

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209604Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 209604 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: N/A Established/Proper Name: Gemcitabine Injection Dosage Form: solution for injection, 100 mg/ml		Applicant: Accord Healthcare, Inc. Agent for Applicant (if applicable): N/A
RPM: Anuja Patel		Division: Division of Oncology Products 2
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> - Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. - Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☒ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: 7/19/2017 <i>Note: 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.</i>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>August 13, 2017</u>		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☒ None
❖ 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		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(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., new listed drug, patent certification revised).

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.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

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

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- ☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)

Subpart I

- ☐ 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

BLAs: Subpart E

- ☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)

Subpart H

- ☐ Approval based on animal studies

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

Comments:

❖ 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
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	☒ No ☐ Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
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 <i>(including approval letter with final labeling)</i>	Action(s) and date(s) Approval 08/03/2017
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	☒ Included Sponsor Submitted labeling (clean) received 7/14/2017
Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	☐ Included
Original applicant-proposed labeling	☐ Included
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
Most-recent draft labeling	☒ Included Sponsor Submitted Received 4/26/2017
❖ Proprietary Name	
- Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> - Review(s) <i>(indicate date(s))</i>	N/A
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: uploaded 12/13/2016 DMEPA: uploaded 2/28/2017 and 5/2/2017 DMPP/PLT (DRISK): ☒ None OPDP: uploaded 6/16/2017 for package insert; uploaded 6/16/2017 for container and container labeling SEALD: ☒ None CSS: ☒ None Product Quality ☐ None Refer to IQA Labeling Review signed 6/22/2017 and TL cleared 6/22/2017 Other: ☐ None
Administrative / Regulatory Documents	

❖ RPM Filing Review⁴/Memo of Filing Meeting (<i>indicate date of each review</i>) ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	RPM Filing Review uploaded 12/13/2016 505(b)(2) Assessment: 7/10/2017 additional information requested by committee 7 17/2017 clearance/minor edit to Q3 of Assessment ☐ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary (<i>signed by Division Director</i>)	☒ Completed
❖ 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 ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) • Date reviewed by PeRC <u>March 29, 2017</u> If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) (<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)	7/13/2017 FDA proposed revisions to PI (minor formatting) 7/11/2017 Regulatory IR from 505b2 Assessment Committee 7/5/2017 Labeling Information request 6/14/2017 CMC Information Request- Request for additional revisions to Comparability Protocol 6/13/2017 Information Request-request for revised labeling in correct format 5/30/2017 FDA Preliminary Edits to PI

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

	5/15/2017 CMC Information Request 4/24/2017 CMC Information Request 4/13/2017 CMC Information Request 4/04/2017 CMC Information Request 3/27/2017 FDA Preliminary Comments on Carton and Container 3/24/2017 CMC Information Request 3/17/2017 Agree iPSP Information Request 2/28/2017 CMC Information Request 12/16/2016 No Filing Review Issues Identified letter 11/18/2016 CMC Information Request 11/08/2016 OSIS Information Request 10/28/2016 Acknowledge NDA letter
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	-Wrap Up Meeting 07/10/17 (uploaded 7/19/2017) -Midcycle Meeting 03/16/2017 (uploaded 7/19/2017) -Planning Meeting Minutes 10/31/2016 (uploaded 11/08/2016)
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☐ No mtg Type B/preNDA Meeting 09/01/2015 (Minutes uploaded 09/23/2015)
• EOP2 meeting (<i>indicate date of mtg</i>)	☒ No mtg
• Mid-cycle Communication (<i>indicate date of mtg</i>)	☒ N/A
• Late-cycle Meeting (<i>indicate date of mtg</i>)	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	03/03/2015 Type C Final Written Responses under IND 107393
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	☒ None
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None Signed and uploaded 7/18/2017; DOP2 Deputy Division Director Concurrence 7/18/2017
PMR/PMC Development Templates (<i>indicate total number</i>)	☒ None

Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) <i>(indicate date for each review)</i>	☒ No separate review
• Clinical review(s) <i>(indicate date for each review)</i>	7/20/2017 Addendum to Clinical Review (for Financial Disclosure) Primary Review uploaded 7/7/2017; TL Concurrence 7/7/2017 Filing Review uploaded 12/8/2016; TL Concurrence 12/8/2016
• Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i>	☒ 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 <i>(indicate date of review/memo)</i>	See 7/20/2017 Clinical Review Addendum
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i> ⁵	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i>	☒ N/A
❖ Risk Management - REMS Documents and REMS Supporting Document <i>(indicate date(s) of submission(s))</i> - REMS Memo(s) and letter(s) <i>(indicate date(s))</i> - Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i>	☒ None
❖ OSI Clinical Inspection Review Summary(ies) <i>(include copies of OSI letters to investigators)</i>	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	☐ No separate review
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	☒ No separate review
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	☒ No separate review
Statistical Review(s) <i>(indicate date for each review)</i>	☐ None Consult review uploaded 6/8/2017; TL concurrence 6/8/2017

⁵ For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	☒ No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	☒ No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	☐ None Primary Review uploaded 7/12/17; TL concurrence 7/12/17 Filing Review uploaded 12/2/2016; TL concurrence 12/2/2016
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	☐ None requested OSIS Review uploaded 12/20/2016
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	☒ No separate review
• Supervisory Review(s) <i>(indicate date for each review)</i>	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	☐ None Primary Review uploaded 7/17/2017; TL concurrence 7/17/2017
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	☒ None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (<i>indicate date for each review</i>)	☒ None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	☐ None uploaded and signed in Panorama 7/14/2017 6/19/2017 Drug Substance, Facility 5/30/2017 Drug Product 5/18/2017 Microbiology 4/26/2017 Labeling 4/25/2017 Drug Product, Microbiology 4/18/2017 Drug Product 4/12/2017 Drug Product, Process 3/29/2017 Labeling 3/29/2017 Drug Substance, Facility 3/21/2017 Microbiology 11/23/2016 Biopharmaceutics 10/13/2016 CMC
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Refer to page 3 of the Executive Summary of the Integrated Quality Assessment Review
☐ Review & FONSI (<i>indicate date of review</i>)	
☐ Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	☒ Acceptable Approval Recommended 7/7/2017 and signed 7/10/2017 in Panorama ☐ Withhold recommendation ☐ Not applicable

⁶ Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity <i>(Notify CDER OND IO)</i>
Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: Notify the CDER BT Program Manager	☐ Done <i>(Send email to CDER OND IO)</i>
❖ For products that need to be added to the flush list (generally opioids): Flush List Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☐ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	
❖ Take Action Package (if in paper) down to Document Room for scanning within two business days	

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

/s/

KRISTIN D JARRELL

08/04/2017

EXCLUSIVITY SUMMARY

NDA # 209604

SUPPL # N/A

HFD # N/A

Trade Name: N/A

Generic Name: GEMCITABINE injection, for intravenous use

Applicant Name: Accord Healthcare Inc.

Approval Date, If Known: PDUFA 8/13/17, target approval date 8/3/17

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)

b) 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.

No efficacy or safety data was submitted for review under this NDA. A pivotal bioequivalence study was conducted by the Applicant to bridge their product with the reference listed product Gemzar; specifically, Study 311-13 was conducted and the final study report was contained in this NDA submission:

Protocol 311-13 entitled "A multicentre, randomized, open label, two-period, two-treatment, two-way crossover, single dose bioequivalence study comparing Gemcitabine

Injection 100 mg/mL (10 mL) (Manufactured by: Intas Pharmaceuticals Ltd.) to the reference listed drug Gemzar 1g/vial (Gemcitabine for Injection 1g/vial, Lilly USA, LLC, Indianapolis, IN 46285, USA) in patients with Pancreatic or Ovarian Cancer.”

Based on the clinical pharmacology review, Study 311-13 showed that Gemcitabine Injection was bioequivalent to the listed drug Gemzar, with the 90% confidence intervals of the geometric mean ratios of gemcitabine C_{max} and AUC falling within 80-125% limits.

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:

N/A

c) Did the applicant request exclusivity?

YES ☐ NO ☒

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

d) 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).

NDA20509, NDA200795, ANDA091594, ANDA079160, A078759, ANDA091365, ANDA202997, ANDA202063, ANDA090799, ANDA090242, ANDA090663, ANDA078339, ANDA079183, ANDA202485, ANDA202031, ANDA200145, ANDA091597, ANDA078433, ANDA077983

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary

should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES ☐ NO ☒

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

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

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

YES ☐ NO ☐

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

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

YES ☐ NO ☐

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☐

If yes, explain:

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

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

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

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved

drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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"):

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 # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # 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: Anuja Patel
Title: Senior RPM
Date: August 2, 2017

Name of Division Director signing form: Joseph Gootenberg, M.D.

Title: Deputy Director, Division of Oncology Products 2

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

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/s/

KRISTIN D JARRELL

08/03/2017

JOSEPH E GOOTENBERG

08/03/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 3, 2017
From: Norma Griffin, Lead Regulatory Health Project Manager DOP2/OHOP
Subject: Financial Disclosure: NDA 209604

Financial disclosure information submitted for this NDA 209604 application 505b2 was reviewed in the clinical review addendum prepared by Dr. Lee Pai-Scherf. Please refer to 07/20/2017 Clinical Review Addendum

Wrap Up Meeting Summary
July 10, 2017

NDA 209604/0

Product: Gemcitabine Injection, solution for injection, 100 mg/ml
Submission Date: October 13, 2016
Received Date: October 13, 2016
Sponsor: Accord Healthcare Inc.

Attendees:

Joseph Gootenberg (Signatory), Monica Hughes (CPMS), Anuja Patel (Sr. RPM), Anamitro Banerjee (CDTL), Edwin Chow (Clinical Pharmacology Reviewer), Paresma Patel (CMC Reviewer), Latonia Ford (OSE RPMS), Lee Pai-Scherf (MO), Erin Larkins (Clinical TL), Ann Marie Trentacosti (Labeling Reviewer), Janine Stewart (DMEPA), Yarery Smith (CMC Micro Reviewer)

Discussion Items:

1. Discipline Specific Reviews of Application

- a. Regulatory Update: *RPM notified the team that the 505(b)(2) RPM assessment was under review (sent to OND IO 6/12/17) and Exclusivity Summary was under CPMS review (sent 7.10.17). The 505b2 Assessment was uploaded in DARRTS 7/19/17.*
- b. CMC: ***Review pending in Platform (last checked 7/7/17)***
 - Facility Inspection- *The facility primary review is completed, it's under secondary review, once facility review is finalized, OMIR could be completed right away.*
 - CMC Micro: Yarery Smith: review complete in DARRTS 6/5/17; *No microbiology deficiencies were identified. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process.*
- c. Nonclinical: *Only a labeling review was needed for this application which was uploaded in DARRTS 7.17.17. There were no pharmacology/toxicology issues that arose during the review period that would prevent approval.*
- d. Clinical: Lee Pai Scherf: review complete in DARRTS 7.7.17
- e. Clinical Pharmacology: Review was pending in DARRTS at the time of wrap up meeting; Review was uploaded in DARRTS 7/12/17

2. Status of Consults

- a. CMC Biostatistics: Meiyu Shen: review complete in DARRTS 6.8.17
- b. OPDP: Nazia Fatima: review complete in DARRTS 6.16.17; no comments on PI or carton container

- c. DMEPA: Otto Townsend: review complete in DARRTS 2.28.17 and 5.2.17
- d. PERC: PeRC Meeting held 3.29.17; PeRC agreed with granting full waiver
- e. OSIS: Li-Hong Yeh: review complete; Uploaded in DARRTS 5/19/17- No 483 issued.
The final inspection classification for all inspected sites is NAI

3. Labeling Discussion

- Final Draft Carton and Container labeling received 4/26/17 SDN 12 -- *copies provided*

Discussion: The team agreed that to the carton container label received on April 26, 2017 was the "final agreed" labeling and should be included in the approval letter.

