CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210565Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 117192

MEETING MINUTES

Kala Pharmaceuticals, Inc.
Attention: Michele LaRussa
SVP, Regulatory Affairs and Quality Assurance
100 Beaver Street, #201
Waltham, MA 02453

Dear Ms. LaRussa:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for KPI-121 (loteprednol etabonate ophthalmic suspension) 1%.

We also refer to the meeting between representatives of your firm and the FDA on May 2, 2017. The purpose of the meeting was to discuss the proposed clinical and non-clinical data presentation for the KPI-121 1% NDA for the treatment of postsurgical inflammation and pain.

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

If you have any questions, call Eithu Z. Lwin, Regulatory Project Manager at (301) 796-0728.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Deputy Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial 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:	May 2, 2017, 1:00 PM– 2:00 PM (EDST)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903
Application Number:	IND 117192
Product Name:	KPI-121 (loteprednol etabonate ophthalmic suspension)
Indication:	Treatment of postoperative inflammation and pain following ocular surgery
Sponsor/Applicant Name:	Kala Pharmaceuticals, Inc.
Meeting Chair:	Wiley A. Chambers, MD
Meeting Recorder:	Eithu Z. Lwin, PharmD

FDA ATTENDEES
Wiley A. Chambers, Deputy Director
William M. Boyd, Clinical Team Lead
Lucious Lim, Clinical Reviewer
Martin Nevitt, Clinical Reviewer
Rhea Lloyd, Clinical Reviewer
Andrew McDougal, Pharmacology/Toxicology Reviewer
Aling Dong, Pharmacology/Toxicology Reviewer
Yunfan Deng, Statistical Reviewer
Amit Somani, Clinical Pharmacology Reviewer
Chunchun Zhang, Product Quality Team Lead (via phone)
Eithu Z. Lwin, Regulatory Health Project Manager

SPONSOR ATTENDEES
Kim Brazzell, Chief Medical Officer
Susan Coultas, Vice President, Clinical Operations
Michele LaRussa, Senior Vice President, Regulatory Affairs and Quality Assurance
Catherine A. Briasco, Senior Director, Project Leader
(b) (4)

BACKGROUND

Kala Pharmaceuticals, Inc. (Kala) is developing KPI-121(loteprednol etabonate ophthalmic suspension), an ester corticosteroid, for the treatment of postoperative inflammation and pain following ocular surgery. Kala claims the new formulation of loteprednol etabonate enhances penetration through the mucous layer of the tear film allowing prolonged drug presence on the ocular surface and increased drug penetration into ocular tissues and thus has potential to reduce either dosing strength or frequency of administration as compared to Lotemax.

Kala submitted a meeting request on February 24, 2017, requesting a Pre-NDA meeting to discuss the proposed clinical and non-clinical data presentation for the KPI-121 1% NDA for the treatment of postsurgical inflammation and pain. A Meeting Granted Letter was issued on March 7, 2017, listing May 2, 2017, as the meeting date. The Division sent Meeting Preliminary Comments in response to the questions posted in the Briefing Package via e-mail on April 26, 2017. Kala emailed presentation slide deck titled "Preliminary KPI-121 Phase 3 Surgical Results Study KPI-121-C-005," on May 1, 2017, and was later submitted to the IND on May 16, 2017, received May 18, 2017.

DISCUSSION

For the purposes of these minutes, the questions posted in the briefing document are in **bold**, FDA preliminary responses are in *italics*, and the meeting discussions are in normal font.

Regulatory

1. **The phase 3 pivotal trials (KPI-121-C-001 and KPI-121-C-005) for Kala's proposed NDA are in patients with inflammation and pain following cataract surgery. Assuming the data are supportive, we will be requesting an indication similar to other approved products for treatment of postoperative inflammation and pain following ocular surgery.**

   Does the Agency agree?

   FDA Response: Agree.

   Meeting Discussion: None

Clinical/Biostatistics

2. **Kala is conducting a number of clinical trials for both the postoperative inflammation and pain program** (b) (4) **In the integrated summary of safety (ISS) for the postoperative inflammation and pain NDA, Kala proposes to describe the safety results from studies of KPI 121 that are complete (ie, have a final study report) at the time of the submission,** (b) (4)

   The primary focus of the ISS for the postoperative inflammation and pain NDA is proposed to be on the safety results from the 2 phase 3 pivotal studies (ie, Protocols KPI-121-C-001 and KPI-121-C-005), which will be described based on summary tables

derived from each individual protocol dataset and from an integrated dataset (ie, a pooled analysis).

[redacted] will be ongoing during the time of the preparation of the NDA submission for the postoperative inflammation and pain indication, and therefore the safety data from these trials will not be included in the ISS.

The safety data from Protocols KPI-121-C-008 and [redacted] (PK studies in healthy volunteers) [redacted]

Table 3 summarizes Kala's proposal for the inclusion clinical study reports (CSRs) and datasets in Module 5 of the planned NDA.

