CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204592Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 10/31/2013
See OMB Statement on Page 3.

NDA NUMBER
NDA 204592

NAME OF APPLICANT/NDA HOLDER
Iroko Pharmaceuticals, LLC

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Zorvolex Capsules

ACTIVE INGREDIENT(S)	STRENGTH(S)
Diclofenac Acid	18 mg and 35 mg

DOSAGE FORM
Capsule

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
US 2010/0092563	NA-pending application	NA-pending application

d. Name of Patent Owner	Address *(of Patent Owner)*	
iCeutica	One Kew Place, 150 Rouse Blvd.	
	City/State: Philadelphia, PA	
	ZIP Code: 19112	FAX Number *(if available)*: (267) 546-3004
	Telephone Number: (267) 546-3019	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
NA	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☒ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☒ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☐ Yes	☒ No
4.2 Patent Claim Number(s) *(as listed in the patent)*	Does (Do) the patent claim(s) referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*		

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☒ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	8 NOV 12

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Anita L. Meiklejohn	
Address Fish & Richardson P.C. One Marina Park Drive	City/State Boston, Massachusetts
ZIP Code 02210-1878	Telephone Number 617-542-5070
FAX Number *(if available)* 877-769-7945	E-Mail Address *(if available)* ALM@FR.COM

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html.*

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 10/31/2013
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PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER
NDA 204592

NAME OF APPLICANT/NDA HOLDER
Iroko Pharmaceuticals, LLC

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Zorvolex Capsules

ACTIVE INGREDIENT(S)	STRENGTH(S)
Diclofenac Acid	18 mg and 35 mg

DOSAGE FORM
Capsule

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
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FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
US 2012/0135047	NA-pending application	NA-pending application

d. Name of Patent Owner
iCeutica

Address *(of Patent Owner)*
One Kew Place, 150 Rouse Blvd.

City/State
Philadelphia, PA

ZIP Code
19112

FAX Number *(if available)*
(267) 546-3004

Telephone Number
(267) 546-3019

E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

NA

Address *(of agent or representative named in 1.e.)*

City/State

ZIP Code

FAX Number *(if available)*

Telephone Number

E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3.**		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☐ Yes	☒ No
4.2 Patent Claim Number(s) *(as listed in the patent)*	Does (Do) the patent claim(s) referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*		

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☒ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide information below)*	Date Signed
	8 NOV 12

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Anita L. Meiklejohn	
Address Fish & Richardson P.C. One Marina Park Drive	City/State Boston, Massachusetts
ZIP Code 02210-1878	Telephone Number 617-542-5070
FAX Number *(if available)* 877-769-7945	E-Mail Address *(if available)* ALM@FR.COM

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

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First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

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2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 10/31/2013
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PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER
NDA 204592

NAME OF APPLICANT/NDA HOLDER
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Zorvolex Capsules

ACTIVE INGREDIENT(S)	STRENGTH(S)
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DOSAGE FORM
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1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
US 2012/0160944	NA-pending application	NA-pending application

d. Name of Patent Owner
iCeutica

Address *(of Patent Owner)*
One Kew Place, 150 Rouse Blvd.

City/State
Philadelphia, PA

ZIP Code
19112

FAX Number *(if available)*
(267) 546-3004

Telephone Number
(267) 546-3019

E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

NA

Address *(of agent or representative named in 1.e.)*

City/State

ZIP Code

FAX Number *(if available)*

Telephone Number

E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

PSC Graphics (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☒ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☒ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☐ Yes	☒ No
4.2 Patent Claim Number(s) *(as listed in the patent)*	Does (Do) the patent claim(s) referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*		

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For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☒ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	8 NOV 12

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Anita L. Meiklejohn	
Address Fish & Richardson P.C. One Marina Park Drive	City/State Boston, Massachusetts
ZIP Code 02210-1878	Telephone Number 617-542-5070
FAX Number *(if available)* 877-769-7945	E-Mail Address *(if available)* ALM@FR.COM

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html.*

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 10/31/2013
See OMB Statement on Page 3.

NDA NUMBER
NDA 204592

NAME OF APPLICANT/NDA HOLDER
Iroko Pharmaceuticals, LLC

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Zorvolex Capsules

ACTIVE INGREDIENT(S)	STRENGTH(S)
Diclofenac Acid	18 mg and 35 mg

DOSAGE FORM
Capsule

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
US 2012/0165323	NA-Pending application	NA-Pending application

d. Name of Patent Owner	Address *(of Patent Owner)*	
iCeutica	One Kew Place, 150 Rouse Blvd.	
	City/State: Philadelphia, PA	
	ZIP Code: 19112	FAX Number *(if available)*: (267) 546-3004
	Telephone Number: (267) 546-3019	E-Mail Address *(if available)*:

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
NA	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☒ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☒ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2 Patent Claim Number(s) *(as listed in the patent)*	Does (Do) the patent claim(s) referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☒ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	8 NOV 12

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Anita L. Meiklejohn	
Address Fish & Richardson, P.C. One Marina Park Drive	City/State Boston, Massachusetts
ZIP Code 02210-1878	Telephone Number 617-542-5070
FAX Number *(if available)* 877-769-7945	E-Mail Address *(if available)* ALM@FR.COM

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html.*

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 10/31/2013
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER
NDA 204592

NAME OF APPLICANT/NDA HOLDER
Iroko Pharmaceuticals, LLC

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Zorvolex Capsules

ACTIVE INGREDIENT(S)	STRENGTH(S)
Diclofenac Acid	18 mg and 35 mg

DOSAGE FORM
Capsule

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
US 2012/0165410	NA - Pending application	NA - Pending application

d. Name of Patent Owner	Address *(of Patent Owner)*	
iCeutica	One Kew Place, 150 Rouse Blvd.	
	City/State: Philadephia, PA	
	ZIP Code: 19112	FAX Number *(if available)*: (267) 546-3004
	Telephone Number: (267) 546-3019	E-Mail Address *(if available)*:

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
NA	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☒ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☒ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☐ Yes	☒ No
4.2 Patent Claim Number(s) *(as listed in the patent)*	Does (Do) the patent claim(s) referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*		

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☒ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	8 NOV 12

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Anita L. Meiklejohn	
Address Fish & Richardson P.C. One Marina Park Drive	City/State Boston, Massachusetts
ZIP Code 02210-1878	Telephone Number 617-542-5070
FAX Number *(if available)* 877-769-7945	E-Mail Address *(if available)* ALM@FR.COM

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
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- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
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- Additional copies of these forms may be downloaded from the Internet at: *http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html.*

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 10/31/2013
See OMB Statement on Page 3.

NDA NUMBER
NDA 204592

NAME OF APPLICANT/NDA HOLDER
Iroko Pharmaceuticals, LLC

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Zorvolex Capsules

ACTIVE INGREDIENT(S)	STRENGTH(S)
Diclofenac Acid	18 mg and 35 mg

DOSAGE FORM
Capsule

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
US 2012/0202964	NA-pending application	NA-pending application

d. Name of Patent Owner	Address *(of Patent Owner)*	
iCeutica	One Kew Place, 150 Rouse Blvd.	
	City/State: Philadelphia, PA	
	ZIP Code: 19112	FAX Number *(if available)*: (267) 546-3004
	Telephone Number: (267) 546-3019	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
NA	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3.**		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☒ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☒ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?		☐ Yes	☒ No
4.2 Patent Claim Number(s) *(as listed in the patent)*	Does (Do) the patent claim(s) referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☐ No
4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*		

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☒ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	8 NOV 12

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Anita L. Meiklejohn	
Address Fish & Richardson P.C. One Marina Park Drive	City/State Boston, Massachusetts
ZIP Code 02210-1878	Telephone Number 617-542-5070
FAX Number *(if available)* 877-769-7945	E-Mail Address *(if available)* ALM@FR.COM

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html.*

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

1.3.5.2 PATENT CERTIFICATION

Paragraph II Certification
Patent has expired/no unexpired patents listed in the Orange Book

Pursuant to 21§314.50(i)(1)((i)(A)(2)), in the opinion and to the best knowledge of Iroko Pharmaceuticals, LLC, there are no unexpired patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

Steven Jensen, Vice President, Regulatory Affairs & Quality

12/01/2012
Date

EXCLUSIVITY SUMMARY

NDA # 204592 SUPPL # NA HFD # 170

Trade Name Zorvolex Capsules

Generic Name diclofenac

Applicant Name Iroko Pharmaceutical LLC

Approval Date, If Known October 18, 2013

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)(2)

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?

3 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#	020142	Cataflam (diclofenac potassium)
NDA#	021234	Flector (diclofenac epolamine)
NDA#	022202	Zipsor (diclofenac potassium)
NDA#	022165	Cambia (diclofenac potassium)
NDA#	021005	Solaraze (diclofenac sodium)
NDA#	022122	Voltaren (diclofenac sodium)
NDA	19201	Voltaren (diclofenac sodium)
NDA	20254	Voltaren -XR(diclofenac sodium)
NDA#	020947	Pennsaid (diclofenac sodium)

See Orange Book for a list of ANDAs.

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:

Study DIC3-08-04 (Phase 3) and Study DIC1-12-07 (Pharmacokinetics)

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:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study DIC3-08-04 (Phase 3) and Study DIC1-12-07 (Pharmacokinetics)

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # 103880 YES ☒ ! NO ☐

! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

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: Swati Patwardhan
Title: Regulatory Project Manager, HFD-170

Date: October 16, 2013

Name of Office/Division Director signing form: Sharon Hertz, MD
Title: Deputy Director, HFD-170

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

SWATI A PATWARDHAN
10/16/2013

SHARON H HERTZ
10/18/2013

1.3.3 Debarment Certification

Iroko 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.

Signed: _____ Date: 12/21/2012

Steve Jensen
Vice President, Regulatory Affairs and Quality
Iroko Pharmaceuticals, LLC

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # **204592** BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: **Zorvolex** Established/Proper Name: **diclofenac** Dosage Form: **Capsules**		Applicant: **Iroko Pharmaceuticals** Agent for Applicant (if applicable):
RPM: **Swati Patwardhan**		Division: **DAAAP**

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(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.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):
NDA 020142 Cataflam 50 mg

Provide a brief explanation of how this product is different from the listed drug.
Zorvolex capsules are a reformulation of diclofenac (in acid form) with reduced particle size. Zorvolex capsules are 20% lower in 'molar' diclofenac dose compared to Cataflam tablets (diclofenac potassium salt).

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☒ This application relies on (explain) Cataflam

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☒ No changes ☐ Updated Date of check: October 18, 2013

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.

❖ Actions	
• Proposed action • User Fee Goal Date is **October 20, 2013**	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[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.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ 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 _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 3 (New Dosage Form)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☒ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action (by OEP)	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[3] 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	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *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.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(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.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• 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.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• 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) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [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).	☒ No paragraph III certification Date patent will expire
• [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). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☒ N/A (no paragraph IV certification) ☐ 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).*

(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? (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). *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*).* *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.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[4]	✓
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AP/ Oct 18, 2013
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Oct 18, 2013
• Original applicant-proposed labeling	✓
• Example of class labeling, if applicable	

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	Oct. 8, 2013
• Original applicant-proposed labeling	Dec. 20, 2012
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	Oct 10, 2013
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	• Apr. 29, 2013 • Apr. 29, 2013, Sep. 6, 2013 • ✓
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM Feb.22, 2013 ☒ DMEPA Sep.13, 2013 ☒ DMPP/PLT (DRISK) Oct. 4, 2013 ☒ ODPD (DDMAC) Oct.3, 2013 ☒ SEALD Oct. 17, 2013 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	Feb.22, 2013 Sep. 16, 2013 Oct. 18, 2013 ☐ Not a (b)(2) ☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC Sep.4, 2013 If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ 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 *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	✓
❖ Internal memoranda, telecons, etc.	✓
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg Jun 7, 2012
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg Nov. 9, 2010
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None Oct. 18, 2013
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None Sep. 30, 2013
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	Sep. 30, 2013
• Clinical review(s) *(indicate date for each review)*	Sep. 17, 2013; Feb. 1, 2013
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	CDTL Memo/Sep. 30, 2013
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None

[6] Filing reviews should be filed with the discipline reviews.

❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested Aug. 29, 2013
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
Statistical Review(s) *(indicate date for each review)*	☐ None Sep. 11, 2013; Feb. 14, 2013
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None Sep. 16, 2013; Feb. 11, 2013
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☒ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None Sep. 17, 2013; Feb. 1, 2013; Dec. 2, 2010; Apr. 17, 2009
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None Feb. 25, 2013; Feb. 27, 2013; Sep. 17, 2013; Sep. 16, 2013
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed Apr. 8, 2013
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	Sep. 16, 2013
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) *(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 sites[7])*	Date completed: Jun. 13, 2013 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

[7] 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.

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/s/

SWATI A PATWARDHAN
10/22/2013

Patwardhan, Swati

From: Jani, Parinda
Sent: Thursday, October 17, 2013 3:09 PM
To: Patwardhan, Swati; Lloyd, Joshua; Hertz, Sharon H
Subject: FW: Environmental assessment for Diclofenac NDA 204592

FYI

From: Peri, Prasad
Sent: Thursday, October 17, 2013 2:59 PM
To: Jani, Parinda
Subject: FW: Environmental assessment for Diclofenac NDA 204592

Parinda,

Looks like we are OK with the categorical exclusion

Prasad

From: Bloom, Raanan
Sent: Thursday, October 17, 2013 2:24 PM
To: Peri, Prasad
Cc: Wang, Ying; Duffy, Eric P; Pinto, Julia
Subject: RE: Environmental assessment for Diclofenac NDA 204592

Prasad,

A categorical exclusion (21CFR25.31(a)) is claimed by the applicant and is supported by the sponsor's argument that Zorvolex approval will "not increase overall use" of diclofenac; rather Zorvolex will compete with existing approved applications (NDAs and ANDAs) and may, in fact, reduce environmental introductions due to lower dosage levels. I have checked the diclofenac approvals at drugs@fda and concur. The categorical exclusion claim can be accepted for this application.

Currently, we do not have concerns about bird deaths from use of this application.

Please let me know if you need additional information or any questions.

Ron

Raanan (Ron) A. Bloom, Ph.D.
Senior Environmental Officer
Environmental Assessment Staff
FDA/CDER/OPS/IO
Ph: 301-796-2185

From: Peri, Prasad

Sent: Thursday, October 17, 2013 10:23 AM
To: Bloom, Raanan
Subject: RE: Environmental assessment for Diclofenac NDA 204592

Thanks

Appreciate your help. Somehow since we have data in house, I think we should be OK that there is no need to provide an environment assessment for all diclofenac applications. [redacted] (b) (4)

Prasad

From: Bloom, Raanan
Sent: Thursday, October 17, 2013 7:53 AM
To: Peri, Prasad
Subject: RE: Environmental assessment for Diclofenac NDA 204592

Peri,

I'll get back to you on this later today.

Happy post-government shutdown day!

Ron

From: Peri, Prasad
Sent: Wednesday, October 16, 2013 3:16 PM
To: Bloom, Raanan
Cc: Wang, Ying; Duffy, Eric P; Pinto, Julia
Subject: Environmental assessment for Diclofenac NDA 204592

Hello Ron,

DPARP received a NDA for diclofenac and is about to take an approval action..

They did provide an environmental assessment and we accepted it.

However note that for a similar application NDA [redacted] (b) (4) we asked them to provide an environmental assessment based on new information available at that time about birds dying.

Since we are about to take an approval action, do you think it would be OK to accept a post approval commitment for them to provide a Environmental impact assessment.

Thanks
Prasad

Prasad Peri, Ph.D.
Branch Chief, Branch VIII ONDQA

Rm 2618, Bldg 21,
10903 New Hampshire Avenue
Silver Spring MD 20993
Prasad.peri@fda.hhs.gov
Ph: 301 796 1730
Fax: 301 796 9749

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/s/

SWATI A PATWARDHAN
10/17/2013

Patwardhan, Swati

From: Borders-Hemphill, Vicky
Sent: Tuesday, October 15, 2013 12:34 PM
To: Patwardhan, Swati
Cc: Walker, Morgan
Subject: RE: re: NDA 204592 revised labeling from Sponsor

Hi Swati,
DMEPA reviewed the revised container label and blister and carton labeling for Zorvolex (diclofenac) capsules, submitted October 10, 2013 under NDA 204592 and find them to be acceptable.

Thanks,
Vicky Borders-Hemphill,PharmD
CDR, USPHS Commissioned Corps
Safety Evaluator
Division of Medication Error Prevention and Analysis
FDA/CDER/OSE/OMEPRM
Bldg 22, Room #4424
Phone: 301-796-2225
Email: Vicky.Borders-Hemphill@fda.hhs.gov

From: Patwardhan, Swati
Sent: Friday, October 11, 2013 11:16 AM
To: Lloyd, Joshua; Galati, Steven; Peri, Prasad; Pinto, Julia; Wang, Ying; Wasserman, Adam; Xu, Zengjun (Alex); Naraharisetti, Suresh; Xu, Yun (CDER); Li, Feng (CDER); Derr, Janice; Caulk, Nathan; Chung-Davies, Eunice; Borders-Hemphill, Vicky
Cc: Sullivan, Matthew
Subject: re: NDA 204592 revised labeling from Sponsor
Importance: High

Greetings,
The Sponsor has submitted revised labels and labeling for NDA 204592 Zorvolex.

The carton container labels are submitted via gateway: \\CDSESUB1\evsprod\NDA204592\0012
They have accepted all our revisions.

The med guide is saved on share drive: \\fdsfs01\ode2\DAAAP\NDA and sNDA\NDA 204592 (Zorvolex_Iroko)\Labeling\~$A 204592 MG revised Oct-8 - Sponsor Response - CLEAN.doc
Again they have accepted all our changes.

The PI is saved on share drive at \\fdsfs01\ode2\DAAAP\NDA and sNDA\NDA 204592 (Zorvolex_Iroko)\Labeling\NDA 204592 draft-labeling-revised-Oct-8 - Sponsor Response.doc
Sponsor has proposed number of revisions to our comments. Please review those changes and provide your comments preferably by COB Today. (apologize to make such a short turn around request).

This is the clean version of the Sponsor's labeling \\fdsfs01\ode2\DAAAP\NDA and sNDA\NDA 204592 (Zorvolex Iroko)\Labeling\NDA 204592 draft-labeling-revised-Oct-8 - Sponsor Response CLEAN.doc

Thank you

Swati Patwardhan
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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/s/

SWATI A PATWARDHAN
10/17/2013

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Wednesday, October 16, 2013 12:46 PM
To: Patwardhan, Swati; 'Steve Jensen'
Subject: RE: Labeling comments for NDA 204592
Attachments: NDA 204592 draft-labeling-revised-Oct-16.doc

Hi Steve,

Attached please find the word version of the revised labeling with our proposed changes. Please review the proposed FDA revisions, and **email** back to me your response. You can email me a

Word version (in track changes). Please accept any changes with which you concur, and then make any revisions you deem necessary. Please DO **NOT** submit final labeling to the NDA at this time, but

send your response to me only via email. If you have any questions, do not hesitate to call me/email me. Please submit the revised labeling, by ~10 am tomorrow, October 16, 2013 .

Thank you

Swati Patwardhan
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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/s/

SWATI A PATWARDHAN
10/16/2013

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Tuesday, October 08, 2013 4:03 PM
To: 'Steve Jensen'
Subject: RE: Labeling comments for NDA 204592
Attachments: NDA 204592 draft-labeling-revised-Oct-8.doc; NDA 204592 MG revised Oct-8.doc

Hi Steve,

Attached please find the word version of the labeling and Med guide, with our proposed changes. Please review the proposed FDA revisions, and **email** back to me your response. You can email me a

Word version (in track changes). Please accept any changes with which you concur, and then make any revisions you deem necessary. Please DO **NOT** submit final labeling to the NDA at this time, but

send your response to me only via email. Once we receive your response to these revisions, we will again review the label and then I will get back to you with any further proposed revisions prior to the action date.

Since there were revisions made, we may have missed typos, cross references, etc., and some of the heading formatting might be off.

For carton and container labels, we request following changes:

- Revise the established name to read “(diclofenac) capsules
- The storage condition is not stated in the blister physician sample labeling (both 18 mg and 35 mg). Please add the following storage condition language to the blister physician sample labeling:
  store at 25°C (77°F) with excursions permitted to 15°C-30°C (59°F-86°F)

If you have any questions, do not hesitate to call me/email me. Please submit the revised labeling, MG, and carton/container blister labels by COB Friday, October 11. 2013

Thank you

Swati Patwardhan
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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

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/s/

SWATI A PATWARDHAN
10/08/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204592

DISCIPLINE REVIEW LETTER

Iroko Pharmaceuticals, LLC
One Kew Place
150 Rouse Boulevard
Philadelphia, PA 19112

Attention: Steve Jensen
Sr. VP, Regulatory Affairs & Quality

Dear Mr. Jensen:

Please refer to your New Drug Application (NDA) submitted and received, December 20, 2012, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zorvolex (diclofenac) Capsules.

Our review of the carton and container labels is complete, and we have identified the following deficiencies:

A. All Container Labels and Carton Labeling (30 capsules, 90 capsules, and physician sample -18 mg and 35 mg strengths)

1. Revise the presentation of the proprietary name so it appears in title case rather than all capital letters to improve the readability.

2. Revise the established name to read "(diclofenac) capsules". Additionally, ensure that the name appears on one line underneath the proprietary name.

3. (b) (4)

4. Revise the color of the line graphic that appears underneath the strength statement so that each strength has a distinct underline color. (b) (4)

B. Bottle Container Labels (30 capsules and 90 capsules -18 mg and 35 mg strengths)

1. Ensure that the image of the capsule on the principal display panel of bottle labels represents the actual capsule and its true size, color and imprint. Ensure that the capsule

image does not compete in size or prominence with the proprietary name and strength information.

2. Remove the statement "See package insert for dosage information" from the principal display panel or relocate it to the side panel.

C. Physician sample Blister Labels

1. Ensure that the appearance of strength on the blister container backing describes the milligram amount of drug per single unit to mitigate medication errors of wrong dose and to appear as follows:

XX mg per capsule

2. Ensure that the name of the manufacturer, packer, or distributor is on the blister label as set forth in 21 CFR 201.10 (i).

D. Physician sample Blister Box holder and Carton Labeling

1. Ensure that the appearance of strength on the principal display panel and other panels of the blister carton labeling describes the milligram amount of drug per single unit to mitigate medication errors of wrong dose and to appear as follows:

XX mg per capsule

2. Consider providing a blank open space on the label so the provider of the drug sample can write or affix a label with the patient name and specific instructions for use.

3. Use a distinct color per strength or delete the purple color on the corners and flaps of the carton to further differentiate between the two strengths and help to minimize errors related to wrong strength selection. As presented, there is little distinction between the boxes when placed side by side (b) (4)

4. Ensure that the strength statement appears directly beneath the proprietary and established names on all panels of the box holder labeling. As presented, the strength statement does not appear on all display panels.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Swati Patwardhan, Regulatory Project Manager, at (301) 796-4085.