- Final Draft Package Insert Labeling received 7/7/17 SDN 18 – *copies provided*

Discussion: The Signatory and RPM stated that further formatting revisions were needed. The labeling was sent back to the Applicant on July 13, 2017 with proposed revisions and the applicant submitted their final label to the NDA on July 14, 2017.

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/s/

ANUJA PATEL
07/19/2017

**Midcycle Meeting Summary
March 16, 2017**

NDA 209604/0

Product: Gemcitabine Injection, solution for injection, 100 mg/ml
Submission Date: October 13, 2016
Received Date: October 13, 2016
Sponsor: Accord Healthcare Inc.
Link to NDA submission:
(SDN 0) EDR Location: <\\CDSESUB1\evsprod\NDA209604\209604.enx>

Proposed Indications:

“Gemcitabine Injection is a nucleoside metabolic inhibitor indicated:

- in combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy;
- in combination with paclitaxel, for first-line treatment of metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated;
- in combination with cisplatin for the treatment of non-small cell lung cancer; and
- as a single agent for the treatment of pancreatic cancer.”

Attendees Present:

Office of New Drugs Review Team:

Jeff Summers, Deputy Director for Safety, DOP2 (Covered for Joseph Gootenberg as Signatory)
Anuja Patel, Sr. Regulatory Health Project Manager, DOP 2
Lee Pai-Scherf, Medical Officer, DOP 2
Erin Larkins, Clinical Team Leader, DOP 2

Office of Clinical Pharmacology

Edwin Chow, Clinical Pharmacology Reviewer
Jeanne Fourie Zirkelbach, Clinical Pharmacology Team Leader

Office of Biostatistics

Meiyu Shen, CMC Stats Reviewer

Office of Product Quality Review Team:

*Paresma Patel, Drug Product (DP) Reviewer
*Anamitro Banerjee, DP, Branch Chief, ADL/CDTL

Office of Safety Evaluation Review Team:

*Latonia Ford, OSE RPM

Discussion During Meeting:

1. Slides were presented by the following disciplines (in order):

- Chemistry, Manufacturing, and Control- Anamitro Banerjee
- Clinical Pharmacology/OSIS Inspection Update- Edwin Chow

2. **Discussion of PMRs/PMCs** – There were no PMRs or PMCs identified for this application.
3. **REMS:** At this point, the team does not anticipate that a REMS will be needed.

Submitted Consults:

- OPDP- consult uploaded in DARRTS 11/1/2016
- OSE-consult uploaded in DARRTS 11/1/2016
- PeRC/ Pediatrics- PeRC meeting held March 8, 2017
- OSIS- review completed 12/19/16
- OSI- No OSI consult is needed for this application.

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/s/

ANUJA PATEL
07/19/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 19, 2017
From: Anuja Patel, M.P.H., Senior Regulatory Health Project Manager
DOP2/OHOP
Subject: NDA 209604: Advisory Committee Meeting

No advisory committee meeting was held for this 505(b)(2) application and no Special Government Employees (SGEs) were consulted.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 19, 2017
From: Anuja Patel, M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 209604: Environmental Assessment

Environmental Assessment review can be found on page 3 of the Executive Summary of the Integrated Quality Assessment Review.

Patel, Anuja

From: Patel, Anuja
Sent: Thursday, July 13, 2017 4:18 PM
To: 'Sabita Nair'
Subject: FDA Revisions to Package Insert- NDA 209604/ Gemcitabine Injection/ Accord Healthcare
Attachments: FDA revisions to Accords 7 7 17 PI labeling.docx

Dear Ms. Nair,

Please refer to your New Drug Application (NDA) dated October 13, 2016, received October 13, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for gemcitabine injection, solution for injection, 100 mg/ml.

We also refer to your July 7, 2017, amendment to the NDA containing your proposed final draft labeling for the package insert.

Attached please find FDA revisions to the label which are mostly formatting and spacing corrections. Please review the attached and accept all changes.

Please submit your final draft labeling to the NDA by COB July 14, 2017.

Please ACK receipt of this communication.

Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎ 301.796.9022 (phone)
anuja.patel@fda.hhs.gov (email)

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Patel, Anuja

From: Patel, Anuja
Sent: Thursday, July 13, 2017 4:18 PM
To: 'Sabita Nair'
Subject: FDA Revisions to Package Insert- NDA 209604/ Gemcitabine Injection/ Accord Healthcare
Attachments: FDA revisions to Accords 7 7 17 PI labeling.docx

Dear Ms. Nair,

Please refer to your New Drug Application (NDA) dated October 13, 2016, received October 13, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for gemcitabine injection, solution for injection, 100 mg/ml.

We also refer to your July 7, 2017, amendment to the NDA containing your proposed final draft labeling for the package insert.

Attached please find FDA revisions to the label which are mostly formatting and spacing corrections. Please review the attached and accept all changes.

Please submit your final draft labeling to the NDA by COB July 14, 2017.

Please ACK receipt of this communication.

Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎ 301.796.9022 (phone)
anuja.patel@fda.hhs.gov (email)

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/s/

ANUJA PATEL
07/13/2017

Patel, Anuja

From: Patel, Anuja
Sent: Tuesday, July 11, 2017 2:16 PM
To: 'Sabita Nair'
Subject: FDA Information Request: NDA 209604/ Gemcitabine Injection/ Accord Healthcare

Dear Ms. Nair:

Please refer to your New Drug Application (NDA) dated October 13, 2016, received October 13, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for gemcitabine injection, solution for injection, 100 mg/ml.

We have the following request for additional information and request that you submit your response via email by 9 AM, EST July 12, 2017, followed with a formal submission to the NDA as “General Correspondence/Response to Information Request”

- **Explain the relationship between the product manufactured by Intas and the proposed commercial product to be marketed by Accord.**

Please confirm receipt.

Thank you,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎ 301.796.9022 (phone)
anuja.patel@fda.hhs.gov (email)

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/s/

ANUJA PATEL
07/11/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 5, 2017
From: Anuja Patel, M.P. H., Sr. Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 209604: FDA Response to Package Insert (PI) received 6/15/17

Accord Healthcare Inc.
Attention: Sabita Nair
Senior Director, Regulatory Affairs
1009 Slater Road, Suite 210-B
Durham, NC 27703

Dear Ms. Nair:

We refer to our May 30, 2017 Memorandum sent via electronic mail, containing FDA preliminary edits on the package insert in response to your revised labeling submitted and received on January 17, 2017, under NDA 209604 for Gemcitabine Injection, solution for injection, 100 mg/ml.

We acknowledge receipt of your June 6, 2017, amendment containing your revised draft labeling in response to our May 30, 2017 communication. As communicated to you via phone and email on June 13, 2017, the labeling submitted on June 6, 2017 did not follow our instructions for submitting revised labeling.

We acknowledge receipt of your amended PI, submitted and received on June 15, 2017, in response to our June 13, 2017 communication.

Please find attached revised labeling including FDA counterproposal to your labeling received on June 15, 2017.

Where you agree with FDA's proposed edits, please accept the tracked change to aid in reviewability. Please include a comment (cite "From Accord" in the comment field) stating your agreement.

For those edits which you do not agree, provide your proposed modifications and a comment (cite "From Accord" in the comment field) that includes a justification for your proposal.

Provide your final draft labeling in response to FDA's proposed revisions as an amendment to the NDA by **close of business, Friday, July 7, 2017**. In addition to submitting your response to the NDA, please email me a MS Word labeling in both clean and redlined versions (showing track changes).

Please let me know if you have any questions.

Regards,

Anuja Patel, M.P.H.
Sr. Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9022, Fax: 301-796-9849

Attachment: FDA proposed revisions to the PI submitted June 15, 2017

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/s/

ANUJA PATEL
07/05/2017

From: Steven Kinsley
To: snair@intaspharma.com
Cc: Anuja Patel
Subject: NDA 209604 CMC Information Request 7-14-17
Date: June 14, 2017

Dear Sabita,

I have received the following information request from our CMC review team. Please respond to the following with a submission to your NDA by Wednesday, June 21, 2017.

1. The proposed testing plan described in the provided Comparability Protocol (CP) appears acceptable; however, since other elements of the CP ([REDACTED] (b) (4)) are unknown at this time, the Agency cannot commit to a CBE-30. Please update the CP to indicate [REDACTED] (b) (4) or additional information, see the FDA "Guidance for Industry: Changes to an Approved NDA or ANDA" (April 2004).

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

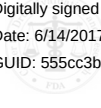
Office of Program and Regulatory Operations
U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov





Steven
Kinsley

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Date: 6/14/2017 03:52:44PM
GUID: 555cc3bc000836e194b17e8bf695ce5f



Patel, Anuja

From: Patel, Anuja
Sent: Tuesday, June 13, 2017 2:09 PM
To: 'Sabita Nair'
Subject: FDA Information Request- NDA 209604/ Gemcitabine Injection/ Accord Healthcare

Importance: High

Dear Sabita,

We refer to our May 30, 2017 Memorandum sent via electronic mail, containing FDA preliminary edits on the package insert in response to your revised labeling submitted and received on January 17, 2017. We acknowledge receipt of your June 6, 2017 amendment containing your revised draft labeling in response to our May 30, 2017 communication.

As I communicated to you via phone on June 13, 2017, the labeling submitted on June 6, 2017 did not follow the instructions in the Memorandum for submitting revised labeling.

Please submit revised labeling in response to our May 30, 2017 communication and as stated in the May 30, 2017 Memorandum:

*"Where you agree with FDA's proposed edits, please accept the tracked change to aid in reviewability. Please include a comment (cite "From Accord" in the comment field) stating your agreement.
For those edits which you do not agree, provide your proposed modifications in tracked changes and a comment (cite "From Accord" in the comment field) that includes a justification for your proposal."*

Please submit your revised labeling as an amendment to the NDA by 10 AM, EST, Thursday, June 15, 2017. In the cover letter, please refer to the May 30, 2017 communication, to your June 6, 2017 amendment, and to this email. Please email me a courtesy copy of your submission once submitted formally.

Please confirm receipt.

Thank you!
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎ 301.796.9022 (phone)
anuja.patel@fda.hhs.gov (email)

From: Sabita Nair [<mailto:snair@intaspharma.com>]
Sent: Tuesday, May 30, 2017 11:00 AM
To: Patel, Anuja
Subject: RE: FDA Preliminary Edits to Package Insert- NDA 209604/ Gemcitabine Injection/ Accord Healthcare

Hello Anuja,

Good Morning. I am acknowledging receipt of the e-mail containing the edits to the package insert for NDA 209604.

Regards,
Sabita

Sabita Nair, RAC
Sr. Director-Regulatory Affairs

INTAS PHARMACEUTICALS LTD./ACCORD HEALTHCARE INC.
1009 Slater Road, Suite 210-B, Durham NC 27703, USA
Tel : 919-941-7880; Fax: 919-941-7885;
E-Mail: snair@intaspharma.com

From: Patel, Anuja [<mailto:Anuja.Patel@fda.hhs.gov>]
Sent: Tuesday, May 30, 2017 10:38 AM
To: Sabita Nair <snair@intaspharma.com>
Subject: FDA Preliminary Edits to Package Insert- NDA 209604/ Gemcitabine Injection/ Accord Healthcare
Importance: High

Dear Ms. Nair,

Please find attached Memorandum containing FDA preliminary edits to the Package Insert received on January 17, 2017. I'm attaching a Word Version of the label to assist in your response which is due as an amendment to the NDA by close of business, June 6, 2017.