The text summary of all safety data is expected to meet the Agency's definition of "small" and is proposed to be included in Module 2.7.4 (Summary of Clinical Safety).

Does the Agency agree with the plan for the studies to be included in the ISS and in the manner described?

FDA Response: The clinical trials you proposed to include in the ISS are acceptable. Safety data are expected to be reported by concentration (i.e., KPI-121 0.25% vs.1%) and dosing regimen (i.e., BID vs. QID). Any adverse event finding from any of the currently ongoing studies which has been reported as a serious and unexpected finding and appears to be inconsistent with the findings from studies KPI-121-C-001 and KPI-121-C-005 should be submitted with the proposed NDA.

Meeting Discussion: The Sponsor proposed to pool/integrate safety data from KPI-121 1% BID dosing arms from studies KPI-121-C-001 and KPI-121-C-005 and not from Study [redacted]

The Sponsor also proposed to present data for all KPI-121 0.25% QID safety data will be presented in table form by study (KPI-121-C-001, [redacted] and will not be integrated. The Division stated it was acceptable.

The Division clarified that that all SAEs for ongoing clinical studies [redacted] regardless of relationship to study product, need to be reported in the NDA.

The Division confirmed that a patient user instruction guide is not needed.

3. **For the integrated (ie, pooled) data presentations in the ISS, Kala proposes to include tabular summaries of demographics, disposition, exposure, AEs (including but not limited to summaries of all AEs, drug-related AEs, serious AEs, AEs leading to discontinuation of treatment, and ocular AEs), and IOP data (including but not limited to summary statistics of raw data and change from baseline, and proportion of subjects with > 5 mmHg changes from baseline) for the pooled safety population of Protocols**

KPI-121-C-001 and KPI-121-C-005. All other data will not be integrated, but will be presented separately for the 2 studies.

Does the Agency agree with the plan for the pooled analyses to be included in the ISS?

FDA Response: Provided the AE and IOP data are pooled by concentrations (i.e., KPI-121 0.25% vs.1%) and dosing regimen (i.e., BID vs. QID), the proposed plan for pooled analyses is acceptable.

Meeting Discussion: None

4. **Medical Dictionary for Regulatory Activities (MedDRA) version 16.1 was used to code all AE data for Protocols KPI-121-C-001 and KPI-121-C-005, the 2 phase 3 pivotal trials. For this reason, the pooled AE analyses for the integrated dataset for the KPI-121-C-001 and KPI-121-C-005 studies are proposed to be presented using the same MedDRA version, 16.1. The AE data from the supportive studies (ie, (b) (4) (b) (4) KPI-121-C-008, and (b) (4) will be presented without pooling, using the MedDRA version that was used for each given study (version 16.1 for Protocols (b) (4) and (b) (4) and version 19.1 for Protocols KPI-121-C-008 and (b) (4) No AE coding was applied for Protocol (b) (4) (which is a synoptic CSR) and these AE results will be described using investigator terms.**

   Does the Agency agree that the pooled AE data, from Protocols KPI-121-C-001 and KPI-121-C-005, can use MedDRA version 16.1?

   FDA Response: Agree.

   Meeting Discussion: None

5. **For all studies submitted in Module 5, Kala proposes including:**

   - **patient narratives for all deaths and other serious AEs (SAEs), all severe ocular AEs in the study eye, and all discontinuations (from treatment or study) due to AEs.**
   - **case report forms (CRFs) for all patients for whom a narrative is submitted, plus all patients who discontinued early (from treatment or study) for any reason.**

   Does the Agency agree with the proposals for narratives and CRFs?

   FDA Response: Agree.

   Meeting Discussion: None

6. **Kala proposes to present the efficacy results of Protocols KPI-121-C-001 and KPI-121-C-005, the 2 phase 3 pivotal trials, in Module 2.7.3 (Summary of Clinical Efficacy), by protocol. No pooled analysis of an integrated dataset is proposed, to allow the reviewer to compare and contrast the outcomes of the 2 independent pivotal studies. A summary of the pharmacokinetic data from Protocol KPI-121-C-008 will also be included. The text summary of all efficacy data is expected to meet the Agency's definition of "small" and is proposed to be included in Module 2.7.3 (Summary of Clinical Efficacy).**

   Does the Agency agree with the plan for the presentation of efficacy data?

FDA Response: Agree.

Meeting Discussion: None

7. **For the clinical data presentation, Kala proposes to produce and submit SDTM compliant datasets and documentation for the 2 phase 3 pivotal studies (KPI 121 C 001 and KPI 121 C 005) and 1 phase 1 pharmacokinetic study (KPI 121 C 008), which were conducted in support of the proposed indication of the treatment of postoperative inflammation and pain following ocular surgery.** (b) (4) (b) (4) **Kala proposes** (b) (4)

   Does the Agency agree?

   FDA Response: Agree.