Sincerely,

{See appended electronic signature page}

Matt Sullivan, MS
Chief, Project Management Staff (acting)
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MATTHEW W SULLIVAN
09/26/2013

PeRC PREA Subcommittee Meeting Minutes
September 4, 2013

PeRC Members Attending:
Lynne Yao
Robert "Skip" Nelson
Karen Davis-Bruno
Rosemary Addy
Patricia Dinndorf
Tom Smith
Julia Pinto
Ethan Hausman
Peter Starke
Wiley Chambers
Andrew Mulberg
Andrew Mosholder
Colleen LoCicero
Dianne Murphy
Gregory Reaman
Dionna Green
Daiva Shetty
Lisa Kammerman
George Greeley
Jane Inglese

Guests Attending:
Robert Guidos
Richard Moscicki
Renan Bonnel (OPT)
Nichella Simms (PMHS)
Gilbert Burckart (OCP)
Courtney Suggs (OCP)
Richard Whitehead (DMEP)
Bradley McEvoy (OB)
Jaya Vaidyanathan (OCP)
Lokesh Jain (OCP)
David Carlson (DMEP)
Margaret Lin (DNP)
Hao Zhu (OCP)
Ellis Unger (ODE4)
Jing Zhang (DPP)
George Kordzakhia (DBI)
Linda Fossom (DPP)
Jenn Sellers (DPP)
Hiren Patel (DPP)
Joshua Lloyd (DAAAP)
Swati Patwardhan (DAAAP)
Juli Tomaino (DGIEP)
Anil Rajpal (DGIEP)
Nitin Mehrotra (OCP)
Karen Mahoney (DMEP)
Andre Jackson (OCP)
Sue-Chih Lee (PMTL)
Jian Wang (OCP)
Russel Fortney (DCRP)
Gail Moreschi (DCRP)
Shari Targum (DCRP)
Vicki Moyer (PMHS)
Amy Taylor (PMHS)
Melissa Tassinari (PMHS)

Agenda

10:00	NDA	(b) (4)	(b) (4)
10:30	NDA	204592	Zorvolex (diclofenac acid) Partial Waiver/Deferral/Plan
11:00	NDA	(b) (4)	(b) (4)
	NDA	(b) (4)	(b) (4)

(b) (4)

(b) (4)

Zorvolex (diclofenac acid) Partial Waiver/Deferral/Plan

- NDA 204592 seeks marketing approval for Zorvolex (diclofenac acid) for the treatment of mild to moderate acute pain in adults.
- The application was submitted on December 20, 2012, and has a PDUFA goal date of October 20, 2013.
- The application triggers PREA as directed to a new dosage form.
- A waiver is being requested for pediatric patients aged birth to less than 1 year because the product would be ineffective and/or unsafe in this age group.
- *Division justification for waiver:* Diclofenac is primarily metabolized by cytochrome P450 (CYP) enzyme CYP2C9. Hepatic CYP-dependent metabolism is immature (low) at birth with maturation occurring gradually over the first 6 to 12 months of life. Overall, children aged less than 1 year have a decreased ability to metabolize drugs via CYP2C9 resulting in prolonged persistence of the drug in the body. Immaturity of CYP enzymes, including CYP2C9, during the first year of life and the inter-individual variability in terms of CYP maturation results in an inability to accurately predict a diclofenac dose for the effective and safe use of the drug in pediatric subjects aged birth to <1 year. Therefore, a waiver is requested for the age group birth to <1 year, on the grounds that the drug would be ineffective or unsafe in this age group because pharmacokinetic pathways for the drug's metabolism are not fully developed in this age group.
- A deferral is being requested for pediatric patients aged 1 to less than 18 years because adult studies have been completed and the product is ready for approval.
- The sponsor plans to conduct the following clinical studies:
    - Study 1: An open-label pharmacokinetic and safety study or studies of an age appropriate formulation of diclofenac in pediatric patients 6 to < 18 years of age with acute pain.
    - Study 2: An open-label pharmacokinetic and safety study or studies of an age appropriate formulation of diclofenac in pediatric patients 2 to < 6 years of age with acute pain.
    - Study 3: A pharmacokinetic, safety, and efficacy study or studies of an age appropriate formulation of diclofenac in pediatric patients 1 to < 2 years of age with acute pain.
- Division comments: (b) (4)

PeRC Recommendations:

- The PeRC did not agree with the Division to grant a partial waiver in pediatric patients aged birth to less than one year because the product would be ineffective

and/or unsafe in this age group. The PeRC acknowledged that this reason has been used for previous NSAID products (immaturity of CYP2C9) but there was concern expressed that granting a waiver for this reason would set a potentially dangerous precedent. The PeRC noted that it may not be worth the "risk" to study this product for this population but that other products metabolized by CYP2C9 may be important to be studied in the 0 to 6 month population.

- The PeRC recommended granting a partial waiver in pediatric patients aged birth to less than one year because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients of this age and is not likely to be used in a substantial number of pediatric patients in this age group. There was concern expressed by the Division and some members of the PeRC that there may not be adequate existing therapies for the treatment of mild to moderate pain in patients 0 to 6 months of age.
- The PeRC agreed with the Division to grant a deferral for pediatric patients aged 1 to less than 18 years because the product is ready for approval in adults.
- Additional items and comments:
  - The PeRC will provide a clinical pharmacology reference to the Division on PK/PD modeling.
  - The PeRC plans to hold a meeting with the Division to discuss pediatric plans for other treatments for mild to moderate pain, including NSAIDS.

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JANE E INGLESE
09/22/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204592 **INFORMATION REQUEST**

Iroko Pharmaceuticals, LLC
Attention: Michelle Wilson, PhD
Senior Consultant
575 E. Swedesford Road, Suite 100
Wayne, PA 19087

Dear Dr. Wilson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) (2) of the Federal Food, Drug, and Cosmetic Act for Zorvolex™ (diclofenac acid) Capsules, 18 mg and 35 mg.

We are reviewing the Product Quality section of your submission and have the following comments and information requests. We request a response in order to continue our evaluation of your NDA by **Thursday, August 15, 2013**.

1. Per ICH guidance Q6A two identification methods are required for drug product. Provide a second identification method for the drug product Zorvolex capsules.
2. The specification limits for trace metals should be based on safety as well as quality. (b) (4) the proposed specification limits for trace metals based on the registration batch data.
3. Diclofenac impurity A is a specified impurity in the drug substance and is listed in the drug substance specifications in the NDA. You need to provide characterization for specified impurities (identity, structure, etc.) in the NDA. Reference to DMF is not sufficient.

If you have any questions, call LCDR Luz E Rivera, Regulatory Project Manager, at (301) 796-4013.

Sincerely,
{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI
07/25/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 204592

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Iroko Pharmaceuticals, LLC
c/o Computer Sciences Corporation (CSC)
575 E. Swedesford Road, Suite 100
Wayne, PA 19087

ATTENTION: Michelle Wilson, Ph.D.
Principal Regulatory Strategist

Dear Dr. Wilson:

Please refer to your New Drug Application (NDA) dated and received December 20, 2012, submitted under section 505(b)(2)of the Federal Food, Drug, and Cosmetic Act for Diclofenac Capsules, 18 mg and 35 mg.

We also refer to:

- Your initial submission requesting review of the proposed proprietary name Zorvolex, dated and received January 30, 2013, and
- Your amendment, dated and received February 4, 2013, for the proposed proprietary name, Zorvolex.

We have completed our review of the proposed proprietary name, Zorvolex and have concluded that it is acceptable.

The proposed proprietary name, Zorvolex, 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 January 30, 2013 and February 4, 2013, submissions 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, contact Teena Thomas, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0549. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Swati Patwardhan at (301) 796-4085.

Sincerely,

{See appended electronic signature page}

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

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/s/

CAROL A HOLQUIST
04/29/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204592 **INFORMATION REQUEST**

Iroko Pharmaceuticals, LLC
Attention: Michelle Wilson, PhD
Senior Consultant
100 Springhouse Drive, Suite 205
Collegeville, PA 19426

Dear Dr. Wilson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) (2) of the Federal Food, Drug, and Cosmetic Act for Zorvolex™ (diclofenac acid) Capsules, 18 mg and 35 mg.

We are reviewing the Product Quality section of your submission and have the following comments and information requests. We request a response in order to continue our evaluation of your NDA by **Thursday, May 1st, 2013**.

Chemistry, Manufacturing and Controls:

1. You have listed 3 individual known impurities in the drug substance in the registration batch results. However, there is only one proposed acceptance criterion for known impurities in the specification. This is not acceptable. Provide an acceptance criterion for each known impurity separately with justification.
2. Your proposed total impurities limit of NMT (b)(4)% for the drug substance is not supported by the batch data. Revise this limit with justification to reflect the actual batch data (release and stability). Provide a retest period for the drug substance.
3. Revise and submit information in every section of the NDA per ICH guidance M4Q (R1). If certain information in a section is referenced to a DMF, list the reference in that section. For module 3 (quality) the following sections are missing as submitted: 3.2.S.1, 3.2.S.3, 3.2.S.6, and 3.2.S.7. Submit the above sections to this NDA. Please note per ICH M4Q (R1) any information provided in module 2 (quality overall summary) is supposed to be the summary of the information already provided in module 3. Any information you summarized in module 2 should also be provided in module 3.
4. Provide general information (nomenclature, structure, general properties, etc) for the drug substance in module 3.
5. Provide in module 3, the characterization for each known impurities listed in the drug substance registration batches.

6. Provide certificates of analyses (CoAs) for the drug substance used for the registration batches submitted in the NDA. Provide a table comparing your incoming acceptance criteria and the specifications from the drug substance suppler in the CoA. Please note the specifications in the CoA have to meet or exceed your acceptance criteria. You also need to notify your supplier whenever you change your acceptance criteria and vice versa.
7. The proposed acceptance criteria for the related substances in the drug product of NMT (b) (4)% (18 mg capsule) and NMT (b) (4)% (35 mg capsule) for Impurities A, B, and C are not acceptable. You should take both safety and quality into consideration when setting the impurity limits. Tighten the proposed acceptance criteria based on the actual data. The acceptance criteria should be the same for both strengths (18 mg and 35 mg) (b) (4) (b) (4).
8. The proposed acceptance criterion for Total Impurities in the drug product of NMT (b) (4)% is not supported by the batch data. Tighten the acceptance criterion based on the actual data (e.g., NMT (b) (4)%).
9. There are (b) (4) trace metal test results ((b) (4)) listed in the primary stability batches. However, only (b) (4) have the acceptance criteria in the drug product specification. Provide acceptance criteria with justification for all trace metals that may potential be present in the drug product. Please note the proposed acceptance criteria should take into consideration of safety and product quality (batch data).

We also want to inform you that DMF (b) (4) you referenced for the drug substance has deficiencies and is not adequate to support your NDA. The deficiencies in the DMF have been communicated to the DMF holder in the letter dated March 26, 2013.

Biopharmaceutics:

10. An internal preliminary analysis showed that the Proof of Concept (POC) product and the Commercial product are not bioequivalent (Mean Ratio of Cmax of POC/Commercial = 0.645) , whereas the f2 values between POC and Commercial Batch dissolution profiles are greater than 50, indicating that your dissolution method is under discriminating. Therefore, you should develop a dissolution method with the discriminating ability to reject batches that are not bioequivalent. To evaluate the discriminating power of the method, note that in general the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e. aberrant formulations and manufacturing conditions) for the most relevant critical manufacturing variables (e.g. (b) (4) etc.).

11. The dissolution data you provided to investigate the impact of particle size on dissolution are not adequate. You have compared [redacted] (b) (4) .
12. We were not able to access the dissolution dataset of the stability data (3.2. P. 8.3. Stability Data Dissolution Dataset). Please provide an accessible file for these stability-dissolution data.

If you have any questions, call LCDR Luz E Rivera, Regulatory Project Manager, at (301) 796-4013.

Sincerely,

{See appended electronic signature page}

Prasad Peri, Ph.D.
Branch Chief, Branch VIII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

PRASAD PERI
04/17/2013

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Thursday, March 28, 2013 4:36 PM
To: 'Michelle L Wilson'
Subject: RE: NDA 204592 Zorvolex Capsules, Information request 3/28/2013

Dear Ms. Wilson,
We are reviewing Clinical Pharmacology section of your review and request additional information as follows:

When we are reviewing the datasets you submitted for the study DIC1-12-07, the randomization scheme and treatment groups are not clearly listed. Hence, include additional columns to indicate the treatment (eg, A, B, C, D or E) and associated sequence and period for both plasma concentrations and PK parameters. For example: include in separate columns the following information, Subject Number, Actual Time, Nominal time, Concentration, Period, Treatment, Sequence etc.

Please acknowledge the email receipt. We request a response preferably by COB, April 08, 2013

Thank you

Swati Patwardhan
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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/s/

SWATI A PATWARDHAN
03/28/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204592

FILING COMMUNICATION

Iroko Pharmaceuticals, LLC
c/o Computer Sciences Corporation (CSC)
100 Springhouse Drive, Suite 205
Collegeville, PA 19426

Attention: Michelle Wilson, Ph.D.
US Agent and Principal Regulatory Strategist for CSC

Dear Dr. Wilson:

Please refer to your New Drug Application (NDA) dated and received December 20, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Zorvolex (diclofenac acid) Capsules, 18 and 35 mg.

