration inhibition study according to OECD Guideline 209.

Based on the results of the study, the EC_{50} (Median Effective Concentration) value was determined to be >1000 mg/L, the highest concentration tested.{4}

6.1.2. Acute Toxicity to Freshwater Green Algae

The influence of darunavir on the green algal species *Pseudokirchneriella subcapitata*, was investigated in a 72-hour static test, according to OECD Guideline 201.

Based on the results of this test, the EC_{50} for both endpoints, growth rate and yield, was empirically estimated to be >43 mg/L. Additional testing at higher concentrations to further define the EC_{50} values was not performed, since the highest nominal concentration of the test substance approximated the water solubility limit of darunavir under the maintained test conditions. The 72-hour No-Observed-Effect Concentration (NOEC) was determined to be 43 mg/L, the highest concentration tested.{5}

6.1.3. Acute Toxicity to the Water-Flea

The acute toxicity of darunavir drug substance to *Daphnia magna* was determined in a 48-hour static test according to OECD Guideline 202.

Since no concentration tested resulted in ≥50% immobilization, the 48-hour EC_{50} value for darunavir and *Daphnia magna* was empirically estimated to be >44 mg/L, the highest mean measured concentration tested. Additional testing at higher concentrations to further define the EC_{50} was not performed, since the highest nominal concentration of the test substance approximated the water solubility limit of darunavir under the maintained test conditions. The NOEC was determined to be 2.6 mg/L.{6}

6.1.4. Acute Toxicity to Fish

The acute toxicity of darunavir drug substance to rainbow trout (*Oncorhynchus mykiss*) was determined in a 96-hour static renewal test according to OECD Guideline 203.

Since no concentration tested resulted in ≥50% mortality, the 96-hour LC_{50} value for darunavir and *Oncorhynchus mykiss* was empirically estimated to

be >38 mg/L, the highest mean concentration tested. Additional testing at higher concentrations to further define the LC_{50} values was not performed, since the highest nominal concentration of the test substance was the approximate water solubility limit of darunavir under the maintained test conditions. The NOEC was determined to be 38 mg/L.{7}

6.2. Conclusion

In accordance with the Tier 1 Testing Criteria described in the *Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications* (July 1998){2}, no further testing is required. After the microbial inhibition test found darunavir to have an EC_{50} >1,000 mg/L, the log K_{ow} was determined to be <3.5, after which acute ecotoxicity studies were reported. The calculated assessment factor for each of the 3 acute toxicity studies is >1,000. No observed effects were seen at the MEEC, therefore no further testing is required. Information related to the tiered approach to environmental effects testing is confidential and is provided in APPENDIX 2 – CONFIDENTIAL TIERED APPROACH TO ENVIRONMENTAL EFFECTS TESTING CALCULATIONS**.**

7. MITIGATION MEASURES

Section 7 is not required when there have been no adverse environmental effects identified.

8. ALTERNATIVES TO THE PROPOSED ACTION

Section 8 is not required when there have been no adverse environmental effects identified.

9. LIST OF PREPARERS

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Education:

- B.S. Environmental Sciences from Rutgers University, NJ USA
- M.S. Environmental Sciences from Rutgers University, NJ USA

Professional Experience:

- January 2012 – Current:

  - Senior Environmental Engineer at Janssen Research & Development, L.L.C. in Beerse, Belgium.
  - Responsibilities include coordination of ecotoxicity fate & effects testing programs and international environmental registration of pharmaceuticals.
- February 2005 – December 2011:
  - Environmental Engineer at Johnson & Johnson Pharmaceutical Research & Development in Raritan, NJ USA.
  - Responsibilities include coordination of ecotoxicity fate & effects testing programs and international environmental registration of pharmaceuticals

REFERENCES

1. DMF 18825 previously submitted for TMC114 Ethanolate, 2 Nov 2005.

2. Guidance for industry-environmental assessment of human drugs and biologics applications. US FDA - Food and Drug Administration, Washington, DC, Jul 1998.

3. [^{14}C]TMC114 Ethanolate - determination of the adsorption coefficient (Koc). McLaughlin SP. OECD Guideline 106; Springborn Smithers Laboratories Report 13844.6106, 25 Oct 2005.

4. TMC114 Ethanolate - activated sludge respiration inhibition. McLaughlin SP. OECD Guideline 209; Springborn Smithers Laboratories Report 13844.6103, 06 Jul 2005.

5. TMC114 Ethanolate - acute toxicity to the freshwater green alga, *Pseudokirchneriella subcapitata*. Hoberg, JR. OECD Guideline 201; Springborn Smithers Laboratories Report 13844.6107, 01 Sep 2005.

6. TMC114 Ethanolate – acute toxicity to water fleas, (*Daphnia* magna) under static conditions. Hoberg JR. OECD Guideline 202; Springborn Smithers Report 13844.6108, 01 Sep 2005.

7. TMC114 Ethanolate – acute toxicity to rainbow trout (*Oncorhynchus mykiss*) under static conditions. Hoberg, JR. OECD Guideline 203; Springborn Smithers Report 13844.6109, 11 Aug 2005.

CONFIDENTIAL APPENDICES

APPENDIX 1: CONFIDENTIAL MEEC CALCULATIONS

APPENDIX 2

CONFIDENTIAL TIERED APPROACH TO ENVIRONMENTAL EFFECTS TESTING CALCULATIONS

SIGNATURES

Signed by	Date	Justification
KELLY QUINLAN	03May2013, 13:22:36 PM, UTC	Document Approval