   Meeting Discussion: None

8. **Kala proposes to produce and submit ADaM compliant datasets for the pooled safety analyses from Protocols KPI 121 C 001 and KPI 121 C 005 (inclusive of study ID), and for the small pharmacokinetic studies in healthy adult subjects, KPI-121-C-008 and** (b) (4)

   Analysis datasets and documentation used for the outputs prepared for the other individual CSRs are proposed to be submitted as non-standard legacy (ie, SAS) datasets (ie, raw CRF data and programs on which the individual CSR tables and listings were based) that are not ADaM compliant.

   Does the Agency agree?

   FDA Response: Agree.

   Meeting Discussion: None

Nonclinical

9. **Kala believes that the company has sufficient nonclinical information to support a 505(b)(2) NDA for the treatment of postoperative inflammation and pain with KPI-121 1% BID, including the publicly available nonclinical toxicology data contained in previous Lotemax** (b) (4) **document and summarized in the Lotemax package inserts, published loteprednol etabonate nonclinical data, Kala's GLP 28-day ocular toxicity study in rabbits conducted with KPI-121 1%, and ocular pharmacokinetic studies in rabbits conducted with KPI-121.**

   Does the Agency agree?

   FDA Response: You are proposing to (b) (4) (b) (4)

(b) (4)

Your approach otherwise appears appropriate. The adequacy of the data will be a review issue.

Meeting Discussion: None

10. In Module 2.4 of the proposed NDA, Kala proposes to make reference to publicly available data including but not limited to: Lotemax package inserts, (b) (4) , and literature to support the nonclinical summary for KPI-121 1%, in addition to the results from a 28-day toxicity study in rabbits conducted with topically administered KPI-121 1%.

Does the Agency agree?

FDA Response: Please refer to our response to Question 9 above regarding reference to the Lotemax (b) (4) *We otherwise concur with your approach.*

The following general advice may be helpful for preparing the nonclinical module of your NDA.

a. All recommended nonclinical elements should be provided, either directly (original studies or published literature) or by relying on the FDA's findings of safety and effectiveness for a listed drug. If literature is being relied upon to support the NDA, published literature relevant to your product should be considered, and relevant data should be summarized in the NDA.

i. Include a summary of all published nonclinical literature being relied upon and *a copy of all publications cited.*

ii. The nonclinical summary is typically organized to address each of the nonclinical elements (e.g. pharmacology, pharmacokinetics, ocular toxicity, systemic toxicity, genotoxicity, reproductive toxicity, carcinogenicity, etc.).

iii. A copy of each cited article should be provided. Please note that review articles cannot be relied upon to support an application; the source articles which contain full study data should be provided or incorporated by reference.

iv. Published data is viewed at the same level of scrutiny as original data and expected to be of comparable/sufficient quality to support an NDA. In your integrated summary, provide discussion of the potential impact of study shortcomings (e.g. insufficient animal numbers, insufficient endpoint analyses, formulation differences, inadequate test article characterization, etc.), if applicable.

v. Please also identify any listed drug(s) described in the published literature (e.g., trade name(s)). Reliance on published literature describing a listed drug(s) is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s).

b. *Please note that non-US labeling or non-US regulatory authority assessments may not be relied upon as they are neither FDA's findings related to a listed drug, nor are they published literature. If the studies upon which the non-US conclusions are based have been published, you may be able to rely upon that literature.*

c. *FDA discipline reviews cannot be relied upon to support an 505(b)(2) NDA application. FDA finding of safety and efficacy is captured in the product labeling, and may include findings that can be inferred from fact of approval. If you intend to rely on FDA's finding of safety and/or effectiveness for a listed drug, you must establish that such reliance is scientifically appropriate. You should establish a "bridge" (e.g., via comparative pharmacokinetic data) between your proposed formulation and the listed drug. If exposure levels using your proposed formulation are less than or equal to that of the listed drug (at approved dose) following ocular administration, then reliance upon the listed drug would be considered scientifically justified. If exposure levels using your formulation exceed those of the listed drug, then additional toxicity studies may be needed to support the increased exposure.*

d. *You should ensure that all nonclinical data needed to support your application are either provided directly, or are adequately bridged if you opt to rely on the FDA's findings of safety and effectiveness for a listed drug(s). A detailed description regarding how you intend to bridge data that you don't own or have right of reference to should be provided in the NDA.*

e. *Impurity specifications that exceed qualification limits specified in the ICHQ3 guidances should be adequately qualified and the supporting safety data should be provided in the NDA submission. Ensure that ocular and systemic safety are addressed.*

f. *Novel excipients should be qualified, and safety data provided.*

g. *For the NDA, labeling should comply with the Pregnancy and Lactation Labeling Rule (PLLR). For more information, please see the final rule.*
https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/labeling/ucm093307.htm

Meeting Discussion: None

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP 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 iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP 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 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: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information and Pregnancy and Lactation Labeling Final Rule websites, which include:

- 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 related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master Files** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

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 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 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. by trade name(s)).