We also refer to your amendment dated February 12, 2013.

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 **Standard**. Therefore, the user fee goal date is October 20, 2013.

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 September 29, 2013.

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

1. Zorvolex has two strengths, 35 mg and 18 mg, based on diclofenac acid. The listed drug you specified, Cataflam, has a tablet of 50 mg based on diclofenac potassium salt. Provide a justification, including calculations, demonstrating how Zorvolex

Capsules have a 20% reduction in the diclofenac dose compared with the Cataflam 50 mg tablets. This calculation should be based on the free base of diclofenac.

Additionally, during our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. The length of Highlights (HL) is more than half a page. It must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement).

2. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet). Currently, the section/subsection is missing at the end of the statement for Indication and Usage Section.

3. All the text in Boxed Warning must be in bold font.

4. In the HL, the WARNING must be centered and the sentence: "See full prescribing information for complete boxed warning." must be centered immediately beneath the heading.

5. In the HL, the text "Patient Counseling Information" should be in uppercase in the following statement: "See 17 for PATIENT COUNSELING INFORMATION and Medication Guide".

6. The title for the Warning must be the same for HL and FPI. It must also appear at the beginning of the table of contents (TOC) in upper case and bolded font. However, we note that the title is missing in the Boxed Warning in the HL section.

7. In the TOC, all section headings must be in bold font and in upper case. Currently, the section headings in the TOC are not in bold font.

8. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk, and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed." Currently, the asterisk symbol is missing next to the heading.

9. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions* (*5.2*)]. Currently, the numerical identifiers are in regular font.

10. In the FPI, all the text in the Boxed Warning is not bolded.

11. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

    "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice." Currently, word "clinical" is missing in the last line.

12. In the Patient Counseling Information, you must include the type of patient labeling and the following statement at the beginning of Section 17:
    "See FDA-approved patient labeling (Medication Guide)"

We request that you resubmit labeling that addresses these issues by March 18, 2013. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for the following pediatric age groups for this application:

1. Birth to less than 1 month
2. (b) (4)
3. (b) (4)

Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We also acknowledge receipt of your request for a partial deferral of pediatric studies, for the age (b) (4) to less than 17 years, for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, contact Swati Patwardhan, Regulatory Project Manager, at (301) 796-4085.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, MD
Director
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

RIGOBERTO A ROCA on behalf of BOB A RAPPAPORT
02/27/2013

Patwardhan, Swati

From: Patwardhan, Swati
Sent: Friday, February 01, 2013 4:53 PM
To: Michelle L Wilson
Subject: Re: Information request for NDA 204592

Dear Dr. Wilson,

We are reviewing your New Drug Application submitted for Diclofenac aid, NDA 204592, and request following information

1. The information you described under Section 2.7.4.11.1 in the Summary of Clinical safety for age, sex, and race is inadequate. Your summary of safety should include an analysis of safety data by gender, age, and racial subgroups [21 CFR 314.50(5)(vi)(a)] based on data from your clinical studies. Provide the analysis as an amendment.

2. For study DIC1-12-07, provide the details surrounding the reasons subjects discontinued for the reasons of other, consent withdrawn, and protocol violations. Alternatively, identify the location within your submission where this information can be found.

3. For study DIC3-08-04, provide case report forms for all subjects who withdrew from the study.

5. Per the End of Phase 2 meeting minutes (refer to the discussion under Question 7), the Phase 3 bunionectomy trial would be conducted with an "empty stomach" food restriction. Clarify whether subjects were administered study medication on an empty stomach or a fed state. If this was not implemented, provide justification for not doing so.

Please acknowledge the receipt of this email, and provide a timeline for your response.

Thank you

Swati Patwardhan
Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Center of New Drug Evaluation and Research
Phone: 301-796-4085
Fax: 301-796-9748

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/s/

SWATI A PATWARDHAN
02/04/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204592

NDA ACKNOWLEDGMENT

Iroko Pharmaceuticals, LLC
c/o Computer Sciences Corporation (CSC)
100 Springhouse Drive, Suite 205
Collegeville, PA 19426

Attention: Michelle Wilson, Ph.D.
US Agent and Principal Regulatory Strategist for CSC

Dear Dr. Wilson:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Zorvolex (diclofenac acid) Capsules, 18 and 35 mg

Date of Application: December 20, 2012

Date of Receipt: December 20, 2012

Our Reference Number: NDA 204592

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 February 18, 2013, 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/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. 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.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

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 Anesthesia, Analgesia, and Addiction Products
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/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

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If you have any questions, call me at (301) 796-4085.

Sincerely,

{See appended electronic signature page}

Swati Patwardhan
Regulatory Health Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
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/

SWATI A PATWARDHAN
01/02/2013

Chiapperino, Dominic

From: Chiapperino, Dominic
Sent: Thursday, August 23, 2012 11:25 AM
To: 'Michelle L Wilson'
Subject: RE: Iroko NDA 204592, Literature Search Question

Dear Michelle,

Regarding your question for the Division concerning the literature search for Iroko's planned 505(b)(2) NDA for diclofenac capsules, we have the following comments in response:

The data in support of efficacy will be mainly from a combination of efficacy trial(s) conducted using investigational drug and relative bioavailability (the PK profile with respect to time after dosing) between the investigational drug and reference product. A review of efficacy from the literature can be restricted to information not available through the clinical studies, if any such literature is relevant. Otherwise a summary of general diclofenac efficacy is not required.

You have conducted a relative BA study with Cataflam as the listed drug. You may rely on the clinical pharmacology information from the Cataflam label, provided that such reliance is scientifically justified. You may also rely on the clinical pharmacology information from literature, provided such reliance is scientifically justified.
If literature is used, copies of the articles must be included and any proprietary names in those reports identified. If a product is identified by proprietary name and the information in the literature article is required for approval, including for the labeling, then that product must be included in the list of products relied upon for approval and the required patent notification and certification procedures followed.

Please contact me if you have further questions.

Kind regards,
Dominic

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
FDA, Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Anesthesia, Analgesia, and Addiction Products
10903 New Hampshire Avenue
Building 22, Room 3134
Silver Spring, MD 20993
Office phone: (301) 796-1183
Facsimile: (301) 796-9723
Dominic.Chiapperino@fda.hhs.gov

-----Original Message-----
From: Michelle L Wilson [mailto:mwilson60@csc.com]
Sent: Monday, July 30, 2012 7:58 AM
To: Chiapperino, Dominic
Subject: Iroko NDA 204592, Literature Search Question

Dear Dominic,

Iroko has a question regarding the literature search that will support their NDA:

Due to the breadth of literature available on diclofenac, Iroko proposes to use Davies 1997 as their anchor review article for the pharmacokinetics of diclofenac and Derry 2009 as their anchor review article for the clinical

aspects of diclofenac. (The full citations and the articles are included below). Using Davies 1997 and Derry 2009 as anchor review articles, Iroko will conduct a literature search with a cut-off date of July 31, 2012; the NDA is targeted for submission in December 2012. Please note that Iroko may also cite relevant primary sources listed in the anchor documents as needed.

Does the Agency concur with Iroko's literature search strategy as outlined above?

Citations

Davies NM, Anderson KE. Clinical pharmacokinetics of diclofenac. Therapeutic insights and pitfalls. Clin Pharmacokinet. 1997 Sep;33 (3):184-213.

Derry P, Derry S, Moore RA, McQuay HJ. Single dose oral diclofenac for acute postoperative pain in adults. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD004768.

Thank you very much for your time.

Best wishes,

Michelle

(See attached file: Derry P 2009 -review.pdf)(See attached file: Davies NM 1997 - review.pdf)

MICHELLE WILSON, PH.D.
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DOMINIC CHIAPPERINO
08/23/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 103880

MEETING MINUTES

Premier Research Group, on behalf
of Iroko Pharmaceuticals, LLC
Centre Square West
1500 Market Street, STE 3500
Philadelphia, PA 19102

Attention: Linda Hibbs
Associate Director, Regulatory Operations, Premier Research Group, Ltd.

Dear Ms. Hibbs:

Please refer to the Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the Act) for Diclofenac Capsules.

We also refer to the meeting between representatives of Iroko Pharmaceuticals and the FDA on June 7, 2012. The purpose of the meeting was to to discuss the development program and planned New Drug Application (NDA) submission for Diclofenac Capsules.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1183.

Sincerely,

{See appended electronic signature page}

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia, Analgesia, and
Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
Attachment 1: Additional Comments for Pre-NDA Stage of Drug Development

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	June 7, 2012, 11:00 AM – 12:00 PM
Meeting Location:	FDA, White Oak Building 22, Rm. 1315 10903 New Hampshire Avenue Silver Spring, MD 20903
Number:	IND 103880
Product Name:	Diclofenac Capsules (to be marketed as "Zorvolex")
Indication:	Treatment of mild to moderate acute pain
Sponsor/Applicant Name:	Iroko Pharmaceuticals, Inc.
Meeting Chair:	Sharon Hertz, M.D., Deputy Director, Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Meeting Recorder:	Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, DAAAP

FDA ATTENDEES

Bob A. Rappaport, M.D. , Director, DAAAP
Sharon Hertz, M.D., Deputy Director, DAAAP
Christina Fang, M.D., Medical Officer, DAAAP
Adam Wasserman, Ph.D., Nonclinical Supervisor, DAAAP
Alex Xu, Ph.D., Nonclinical Reviewer, DAAAP
Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, DAAAP
Yun Xu, Ph.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II (DCP2)
Suresh B. Naraharisetti, Ph.D., Clinical Pharmacology Reviewer, DCP2
Dionne Price, Ph.D., Statistics Team Leader, Division of Biometrics II (DB2)
David Petullo, Ph.D., Statistics Reviewer, DB2
Danae Christodoulou, Ph.D., CMC Lead, Office of New Drug Quality Assessment (ONDQA)
Arthur B. Shaw, Ph.D., Product Quality Reviewer, ONDQA
Sandra Suarez, Ph.D., Biopharmaceutics Team Leader (acting), ONDQA
Kareen Riviere, Ph.D., Biopharmaceutics Reviewer, ONDQA

IROKO ATTENDEES

David A. Dickason, Senior Director, Technical Development
Steven Jensen, Vice President, Regulatory Affairs & Compliance
(b) (4)
Juliana Schwarz-Rocha, Sr. Manager, Regulatory Affairs

Michelle Wilson, Ph.D., Principal Regulatory Strategist (CSC)
Clarence Young, M.D., Chief Medical Officer
Linda Hibbs, Associate Director, Regulatory Operations (Premier Research)
(b) (4)

1.0 BACKGROUND

The purpose of the meeting between FDA and Iroko Pharamaceuticals was to discuss Iroko's development program for diclofenac capsules, now at pre-NDA stage of development. The proposed indication is the "treatment of mild to moderate acute pain." Iroko intends to submit their NDA via the 505(b)(2) regulatory pathway, with Cataflam (NDA 020142) as the reference listed product.

2.0 DISCUSSION

DAAAP provided preliminary comments to Iroko on June 5, 2012, containing responses to Iroko's questions in their meeting briefing package dated April 30, 2012. Iroko responded via email on June 6, 2012, indicating the questions/responses requiring further discussion at the meeting and providing additional comments and revised proposals as the basis for further discussion. Below are Iroko's original questions in italic font, DAAAP's responses in bold font, as provided in the June 5, 2012 preliminary comments, and Iroko's additional comments and revised proposals in normal font, followed by discussion during the meeting, also in normal font.

Chemistry, Manufacturing, and Controls
Question 1: Iroko proposes to file nine months long-term and six months accelerated stability data on three Primary Stability Batches with 12 months long-term and six months accelerated data on three supportive Demonstration Batches in support of the expiry date of 24 months. Does the Division concur?