Please confirm receipt of this email and attachments.

Thank you,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎ 301.796.9022 (phone)
anuja.patel@fda.hhs.gov (email)

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/s/

ANUJA PATEL
06/13/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 30, 2017
From: Anuja Patel, M.P. H., Sr. Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 209604: FDA Preliminary Comments on Package Insert (PI)

Accord Healthcare Inc.
Attention: Sabita Nair
Senior Director, Regulatory Affairs
1009 Slater Road, Suite 210-B
Durham, NC 27703

Dear Ms. Nair:

We refer to your amended prescribing information (PI), submitted on January 16, 2017, and received on January 17, 2017, under NDA 209604 for Gemcitabine Injection, solution for injection, 100 mg/ml.

Please find attached revised labeling including FDA preliminary edits to the PI.

Where you agree with FDA's proposed edits, please accept the tracked change to aid in reviewability. Please include a comment (cite "From Accord" in the comment field) stating your agreement.

For those edits which you do not agree, provide your proposed modifications and a comment (cite "From Accord" in the comment field) that includes a justification for your proposal.

Provide a response to FDA's proposed changes as an amendment to the NDA by **close of business, Tuesday, June 6, 2017**. In addition to submitting your response to the NDA, please email me a MS Word labeling in both clean and redlined versions (showing track changes). Please let me know if you have any questions.

Regards,

Anuja Patel, M.P.H.
Sr. Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9022, Fax: 301-796-9849

Attachment: FDA proposed revisions to the PI submitted January 16, 2017

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/s/

ANUJA PATEL
05/30/2017

From: Steven Kinsley
To: snair@intaspharma.com
Cc: Anuja Patel
Subject: NDA 209604 CMC Information Request 5-15-17
Date: May 15, 2017

Dear Sabita,

I have received the following information request from our CMC review team. Please respond to the following with a submission to your NDA by Friday, May 19, 2017.

Microbiology:

1. In your response to the April 4, 2017 Information request, received April 25, 2017, you stated that you have initiated the antimicrobial effectiveness testing of finished product (b) (4) and the study will be completed by [REDACTED] is testing will be submitted by

Wednesday, May 24, 2017.

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

Office of Program and Regulatory Operations
U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov





Steven
Kinsley

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Date: 5/15/2017 11:23:25AM
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PeRC Meeting Minutes
March 29, 2017

PeRC Members Attending:

Lynne Yao
John Alexander
Meshaun Payne
Jacqueline Yancy
Hari Cheryl Sachs
Wiley Chambers
Lily Mulugeta
Skip Nelson
Gil Burkhart
Dionna Green
Rosemary Addy
James Travis
Antonia Dow
Daiva Shetty
Gettie Audain
Mark Rothmann
Julia Pinto
Adrienne Hornatko-Munoz
Barbara Buch

Agenda

(b) (4)

9:00

9:50

10:10

10:30

10:40

11:00

11:10

11:30

NDA
209604

Gemcitabine Injection (Full Waiver) with
Agreed iPSP

DOPII

Anuja Patel

(1) in combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy (2) in combination with paclitaxel, for first-line treatment of metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated(3)in combination with cisplatin for the treatment of non-small cell lung cancer; and (4) as a single agent for the treatment of pancreatic cancer

(b) (4)

Gemcitabine Injection (Full Waiver) with Agreed iPSP

- Proposed Indication: (1) in combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy (2) in combination with paclitaxel, for first-line treatment of metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated (3) in combination with cisplatin for the treatment of non-small cell lung cancer; and (4) as a single agent for the treatment of pancreatic cancer
- This product triggers PREA as a new indication
- *PeRC Recommendations:*
 - The PeRC agrees with granting a full waiver.

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/s/

JACQUILINE A YANCY
05/05/2017

From: Steven Kinsley
To: snair@intaspharma.com
Cc: Anuja Patel
Subject: NDA 209604 CMC Information Request 4-24-17
Date: April 24, 2017

Dear Sabita,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Tuesday, May 30, 2017.

- 1) Your response to Drug Product information request received on 18-Apr-2017 is inadequate. The submitted in-use stability data (b) (4)
(b) (4)
(b) (4)
(b) (4) Conduct in-use stability studies (b) (4)
(b) (4)
(b) (4) over the proposed 28-day in-use storage time. Provide data for the following time points: initial (t=0), 14 days, and 28 days.
- 2) You have indicated that a (b) (4)
(b) (4) (b) (4). Provide a quantitative estimate of the (b) (4)
(b) (4) provided in Attachment 1 and Attachment 3 of the Study Report 8-28-8444-2 (Section 3.2.P.2, Appendix 3).

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

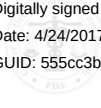
Office of Program and Regulatory Operations
U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov





Steven
Kinsley

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Date: 4/24/2017 11:01:39AM
GUID: 555cc3bc000836e194b17e8bf695ce5f



From: Steven Kinsley
To: snair@intaspharma.com
Cc: Anuja Patel
Subject: NDA 209604 CMC Information Request 4-13-17
Date: April 13, 2017

Dear Sabita,

I have received the following information request from our CMC review team. Please respond to the following with a submission to your NDA by Thursday, April 27, 2017.

1. Your response to Drug Product information request (comment 4) received on 12-Apr-2017 is inadequate. (b) (4)

use stability studies

Provide data for in-

(b) (4)

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

Office of Program and Regulatory Operations
U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov





Steven
Kinsley

Digitally signed by Steven Kinsley
Date: 4/13/2017 01:34:22PM
GUID: 555cc3bc000836e194b17e8bf695ce5f



From: Steven Kinsley
To: snair@intaspharma.com
Cc: Anuja Patel
Subject: NDA 209604 CMC Information Request 4-4-17
Date: April 4, 2017

Dear Sabita,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Tuesday, April 25, 2017.

Drug Product

1. Provide data to demonstrate that elemental impurity levels for the registration batches do not exceed PDE levels per ICH Q3D or USP <232>. Include an adequate risk assessment that demonstrates an understanding of elemental impurities that may leach into the drug product including risk factors for the manufacturing process. Alternatively, you can test and control for elemental impurities in your proposed drug product specifications.

Microbiology

2. With regard to the information provided from the antimicrobial effectiveness testing

(b) (4)





- b. The updated sterility test protocol is dated 2017; however, the actual results are dated 2012. Please explain.

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

Office of Program and Regulatory Operations
U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov





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Steven
Kinsley

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 27, 2017
From: Anuja Patel M.P.H., Sr. Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 209604/ Gemcitabine Injection/ Accord Healthcare Inc.
FDA Preliminary Comments on Carton and Container Labeling

Accord Healthcare Inc.
Attention: Sabita Nair
Senior Director, Regulatory Affairs
1009 Slater Road, Suite 210-B
Durham, NC 27703

Dear Ms. Nair,

Please find attached FDA's preliminary comments to your carton and container labeling submitted on October 13, 2016.

Below are our preliminary comments on your proposed carton and container labeling.

Provide a response to FDA's proposed changes by close of business on March 31, 2017, or sooner. In addition to formally submitting your response to the NDA, please email me a copy of your responses to our comments and questions below as well as the revised carton and container labeling.

FDA General Comments regarding the carton and container labeling:

1. Indicate sterility of your drug product on the container label and carton labeling.
2. The proposed carton and immediate container labels indicate that the (b) (4) data submitted in the NDA, Gemcitabine injection 100 mg/mL (b) (4) Provide a justification for the statement (b) (4) on the container and carton labeling.
3. Revise the NDC so the product codes (middle digits) are differentiated and not sequential. Injectable products might contain the same product concentration but contain a different total amount of drug in the container because of differences in the fill volume (e.g., 20 mg/2 mL (10 mg/mL), 40 mg/4 mL (10mg/mL)). When the same product code number is used for all of the different containers, healthcare practitioners have had difficulty distinguishing the difference in total drug content.
4. Since the vials are intended for multiple doses and should be discarded 28 days after initial puncture, revise the statement (b) (4) to read "Discard 28 days after initial puncture".

(b) (4)



FDA Comments on Carton Labeling:

1. Delete the statement (b) (4) as it crowds the carton labeling and is duplicative with the statement “Must Be Diluted Before Use”. The statement “Must Be Diluted Before Use” on the PDP and back panel already instructs end users that the drug product must be (b) (4) before administration.
2. Change the statement, (b) (4) to read, “See Prescribing Information for complete dilution information.”
3. Change the statement, (b) (4) to read, “Usual Adult Dose: See Prescribing Information.”

4. Include the unit of measurement after each number in the temperature range. For example, change "...room temperature 20° to 25°C (68° to 77°F)..." to read, "...room temperature 20°C to 25°C (68°C to 77°F)...".
5. The flag, "New Concentration and Preparation" may only remain in place for six months.

Carton Labels: 200 mg/2mL, 1 g/10mL, 1.5 g/15mL, and 2 g/20mL (100 mg/mL)

(b) (4)



Please let me know if you have any questions.

Regards,

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-9022, Fax: 301-796-9849

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/s/

ANUJA PATEL
03/27/2017

From: Steven Kinsley
To: snair@intaspharma.com
Cc: Anuja Patel
Subject: NDA 209604 CMC Information Request 3-24-17
Date: March 23, 2017

Dear Sabita,

I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Friday, April 14, 2017.

Drug Product

1. Perform and provide data from the extraction studies of the container closure elements ((b) (4) stoppers and vials). (b) (4)
(b) (4)
correlate the impurities detected in the extraction studies to the observed leachables in the Study 8-28-8444-2 (Section 3.2.P.2, Appendix 3).
2. The container volumes measured in the submitted batch release data are (b) (4)
(b) (4) as recommended in USP <1151> Pharmaceutical Dosage Forms. As per 21 CFR 201.51 (g), revise your specifications to comply with USP <1151>. Alternatively, provide an adequate justification for the (b) (4)
(b) (4)
(b) (4).
3. Tighten the acceptance criteria for (b) (4) to reflect the maximum clinical dose of 1250 mg/m². Adequately justify the acceptance criteria based on batch release and shelf life data.
4. Provide data to demonstrate that the drug product meets specifications through the in-use storage time of 28 days following removal of clinically relevant aliquots (doses) of drug product. You may implement a bracketing design for the (b) (4) closure presentations with adequate justification.
5. Provide the drug product batch numbers and presentations tested in the (b) (4)
(b) (4) provided in the submission. You may implement a bracketing design for the (b) (4).

Process

(b) (4)

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

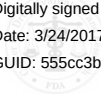
Office of Program and Regulatory Operations
U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov





Steven
Kinsley

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Date: 3/24/2017 12:56:51PM
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Patel, Anuja

From: Patel, Anuja
Sent: Friday, March 17, 2017 11:20 AM
To: 'snair@intaspharm.com'
Subject: FDA Information Request- Agreed iPSP- NDA 209604

Importance: High

Dear Ms. Nair,

I am writing to you in follow-up to the March 17, 2017 phone call requesting that a copy of your Agreed iPSP under IND 107393 be formally submitted to the NDA by close of business March 20, 2017. In addition, please email me a Word copy of the Agreed iPSP.

Please confirm receipt of this email.

Thank you!
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎ 301.796.9022 (phone)
anuja.patel@fda.hhs.gov (email)

Secure Electronic Mail

Secure e-mail between CDER and industry is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). Secure e-mail should not be used for formal regulatory submissions (for example, NDAs, INDs, amendments and supplements). For more information on establishing a Secure Electronic Mail link with CDER, contact SecureEmail@fda.hhs.gov.