If you intend to rely 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 FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such

pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

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 is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). 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 the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the 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 effectiveness 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)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
4.	

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
None

ACTION ITEMS
None

ATTACHMENTS AND HANDOUTS
Please refer to Kala's presentation slide deck titled "Preliminary KPI-121 Phase 3 Surgical Results Study KPI-121-C-005," submitted on May 16, 2017, and received on May 18, 2017. These slides were emailed to the Division on May 1, 2017, and were presented during the May 2, 2017, meeting.

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

/s/

WILEY A CHAMBERS
05/22/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 117192

MEETING MINUTES

Kala Pharmaceuticals, Inc.
Attention: Michele LaRussa
SVP, Global Head of Regulatory Affairs and Quality Assurance
100 Beaver Street
Waltham, MA 02453

Dear Ms. LaRussa:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for KPI-121 (loteprednol etabonate ophthalmic suspension).

We also refer to the meeting between representatives of your firm and the FDA on May 12, 2017. The purpose of the meeting was to gain agreement on commercial manufacturing plans and NDA content and format for quality/chemistry, manufacturing and controls.

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

If you have any questions, call Teshara G. Bouie, Quality Assessment Lead (Acting) at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Balajee Shanmugam, Ph.D.
Branch Chief (Acting)
Branch III, Division of New Drug Products I
Office of New Drug Products
Office of Pharmaceutical Quality
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 – CMC

Meeting Date and Time: May 12, 2017; 11:00 am – 12:00 pm
Meeting Location: White Oak Building 22, Conference Room: 1421

Application Number: IND 117192
Product Name: KPI-121 (loteprednol etabonate ophthalmic suspension)
Indication: Postoperative inflammation and pain following ocular surgery
Sponsor/Applicant Name: Kala Pharmaceuticals, Inc.

Meeting Chair: Balajee Shanmugam, Ph.D.
Meeting Recorder: Teshara G. Bouie

FDA ATTENDEES

Balajee Shanmugam, Ph.D.	Branch Chief (Acting), OPQ/ONDP
Chunchun Zhang, Ph.D.	CMC Lead (Acting), OPQ/ONDP
Milton Sloan, Ph.D.	Drug Product Reviewer, OPQ/ONDP
Ash Bekele, Ph.D.	Product Quality Microbiology Reviewer, OPQ/OPF
Jonathan Swoboda, Ph.D.	Facilities Reviewer, OPQ/OPF
Maotang Zhou, Ph.D.	Quality Assessment Lead (Acting), OPQ/OPF
Wiley A. Chambers, MD.	Deputy Director, DTOP
William Boyd, MD.	Medical Team Lead, DTOP
Teshara G. Bouie, MSA, RAC	Quality Assessment Lead (Acting), OPQ/OPRO

SPONSOR ATTENDEES

Hongming Chen, ScD, Chief Scientific Officer
Raj Kewalramani, VP Manufacturing & Process Development
Jim Bourassa, PhD, Director of Analytical Development
Catherine A. Briasco, PhD, Senior Director & Project Leader
Elizabeth Enlow, PhD, Principal Scientist, Formulation Development
Ed Sopp, Senior Director of Quality Assurance
Kelly Webster, Senior Manager, Regulatory Affairs
Michele LaRussa, Senior VP of Regulatory Affairs & QA

1.0 BACKGROUND

IND 117192 is being developed for postoperative inflammation and pain following ocular surgery. On March 3, 2017, the Sponsor submitted a Type B Pre-NDA CMC meeting to gain agreement on commercial manufacturing plans and NDA content and format for quality/chemistry, manufacturing and controls. Background packages were received on April 11, 2017. FDA sent Preliminary Comments to the Sponsor on May 9, 2017. Kala provided responses to the FDA preliminary comments for questions #'s 1 - 6 and Additional Comment # 1 below on May 11, 2017.

2. DISCUSSION

Question 1

Kala proposes that the (b) (4) for KPI-121 1% drug product to be submitted in NDA section 3.2.P.3.2 will use a (b) (4) (b) (4) In the commercial Manufacturing Batch Record, (b) (4) (b) (4) being processed in that batch. This practice will continue until sufficient manufacturing experience is obtained (b) (4) (b) (4)

Does the Agency agree with this proposal?

FDA Response:

We agree that (b) (4) *can be used* (b) (4) *Please indicate how many batches you plan to use this interim practice. In addition, we recommend that you clearly provide the detailed calculation instruction in the process description as well as the master batch record (MBR).*

Kala Response:

In the NDA, Kala will propose the number of batches for this interim practice, (b) (4) We are tentatively proposing to use this interim practice for the process validation batches, plus 10 additional commercial batches ofKPI-1 211% drug product. Also, we will put the detailed calculation in the MBR, but we do not plan to file the commercial MBR in the NDA, because the commercial MBR will be finalized at the time of process validations. Does the Agency have any further comments?