FDA Response:
No. Earlier stability studies for batches 16105-001A and 16106-001B showed that Impurity B reached (b) (4) % after only 12 months of storage. Therefore, include sufficient stability data at the time of submission to be able to assess the changes in impurities at the proposed expiration date. We recommend that you provide the following information:

1. **A side-by-side comparison of the formulation, process, and scale of the following batches:**
   - **Batches used for earlier stability studies**
   - **Demonstration Batches**
   - **Primary Stability Batches**
   - **Proposed Commercial Formulation**

2. **A comparison of the stability data (including under accelerated storage conditions) for earlier batches (including batches 16105-001A and 16106-001B) and the batches to be submitted in the NDA.**

Sponsor Response: Regression analysis of the 18 months long term stability data (25°C/60% RH) for batches 16105-001A and 16106-001A projects that Impurity B would exceed the (b)(4)% ICH threshold at approximately 33 months. (Data submitted to IND 103880/S-0018.) Iroko is confident the stability data included in the NDA will be sufficient to assess the changes in impurities and support the proposed expiration date.

Iroko intends to include in the NDA each of the comparisons recommended by the Division in response to sub-items 1 and 2 above.

Discussion:
Regarding differences in manufacturing for early batches versus the to-be-marketed formulation, Iroko explained that (b)(4) The product dissolution profile was monitored during the optimization activities to ensure that the dissolution profile between the Phase 1/2 and the Phase 3 (which is also the to-be-marketed) formulation remained comparable. Formulation and manufacture optimization successfully reduced the level of Impurity B based on the 6-month accelerated and long-term stability data. The Division highlighted that what was notable about the Phase 1/2 batches was that the impurity levels increased at 12 months. Iroko explained that the Phase 1/2 product impurity levels had an upward trend throughout the stability program and that this trend has not been observed in the stability studies with the Phase 3 formulation.

Iroko proposed to rely on in vitro dissolution data to establish a bridge between the Phase 1/2 and Phase 3 formulations. The Division stated that the modifications made are Level 3 changes per the SUPAC guidance and, therefore, in vitro dissolution comparison is not sufficient to ensure that the biopharmaceutic properties remain unchanged. Due to the nature of the manufacturing changes, the Division stated that an in vivo/in vitro correlation (IVIVC) model or an in vivo bioequivalence study would be required to establish a bridge between the Phase 1/2 formulation and the Phase 3 formulation. The Division further explained that submission of an NDA with only in vitro bridging data, accompanied by a rationale for this bridging strategy, might be possible. FDA would review bridging data and rationale, but the acceptability of such an approach would be unlikely and thus a highly risky strategy.

Additionally, the Division questioned whether the food effect seen with the Phase 1/2 formulation would be similar with the Phase 3 formulation and noted also that the BA study comparing to the reference drug Cataflam was conducted with the Phase 1/2 formulation and not the Phase 3 formulation. On the latter point, Iroko proposed conducting a replacement comparative bioavailability study of the Phase 3 formulation against the reference drug, Cataflam. The Division agreed to this proposal. See the related meeting discussion and comments for Question 5.

Question 2: Included in this meeting package are the proposed release specifications for the drug product (see Table 2.10.3.2.6.1-1) as well as the in-process specifications (see

Figure 2.10.3.2.5-1). Does the Division have any comments to the drug product and in-process specifications presented?

FDA Response:
Yes, we have the following comments:

1. **Provide data to support the proposed acceptance criteria for the individual identified impurities (NMT (b) (4)%).**

2. **In your Particle Size Distribution (PSD) control, define SSA and provide a range. Monitor PSD (b) (4)**

3. **Note that the in-process controls will be evaluated during review of the NDA.**

4. **There is insufficient information to comment on the dissolution acceptance criterion for your product. Final acceptability of the proposed dissolution acceptance criterion for your product will be made during the NDA review process based on the totality of the provided dissolution data. See additional Biopharmaceutics comments.**

Sponsor Response: FDA's response is clear.

Discussion: No further discussion was necessary.

Additional Biopharmaceutics comments:
We have the following comments regarding the dissolution information to be provided in your NDA.

1. **Dissolution Test: Include the dissolution method report supporting the selection of the proposed dissolution test. Include the following information in the dissolution report:**

a. **Solubility data for the drug substance covering the pH range**

b. **Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) used to select the proposed dissolution method as the optimal test for your product. If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions**

used for each test should be clearly specified. The dissolution profile should be complete and cover at least (b)(4)% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable.

c. **Provide the complete dissolution profile data (individual, mean, SD, profiles) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim.)**

d. **Include the testing conducted to demonstrate the discriminating capability of the selected dissolution test. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e. aberrant formulations and manufacturing conditions) for the most relevant critical manufacturing variables (e.g. drug substance particle size, etc.). Additionally, if available, submit data showing the capability of the selected dissolution method to reject batches that are not bioequivalent.**

e. **Provide the supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).**

2. **Dissolution Acceptance Criterion: For the selection of the dissolution acceptance criterion of your product, the following points should be considered:**

   a. **The dissolution profile data from the pivotal clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criterion of your product (i.e., specification-sampling time point and specification value).**

   b. **The in vitro dissolution profile should encompass the timeframe over which at least (b)(4)% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.**

   c. **For immediate release product the selection of the specification time point should be where Q= (b)(4) % dissolution occurs.**

Note that the final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA. However, the acceptability of the

proposed dissolution criterion for your product will be made during the NDA review process based on the totality of the dissolution data provided.

Sponsor Response to Additional Biopharmaceutics Comments: FDA's comments are clear.

Discussion: No further discussion was necessary.

Question 3: Iroko proposes to submit sections of Module 3 through the use of a Type II Drug Master File and reference it in the NDA. Does the Division concur?

FDA Response:
Yes.

Please note that all changes in a DMF are required to be reported to the DMF when they occur (21 CFR 314.420(c)) and the holder is required to notify the applicant that changes have been made. It is the applicant's responsibility to report all changes appropriately as required under 21 CFR 314.70 and following the recommendations in the guidance for industry, *Changes to an Approved NDA or ANDA*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm077097.pdf

We recommend that you take measures to ensure that information in the NDA (e.g. in-process controls) is referenced to specific sections in the DMF, e.g., specific sections of P.2.

Sponsor Response: FDA's response is clear.

Discussion: No further discussion was necessary.

Nonclinical
Question 4: Does the Division confirm that the nonclinical studies with the existing safety data in the public domain are adequate to support the filing of an NDA?

FDA Response:
We agree that additional non-clinical studies are not needed to support the filing of an NDA if all impurities and degradants are within the ICH threshold in your drug product. Any impurity or degradation product that exceeds ICH thresholds by the expiry date must be adequately qualified for safety. For additional information, you may refer to the EOP2 meeting minutes and ICH guidance for industry, *Q3A(R2) Impurities in New Drug Substances*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073385.pdf and *Q3B(R2) Impurities in New Drug Products*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073389.pdf.

Sponsor Response: FDA's response is clear. We confirm that data generated to date from the Demonstration Batches through six months stability (25°C/60% RH and 40°C/75% RH) and Primary Stability batches through three months stability (25°C/60% RH, 30°C/65% RH and 40°C/75% RH) do not show any impurities or degradants that exceed ICH threshold levels. Additionally, there does not appear to be any trending in that direction.

Discussion: No further discussion was necessary.

Clinical
Question 5: Does the Division concur that the positive results from the Phase 2 and Phase 3 studies are adequate to support the filing of an NDA for Zorvolex Capsules for the treatment of mild to moderate acute pain?

FDA Response:
Yes.

You have indicated that the formulation used in the Phase 3 study is the same as the final to-be-marketed formulation. However, the drug product formulation used in Phase 1/2 studies is considerably different than the final to-be-marketed formulation used in the Phase 3 study. Therefore, the results obtained from Phase 1/2 studies may not apply to your final to-be-marketed product. You must conduct an in vivo BA/BE bridging study between these formulations and use the bioequivalence criteria to analyze the data in order for the Phase 1/2 study results to be used to support your final to-be-marketed product. In addition, you must conduct another food effect study with your final to-be-marketed product, as BE in the fasting state does not necessarily mean two formulations will have the same food effect.

Sponsor Response: Iroko formulation and process activities were undertaken for the purpose of optimizing the stability and large scale processability of the Phase 3 and to-be-marketed formulation. The critical processing (b) (4) in both formulation and process, between Phase 1/2 and Phase 3 products. Further, the process change between the Phase 1/2 and Phase 3 to-be-marketed formulation consisted (b) (4) of only minor formulation changes and process parameters to assure a robust and reproducible product. The details of these formulation and process optimizations are included in IND 103880/S-0018.

Numerous in vitro bridging studies were conducted to ensure the performance characteristics of the drug product remained consistent over the course of development. F_2 similarity calculations confirm that the release characteristics are comparable for the two formulations and that performance is unchanged. These values are summarized in the table below. Details of the bridging studies are intended for inclusion in the NDA.

Summary of F_2 Similarity Values
Phase 1/2 and Phase 3 to-be-marketed Drug Products

18 mg Phase 1/2 to Phase 3 (Avg)	73
18 mg Phase 1/2 (16105-001A) to Phase 3 (L0306589)	77
18 mg Phase 1/2 (16105-001A) to Phase 3 (L0306925)	56
18 mg Phase 1/2 (16105-001A) to Phase 3 (L0306926)	70
35 mg Phase 1/2 to Phase 3 (Avg)	78
35 mg Phase 1/2 (16106-001A) to Phase 3 (L0306590)	60
35 mg Phase 1/2 (16106-001A) to Phase 3 (L0306927)	88
35 mg Phase 1/2 (16106-001A) to Phase 3 (L0306928)	86

These data demonstrate comparability between the two formulations and there is no expectation that the implemented changes would result in a meaningful in vivo performance change. Iroko feels strongly that an in vivo study is not necessary to bridge the Phase 1/2 and Phase 3 formulations for this immediate release drug product. We believe the in vitro bridging studies support the relevance of the Phase 1/2 studies and apply to the final to-be-marketed product.

Discussion:
Regarding the conduct of an in vivo BA/BE bridging study between the Phase 1/2 and the Phase 3/to-be-marketed formulations, the Division proposed that the food effect of the Phase 3/to-be-marketed formulation could be studied as an additional arm to this BA/BE bridging study, instead of performing a separate food effect study with the Phase 3 formulation.

An alternative approach was discussed, in which a new Phase 1 PK study, similar in design and assessments to the original Phase 1 study, e.g., establishing dose proportionality from low-dose to high-dose, would be conducted to directly compare the bioavailability of the Phase 3/to-be-marketed formulation and the listed drug, Cataflam. These new PK data from the Phase 3/to-be-marketed formulation could potentially remove the need for any bridging between the Phase 1/2 and the Phase 3/to-be-marketed formulation, depending on the overall completeness of the clinical package with studies conducted using the Phase 3 formulation.

This proposal was also discussed in the context of the efficacy data derived from the Phase 2 study to support the clinical package. The Division commented that, if the Phase 3 pivotal trial was sufficiently robust, the Phase 2 proof-of-concept study might not be necessary to support NDA approval, thus removing another potential for need of bridging between the Phase 1/2 and Phase 3 formulations.

The Division proposed that the new Phase 1 PK protocol synopsis and overview of the revised clinical package be submitted to the Division for review. The Division agreed to provide feedback on the protocol synopsis and the completeness of the clinical package for NDA submission via the 505(b)(2) regulatory pathway.

Post-Meeting Note:
Based on your submission dated June 14, 2012, containing your minutes, the new Phase 1 PK study synopsis (Study DIC1-12-07), and an updated description of your proposed clinical package for NDA submission, we have the following comments:

1. The Phase 2 study DIC2-08-03 will be considered as supportive information for approval of your product. Therefore, a within-study comparison between the Phase 3/to-be-marketed formulation and the Phase1/2 formulation is not necessary. The results of your proposed Study DIC1-12-07 will provide pharmacokinetic information on the Phase 3/to-be-marketed formulation, which can be used to bridge data (cross-study comparison) generated for the Phase1/2 formulation of your drug product development.

2. In your proposed Study DIC-12-07, your inclusion of "Treatment E" arm (Cataflam, fed conditions) is acceptable; however, this arm is not necessary. You may instead make food effect comparisons using the data from your previously conducted Phase 1 study (DIC1-08-01) or from the Cataflam label versus your Phase 3 formulation.