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/s/

ANUJA PATEL
03/17/2017

From: Steven Kinsley
To: snair@intaspharma.com
Cc: Anuja Patel
Subject: NDA 209604 CMC Information Request 2-28-17
Date: February 28, 2017

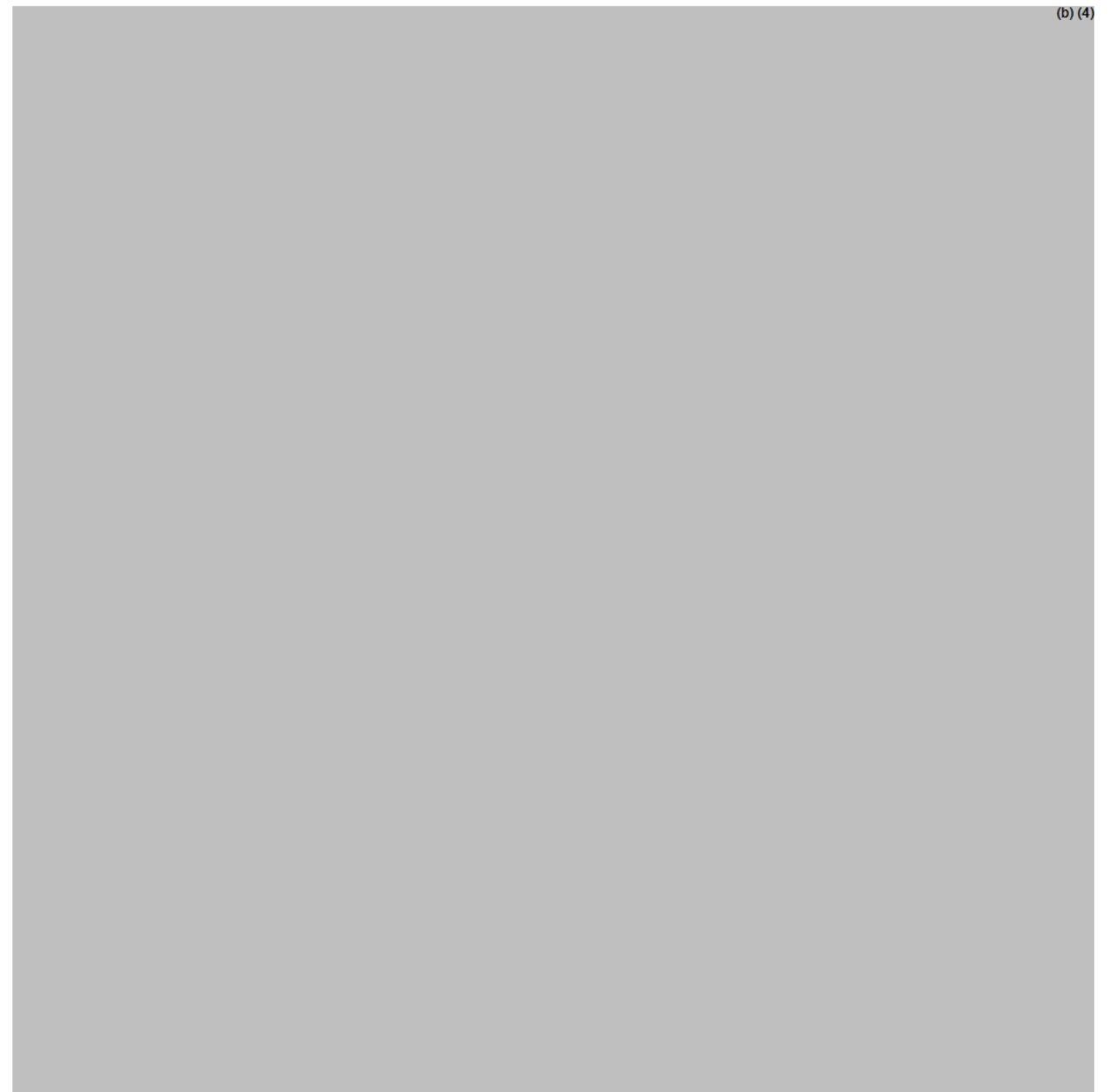
Dear Sabita,

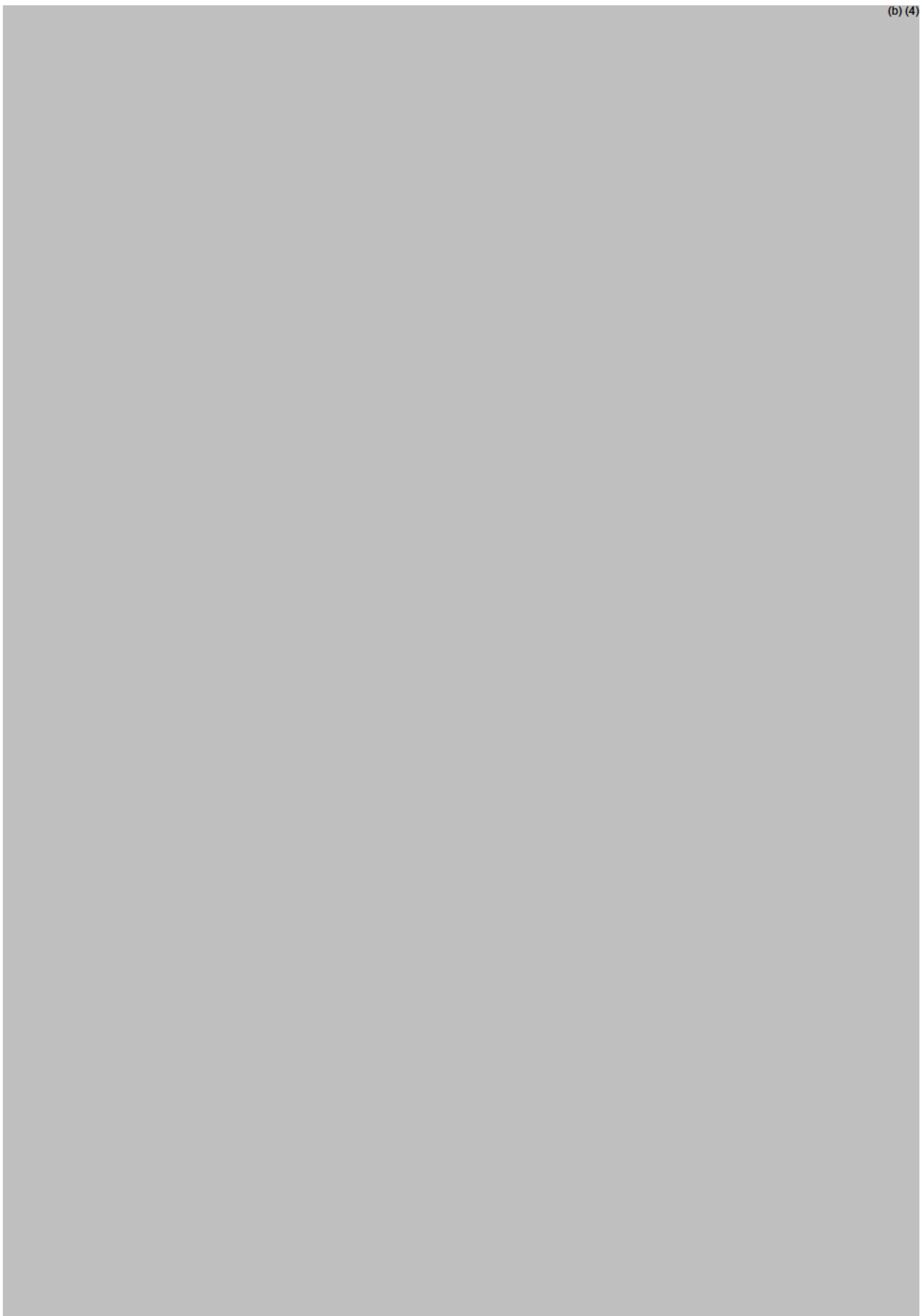
I have received the following information requests from our CMC review team. Please respond to the following with a submission to your NDA by Tuesday, March 21, 2017.

Microbiology

1. The information regarding the Antimicrobial Effectiveness Testing (AET) to demonstrate the efficacy of the preservative system is acknowledged. Please address the following:

(b) (4)





If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

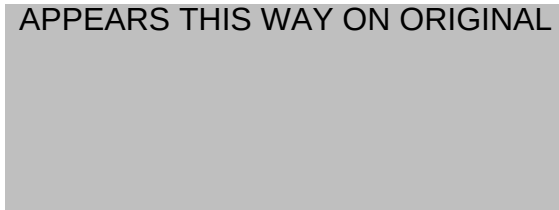
Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

Office of Program and Regulatory Operations
U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov



APPEARS THIS WAY ON ORIGINAL





Steven
Kinsley

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NDA 209604

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Accord Healthcare Inc.
Attention: Sabita Nair
Senior Director, Regulatory Affairs
1009 Slater Road, Suite 210-B
Durham, NC 27703

Dear Ms. Nair:

Please refer to your New Drug Application (NDA) dated October 13, 2016, received October 13, 2016, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for gemcitabine injection, solution for injection, 100 mg/ml.

We also refer to your amendments dated November 9, and 23, 2016.

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 August 13, 2017.

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 July 16, 2017.

At this time, we are notifying you that, we have not identified any potential review issues. Note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified labeling issues and have included our labeling comments and questions for you to address in the attached labeling.

We request that you resubmit labeling (in both redlined (track-changes shown) and clean Microsoft Word formats) that addresses these issues by January 16, 2017. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

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.

PROMOTIONAL MATERIAL

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). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) 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.

REQUIRED PEDIATRIC ASSESSMENTS

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

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

If you have any questions, call Anuja Patel, Regulatory Project Manager, at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

JOSEPH E GOOTENBERG on behalf of PATRICIA KEEGAN
12/16/2016

From: Steven Kinsley
To: snair@intaspharma.com
Cc: Anuja Patel
Subject: NDA 209604 CMC Information Request 11-18-16
Date: November 18, 2016

Dear Ms. Nair,

My name is Steve Kinsley and I am your point of contact for CMC related material for NDA 209604. I have received the following information request from our CMC review team. Please respond to the following with a submission to your NDA by Monday, November 28, 2016.

1. Although you conducted a bioequivalence study and submitted the final report within the NDA, a biowaiver request is included in Application. Please clarify the purpose of "Request for Waiver" section in Module 1.12. It is also pertinent to mention that the section does not specifically state whether or not a waiver of in vivo bioavailability studies is being requested for the drug product.

If you have any questions, contact me. Also, please verify receipt of this Information Request via return e-mail.