Meeting Discussion:

The sponsor was advised that commercial Master Batch Records are required in the NDA per 21 CFR 314.54(a)(1)(i) [Note: This is the correct CFR citation for 505(b)(2) applications. During the meeting, 21 CFR 50(d)(1)(ii)(c) was incorrectly cited. The latter is meant for 505(b)(1) applications]. In addition, the Sponsor was referred to the Process Validation guidance (2011), Pre-Approval Inspection guidance, Changes to an Approved A/NDA guidance, and SUPAC guidance. The sponsor was reminded that process validation is to confirm the process design and demonstrate that the commercial manufacturing process performs as expected, rather than to develop and/or finalize the commercial manufacturing process. In the NDA submission, the sponsor is expected to propose all operation parameters (set point and/or ranges with lower and upper limits) based on data collected from the manufacturing of development and registration batches, and discuss how scalability issues for all scale dependent parameters have been taken into account. The Sponsor was also reminded that all facilities are expected to be ready for inspection at the time of NDA submission. Kala expressed concerns that their Master Batch Records are too large and detailed but will work with the manufacturer.

Question 2

Are the proposed release specifications for the drug product (b) (4) (KPI-121 (b) (4)) acceptable to the Agency?

FDA Response:

The proposed release specification appears reasonable. Confirm that the (b) (4) product is sterile and meets USP chapter <71> or equivalent sterility test requirements. Also, the acceptance criteria for particle size should be included.

Kala Response:

(b) (4)

Is this overall approach acceptable to the Agency?

Meeting Discussion:
Based on the adequacy of the sterilization validation and the [redacted], [redacted] of the [redacted] product may not be requested.

The sponsor agreed to provide details of the manufacturing processes [redacted] to the NDA as there is no DMF on file.

Kala Response:
Regarding release acceptance criteria for particle size [redacted] Therefore Kala proposes that we will not set a particle size specification for release of the drug product [redacted] Does the Agency agree?

Meeting Discussion: The Agency concurs.

Question 3

Are the proposed release specifications for the finished drug product acceptable to the Agency?

***FDA Response**:*
The tests proposed for the release testing are typical for the ophthalmic suspension dosage form. We recommend including tests for fill volume, content uniformity and particulate matter. Please give rationale for reporting the specified impurities in the way you have presented. Adequacy of the specification will be evaluated during NDA review. Additional tests and/or tightening of the proposed acceptance limits may be necessary.

Kala Response:
Fill volume: [redacted]. Is this acceptable instead of adding a release test?

Meeting Discussion:
The current release specifications do not include fill volume. The Agency strongly recommends adding a specification for fill volume (i.e., not less than…).

Kala Response:
Content uniformity: As part of characterizing the consistency of units across the entire filled batch, Kala performed testing of units from the beginning, middle and end of the batch for the 3 registration batches. For commercial release testing, Kala's understanding is that USP <905> (Uniformity of Dosage Forms) does not apply to multi-dose containers of suspensions. In a Feb 2016 briefing document submitted to FDA, Kala proposed continuing this characterization testing through process validation batches only. In written responses (dated Feb 26, 201 6), FDA agreed to Kala's sampling plan for this testing. Is Kala 's proposal still acceptable to the Agency?

Meeting Discussion:
The Agency concurs.

Kala Response:
Particulate Matter: Kala's understanding is that, per USP <789>, particulate matter testing does not apply to ophthalmic suspensions. KPI-12 1 1% is a (b) (4) suspension of (b) (4), thus the methods in USP <789> (light obscuration and microscopic particle count) do not apply. Does the Agency agree?

Meeting Discussion:
The Agency clarified testing should be done to describe the (b) (4) the limits described in USP <789> do not apply.

Question 4

Are the stability specifications for the drug product (b) (4) (KPI-121 (b) (4)) acceptable to the Agency?

FDA Response:
The proposed stability specification for the drug product (b) (4) appears reasonable. We recommend including an acceptance limit for particle size.
Provide justification for not including a test for other quality attributes (such as pH, (b) (4) resuspendability).

Kala Response

(b) (4)

Meeting Discussion: The Agency concurs and advised that any later changes in manufacturing will have to match.

For the other quality attributes listed by the Agency, Kala will provide justification in the NDA for not including them as additional stability tests. Briefly, these justifications are:

- (b) (4) (b) (4) .
- pH: Factors that could result in pH (b) (4) include (b) (4) As noted above, (b) (4) prevents (b) (4) . Additionally, (b) (4)
- (b) (4) (b) (4) (b) (4) (b) (4)

Does the Agency have any comments on these justifications?

Meeting Discussion:
As noted above, the Agency recommends a minimum fill volume and (b) (4) (b) (4) The pH has the potential to (b) (4) so it should be monitored. The (b) (4) should be determined so that it can be described in the labeling. If there is any reason to believe that it may change over the course of the stability studies, it should be monitored.