3. The inclusion of the lower strength arm (18 mg) in your proposed Study DIC-12-07 may not be necessary; you will have the option to request a biowaiver for the proposed 18 mg strength instead. The CFR BA/BE requirements for the proposed lower strength of your proposed product may be waived if the following criteria are met:
    - Inclusion of a biowaiver request in the NDA submission for the lower strength
    - There is BA/BE data for the highest strength
    - The lower and higher strengths of your product are the same dosage form
    - The lower strength product is proportionally similar in its active and inactive ingredients to the highest strength product, and
    - Dissolution profile comparisons between the highest and lower strengths meet the *f2* similarity requirements

The Division noted that the preliminary data from the Phase 3 bunionectomy trial suggest that the lower dose seems to be effective when taken without food; however, the impact of food was not evaluated.

Question 6: Does the Division agree with the approach that the Integrated Summaries of Effectiveness and Safety will comprise the data from each of the individual studies along with an overview of the literature?

FDA Response:
Yes.

Sponsor Response: The Division's response is clear.

Discussion: No further discussion was necessary.

Question 7: Does the Division agree that CRFs will be included only for patients with reported deaths, patients that discontinued due to adverse events and SAEs?

FDA Response:
Yes. Also, provide case summaries for deaths, SAEs, and discontinuations due to AEs, where the summaries include the time relationship between dosing and the event occurrence.

Sponsor Response: The Division's response is clear. Iroko confirms that the requested case summaries will be included in the NDA.

Discussion: No further discussion was necessary.

Question 8a: Does the Division agree with Iroko's plan to submit the Pediatric Plan at the time of NDA submission?

FDA Response:
Yes.

Question 8b: Is the Division in accordance with the waiver for ages Birth to age 1 year?

FDA Response:
Waivers for pediatric studies are determined by the Pediatric Research Committee. However, it appears reasonable to consider a waiver of studies for pediatric patients up to one year of age.

Sponsor Response: The Division's responses to Questions 8a and 8b are clear.

Discussion: No further discussion was necessary.

Question 9: Does the Division concur with Iroko's plan to not include a formal REMS in the NDA for the acute use of diclofenac capsules as outlined above?

FDA Response:
Yes.

Sponsor Response: The Division's response is clear.

Discussion: No further discussion was necessary.

Data Format
Question 10: Following the Center of Drug Evaluation and Research (CDER) common data standard issues document updated in December 2011, Iroko plans to submit the clinical trial datasets for the Phase 2 and Phase 3 efficacy studies in SDTM format. All SDTM datasets will be provided as SAS Version 5 Transport (.XPT) files. SDTM datasets will be provided following the SDTM version 1.2/SDTM Implementation Guide (IG) v. 3.1.2. ADaM analysis datasets will be

provided for the Phase 2 and Phase 3 studies following ADaM 2.1/ADaM IG v.1. Does the Division agree with Iroko's data submission plans?

FDA Response:
Yes.

Sponsor Response: The Division's response is clear.

Discussion: No further discussion was necessary.

Question 11: Iroko intends to submit Define documents for both SDTM and ADaM (separately) as Define.xml files. Does the Division agree with Iroko's plan to submit the Define document for both SDTM and ADaM as Define.xml files only?

FDA Response:
Yes.

Sponsor Response: The Division's response is clear.

Discussion: No further discussion was necessary.

Question 12a: Iroko plans to submit the Phase 2 (DIC2-08-03) Clinical Study Report (CSR) as a legacy report. Does the Division concur?

FDA Response:
No. In order to use Study DIC2-08-03 to support your application, a modular (b) (4) report is more appropriate.

Sponsor Response: The Division's response is clear.

Discussion: No further discussion was necessary.

Question 12b: Iroko plans to submit the Phase 3 (DIC3-08-04) CSR as a modular report in compliance with ICH E3 guideline. Does the Division concur?

FDA Response:
Yes.

Sponsor Response: The Division's response is clear.

Discussion: No further discussion was necessary.

Question 13a: Does the Division agree with Iroko's plan to submit only the PK concentration source data for the Phase 1 study?

FDA Response:
Your proposal to submit the tables, listings, and figures (including demographic, PK, adverse event (AE) and concomitant medications) in the final study report and the individual subject concentration source data in SAS (.XPT) format is acceptable.

Sponsor Response: The Division's response is clear.

Discussion: No further discussion was necessary.

Question 13b: Iroko plans to submit the Phase 1 CSR (DIC1-08-01) as a legacy report. Does the Division concur?

FDA Response:
In order to use Study DIC1-08-01 to support your application, we highly recommend that you submit a modular (b) (4) report for your Phase 1 study report.

Sponsor Response: The Division's response is clear.

Discussion: No further discussion was necessary.

Regulatory
Question 14: Does the Division have any comments on the draft Prescribing Information?

(b) (4)

(b) (4)

Question 15: Iroko has submitted a draft table of contents for NDA in section 5 of this meeting package. Does the Division have any comments on the draft table of contents?

FDA Response:
Refer to the response to Question 12a as it applies to the content under 5.3.5.1 Study Reports.

Sponsor Response: The Division's response is clear.

Discussion: No further discussion was necessary.

Question 16: Does the Division have any additional comments to the information provided in this meeting package?

FDA Response:
As discussed previously, it is unusual for an NSAID to be dosed on an empty stomach, and it is likely that patients may not follow this advice. We have no information on the effect on the efficacy of the product when taking your formulation of diclofenac capsules with food. Therefore, it is likely that we will take this NDA to advisory committee for review of this issue and to determine if this is of sufficient concern to impact approval of the application. Refer to Attachment 1 for additional general comments for pre-NDA stage of drug development.

Sponsor Response: Oral diclofenac has been available in the United States since 1988. The effect of food upon diclofenac absorption kinetics is well characterized for multiple dosage formulations. In the United States more than (b) (4) units of diclofenac have been dispensed in the past five years (reference IMS data May 2012). Based upon the Division's recommendations at the End of Phase 2 meeting, food restrictions were included in the protocol for the Phase 3 pivotal study. Furthermore, while the Division states that it is "unusual for an NSAID to be dosed on an empty stomach" there are recently approved diclofenac drug products for acute use with food restrictions and statements describing the potential impact upon the rate of absorption kinetics and/or efficacy when taken with food (reference Zipsor, Cambia prescribing information labels). (b) (4)

Discussion: See discussion of Question 14.

3.0 OTHER GENERAL PRE-NDA MEETING ADVICE

3.1 Prescribing Information

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

3.2 Manufacturing Facilities

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

4.0 ACTION ITEMS

Iroko was to submit an updated description of their proposed clinical package for the NDA submission, including a synopsis of a new Phase 1 study with the to-be-marketed formulation, which might preclude the need for a BA study to bridge between formulations used in previous Phase 1 studies and the Phase 3/to-be-marketed formulation. Iroko has submitted this new information, dated June 14, 2012. See the Division's post-meeting note on page 10.

5.0 ATTACHMENTS AND HANDOUTS

Appended is a copy of "Attachment 1: Additional Comments for Pre-NDA Stage of Drug Development," which was also provided to Iroko with FDA's preliminary meeting comments on June 5, 2012.

Attachment 1:
Additional Comments for Pre-NDA Stage of Drug Development

Nonclinical Comments

1. Include a detailed discussion of the nonclinical information in the published literature in your NDA submission and specifically address how the information within the published domain impacts the safety assessment of your drug product. Include this discussion in Module 2 of the submission. Include copies of all referenced citations in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.

2. We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 draft guidance for industry, *Applications Covered by Section 505(b)(2),* available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

   In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408, available at http://www.fda.gov/ohrms/dockets/dailys/03/oct03/102303/02p-0447-pdn0001-vol1.pdf).

   Note that you may only rely on the Agency's finding of safety and/or effectiveness as it is reflected in the approved labeling for the listed drug(s). You may not reference data in the Summary Basis of Approval or other FDA reviews obtained via the Freedom of Information Act or publically posted on the CDER website to support any aspect of your development program or proposed labeling of your drug product. Reviews are summary data only and do not represent the Agency's previous finding of safety and effectiveness.

   If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). Establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

3. The nonclinical information in your proposed drug product label must include relevant exposure margins with adequate justification for how these margins were obtained. If you intend to rely upon the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label must be updated to reflect exposures from your product. If the referenced studies employ a different route of administration or lack adequate information to allow scientifically justified extrapolation to your product, you may need to conduct additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product label.

4. New excipients in your drug must be adequately qualified for safety. Studies must be submitted to the IND in accordance as per the following guidance for industry, *Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients*.

   As noted in the document cited above, "the phrase ***new excipients*** means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently **proposed level of exposure**, **duration of exposure**, or **route of administration**." (emphasis added).

5. Any impurity or degradation product that exceeds ICH qualification thresholds must be adequately qualified for safety as described in ICHQ3A(R2) and ICHQ3B(R2) guidances at the time of NDA submission.

   Adequate qualification would include:

   a. Minimal genetic toxicology screen (two *in vitro* genetic toxicology studies; e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.

   b. Repeat dose toxicology of appropriate duration to support the proposed indication.

6. Genotoxic, carcinogenic or impurities that contain a structural alert for genotoxicity must be either reduced to NMT (b) (4) in the drug substance and drug product or adequate safety qualification must be provided. For an impurity with a structural alert for mutagenicity, adequate safety qualification requires a negative in vitro bacterial reverse mutation assay (Ames assay) ideally with the isolated impurity, tested up to the appropriate top concentration of the assay as outlined in ICHS2A guidance document titled "Guidance on Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals." Should the Ames assay produce positive or equivocal results, the impurity specification must be set at NMT (b) (4), or otherwise justified. Justification for a positive or equivocal Ames assay may require an assessment for carcinogenic potential in either a standard 2-year rodent bioassay or in an appropriate transgenic mouse model.

7. In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product, and how these levels compare to ICHQ3A and Q3B qualification thresholds along with a determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification threshold should be adequately justified for safety from a toxicological perspective.

8. The NDA submission must contain information on potential leachables and extractables from the drug container closure system and/or drug product formulation as outlined in the FDA Guidance for Industry titled "Container Closure Systems for Packaging Human Drugs and Biologics." The evaluation of extractables and leachables from the drug container closure

system or from a transdermal patch product must include specific assessments for residual monomers, solvents, polymerizers, etc.). Based on identified leachables provide a toxicological evaluation to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). As many residual monomers are known genotoxic agents, your safety assessment must take into account the potential that these impurities may either be known or suspected highly reactive and/or genotoxic compounds. The safety assessment should be specifically discussed in module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. For additional guidance on extractables and leachables testing, consult the FDA Guidance documents "Container Closure Systems for Packaging Human Drugs and Biologics" and "Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation." Additional methodology and considerations have also been described in the PQRI leachables/extractables recommendations to the FDA, which can be found at http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf.

9. Failure to submit adequate impurity qualification, justification for the safety of new excipient use, or an extractable leachable safety assessment at the time of NDA submission can result in a Refusal-to-File or other adverse action.

Chemistry, Manufacturing and Control (CMC) Comments

1. Include a well documented Pharmaceutical Development Report as per the ICH-Q8 guideline and highlight how critical quality attributes and critical process parameters are identified and controlled.

2. Include at least 12 months of real time data and 6 months of accelerated data in the NDA. Alternatively, submit an appropriate amount of satisfactory stability data to cover the proposed expiry dating.

3. Provide a list of all manufacturing and testing facilities and their complete addresses in alphabetical order, and a statement about their cGMP status. For all sites, provide a name contact and address with telephone number and facsimile number at the site. Clearly specify the responsibilities (e.g., manufacturer, packager, release tester, stability tester etc.) of each facility, the site CFN numbers and designate which sites are intended to be primary or alternate sites. Note that facilities with unacceptable cGMP compliance may risk approvability of the NDA

4. Ensure that all of the above facilities are ready for inspection by the day the application is submitted, and include a statement confirming to this in the NDA cover letter.

5. Provide summary stability data on a parameter-by-parameter basis (instead of only on a batch to batch basis), and in addition, provide graphical plots of critical parameters and trending parameters. The graphical plots should indicate the proposed acceptance criteria, and they should include both mean and individual data points.

The Abuse Potential section of the NDA is submitted in the eCTD as follows:

Module 1: Administrative Information and Prescribing Information
1.11.4 Multiple Module Information Amendment
This section should contain:

- A summary, interpretation and discussion of abuse potential data provided in the NDA.
- A link to a table of contents that provides additional links to all studies (nonclinical and clinical) and references related to the assessment of abuse potential.
- A proposal and rationale for placement, or not, of a drug into a particular Schedule of the CSA.