Best Regards,
Steve

Steven Kinsley, Ph.D.
Regulatory Business Process Manager

Office of Program and Regulatory Operations
U.S. Food and Drug Administration
Tel: 240-402-2773
Steven.Kinsley@fda.hhs.gov





Steven
Kinsley

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Patel, Anuja

From: Patel, Anuja
Sent: Tuesday, November 08, 2016 1:43 PM
To: Sabita Nair (snair@intaspharma.com)
Subject: FDA Information Request- Contact Information for Sites- NDA 209604 -Gemcitabine Injection 100 mg/mL, 2 mL, 10 mL, 15 mL and 20 mL for intravenous infusion use only

Importance: High

Hi Sabita,

We refer to your new NDA 505b(2) application (NDA 209604)for Gemcitabine Injection 100 mg/mL, 2 mL, 10 mL, 15 mL and 20 mL for intravenous infusion use only

We have the following request for information:

Please provide name of point of contact and contact information, specifically, the phone number and email address for the following:

- 1. Srinivasam Cancer Care
Hospitals India Pvt. Ltd.
236/1, Vijayashree Layout,
Arekere, Bannerghatta Main Road,
Bangalore - 560 076, Karnataka, India
Clinical Investigator: Dr. K. C. Lakshmaiah**
- 2. Nirmal Hospital Pvt Ltd.
Ring Road, Civil Street, Near
Kadiwala School, Surat - 395002, Gujarat, India
Clinical Investigator: Dr. Jayanti G Patel**
- 3. City Cancer Centre
33-25-33, Ch. Venkata
Krishnayya Street, Suryarao Pet,
Vijayawada -520002,
Andhra Pradesh, India
Clinical Investigator: Dr. Gopichand Mamillapalli**
- 4. Meenakshi Mission Hospital and Research Center
Lake Area, Melur Road, Madurai-625107,
Tamil Nadu, India
Clinical Investigator: Dr. Ananda Selvakumar**
- 5. Unique Hospital Multispeciality & Research Institute
Opp. Kiran Motor, Nr. Canal, Civil Char Rasta,
Sosyo Circle Lane, Surat -395002,
Gujarat, India
Clinical Investigator: Dr. Tanveer Mohibbhai Maksud**
- 6. Curie Manavta Cancer Center
Opp. Mahamarg Bus Stand,**

**Mumbai Naka, Nasik - 422004,
Maharashtra, India
Clinical Investigator: Dr. Rajnish Vasant Nagarkar**

A response (e-mail) is requested by close of business, November 9, 2016. Please confirm receipt and submit your response formally to the NDA.

Regards,
Anuja

Anuja Patel, MPH
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology & Oncology Products, CDER, FDA
White Oak Complex, Bldg. 22, Room 2365
10903 New Hampshire Avenue
Silver Spring, MD 20993
☎ 301.796.9022 (phone)
301.796.9872 (fax)
anuja.patel@fda.hhs.gov (email)

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/s/

ANUJA PATEL
11/08/2016

**Initial Planning Meeting Agenda
October 31, 2016**

NDA 209604/0

Product: Gemcitabine Injection, solution for injection, 100 mg/ml
Submission Date: October 13, 2016
Received Date: October 13, 2016
Sponsor: Accord Healthcare Inc.

Link to NDA submission:

(SDN 0) EDR Location: <\\CDSESUB1\evsprod\NDA209604\209604.enx>

Proposed Indications:

“Gemcitabine Injection is a nucleoside metabolic inhibitor indicated:

- in combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy;
- in combination with paclitaxel, for first-line treatment of metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated;
- in combination with cisplatin for the treatment of non-small cell lung cancer; and
- as a single agent for the treatment of pancreatic cancer.”

Review Team/Collaborators for NDA 209604/0:

(* denotes attendee at planning meeting)

Office of New Drugs Review Team:

*Joseph Gootenberg, Deputy Director DOP2, Signatory
*Anuja Patel, Sr. Regulatory Health Project Manager, DOP 2
*Monica Hughes, CPMS, DOP 2
*Lee Pai-Scherf, Medical Officer, DOP 2
*Gideon Blumenthal, CDTL, DOP 2
*Stephanie Aungst, Nonclinical Reviewer, DHOT, OHOP
*Whitney Helms, Nonclinical TL, DHOT, OHOP
* Jennie Change, Safety Labeling Reviewer

Office of Clinical Pharmacology

*Edwin Chow, Clinical Pharmacology Reviewer
*Jeanne Fourie Zirkelbach, Clinical Pharmacology Team Leader

Office of Product Quality Review Team:

*Steven Kinsley, RHBPM, OPRO
*Paresma Patel, Drug Product (DP) Reviewer
*Anamitro Banerjee, DP, Branch Chief
*Haripada Sarkar, Drug Substance (DS) Reviewer
*Kasturi Srinivasachar, DS, Branch Chief
*Yarery Smith, Primary CMC Micro Reviewer
Jesse Wells, Secondary CMC Micro Reviewer
*John Arigo, CMC Micro Branch Chief
Wendy Zhang, Primary Facility Reviewer

Christina Cappaci-Daniel, Secondary Facility Reviewer
*Huiquan Wu, Process Reviewer
*Rakhi Shah, Process Review Branch Chief
*Parnali Chatterjee, Primary Biopharmaceutics Reviewer
*Okpo Eradiri, Biopharmaceutics Team Leader

Office of Safety Evaluation Review Team:

Latonia Ford, OSE RPM
Otto Townsend, OSE/DMEPA
Chi-Ming (Alice) Tu, OSE/DMEPA (TL)
Steve Bird, DEPI TL
Afrouz Nayerma, DPV TL

*A standard **reminder** that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss.

Regulatory Background

Gemcitabine Injection, is a sterile, clear, colorless to pale yellow solution in a multi-dose clear glass vial formulated as 100 mg/mL gemcitabine freebase with USP/NF grade PEG-300, propylene glycol and dehydrated alcohol. Sodium hydroxide and hydrochloric acid are added to obtain pH (b) (4). Clinical presentations are 2 mL, 10 mL, 15 mL and 20 mL vials with (b) (4) stopper and color-coded (b) (4). Drug product is intended to be admixed with 0.9% sodium chloride, USP for intravenous infusion over 30 minutes.

The Listed Drug (LD) for the proposed 505 (b)(2) application is GEMZAR® [Gemcitabine for Injection (Lyophilized)], a product of Eli Lilly and Company Limited, USA.

The proposed formulation differs from the formulation of the LD in terms of its form (ready to use formulation as compared to the lyophilized formulation of the LD).

IND 107393 was first submitted on October 17, 2011, with clinical study # 655-10, entitled “A Multi-Center, Randomized, Open-Label, Two-Period, Two-Treatment, and Two-Way Crossover, Single Dose Bioequivalence Study Comparing Gemcitabine Injection (Manufactured by Intas Pharmaceuticals Ltd.) to the reference listed drug Gemzar injection (Eli Lilly and Co) in patients with Pancreatic or Ovarian Cancer”, intended to support a 505(b)(2) application for Gemcitabine Injection. A summary of the study results submitted on July 2014 with the IND Annual Report (amendment 11) indicated that the study failed to meet the bioequivalence acceptance criteria. On August 19, 2013, Accord submitted a second bioequivalence (BE) protocol, study # 311-13 (b) (4)

Refer to DARRTS IND 107393 for detailed regulatory history, including advice letters and issued communications.

Agenda Items:

1. **Review Status:**
 - a. Standard 10 Month Review
 - b. Categorical Exclusion requested
 - c. Requested for Waiver from in vivo Bioequivalence Studies
 - d. Requested full waiver of pediatric studies

Discussion: The RPM suggested that the team review previous communications under IND 107 393 in regards to previous communications regarding the BE protocol submitted with this application. The team acknowledged applicant's request for waiver but determined that the need for a waiver was not applicable because a solubilizing agent is present in the proposed drug product. The biowaiver request in the application is redundant because the BE study was conducted and is included in the submission.

The team identified that the submission only contained summary PK reports. Whether this will be considered a filing issue will be discussed internally within OCP and an update will be provided at the filing meeting.

2. **Dates Milestone Letters Must Issue**

Discussion: The team acknowledged the timeline below and will update calendar with planned leave for the holiday. The team agreed that application will mostly be reviewed by OPQ and per the MOUs the CDTL will be identified by OPQ and communicated to the OND RPM.

Milestone	Standard review 10-month PDUFA review	Comments
Application Received	October 13, 2016	
Acknowledgment Letter	October 27, 2016	Issued October 28, 2016
Planning Meeting (Day 45)	Planner Target Date: Monday, November 10, 2016	Held October 31, 2016
Filing Meeting	Planner Target Date: November 27, 2016	Scheduled for Thursday, November 17, 2016 due to holidays
Filing Action Letter (Day 60) (Inform applicant of review designation, filing determination) •Do we have any filing issues that we should discuss today? •Do we need to have teleconference with the Applicant before the filing meeting? •If the filing issues are not identified, we will need to send a "Notification of Review Status/Priority Review Determination" letter.	PDUFA DATE: Monday, December 12, 2016	Planned date is November 21, 2016

Milestone	Standard review 10-month PDUFA review	Comments
Deficiencies Identified Letter (74 Day Letter)	Planner Target Date: Monday, December 26, 2016 (HOLIDAY)	<i>Planned date is December 19, 2016 due to holiday</i>
Hold Mid-Cycle Meeting	Planner Target Date: Monday, March 13, 2017	<i>Scheduled for Thursday, March 16, 2017</i>
Hold Wrap-Up meeting	Planner Target Date: Sunday, July 9, 2017	<i>Scheduled for Monday, June 19, 2017</i>
Send proposed labeling to applicant (with 1 week response)	Planner Target Date: Sunday, July 16, 2017	Actual Due Date: Friday, June 16, 2017 *scheduled earlier to allow for negotiations
Review Target Due Dates: <i>Primary Review Due</i> <i>Secondary Review Due</i> <i>CDTL Review Due (OPQ)</i> <i>Deputy Director Review Due</i>	Planner Target Dates: Sunday, July 9, 2017 Sunday, July 16, 2017 Sunday, July 23, 2017 August 13, 2016	Actual Due Dates: Friday, July 7, 2017 Friday, July 14, 2017 Friday, July 21, 2017
Compile and circulate Action Letter and Action Package	Planner Target Date: Sunday, July 23, 2017	Actual Due Date: Friday, July 21, 2017
FINAL Action Letter Due	Planner Target Date: Sunday, August 13, 2017	Actual Due Date: Friday, August 11, 2017

3. **Consults to be requested per discussion during meeting**
- *OPDP- consult uploaded in DARRTS 11/1/2016*
 - *OSE-consult uploaded in DARRTS 11/1/2016*

- *PeRC/ Pediatrics- PeRC meeting scheduled for March 8, 2017; meeting materials due 2 weeks prior to PERC meeting.*
- *OSIS- consult uploaded 11/8/2016*
- *OSI- No OSI consult is needed for this application.*

4. Upcoming/TBD Internal Team Meetings:

- a. **Filing Meeting:** Scheduled for Thursday, November 17, 2016
- Please bring Filing review and Interim Deliverables
 - Please be prepared to identify and discuss significant filing issues for either a day 60 or a day 74 letter.

Discussion: Labeling Reviewer's Preliminary edits to the PI will be posted on sharepoint for disciplinary review by November 21, 2016. The team agreed to include any additional edits as time permits. The labeling with FDA proposed edits will be sent to applicant with Day 60 or 74 letter.

- b. **Mid-Cycle Meeting:** TBD
- Discuss how long the internal meeting needs to be and who will need to be present
 - Slides to CDTL 1 week prior to mid-cycle

Discussion: RPM stated that the Midcycle meeting will be scheduled this week.

- c. **Labeling Meetings (refer to suggested section groupings):**
- When should we begin labeling meetings?
 - **Labeling submitted in the application included:**
Draft PI Labeling (Word)
Annotated PI in comparison with LD PI
Container Label/Carton: 2ml pack, 10mL pack, 15mL pack, 20 mL pack

Discussion: During the meeting, the labeling reviewer stated that the package insert for the LD for updated June 2014; therefore the proposed draft labeling should be very similar to the PLLR format. Nevertheless, the labeling reviewer will review the submitted labeling for PLR and PLLR compliance.

The team agreed to scheduling labeling meeting end May/early June 2017.

- d. **Team Meetings:** Do we want to schedule once per month?