Question 5

Kala intends to store [redacted] (KPI-121 [redacted] In the NDA, Kala will provide data to support this proposed storage period, including [redacted] stability and maintenance of sterility.

Is Kala's plan for the NDA data package to support shelf-life and storage of KPI-121 [redacted], acceptable to the Agency?

FDA Response:

The propose plan is reasonable but should be supported with adequate stability data Furthermore, the [redacted] will be subject to NDA review and/or GMP inspection. Additionally, indicate which facility(ies) will be used for commercial storage and any development facilities (if different) that performed [redacted] These sites should be identified on the FDA Form 356h and Module 3.2.P.3.1 for the proposed submission. Please clarify the storage orientation of the drug product [redacted] and if any quality attribute will be impacted by it.

Kala Response:

Kala assumes that FDA's use of the term [redacted] refers to the stability studies of the DPI described in Kala's briefing document. Please confirm.

Meeting Discussion:

The Agency clarified the term [redacted] is the [redacted] the sponsor plans [redacted] hours.

Question 6

Are the stability specifications for the finished drug product acceptable to the Agency?

FDA Response:

The proposed drug product stability specification appears reasonable. We recommend that you include tests for resuspendability, antimicrobial effectiveness testing, and particulate matter. The antimicrobial effectiveness testing should include the USP listed microorganisms and meet the acceptance criteria as per USP <51> or equivalent methodology. The adequacy of the specification, including analytical procedures and acceptance criteria will be determined upon review of the NDA. Additional tests and/or tightening of the acceptance limits may be required.

Kala Response:
Resuspendability: Kala's loteprednol etabonate (LE) assay employs standardized agitation of the DP bottles with a [redacted] (b) (4) An acceptance criterion has been set for LE assay, which is measured throughout the stability studies. Therefore the LE assay result is also a measure of resuspendability. Is this acceptable for characterizing resuspendability?

Particulate matter: Please see Kala's response to Q. 3 regarding particulate matter. Does the Agency agree that particulate testing during stability studies is not applicable to our product?

Meeting Discussion:
Refer to the Agency's response to question #3 in regards to particulate matter.
The Agency stated the labeling should match how the product is tested. Specify the number of shakes or time. The Sponsor was advised to conduct a [redacted] (b) (4) on one stability batch for the Agency to evaluate the justification for [redacted] (b) (4)

Question 7

As of Feb 2017, Kala has 6 months of stability data for the registration drug product batches (Appendix 2, Tables A-1 – A-3), and all data meet stability specifications for all three bottle orientations. However, Kala's development stability data suggest that samples stored in the inverted orientation might fail for LE Assay at upcoming timepoints, likely due to difficulty in re-suspending drug particles that have settled in the bottle tips. Kala proposes that if this occurs, we will terminate all inverted orientation studies after a single OOS result in any one lot is observed. In such a case, product labeling would then include a statement to store the product upright, and procedures would be developed to avoid inverted orientation of the product during storage and shipment.

Is this plan acceptable to the Agency?

***FDA Response**:*
We recommend that you continue to evaluate the inverted orientation to determine how long the product may be inverted before it is likely to fall out of specifications. We recommend that you provide a justification, with supportive data, for not being able to pursuing stability studies of samples stored in the inverted position. If the efforts to mitigate the issue in resuspending the

drug product persist, we recommend that you provide clear labeling and diagrams on the container box to encourage upright storage.

Meeting Discussion: No further discussion at the meeting.

Question 8

On Jan 30, 2017, Kala submitted an "Expiry Dating and Stability Plan Proposal" to the KPI-121 IND 117192.

Does the Agency agree with Kala's proposal for expiry dating and the stability plan to support the shelf life?

***FDA Response**:*
The proposed plan appears to be reasonable. Please provide justification in the NDA. Please see additional comments.

Meeting Discussion: No further discussion at the meeting.

Question 9

Kala plans to (b) (4)

Does the Agency agree with this approach?

***FDA Response**:*
The FDA does not approve process validation approaches, protocols, or number of specific batches used in process validation studies. The actual protocols, acceptance criteria, and study outcomes (as applicable) will be evaluated during a pre-approval inspection of your manufacturing facilities. The product design and the suitability of manufacturing processes and control strategy will be evaluated during the NDA review cycle. It is your company's responsibility to conduct all studies necessary to assure your commercial manufacturing process is capable of consistently delivering quality product.

The FDA requires that drug manufacturers validate their manufacturing processes [21 CFR 211.100(a) and 211.110(a)] but does not prescribe how that is to be accomplished as it will

depend on multiple factors, some of which are specific to the complexity of the product and process. The process validation protocol should be built on an understanding of the process gathered from experience executing development batches (Process Validation Stage 1). Subsequent design of the facility and qualification of equipment/utilities and operational performance qualification (Process Validation Stage 2) should be incorporated into the proposed commercial scale manufacturing process and control strategy. Likewise, knowledge obtained during transfer and scale up activities can be useful in further developing the control strategy. Successful process validation should also include a plan for continued process verification (Stage 3).