Module 2: Summaries
2.4 Nonclinical Overview
This section should include a brief statement outlining the nonclinical studies performed to assess abuse potential.

2.5 Clinical Overview
This section should include a brief statement outlining the clinical studies performed to assess abuse potential.

Module 3: Quality
3.2.P.1 Description and Composition of the Drug Product
This section should describe any additional studies performed to examine the extraction of the drug substance under various conditions (solvents, pH, or mechanical manipulation).

3.2.P.2 Description and Composition of the Drug Product
This section should describe the development of any components of the drug product that were included to address accidental or intentional misuse.

Module 4: Nonclinical Study Reports
4.2.1 Pharmacology

4.2.1.1 Primary Pharmacodynamics
These sections should contain study reports (*in vitro* and *in vivo*) describing the binding profile of the parent drug and all active metabolites.

4.2.3.7.4 Dependence
This section should include:

- A complete discussion of the nonclinical data related to abuse potential.
- Complete study reports of all preclinical abuse potential studies.

Module 5: Clinical Study Reports
5.3.5.4 Other Study Reports
This section should contain complete study reports of all clinical abuse potential studies.

5.3.6.1 Reports of Postmarketing Experience
This section should include information to all postmarketing experience with abuse, misuse, overdose, and diversion related to this product

General Clinical Comments

The NDA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP 6010.3R).

To facilitate the review, we request you provide analyses, where applicable, that will address the items in the template, including:

1. Section 2.6 Other Relevant Background Information - Important regulatory actions in other countries or important information contained in foreign labeling.
2. Section 4.4 – Clinical Pharmacology- Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.
3. Section 7.5.1 Dose Dependency for Adverse Events
4. Section 7.5.2 Time Dependency for Adverse Events
5. Section 7.5.3 Drug-Demographic Interactions
6. Section 7.5.4 Drug-Disease Interactions
7. Section 7.5.5 Drug-Drug Interactions
8. Section 7.6.4 – Overdose, Drug Abuse Potential, Withdrawal and Rebound

Sites for Inspection

To assist the clinical reviewer in selecting sites for inspection, include a table in the NDA that has the following columns for each of the completed Phase 3 clinical trials:

1. Site number
2. Principle investigator
3. Location: City State, Country
4. Number of subjects screened
5. Number of subjects randomized
6. Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites
7. Number of protocol violations (Major, minor, definition)

Pediatric Plan

You must submit a pediatric plan with the NDA submission regarding studies in pediatric patients to be conducted to fulfill the requirements of the Pediatric Research Equity Act (PREA). The plan must include the studies to be conducted; a timeline for the studies that states for each study, the date of final protocol submission, date of study start, date of study completion, and date of final study report to be submitted to the Agency; requests for waivers and deferrals with justifications; and, where possible, protocol synopses of the proposed studies.

Common PLR Labeling Errors

Highlights:

1. Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]

2. The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]

3. The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]

4. The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]

5. The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).

6. Recent major changes apply to only 5 sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions)

7. For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance].

8. The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

   "(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."

9. Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.

10. Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).

11. A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)]

12. Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights. [See comment #34 Preamble]

13. The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]

14. A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.

15. A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

Contents (Table of Contents):

16. The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]

17. The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]

18. Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.

19. Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.

20. When a subsection is omitted, the numbering does not change. [See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:

    8.1 Pregnancy
    8.3 Nursing Mothers (not 8.2)
    8.4 Pediatric Use (not 8.3)

8.5 Geriatric Use (not 8.4)

21. When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading "Full Prescribing Information: Contents" must be followed by an asterisk and the following statement must appear at the end of the Contents:

"*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI):

22. Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).

23. Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline. Refer to http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

24. Do not refer to adverse reactions as "adverse events." Refer to the guidance for industry, *Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format*, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm .

25. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Use in Specific Populations (8.4)] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance]

26. Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]

27. Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)].

28. The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.

29. Since SPL Release 4 validation does not permit the inclusion of the Medication Guide as a subsection, the Medication Guide or Patient Package Insert should not be a subsection under the Patient Counseling Information section. Include at the end of the Patient Counseling Information section without numbering as a subsection.

30. The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.

31. Company website addresses are not permitted in labeling (except for a web address that is solely dedicated to reporting adverse reactions). Delete company website addresses from package insert labeling. The same applies to PPI and MG.

32. If the "Rx only" statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. See guidance for industry, *Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements*. The same applies to PPI and MG.

33. For fictitious examples of labeling in the new format, refer to http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

34. For a list of error-prone abbreviations, symbols, and dose designations, refer to the Institute of Safe Medication Practices' website, http://www.ismp.org/Tools/abbreviationslist.pdf

SPL Submission

Structured product labeling (SPL) must be submitted representing the content of your proposed labeling. By regulation [21 CFR 314.50(l), 314.94(d), and 601.14(b); guidance for industry, *Providing Regulatory Submissions in Electronic Format — Content of Labeling,* available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm], you are required to submit to FDA prescribing and product information (i.e., the package insert) in SPL format. FDA will work closely with applicants during the review cycle to correct all SPL deficiencies before approval. Please email spl@fda.hhs.gov for individual assistance.

Integrated Summary of Effectiveness

Please refer to the guidance for industry, *Integrated Summary of Effectiveness,* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf

Please refer to guidance for industry, *Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document,* available at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf

CDER Data Standards Reference Guide/Checklist

The following resources are intended to assist submitters in the preparation and submission of standardized study data to CDER.

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

Dataset Comments

1. Provide an integrated safety (adverse event) dataset for all Phase 2 and 3 trials. If the studies are of different design or duration, discuss with the division which studies are most appropriate for integration.

   The integrated safety dataset that must include the following fields/variables:

   a. A unique patient identifier
   b. Study/protocol number
   c. Patient's treatment assignment
   d. Demographic characteristics, including gender, chronological age (not date of birth), and race
   e. Dosing at time of adverse event
   f. Dosing prior to event (if different)
   g. Duration of event (or start and stop dates)
   h. Days on study drug at time of event
   i. Outcome of event (e.g., ongoing, resolved, led to discontinuation)
   j. Flag indicating whether or not the event occurred within 30 days of discontinuation of active treatment (either due to premature study drug discontinuation or protocol-specified end of active treatment due to end of study or crossover to placebo).
   k. Marker for serious adverse events
   l. Verbatim term

2. The adverse event dataset must include the following MedDRA variables: lower level term (LLT), preferred term (PT), high level term (HLT), high level group term (HLGT), and system organ class (SOC) variables. This dataset must also include the verbatim term taken from the case report form.

3. See the attached mock adverse event data set that provides an example of how the MedDRA variables should appear in the data set. Note that this example only pertains to how the MedDRA variables must appear and does not address other content that is usually contained in the adverse event data set.

4. In the adverse event data set, provide a variable that gives the numeric MedDRA code for each lower level term.

5. The preferred approach for dealing with the issue of different MedDRA versions is to have one single version for the entire NDA. If this is not an option, then, at a minimum, it is important that a single version of MedDRA is used for the ISS data and ISS analysis. If the version that is to be used for the ISS is different than versions that were used for individual study data or study reports, it is important to provide a table that lists all events whose preferred term or hierarchy mapping changed when the data was converted from one MedDRA version to another. This will be very helpful for understanding discrepancies that may appear when comparing individual study reports/data with the ISS study report/data.

6. Provide a detailed description for how verbatim terms were coded to lower level terms according to the *ICH MedDRA Term Selection: Points to Consider* document. For example, were symptoms coded to syndromes or were individual symptoms coded separately.

7. Perform the following SMQ's on the ISS adverse event data and include the results in your ISS report: 1. Severe cutaneous adverse reactions SMQ and 2. Possible drug related hepatic disorders – comprehensive search SMQ. Also, provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds to the same version of MedDRA used for the ISS adverse event data.

8. The spelling and capitalization of MedDRA terms must match the way the terms are presented in the MedDRA dictionary. For example, do not provide MedDRA terms in all upper case letters.

9. For the concomitant medication dataset, you must use the standard nomenclature and spellings from the WHO Drug dictionary and include the numeric code in addition to the ATC code/decode.

10. For the laboratory data, be sure to provide normal ranges, reference ranges, and units as well as a variable that indicates whether the lab result was from the local lab or central lab. Also, the variable for the laboratory result must be in numeric format.

11. Perform adverse event rate analyses at all levels of MedDRA hierarchy (except for LLT) and also broken down by serious versus non-serious.

12. Across all datasets, the same coding must be used for common variables, e.g. "PBO" for the placebo group. Datasets must not incorporate different designations for the same variable, e.g. "PBO" in one dataset, and "0 mg" or "Placebo," in another datasets. If the coding cannot be reconciled, another column using a common terminology for that variable must be included in the datasets.

13. All datasets must contain the following variables/fields (in the same format and coding):
    a. Each subject must have one unique ID across the entire NDA
    b. Study number
    c. Treatment assignment

d. Demographic characteristics (age, race, gender, etc.)

14. A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities must be provided. A listing must be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in an SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. The NDA analyses of the frequency of abnormalities across treatment groups is not sufficient without ready identification of the specific patients with such abnormalities. Analyses of laboratory values must include assessments of changes from baseline to worst value, not simply the last value.

15. Provide CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events.

16. For patients listed as discontinued to due "investigator decision," "sponsor request," "withdrew consent," or "other," the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated.

17. With reference to the table on the following page, note that the HLGT and HLT level terms are from the primary MedDRA mapping only. There is no need to provide HLT or HLGT terms for any secondary mappings. This mock table is intended to address content regarding MedDRA, and not necessarily other data.

Unique Subject Identifier (USUBJID)	Sequence Number (AESEQ)	Study Site Identifier (SITEID)	Unique Subject Identifier	Coding Dictionary Information	Reported Term for AE (Verbatim)	Lower Level Term MedDRA Code	Lower Level Term (LLT)	Preferred Term High Level Term (HLT)	High Level Group Term (HLGT)	System Organ Class (SOC)	Secondary System Organ Class 2 (SOC2)	Secondary System Organ Class 3 (SOC3)	Secondary System Organ Class 4 (SOC4)
01-701-1015	1	701	1015	MedDRA version 8.0	redness around application site	10003058	Application site redness	Application site redness	Administration site reactions	General disorders and administration site conditions	Skin and subcutaneous tissue disorders		

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/s/

DOMINIC CHIAPPERINO
07/06/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 103880

MEETING MINUTES

Premier Research Group, on behalf
of Iroko Pharmaceuticals, LLC
Centre Square West
1500 Market Street, STE 3500
Philadelphia, PA 19102

Attention: Linda Hibbs
Associate Director, Regulatory Operations, Premier Research Group, Ltd.

Dear Ms. Hibbs:

Please refer to the Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the Act) for Diclofenac (b) (4) formulation Capsules.

We also refer to the meeting between representatives of Iroko Pharmaceuticals and the FDA on November 9, 2010. The purpose of the meeting was to discuss the development program for Diclofenac (b) (4) formulation Capsules, now at the End of Phase 2.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1183.

Sincerely,

{See appended electronic signature page}

Dominic Chiapperino, Ph.D.
Senior Regulatory Health Project Manager
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Memorandum of meeting minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2
Teleconference Date and Time:	November 9, 2010, 11:00 AM to 12:00 PM
Application Number:	IND 103880
Product Name:	Diclofenac (b) (4) formulation Capsules
Indication:	Acute (b) (4) pain
Sponsor/Applicant Name:	Iroko Pharmaceuticals, L.L.C.
Meeting Chair:	Sharon Hertz, M.D., Deputy Director, Division of Anesthesia and Analgesia Products (DAAP)
Meeting Recorder:	Dominic Chiapperino, Ph.D., Senior Regulatory Health Project Manager, DAAP

Attendees:

FDA Participants	Title
Bob A. Rappaport, M.D.	Director, Division of Anesthesia and Analgesia Products (DAAP)
Sharon Hertz, M.D.	Deputy Director, DAAP
Frank Pucino, Pharm.D., M.P.H.	Clinical Reviewer, DAAP
Dominic Chiapperino, Ph.D.	Senior Regulatory Health Project Manager, DAAP
Suresh Doddapaneni, Ph.D.	Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II (DCP2)
Suresh B. Naraharisetti, Ph.D.	Clinical Pharmacology Reviewer, DCP2
Iroko Participants	**Title**
Steven Jensen	Vice President, Regulatory and Compliance
(b) (4)	
Linda Hibbs	Associate Director, Regulatory Operations, Premier Research (consultant)
Garen Manvelian, M.D.	Iroko Medical Consultant

Background:
Iroko Pharmaceuticals is seeking feedback from FDA on the development program under IND 103880 for Diclofenac (b) (4) formulation Capsules. Preliminary comments were provided to Iroko in a November 5, 2010, communication that included DAAP's responses to questions from the September 29, 2010, briefing package submitted by Iroko. The meeting on November 9, 2010, focused on a subset of questions for which Iroko desired some clarification. In an email communication sent November 8, 2010, Iroko provided written comments that were intended to initiate discussion of these topics of interest.