Discussion: OPQ will review the application and if clinical consult is needed, the RHBPM will inform the OND RPM and include the OND review team members in meetings as needed.

- e. **Wrap- Up Meeting:** TBD

Discussion: RPM stated that the Wrap up meeting will be scheduled.

8. Miscellaneous Items or Issues:

- Status of OSIS inspections
- Status of facility review inspections

*Discussion: Both inspections are pending as of date of the planning meeting.
OND RPM will be the primary contact for the OSIS inspection within OND and
RHBPM will be the primary contact for the facility inspections.*

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/s/

ANUJA PATEL
11/08/2016



NDA 209604

NDA ACKNOWLEDGMENT

Accord Healthcare Inc.
Attention: Sabita Nair
Senior Director, Regulatory Affairs
1009 Slater Road, Suite 210-B
Durham, NC 27703

Dear Ms. Nair:

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: gemcitabine injection, solution for injection, 100 mg/ml

Date of Application: October 13, 2016

Date of Receipt: October 13, 2016

Our Reference Number: NDA 209604

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 December 12, 2016, 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 Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Ms. Anuja Patel, Senior Regulatory Health Project Manager, at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Monica Hughes, M.S.
Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

MONICA L HUGHES
10/28/2016



IND 107393

MEETING MINUTES

Accord Healthcare, a wholly owned subsidiary of Intas Pharmaceuticals
Attention: Sabita Nair
Director, Regulatory Affairs
1009 Slater Road, Suite 210-B
Durham, NC 27703

Dear Ms. Nair:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Gemcitabine injection, 100 mg/mL.

We also refer to the teleconference between representatives of your firm and the FDA on September 1, 2015. The purpose of the meeting was to discuss the completeness and appropriateness of the submitted information intended to support NDA approval.

A copy of the official minutes of the teleconference 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) 796-9022.

Sincerely,

{See appended electronic signature page}

Anuja Patel, M.P.H.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: Tuesday, September 1, 2015 from 12 Noon to 1:00 PM, EST
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Room 1309

Application Number: IND 107393
Product Name: Gemcitabine
Indication: All approved indications for Gemzar
Sponsor/Applicant Name: Accord Healthcare, a wholly owned subsidiary of Intas Pharmaceuticals
Regulatory Pathway: 505(b)(2) of the Public Health Service Act

Meeting Chair: Dr. Joseph Gootenberg
Meeting Recorder: Anuja Patel

FDA ATTENDEES

Division of Oncology Products 2 (DOP 2), OHOP

Joseph Gootenberg, M.D., Deputy Division Director
Anuja Patel, M.P.H., Senior Regulatory Health Project Manager
Idara Udoh, M.S., Senior Regulatory Health Project Manager
Gideon Blumenthal, M.D., Clinical Team Leader
Lee Pai-Scherf, M.D., Clinical Reviewer

Office of Surveillance and Epidemiology (OSE), Division of Medication Error Prevention and Analysis (DMEPA)

Alice Tu-Chi Ming, Pharm. D., Safety Team Leader, OSE, DMEPA

Office of Product Quality (OPQ)

Olen Stephens, Ph.D., Branch Chief, Office of Product Quality

Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP)

Hong Zhao, Ph.D., Clinical Pharmacology Team Leader
Jun Yang, Ph.D., Clinical Pharmacology Reviewer

SPONSOR ATTENDEES

Sabita Nair, Senior Director, Regulatory Affairs, Accord Healthcare Inc.
Darshit Patel, Assistant General Manager, Regulatory Affairs, Accord Healthcare Inc.
Kanishka Pathak, Manager, Regulatory Affairs, Accord Healthcare Inc.
Ashish Sehgal, Senior Vice President, Formulation Development, Intas Pharmaceuticals Ltd.
Sanjay Shrivastava, Senior Vice President, Regulatory Affairs, Intas Pharmaceuticals Ltd.

BACKGROUND

The Listed Drug (LD) for the proposed 505 (b)(2) application is GEMZAR® [Gemcitabine for Injection (Lyophilized)], a product of Eli Lilly and Company Limited, USA.

Gemcitabine Injection, developed by Intas, is a sterile, clear, colorless to pale yellow solution in a multi-dose clear glass vial formulated as 100 mg/mL gemcitabine freebase with USP/NF grade PEG-300, propylene glycol and dehydrated alcohol. Sodium hydroxide and hydrochloric acid are added to obtain pH (b) (4). Clinical presentations are 2 mL, 10 mL, 15 mL and 20 mL vials with (b) (4) stopper and color-coded (b) (4). Drug product is intended to be admixed with 0.9% sodium chloride, USP for intravenous infusion over 30 minutes. The proposed formulation differs from the formulation of the LD in terms of its form (ready to use formulation as compared to the lyophilized formulation of the LD).

The LD is available in sterile single-dose vials of white lyophilized powder intended to be reconstituted with 0.9% sodium chloride solution followed by dilution with 0.9% sodium chloride solution for intravenous infusion.

Accord lists the following indications in section 3.3, page 8 of the meeting package:

- Ovarian Cancer: Gemcitabine for Injection in combination with carboplatin is indicated for the treatment of patients with advanced ovarian cancer that has relapsed at least 6 months after completion of platinum-based therapy.
- Breast Cancer: Gemcitabine for Injection in combination with paclitaxel is indicated for the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.
- Non-Small Cell Lung Cancer: Gemcitabine for Injection is indicated in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB), or metastatic (Stage IV) non-small cell lung cancer.
- Pancreatic Cancer: Gemcitabine for Injection is indicated as first-line treatment for patients with locally advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas. Gemcitabine for Injection is indicated for patients previously treated with 5-FU.

Regulatory Background

IND 107393 was first submitted on October 17, 2011, with clinical study # 655-10, entitled “A Multi-Center, Randomized, Open-Label, Two-Period, Two-Treatment, and Two-Way Crossover, Single Dose Bioequivalence Study Comparing Gemcitabine Injection (Manufactured by Intas Pharmaceuticals Ltd.) to the reference listed drug Gemzar injection (Eli Lilly and Co) in patients with Pancreatic or Ovarian Cancer”, intended to support a 505(b)(2) application for Gemcitabine Injection. The study was a multi-center, randomized, open-label, two-period, two-treatment, two-way crossover, single dose bioequivalence study to evaluate the bioavailability of the test product in comparison to the LD, Gemzar. The primary objective was to characterize the pharmacokinetic profile of Intas test formulation relative to that of Gemzar in patients and to assess the bioequivalence. The study proposed to [REDACTED] (b) (4)

[REDACTED] The study was found to be acceptable and was allowed to proceed on November 17, 2011.

A summary of the study results submitted on July 2014 with the IND Annual Report (amendment 11) indicated that the [REDACTED] (b) (4)

On August 19, 2013, Accord submitted a second bioequivalence (BE) protocol, study # 311-13 [REDACTED] (b) (4)

1. Clear specification in the protocol that gemcitabine infusion has to be completed within the specified time of 30 minutes (+5 min), patient data will be excluded from analysis if there is any deviation from the specified infusion time; and

2. Study sample size would be based on an adaptive sequential design (b) (4). The initial planned sample size (stage-I) was to be 44 patients based on the following assumptions: T/R ratio: 88.00 – 112.00%; intra patient variability: 16%; power $\geq$ 80%. The final sample size (stage-II) was to be decided based on the intra-patient variability and the point estimate for the ratio of the test and reference products obtained from stage-I. The proposed adaptive sequential design was based initially on (b) (4).
(b) (4)
These designs were considered unacceptable by the FDA (b) (4).

On August 6, 2014, a teleconference was held between FDA and Accord concerning the acceptability of the study design and the overall development plan for study #311-13. Accord stated that the study was open for accrual and estimated that approximately 44 patients would be enrolled by the end of October 2014. FDA informed Accord that an agreement concerning the sample size re-estimation for the new protocol # 311-13 had not been reached, and that the (b) (4) was not acceptable, since (b) (4).

On October 29, 2014, FDA issued an Advice letter containing advice that neither the proposed (b) (4) was acceptable. This Advice letter provided reference to the appropriate FDA Guidance for Industry to aid Accord in the development of Gemcitabine injection following the 505 (b)(2) pathway.

On December 17, 2014, Accord submitted a Type C Written Response Only meeting request to seek guidance regarding a path forward for the ongoing bioequivalence study 311-13, entitled “A Multicenter, Randomized, Open-Label, Two-Period, Two-Treatment, Two-Way Crossover, Single Dose Bioequivalence Study Comparing Gemcitabine Injection 100 mg/ml (manufactured by Intas Pharmaceuticals Ltd) to the Listed Drug Gemzar 1g/vial (Lilly USA, LLC) in Patients with Pancreatic or Ovarian Cancer”. Results from study 311-13 are intended to support a 505(b)(2) application for Gemcitabine Injection, manufactured by Intas, LD. Intas stated that the expiry date of the LD (Gemzar 1 g/vial) used in study 311-13 was October 2014, and that only 30 out of 44 planned patients in stage-I of the study have been enrolled.

On March 3, 2015, FDA issued final written response and also asked the sponsor to address the issue of controlling type I error rate in the sample size re-estimation.

On March 20, 2015, Accord submitted an amendment in response to FDA’s March 3, 2015, final written response and to FDA’s October 29, 2014, Advice letter for their amended bioequivalence protocol # 311-13. The amendment also contained a request for initial pediatric study plan (iPSP) waiver; however the format of the request did not follow the requirements as outlined in FDA’s March 3, 2015, letter.

On June 8, 2015, FDA held an informal teleconference an update on study # 311-13 and to confirm that they intend to stop enrolling patients with the present 30 patients, as indicated in their March 20, 2015, amendment, and that Accord will analyze the data based on Option 2 of our March 3, 2015, minutes. Accord acknowledged and confirmed that the data will be analyzed with the 30 patients and that no new patients will be enrolled. FDA further instructed Accord to include in their NDA application a detailed regulatory history and an overall summary with top line data for both BE studies conducted under the IND.

On July 8, 2015, Accord Healthcare Inc., a wholly owned subsidiary of Intas Pharmaceuticals Ltd, submitted a Type B, pre-NDA meeting to discuss the completeness and appropriateness of the submitted information intended to support NDA approval.

On July 20, 2015, FDA contacted Accord via phone and requested clarification regarding the relationship between Accord Healthcare and Intas Pharmaceuticals, Ltd. Accord informed FDA that the July 8, 2015 meeting request was submitted by Accord Healthcare, a wholly owned subsidiary of Intas Pharmaceuticals, and the forthcoming NDA will also be submitted by Accord Healthcare. An amendment was submitted on July 21, 2015, and received on July 22, 2015.

On July 28, 2015, FDA issued an Advice letter to Accord reiterating the agreements made during the June 8, 2015, teleconference and reminded Accord that Accord must submit an Initial Pediatric Study Plan (iPSP) no less than 210 days prior to submission of the 505(b)(2) marketing application for Gemcitabine injection and that failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

On August 18, 2015, FDA sent an email communication requesting specific questions regarding eCTD questions for FDA response. Accord emailed their response with questions on August 20, 2015. The formal submission, dated August 21, 2015, was received on August 24, 2015.