For additional information on process validation, please refer to "Guidance for Industry, Process Validation: General Principles and Practices" posted at the following link.

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf.

For further information on Agency's drug compliance and pre-approval inspection programs please refer to the following links on FDA's website:

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm252671.htm

Meeting Discussion: No further discussion at the meeting.

Question 10

The KPI-121 (b) (4) . Kala proposes that most of the information related specifically and solely to the KPI-121 (b) (4), will be provided in (b) (4) (b) (4) Information that is common to both the drug product (b) (4) or that is better presented together, will be provided in the usual drug product sections, as described in the table provided.

Does the Agency agree with Kala's proposal?

***FDA Response**:*
We agree. However, for ease of review, the relevant information should be clearly referenced if it is not provided in its usual location.

Meeting Discussion: No further discussion at the meeting.

Question 11

Kala intends to propose 24 month expiry dating (from date of labeling/packaging) at controlled room temperature for the commercial configuration (b) (4) and 12 month expiry dating (from date of labeling/packaging) at controlled room temperature for the physician sample configuration (b) (4)

Is Kala's plan for the stability data that will be provided in the NDA acceptable to support the proposed shelf life for finished drug product?

***FDA Response**:*
The stability package will be evaluated during NDA review and a determination of expiration date will be made at that point.

Meeting Discussion: No further discussion at the meeting.

Question 12

Kala plans to include manufacturing facilities and equipment information in 3.2.A.1, with a summary in 2.3.A.1. The extent of information provided will follow the recommendations in FDA's "*Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*" (Nov 1994). Kala also plans to provide executed batch records in section 3.2.R.1 for the 2 batches of KPI-121 1% that were used in the clinical trials.

Is Kala's plan for the location and extent of this information acceptable?

***FDA Response**:*
The plan regarding the location of the manufacturing facilities and equipment information is adequate. Also, include information for facilities involved in the manufacture and testing of all drug substances and drug products associated with this application in Module 3.2.S.2.1 and Module 3.2.P.3.1, accordingly, as well as in the FDA Form 356h.

Meeting Discussion: No further discussion at the meeting.

Question 13

PDUFA V states that a limited number of minor components can be submitted 30 days after the main NDA filing for NMEs and biologics. Kala plans to file the NDA for KPI-121 1% as a 505(b)(2) application. Would it be acceptable for Kala to file the following data within 30 days after the NDA filing: [redacted] (b) (4)

FDA Response:
Since this NDA will not be under the program, we recommend the NDA to be complete at the time of submission.

Meeting Discussion: No further discussion at the meeting.

Additional comments:

1. *Regarding the container closure integrity test to be conducted on the* [redacted] (b) (4) *containing the* [redacted] (b) (4)

   Kala Response:
   [redacted] (b) (4)

   Meeting Discussion:
   There is no DMF on file for the [redacted] (b) (4). Kala will provide details regarding the [redacted] (b) (4) material composition, compliance with USP monographs, validation package, etc. in the NDA. Extractable/leachable data will be provided in the NDA. [redacted] (b) (4) agreed to provide mock labeling for the [redacted] (b) (4) and stated the labels do not make contact with the [redacted] (b) (4)

2. *Similarly,* [redacted] (b) (4) *should be included in the dye and microbial ingress tests used for finished drug product containers.*

   Meeting Discussion: No further discussion at the meeting.

3. *The new drug application should include a commitment to conduct antimicrobial effectiveness testing according to USP <51> or equivalent methodology on at least one primary stability batch at the end of the proposed shelf life (see ICH Q1A: Stability*

Testing of New Drug Substances and Products).

Meeting Discussion: No further discussion at the meeting.

4. *Reporting of impurities should be per ICH Q3B (R2).*

   Meeting Discussion: No further discussion at the meeting.

5. *Detailed information on all container closures (including the* (b) (4) *) should be provided either in the NDA or by way of reference to a DMF.*

   Meeting Discussion: No further discussion at the meeting.

6. *Conduct a one-time extractables and leachables study over the storage period for all container closure that will come in contact with the drug product.*

   Meeting Discussion: No further discussion at the meeting.

7. *Submit labeling information for all containers.*

   Meeting Discussion: No further discussion at the meeting.

8. *Since you plan to use* (b) (4) *. We recommend that you provide supporting data to demonstrate that the drug product is not contaminated with any* (b) (4) (b) (4) *if necessary.*

   Meeting Discussion: No further discussion at the meeting.

Additional Meeting Discussion:

- Shelf-life starts when the API is mixed with the excipients.
- The agency recommended an (b) (4) study given the proposed stability protocol. A commitment to conducting the recommended study can be provided in the NDA.
- The agency reminded the sponsor that any individual unspecified degradation product/impurity should be NMT (b) (4)% and that each identified impurity should be reported separately.
- The Agency referred the sponsor to ICH Q1A (R2) guidance for setting stability specification for weight.