Meeting Discussion:
Below are the questions from the September 29, 2010, briefing package with the Division's responses as sent in our November 5, 2010, communication. The questions are in italicized font, and the Division's responses are in bolded font. Iroko's written comments from their November 8, 2010, email communication and discussion during the meeting are shown below in normal font.

Regulatory
Question 1: Does the FDA agree that a 505(b)(2) NDA is the appropriate submission pathway for Diclofenac (b) (4) *formulation Capsules (18 mg & 35 mg)?*

FDA Response:
Yes. This may be an appropriate product for the 505(b)(2) regulatory pathway. We recommend that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at: http://www.fda.gov/cder/guidance/index.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at: http://www.fda.gov/ohrms/dockets/dailys/ 03/oct03/102303/02p-0447-pdn0001-vol1.pdf).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability (BA) data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

Iroko Comment:
The Division's response is clear. No further discussion necessary.

Question 2: (b) (4)

(b) (4)

(b) (4)

[redacted]

Nonclinical

Question 3: *Does the FDA agree that data generated in the 1roko clinical development plan, in combination with existing safety data available in the public domain, are adequate to support the new Diclofenac* (b) (4) *formulation and that additional nonclinical safety studies are not required?*

FDA Response:

As we indicated in the previous advice letter on May 11, 2009, we agree that additional nonclinical studies are not required to support the safety of diclofenac for an NDA, provided clinical exposure to diclofenac with the proposed formulation is within the approved limits of the listed drug Cataflam. However, it should be noted that, at the time of NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per (ICHQ3A(R), ICHQ3B(R)). Impurity (b) (4) [redacted] (b) (4) **was shown to above the ICH qualification threshold based on your stability data. Additional non-clinical studies are required for qualification of this compound. These include two in vitro genotoxicity assays (Ames assay and chromosomal aberration assay) and one general toxicity study in a relevant animal species the duration of which is dependent on your clinical indication. A 14-day general toxicology**

study will be adequate for the acute indication; [redacted]

Iroko Comment:
The Division's response is clear. No further discussion necessary.

CMC
Question 4: *Does the FDA agree controlling for in-process particle size distribution and finished product discriminatory dissolution testing are sufficient assurance of product performance and that a finished product particle size distribution test is not necessary?*

FDA Response:
Your approach appears reasonable; however, you must provide sufficient justification and supporting data in your NDA Pharmaceutical Development Report. We remind you that in-process controls and end-product testing specifications will be assessed upon NDA review.

Be advised that the current Agency thinking for " [redacted] **Therefore, your drug product does not meet the Agency definition of a "** [redacted] **."**

In addition, refer to the CMC advice provided for your IND [redacted] **in July 2, 2010 End of Phase 2 meeting minutes.**

Discussion:
Iroko inquired as to the Agency's definition of "[redacted]" and the regulatory guidance source from which that definition derives. It was agreed that this information would be provided in a post-meeting note as part of the meeting minutes.

Post-Meeting Note:
The [redacted] upper limit for the particle size [redacted] is the Agency's current thinking; there is no regulatory document at present that defines [redacted].

Question 5: *Does the agency agree that this scale-up approach is acceptable and that stability registration batches conducted at the Phase 3 scale are appropriate for filing in the NDA?*

FDA Response:
Your scale-up approach is acceptable.

Iroko Comment:
The Division's response is clear. No further discussion necessary.

Clinical

Question 6: *Does the Division agree that the executed single dose study is sufficient to determine the PK characteristics of the new formulation and to support submission of an NDA?*

FDA Response:
The type of information (relative BA against the reference drug, dose proportionality between 18 mg and 35 mg strengths and food effect on the 35 mg strength) obtained from the single-dose study is sufficient to support the clinical pharmacology requirements for filing an NDA.

In the Phase 3 trial, DIC3-08-04, you propose assessing single-dose diclofenac PK information in patients after the first dose and conducting a descriptive PK analysis by dose in the overall population and by gender. As planned, other than the PK-gender differences, the PK information in patients after the first dose may not yield any additional information as the single-dose PK, and dose-proportionality were already assessed in study DIC1-08-01. In lieu of this, consider incorporating a population pharmacokinetics analysis by including hepatic impairment, renal impairment, concomitant medications, age, gender, and other relevant factors as co-variates.

Iroko Comment:
For clarity, pivotal bunionectomy trial DIC3-08-04 will be a homogeneous population. Relative to the population PK analysis referenced above, the co-variates will not be represented in meaningful numbers. As the Agency notes, the PK plan included in the original pivotal trial will not yield any additional information beyond the single-dose PK study (DIC1-08-01). Iroko sees no value including PK within the bunionectomy trial (DIC3-08-04) and would prefer to delete from the study protocol. As such only PK data from the relative BA study DIC1-08-01 will be presented in the NDA. Does the Division find this agreeable?

Discussion:
The Sponsor explained that the bunionectomy trial population will consist of a homogeneous, mostly female patient population, and will exclude participants with the conditions (e.g., hepatic and renal impairment) useful for additional PK analysis. The Division agreed that, since further PK data would unlikely yield any meaningful data, further PK analysis is not necessary. It was agreed that the PK data from the single-dose comparative BA study (DIC1-08-01) is sufficient to support a future NDA submission.

Question 7: *Does the FDA agree that the Phase* 2 *dental impaction pain model trial and the planned, single pivotal Phase* 3 *bunionectomy pain model trial are sufficient to support an NDA for Diclofenac* (b) (4) *formulation for the indication of mild to moderate acute pain?*

FDA Response:
Yes. However, a single-dose study such as DIC2-08-03 cannot be used to support an indication for the treatment of mild to moderate acute pain for a product intended for multiple-dose use. Reliance on prior findings of efficacy for another diclofenac product for acute pain and the proposed Phase 3 study (DIC3-08-04) for the treatment of acute post-

operative pain after bunionectomy may be adequate to support an efficacy claim for this indication.

Additionally, it should be noted that the pharmacokinetics of your product behave differently under fasting and fed states, such that the maximum plasma concentration (C_{pmax}) is approximately 50% lower and the time to maximum plasma concentration (T_{max}) is approximately 20 minutes longer than the RLD in the fed state. Based on the food effect demonstrated by your product, dosing instructions are expected to recommend dosing on an empty stomach to avoid the reduction in Cmax and AUC that results from dosing in the fed state; and this could negatively impact efficacy. Therefore, conduct the planned Phase 3 efficacy and safety studies with the final planned dosing instructions to take on an empty stomach.

Iroko Comment:
Relative BA study DIC1-08-01 demonstrated that food has a statistically significant effect on maximum plasma concentration (C_{max}) for both the Iroko diclofenac test product and the Cataflam® RLD. Furthermore, food had no significant effect on the extent of diclofenac absorption from either the test or reference product. Iroko wishes to clarify that the required dosing instructions for the Iroko commercial product would be comparable and not more restrictive than the Cataflam® label.

Discussion:
The Division noted that the extent of the food effect for the Sponsor's test product is substantially greater than the food effect for Cataflam, the reference drug (i.e., approximately a 60% decrease versus a 30% decrease in C_{max}), and will warrant restrictions regarding administration of this product. This effect is of particular concern with the low-dose formulation, in which patients with pain may be exposed to subtherapeutic concentrations of active drug.

The Sponsor questioned whether the use of food diaries in a study without food restrictions would be acceptable. The Division responded no, and advised that, if the sponsor wanted to show that the food effect did not have a clinical impact, they would need to conduct a study in which patients are randomly assigned to take study medication on an empty stomach or with meals.

The Division noted that product labeling and promotional material will be an outcome of what is studied in development. Should Iroko choose to conduct the efficacy study without food intake restrictions, this would not be sufficient to demonstrate the lack of a clinical food effect. The Sponsor responded that this would be difficult to assess in the Phase 3 bunionectomy trial, which will not have any food restrictions. The difficulty of defining the term, "empty stomach," and monitoring food intake for long-term studies are also problematic. The Division acknowledged these difficulties, as well as the general reluctance people have with taking NSAIDs on an empty stomach, but wanted to be very clear at this early stage of the clinical development program that the PK data supported that the product be taken on an empty stomach. The Division questioned the utility of the (b) (4) formulation for diclofenac since it created this problem with a food effect, but offered no advantage in bioavailability, as diclofenac was already 100% bioavailable.

The Division noted the possibility of an Advisory Committee meeting if the food effect was not studied or a food restriction was not included in the clinical efficacy studies or in the proposed labeling. The Sponsor acknowledged that the presence of a significant food effect (b) (4) agreed to implement the "empty stomach" food restriction (administration of study medication 1 hour before or 2 hours after a meal) in the Phase 3 bunionectomy trial.

Question 8: *Does the FDA agree that a total safety data base of 350 subjects is sufficient to assess the safety of Diclofenac* (b) (4) *formulation Capsules and to support an NDA?*

FDA Response:
Yes. Exposure data on 350 patients may be adequate. (b) (4)

Considering the extent of use with other diclofenac products, you will need to provide safety data on at least 300 patients treated for at least 6 months and at least 100 patients treated for at least one year.

Iroko Comment:
Market research data indicate that more than (b) (4) patients worldwide have been exposed over the last 25 years to diclofenac administered as Voltaren® (diclofenac sodium) launched in 1974 or Cataflam® (diclofenac potassium) launched in 1986 (reference Submission to New Zealand by Pharmacy Solutions Ltd. on behalf of Novartis, July 2002). In addition, "the marketed use of diclofenac sodium (Voltaren®, Geigy Pharmaceuticals) began in 1974 in Japan and has extended to 120 countries and more than 150 million patient-months therapy. Clinical trials have been performed in 21 countries, resulting in 422 publications based on results in 18,000 patients in controlled trials and 85,000 patients in open label studies" (reference Worldwide Safety Experience with Diclofenac" Michael A. Catalano, M.D., The American Journal of Medicine, April 28, 1986, Volume 80; supp 4B).

Iroko's new diclofenac formulation is formulated at a dose 20% lower than both Voltaren® and Cataflam® with corresponding 80% relative systemic exposure (AUC). Testing 300 patients for six months and 100 patients for one year, even dosed on an empty stomach, is unlikely to gain any new or significant information on this well established drug. Does the Division agree with this view?

Discussion:
The Division noted that the requirements discussed did reflect that the program would be relying on the Agency's prior findings for diclofenac, and that, had this been a new molecular entity

(NME), the safety database would need to be at least 1500 patients, and that a cardiovascular outcome study would also be required. (b) (4)

(b) (4)

Iroko Comment:
See Iroko comment to Question 8.

Meeting outcomes and final understandings:

1. FDA agreed to provide in a post-meeting note a definition of "(b) (4)" and note the source guidance for the definition.

2. It was agreed that, since special populations would not be well-represented in the Phase 3 bunionectomy trial, DIC3-08-04, collection of the recommended PK data would not be a requirement in support of the NDA.

3. Iroko stated its understanding of the Division's concerns regarding the strong food effect of Diclofenac (b) (4) formulations Capsules, and intended to address the effect with labeling language that advised dosing on an empty stomach (versus clinical study to demonstrate that the food effect had no impact on patient outcome/efficacy). Further, the Sponsor agreed to implement a food restriction in the proposed Phase 3 bunionectomy trial (DIC3-08-04).

4. (b) (4)

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/s/

DOMINIC CHIAPPERINO
12/07/2010