Product Quality

The proposed product, Gemcitabine Injection 100 mg/mL, is a ready to use solution for injection, whereas the LD is a lyophilized powder for injection. Accord intends to reference product quality information for the gemcitabine hydrochloride drug substance through DMF (b) (4), held by (b) (4). (u) (4) is listed as the intended commercial manufacturing and testing site. The proposed product is formulated with (b) (4) and (u) (4). The product strengths will be supplied in Type I glass containers with (u) (4) rubber stoppers (b) (4) as given below. (b) (4)

- 2 mL vial [200 mg / 2 mL]
- 10 mL vial [1 g / 10 mL]
- 15 mL vial [1.5 g / 15 mL]
- 20 mL vial [2 g / 20 mL]

The meeting package contains an extensive description of formulation development and manufacturing process development:



Summary of Bioequivalence Studies

Intas provided the following table to summary the results of study # 311-13. The analysis results obtained in 30 subjects appear to meet the bioequivalence criteria (80 -125%) with respect to C_{max} , AUC_{0-t} and AUC_{inf} for gemcitabine.

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Patient CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%			
$\ln C_{max}$	28.028	26.773	104.7	94.13 - 116.43	24.4	96.4
$\ln AUC_{0-t}$	14.363	13.281	108.1	101.43 - 115.30	14.6	100.0
$\ln AUC_{0-\infty}$	14.496	13.328	108.8	101.83 - 116.17	14.7	100.0

FDA sent Preliminary Comments to Accord on August 28, 2015. Accord responses to the FDA Preliminary Comments were received via email on August 31, 2015, and Accord informed the FDA that they would like to convert the meeting format from a face to face to a teleconference. FDA responded via email on August 31, 2015 to converting the meeting format to a teleconference.

DISCUSSION OF SPONSOR QUESTIONS AND FDA RESPONSES

Product Quality

1. In this NDA application, can the applicant propose an additional batch size for the commercial which would be within (b) (4) of the exhibit batch size?

FDA Preliminary Response sent August 28, 2015: Yes, a (b) (4) from the registration batches can be acceptable with appropriate supportive data. In the NDA submission, describe differences in equipment type and scale that will be used in the proposed commercial process and provide a risk assessment regarding the planned scale-up activities.

Accord's Response received via e-mail on August 31, 2015: Accord acknowledged and accepted the FDA's response.

Discussion during teleconference: No discussion occurred.

2. If the above proposal is acceptable, can the Agency provide any recommendations on the amount of data needed to support the new batch size?

FDA Preliminary Response sent August 28, 2015: The formulation and manufacturing process are appropriate for the subject drug product described in the NDA. Please address the following comments in the NDA submission:

a

(b) (4)



Accord's Response received via e-mail on August 31, 2015: Accord acknowledged and accepted the FDA's response.

Discussion during teleconference: No discussion occurred.

b.



Accord's Response received via e-mail on August 31, 2015: Accord acknowledged and accepted the FDA's response.

Discussion during teleconference: No discussion occurred.

- c. FDA refers Accord to the literature source, "The degradation of the antitumor agent gemcitabine hydrochloride in an acidic aqueous solution at pH 3.2 and identification of degradation products, 885 - 891, Vol 89, No 7, July 2000, J. of Pharm. Sci." (b) (4)



The analytical methods are not described in the meeting package and common HPLC methods for gemcitabine do not monitor for degradants at (b) (4). Regarding the stability data and in-use data used to support the dilution study, provide data in the NDA to demonstrate these impurities are monitored and controlled. Alternatively, provide a risk based justification, supported by data, to omit control of these degradants in the drug product.

Accord's Response received via e-mail on August 31, 2015: Accord acknowledged and accepted the FDA's response.

Discussion during teleconference: No discussion occurred.

- d. In the NDA submission, provide batch data to demonstrate elemental impurity levels do not exceed corresponding PDE levels as per ICH Q3D or USP <232>. Include a risk assessment that demonstrates an understanding of the potential sources of elemental impurities [REDACTED] (b) (4)
[REDACTED] Alternatively, include testing and control for elemental impurities in the proposed drug product specification.

Accord's Response received via e-mail on August 31, 2015: Accord acknowledged and accepted the FDA's response.

Discussion during teleconference: No discussion occurred.

- e. Additional information that may be submitted in the NDA can be found in the November 1994, "Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" available at:
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf>

Accord's Response received via e-mail on August 31, 2015: Accord acknowledged and accepted the FDA's response.

Discussion during teleconference: No discussion occurred.

Regulatory- Initial Pediatric Study Plan (iPSP) Waiver

3. As Gemcitabine Injection 100 mg/mL is not intended to be used in the pediatric population, the applicant is proposing to request for a waiver from conducting the studies. Therefore in this context, can the applicant waive off the requirement of submission of an Initial Pediatric Study Plan (iPSP) no less than 210 days prior to submission of 505(b)(2) marketing application? Can the applicant propose to submit a waiver request for the pediatric study plan along with the 505(b)(2) NDA submission?

FDA Preliminary Response sent August 28, 2015: Refer to FDA Advice letter sent on July 28, 2015 and to the March 3, 2015, written response only meeting minutes. As stated in these written communications under the Food and Drug Administration Safety and Innovation Act (FDASIA), Accord must submit an Initial Pediatric Study Plan (iPSP) no less than 210 days prior to submission of a 505(b)(2) marketing application for

Gemcitabine injection. The iPSP must contain an outline of the pediatric study or studies that Accord plans to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. Submit the iPSP in PDF and Word format. Failure to include an agreed-upon iPSP with a marketing application could result in a refuse to file action. In addition, Accord may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov.

For further guidance on pediatric product development, please refer to the FDA webpage entitled "Pediatric Product Development" found at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

Accord's Response received via e-mail on August 31, 2015: Accord needed further guidance on Initial Pediatric Study Plan (iPSP) template for iPSP waiver request, specifically on the completion of the iPSP.

Discussion during teleconference: FDA referred to the *Guidance for Industry Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* that was provided as an attachment with the Preliminary Comments sent August 28, 2015. Accord requested clarification regarding information to include in their iPSP as in Appendix 2 of the guidance. FDA addressed each item in Appendix 2 and Accord stated that their understanding of the requirements and acknowledged that the iPSP should be submitted no less than 210 days prior to submission of 505(b)(2) marketing application

4. The applicant requests to obtain the Agency's agreement with the proposals intended to support 505 (b) (2) NDA approval for the proposed product.

FDA Preliminary Response sent August 28, 2015: FDA agrees that Accord's proposals for the content of the proposed 505(b)(2) NDA appear reasonable; however, final determination of the sufficiency of the contents will be made during review of the NDA.

Accord's Response received via e-mail on August 31, 2015: Accord acknowledged and accepted the FDA's response.

Discussion during teleconference: No discussion occurred

ADDITIONAL FDA COMMENTS

Additional Carton and Container Labeling Comments:

5. In the NDA submission, include a plan to mitigate the potential risk of overdose due to concentration confusion (38 mg/mL vs. 100 mg/mL) if the proposed 100 mg/mL concentration gemcitabine product is introduced to the market.

Accord's Response received via e-mail on August 31, 2015: Accord requested further guidance on the risk assessment parameters to be included in the plan as proposed by the Agency.

Discussion during teleconference: Accord acknowledged FDA advice that labeling would have to be strength prominent. Among the strategies to make the label strength prominent, Accord will use color differentiation. The label and vial label would be reviewed after the NDA submission. FDA proposed, if feasible, to review other 505b(2) applications that proposed differing concentrations and provide post meeting comments.

FDA Post Meeting Follow-up Comment: Following FDA review of other 505b(2) applications, FDA refers to discussion under Question 5 and has no additional post-meeting comments to add.

6. Prior to the face to face meeting, provide a statement whether the four vial presentations planned to be marketed (200 mg/2 mL, 1 g/10 mL, 1.5 g/15 mL, and 2g/20 mL) are single or multiple dose vials.

Accord's Response received via e-mail on August 31, 2015: Accord herewith provides a statement that four vial presentations (200 mg/2 mL, 1 g/10 mL, 1.5 g/15 mL, and 2g/20 mL) are multiple dose vials.

Discussion during teleconference: FDA acknowledged Accord's response that four vial presentations (200 mg/2 mL, 1 g/10 mL, 1.5 g/15 mL, and 2g/20 mL) are multiple dose vials. No further discussion occurred.

Additional Clinical Pharmacology Comments:

Address the following clinical pharmacology recommendations in the NDA submission:

7. Submit bioanalytical method(s) and validation reports for clinical pharmacology and biopharmaceutics studies.

Accord's Response received via e-mail on August 31, 2015: Accord acknowledged and accepted the FDA's response.

Discussion during teleconference: No discussion occurred.

8. Provide complete datasets for clinical pharmacology and biopharmaceutics studies. Provide all concentration-time and derived pharmacokinetic (PK) parameter datasets as SAS transport files (*.xpt). Provide a description of each data item in a Define.pdf file. Flag and maintain in the datasets any concentrations and/or subjects that have been excluded from the analysis.

Accord's Response received via e-mail on August 31, 2015: Accord acknowledged and accepted the FDA's response.

Discussion during teleconference: No discussion occurred.

Additional eCTD questions were submitted by Accord via e-mail on August 20, 2015. The formal amendment was received on August 25, 2015.

9. Proposed 505(b)(2) eCTD Application will be based on eCTD specification of ICH DTD version 3.2 & Style sheet Type "ectd-2-0.xml" and FDA US Regional DTD version 2.01 and Style sheet Type "us-regional.xml". Is this acceptable for the proposed 505(b)(2) application?

FDA Preliminary Response sent August 28, 2015: Yes. Accord's proposal is acceptable.

Accord's Response received via e-mail on August 31, 2015: Accord acknowledged and accepted the FDA's response.

Discussion during teleconference: No discussion occurred.

10. For validation of proposed 505(b)(2) eCTD Application, we will follow FDA's Specifications for eCTD Validation Criteria Version 3.0. Is this acceptable?

FDA Preliminary Response sent August 28, 2015: Yes. Accord's proposal is acceptable.

Accord's Response received via e-mail on August 31, 2015: Accord acknowledged and accepted the FDA's response.

Discussion during teleconference: No discussion occurred.

11. In Module 5 of proposed 505(b)(2) eCTD Application, we will submit M5.3.1.2 for Comparative BA/BE Study Reports & 5.3.1.4 for Reports of Bioanalytical and Analytical Methods in two separate Study Tagging File as per FDA specification. Would this be acceptable?

FDA Preliminary Response sent August 28, 2015: Yes, with each study having its own STF

Accord's Response received via e-mail on August 31, 2015: Accord acknowledged and accepted the FDA's response.

Discussion during teleconference: No discussion occurred.

12. In Module 2 of proposed 505(b)(2) eCTD Application, we will submit PDF format and MS Word format consolidated BE summary tables (Table 1 to 4, 6 to 17) instead of submitting separate section 2.7.1 (2.7.1.1, 2.7.1.2, 2.7.1.3, 2.7.1.4) & 2.7.4 (2.7.4.1.3, 2.7.4.2.1.1). Is this acceptable?

FDA Preliminary Response sent August 28, 2015: Yes, with clear leaf titles that includes the table numbers (e.g. BE summary tables 1-4, or something similar).

Accord's Response received via e-mail on August 31, 2015: Accord acknowledged and accepted the FDA's response.

Discussion during teleconference: No discussion occurred.

13. For the navigation of PDF documents in proposed 505(b)(2) eCTD Application, what are the Agency's expectations on Bookmarks and Hypertext links?

FDA Preliminary Response sent August 28, 2015: Please refer to Pages 5 and 6 of the PDF Specification, under "Document Navigation" heading, located at:
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163565.pdf>

Accord's Response received via e-mail on August 31, 2015: Accord acknowledged and accepted the FDA's response.

Discussion during teleconference: No discussion occurred.