- The sponsor is recommended to confirm that all formulation [redacted] (b) (4)
- The sponsor is recommended to provide statement of compliance to pertinent CFR sections for [redacted] (b) (4) used in the manufacturing of the drug product.
- The sponsor was advised to include complete facility information for all sites on the 356h form. All facilities should be ready for inspection at the time of the NDA submission.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

4.0 ATTACHMENTS AND HANDOUTS

See attached.

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

/s/

TESHARA G BOUIE
06/06/2017

BALAJEE SHANMUGAM
06/06/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 117192

MEETING MINUTES

Kala Pharmaceuticals, Inc.
Attention: R. Kim Brazzell, Ph.D.
Chief Medical Officer
100 Beaver Street, #201
Waltham, MA 02453

Dear Dr. Brazzell:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for KPI – 121 (loteprednol etabonate) Ophthalmic Suspension.

We also refer to the teleconference between representatives of your firm and the FDA on May 3, 2016. The purpose of the meeting was to discuss and clarify two of the FDA's, February 26, 2016, responses to Kala's briefing package for KPI-121 submitted on January 28, 2016.

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 Erin Andrews, Pharm.D., at (240) 402-5878 or email at Erin.andrews@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Kristine Leahy, RPh.
Regulatory Business Process Manager
Office of Pharmaceutical Quality
Office of Program and Regulatory Operations
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 C
Meeting Category: End of Phase 2

Meeting Date and Time: May 3, 2016 at 10:00 -10:30 am, EST
Meeting Location: Teleconference

Application Number: IND 117192
Product Name: KPI – 121 (loteprednol etabonate) Ophthalmic Suspension
Indication: Treatment of post-operative inflammation and pain following surgery; (b) (4)

Sponsor/Applicant Name: Kala Pharmaceuticals, Inc.

Meeting Chair: Balajee Shanmugam, Ph.D.
Meeting Recorder: Kristine Leahy, RPh.

FDA ATTENDEES (tentative):
Balajee Shanmugam, Ph.D., Branch Chief (Acting), Branch III, ONDP
Chunchun Zhang, Ph.D., CMC Lead (Acting), ONDP
Milton Sloan, PhD., Drug Product Reviewer, ONDP
Wiley Chambers, M.D., Deputy Director, DTOP
William Boyd, M.D., Clinical Team Leader, DTOP
Kristine Leahy, RPh., Regulatory Business Process Manager, OPRO

SPONSOR ATTENDEES:
Kim Brazzell, Ph.D., Chief Medical Officer
Hongming Chen, Ph.D., Chief Scientific Officer
Cathy Briasco, Ph.D., Sr. Director Project Management
(b) (4)

1.0 BACKGROUND

The purpose of the meeting was to discuss and clarify two of the FDA's, February 26, 2016, responses to Kala's briefing package for KPI-121 submitted on January 28, 2016. Kala Pharmaceuticals, Inc. (Kala) is developing a novel topical ocular formulation of loteprednol etabonate (LE), KPI-121, for various ophthalmic conditions.

FDA sent preliminary comments to Kala Pharmaceuticals, Inc., on April 26, 2016.

2.0 QUESTIONS

Question 2:

Kala recognizes that expiry dating is an NDA review topic. However, the intent of this question is to understand expectations as we design the registration stability studies. Kala proposes [redacted] Does the Agency agree with this

FDA Response (sent 2/26/19):

We could not locate the rationale for the proposed plan in the briefing document. [redacted] *Determination of expiration date will be an NDA review issue.*

Kala's Comments

Kala's planned registration stability studies include [redacted]

Kala proposes that [redacted]

(b) (4)

The expiry period of drug product starts from the date of manufacture. In our proposal, (b) (4)

(b) (4)

Question 2A: Is the proposed plan for commercial storage, labeling and distribution acceptable to the agency?

Question 2B: Is the proposed stability plan acceptable to support the commercial storage, labeling and distribution plan?

FDA Response to Question 2A and 2B:
No, the proposed stability plan is not acceptable.

Meeting Discussion 5/3/16:
FDA is not prepared to accept the stability plan at this time (b) (4)

(b) (4)

Question 4:
Is Kala's leachables testing plan for trade and physician sample bottles (single lot of each strength, horizontal orientation, and 2 storage conditions) acceptable?

FDA Response (sent 2/26/2016):
Yes, your proposed leachables testing plan appears reasonable with testing done through expiry on commercial lots.

Kala's Comments
Kala's briefing document presented a plan for leachables testing of samples from the formal NDA stability studies, which will be conducted with the registration lots. Please clarify the phrase in your response "with testing done through expiry on commercial lots." Does this refer to NDA registration lots?

FDA Response to Question 4:
Yes, we refer to NDA registration lots.

Discussion
Topic not discussed.

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/s/

KRISTINE F LEAHY
05/31/2016

BALAJEE SHANMUGAM
06/02/2016