PREA REQUIREMENTS

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an end-of-phase 2 meeting, you should submit the initial PSP as early as practicable but before the initiation of any phase 3 studies, or any combined phase 2 and phase 3 study, of the drug that is the subject of the initial PSP. If a phase 3 study, or a combined phase 2 and phase 3 study, will not be conducted, the sponsor should submit the initial PSP no later than 210 calendar days before the marketing application is submitted. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>

In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled "Position on Use of SI Units for Lab Tests" found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

505(b)(2) REGULATORY PATHWAY

The Division recommends 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 draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), 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 that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, 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 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, in part, 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 or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
<i>4.</i>	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

ACTION ITEMS

Action Item/Description	Owner	Due Date
If feasible, review other 505b(2) applications that proposed differing concentrations and provide post meeting comments to sponsor	FDA	Completed (please refer to Post Meeting Follow-up Comment under Question 5)
Submit the initial PSP no later than 210 calendar days before the marketing application is submitted	Sponsor	To be determined by Sponsor

ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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

/s/

ANUJA PATEL
09/23/2015



IND 107393

**MEETING REQUEST-
WRITTEN RESPONSES**

Intas Pharmaceuticals Limited
Attention: Sabita Nair
Director, Regulatory Affairs
1009 Slater Road, Suite 210-B
Durham, NC 27703

Dear Ms. Nair:

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

We also refer to your submission submitted December 17, 2014, received December 18, 2014, containing a Type C Written Response Only meeting request. The purpose of the requested meeting is to seek guidance for an issue relating to an expired reference product for your bioequivalence study.

Further reference is made to our Meeting Granted letter dated January 7, 2015, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your January 23, 2015, background package, received on January 27, 2015.

If you have any questions, call me at (301) 796-9022.

Sincerely,

{See appended electronic signature page}

Anuja Patel, M.P.H.
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Written Responses



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: Type C Written Response Only
Meeting Category: Guidance

Application Number: IND 107393 505b(2)
Product Name: Gemcitabine
Indication: All approved indications for Gemzar

Sponsor/Applicant Name: Intas Pharmaceuticals Ltd
Regulatory Pathway: 505(b)(2) of the Public Health Service Act

1.0 BACKGROUND

On December 17, 2014, Intas Pharmaceuticals Ltd (Intas) submitted a Type C Written Response Only meeting request to seek guidance regarding a path forward for the ongoing bioequivalence study 311-13, entitled “A Multicenter, Randomized, Open-Label, Two-Period, Two-Treatment, Two-Way Crossover, Single Dose Bioequivalence Study Comparing Gemcitabine Injection 100 mg/ml (manufactured by Intas Pharmaceuticals Ltd) to the Listed Drug Gemzar 1g/vial (Lilly USA, LLC) in Patients with Pancreatic or Ovarian Cancer”. Results from study 311-13 are intended to support a 505(b)(2) application for Gemcitabine Injection, manufactured by Intas, as an alternative to the Listed Drug (LD) Gemzar® for Injection (Gemcitabine Hydrochloride). Intas states that the expiry date of the LD (Gemzar 1 g/vial) used in study 311-13 was October 2014, and that only 30 out of 44 planned patients in stage-I of the study have been enrolled.

Gemcitabine Injection, developed by Intas Pharmaceuticals, Ltd., is a sterile, clear, colorless to pale yellow solution in a clear glass multi-dose vial formulated as 100 mg/mL gemcitabine freebase with USP/NF grade PEG-300, propylene glycol and dehydrated alcohol. Sodium hydroxide and hydrochloric acid are added to obtain pH (b) (4). Clinical presentations are 2 mL, 10 mL, 15 mL and 20 mL vials with (b) (4) stopper and color-coded (b) (4). Drug product is intended to be admixed with 0.9% sodium chloride, USP for IV infusion over 30 minutes.

The LD, Gemzar for Injection, manufactured by Eli Lilly and Company, is available in sterile single-dose vials of white lyophilized powder intended to be reconstituted with 0.9% sodium chloride solution followed by dilution with 0.9% sodium chloride solution for intravenous infusion.

Intas states that the proposed indication for Gemcitabine Injection is the same as that of the LD, Gemzar. Intas lists the following indications in section 3.3, page 7 of the meeting package:

- Breast Cancer: Indicated in combination with paclitaxel for the first-line treatment of patients with metastatic cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.
- Non-Small Cell Lung Cancer: Indicated in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB), or metastatic (Stage IV) non-small cell lung cancer.

IND 107393 was first submitted on October 17, 2011 with clinical study # 655-10, entitled “A Multi-Center, Randomized, Open-Label, Two-Period, Two- Treatment, and Two-Way Crossover, Single Dose Bioequivalence Study Comparing Gemcitabine Injection (Manufactured by Intas Pharmaceuticals Ltd.) to the reference listed drug Gemzar injection (Eli Lilly and Co) in patients with Pancreatic or Ovarian Cancer”, intended to support a 505(b)(2) application for Gemcitabine Injection. The study was a multi-center, randomized, open-label, two-period, two-treatment, two-way crossover, single dose bioequivalence study to evaluate the bioavailability of the test product in comparison to the LD, Gemzar. The primary objective was to characterize the pharmacokinetic profile of Intas test formulation relative to that of Gemzar in patients and to assess the bioequivalence. The study proposed to (b) (4)

The study was found to be acceptable and was allowed to proceed on November 17, 2011.

A summary of the study results submitted on July 2014 with the IND Annual Report (amendment 11) indicated that the (b) (4)

On August 19, 2013 Intas submitted a second bioequivalence protocol, study # 311-13 with (b) (4) with two key changes:

1. Clear specification in the protocol that gemcitabine infusion has to be completed within the specified time of 30 minutes (+5 min), patient data will be excluded from analysis if there is any deviation from the specified infusion time; and

2. Study sample size would be based on an adaptive sequential design (b) (4). The initial planned sample size (stage-I) was to be 44 patients based on the following assumptions: T/R ratio: 88.00 – 112.00%; intra patient variability: 16%; power $\geq$ 80%. The final sample size (stage-II) was to be decided based on the intra-patient variability and the point estimate for the ratio of the test and reference products obtained from stage-I. The proposed adaptive sequential design was based initially on (b) (4).
[REDACTED]
[REDACTED] These designs were considered unacceptable by the FDA (b) (4).
[REDACTED].

On August 6, 2014, a teleconference was held between FDA and Intas concerning the acceptability of the study design and the overall development plan for study #311-13. Intas stated that the study was open for accrual and estimated that approximately 44 patients would be enrolled by the end of October 2014. FDA informed Intas that an agreement concerning the sample size re-estimation for the new protocol # 311-13 had not been reached, and that the proposed sample size re-estimation using (b) (4) was not acceptable, (b) (4).
[REDACTED]

On October 29, 2014, FDA issued an Advice letter containing advice that neither the proposed (b) (4) was acceptable. This Advice letter provided reference to the appropriate FDA Guidance for Industry to aid Intas in the development of Gemcitabine injection following the 505 (b)(2) pathway.

2.0 **FDA RESPONSE TO SPONSOR QUESTIONS**

1. Expiry date for Reference listed drug (Gemzar 1g/vial) used in the study was October 2014. Considering lengthy screening procedures and stringent approval criteria for Clinical Trials in India, we could dose only 30 patients for stage-I till October 2014.

As the reference product got expired in October 2014, as on date we have stopped the dosing procedure and we have the following two options to proceed further:

- a. Option 1: With 30 completers, we will proceed to the Bio analytical phase followed by statistical analysis.

If with 30 completers, we are able to pass Bioequivalence Criteria for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-∞} with sufficient power, we will end the study and conclude bioequivalence between test and reference product. A protocol deviation would be filed accordingly with justification.

FDA Response: The Option 1 proposal to proceed with sample and data analyses with a sample size of 30 (versus the planned 44) and to end the study if results pass FDA Bioequivalence Criteria is acceptable. Amend the study protocol before the analysis of the samples is initiated. In the study report included in the NDA, provide a detailed description of the validation of the bio-analytical methodology and the PK and statistical analyses. Please see Additional FDA Comments 2 and 4. Although not explicitly stated, FDA assumes that under Option 1, in the event that bioequivalence is not demonstrated, Intas will end the study and will not proceed to accrue additional patients to study 311-13.

- b. **Option 2:** We will procure a new lot of Reference listed drug (Gemzar 1g/vial). Analysis of a new lot would be done with respect to assay value. If assay value for expired reference lot and new reference lot and between test lot and new reference lot is within $\pm 5\%$, we will go ahead with dosing procedure of remaining 14 patients and data analysis would be done for stage-I Clinical Trials in India, Intas could dose only 30 patients for stage-I till October 2014.

FDA Response: The Option 2 proposal to use a new non-expired lot of the same Listed Drug Product to complete the BE study with 44 patients is acceptable. Amend the study protocol before continuing the study. In the study report included in the NDA, provide complete information for the QC lot-assay values, validation of the bio-analytical methodology, and the PK and statistical analyses. Please see Additional FDA Comments 3 and 4.

ADDITIONAL FDA COMMENTS:

Bioequivalence and CMC Statistics Comments:

2. Under Option 1, Intas assumes the development risk that, in the event that the study results (n=30) do not meet bioequivalence criteria, Study 311-13 will not be adequate to support an NDA submission.
3. Under Option 2, Intas assumes the development risk posed by combining two groups for final statistical analyses. If the two subject groups demonstrate heterogeneity of variance or a shift in the mean, data from the two groups cannot be combined.
4. A third option is to manufacture a new batch of Gemcitabine injection and initiate a new BE study using a new batch of the LD Gemzar.
5. Refer to FDA letter issued on October 29, 2014: address the issue of controlling the experimental wise type I error rate in re-estimating study sample size based on the variability obtained from 44 subjects in Stage 1. Submit a response by March 27, 2015.

Clinical Comment:

6. FDA refers to page 7, Section 3.3 Proposed Indications of the meeting package, which states

“The indications proposed for this product are the same as that of the RLD GEMZAR® [Gemcitabine Hydrochloride]

The proposed indications are described below:

Breast Cancer: Indicated in combination with paclitaxel for the first-line treatment of patients with metastatic cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.

Non-Small Cell Lung Cancer: Indicated in combination with cisplatin for the first-line treatment of patients with inoperable, locally advanced (Stage IIIA or IIIB), or metastatic (Stage IV) non-small cell lung cancer.”

The Listed Drug, Gemzar has two additional Indications: for the treatment of advanced ovarian cancer; and for the treatment of pancreatic cancer. Please clarify Intas’s choice of proposed indications for Gemcitabine Injection 100 mg/mL, especially in light of the population accrued to studies 311-13 and 655-10.

7. FDA strongly recommends that Intas request a pre submission meeting with FDA 3 months or more prior to any planned NDA submission to assure the completeness and appropriateness of the information intended to support approval. In addition, refer to section 6.0 505(b)(2) REGULATORY PATHWAY of this letter and to the FDA Draft Guidance for Industry entitled “Applications Covered by Section 505(b)(2)” found at <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm079345.pdf>.

3.0 PREA REQUIREMENTS

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an end-of-phase 2 meeting, you should submit the initial PSP as early as practicable but before the initiation of any phase 3 studies, or any combined phase 2 and phase 3 study, of the drug that is the subject of the initial PSP. If a phase 3 study, or a combined phase 2 and phase 3 study, will not be conducted, the sponsor should submit the initial PSP no later than 210 calendar days before the marketing application is

submitted. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

4.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

5.0 LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm) (<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>).

6.0 505(b)(2) REGULATORY PATHWAY

The Division recommends 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 draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), 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 that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, 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 data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

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If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

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published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

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<i>4.</i>	

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/s/

ANUJA PATEL
03/03/2015