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APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	(electronic stamp)
From	Kendall A. Marcus, MD
Subject	Office Director Decisional Memo
NDA/BLA # **Supplement #**	BLA 761055
Applicant Name	Regeneron Pharmaceuticals, Inc.
Date of Submission	29 July 2016
PDUFA Goal Date	29 March 2017
Proprietary Name / **Established (USAN) Name**	Dupixent injection dupilumab
Dosage Forms / Strength	Single-dose prefilled syringe for subcutaneous injection/300 mg of dupilumab in 2.0 mL solution (150 mg/mL)
Applicant Proposed Indication(s)/Populations	Treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable
Action:	Approval
Approved Indication(s)/Populations (if applicable)	Treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable

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Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Brenda Carr, MD
Statistical Review	Carin Kim, PhD
Pharmacology Toxicology Review	Renquin Duan, PhD
OPQ Review	Gunther Boekhoudt, PhD (DS, DP); Lakshmi Narasimhan, PhD (DP micro); Maria Jose Lopez-Barragan, PhD (DS micro); Wayne Seifert (facilities); Jibril Abdus-Samad (labeling); Melinda Bauerlein (RBPM), Truong Quach (RBPM)
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OSI	Roy Blay, PhD
CDTL Review	Snezana Trajkovic, MD
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COA	Ebony Dashiell-Aje, PhD

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

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1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The subject of this application, Dupixent (dupilumab), is a recombinant human immunoglobulin-G4 (IgG4) monoclonal antibody (mAb) that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by specifically binding to the IL-4 receptor alpha (IL-4Rα) sub-unit shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the Type I receptor, and both IL-4 and IL-13 signaling through the Type II receptor. The proposed indication for dupilumab is for the treatment of adult patients with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Atopic dermatitis (AD) is a chronic, relapsing, pruritic inflammatory skin disorder which is typically characterized by intensely pruritic, xerotic skin. Other clinical features may include erythema, edema, papules, vesicles, erosions, oozing, crusting and lichenification. Presentations vary widely; acute eczema is characterized by intensely pruritic erythematous papules and vesicles with exudation and crusting, whereas subacute or chronic lesions present as dry, scaly, or excoriated erythematous papules. Skin thickening from chronic scratching (lichenification) and fissuring may develop over time. In many patients, lesions in different stages may be present at the same time. AD predominantly occurs in children, although for some patients, it persists into adulthood. The estimated prevalence in adults is about 3%.

Standard treatment for AD begins with non-pharmacologic measures such as bathing practices and use of emollients. In addition to emollients, topical corticosteroids, topical calcineurin inhibitors and a topical phosphodiesterase-4 inhibitor are potential therapeutic options for patients with mild to moderate disease. Phototherapy is also a potential treatment option, but drawbacks include a potentially time-intensive, in-office treatment schedule. Risks from phototherapy may vary according to the type of phototherapy and may include actinic damage, sunburn like reactions, skin cancer (non-melanoma and melanoma), and cataracts. Currently, the only available FDA-approved systemic treatment for AD is corticosteroids; however, the American Academy of Dermatology (AAD) recommends that systemic corticosteroids generally be avoided because of the potential for short and long-term adverse reactions. Systemic products that are used off-label to treat moderate-to-severe AD include cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil. All of these products are associated with potentially serious risks and data supporting their efficacy is limited. Clearly, patients with moderate to severe AD not responsive to optimized topical therapy need additional therapeutic options that have been adequately characterized and possess more favorable benefit-risk profiles.

In support of the application for Dupixent (dupilumab) for the treatment of patients with moderate to severe AD, the Applicant provided substantial evidence of effectiveness from 3 adequate and well-controlled studies that evaluated dupilumab for treatment of adult subjects with moderate-to-severe atopic dermatitis whose disease was not adequately controlled with topical prescription therapies or when those therapies were not advisable. Two identical studies evaluated dupilumab as monotherapy, and the third study evaluated dupilumab with protocol-specified,

concomitant use of topical corticosteroids (TCS). Dupilumab was statistically superior to placebo in all 3 studies in the target AD population for the primary endpoint, the proportion of subjects with both Investigator's Global Assessment (IGA) 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 16. The treatment response was generally similar across the 3 studies. The proportion of subjects receiving dupilumab 300 mg Q2W who achieved IGA success in the two monotherapy trials was 37% as compared to 9% of placebo-treated subjects. In the combination trial in which concomitant TCS use was allowed, 39% of dupilumab-treated subjects as compared to 12% of placebo-treated subjects achieved IGA success. A regimen of 300 mg weekly (QW) was also studied, but efficacy appeared to be similar to the 300 mg Q2W dose.

Use of dupilumab was generally well tolerated. During the first 16 weeks of treatment, adverse drug reactions (ADRs) that occurred with a ≥1% overall incidence rate in the dupilumab group (with or without TCS) and that occurred more frequently than in the placebo group were injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infections, and dry eye. Serious adverse events (SAEs) were reported in 5% of placebo subjects and 2.3% of dupilumab-treated subjects. Hypersensitivity reactions, including generalized urticaria, and serum sickness or serum sickness-like reactions, were reported in less than 1% of subjects who received Dupixent (dupilumab). Two subjects experienced serum sickness or serum sickness-like reactions that were associated with high titers of antibodies to dupilumab.

I concur with the recommendation of the Division of Dermatology and Dental Products, to approve Dupixent (dupilumab) for the treatment of adult patients with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupixent (dupilumab) solution for subcutaneous (SQ) administration is supplied as a sterile, colorless to pale yellow, preservative-free liquid solution in a single-dose pre-filled syringe with needle shield. The recommended dose of Dupixent (dupilumab) for adult patients is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week (Q2W).

The safety concerns identified with use of Dupixent (dupilumab) can be adequately managed by professional labeling and routine pharmacovigilance in the postmarket setting. Product labeling will include warnings about hypersensitivity reactions, conjunctivitis and keratitis, use in patients with comorbid asthma, and use in patients with helminth infections. A Risk Evaluation and Mitigation Strategy (REMS) will not be required for Dupixent (dupilumab) to ensure that the benefits of the drug outweigh the risks.

An FDA Advisory Committee Meeting was not held to discuss this application because the application did not raise significant safety or efficacy Issues.

The safety and effectiveness of Dupixent in patients less than 18 years of age have not been established.

Dimension	Evidence, Uncertainties and Conclusions
Analysis of Condition	Atopic dermatitis (AD) is a chronic, relapsing, pruritic inflammatory skin disorder which is typically characterized by intensely pruritic, xerotic skin. Other clinical features may include erythema, edema, papules, vesicles, erosions, oozing, crusting and lichenification. Presentations vary widely; acute eczema is characterized by intensely pruritic erythematous papules and vesicles with exudation and crusting, whereas subacute or chronic lesions present as dry, scaly, or excoriated erythematous papules. Skin thickening from chronic scratching (lichenification) and fissuring may develop over time. In many patients, lesions in different stages may be present at the same time. Common comorbidities include asthma, allergic rhinitis/rhinoconjunctivitis, food allergies, and cutaneous infections. Sleep disturbances are common during disease flares, which may also negatively impact mood, behavior, and cognition. Although it may affect all age groups, AD is most common in children. Onset is typically between the ages of 3 and 6 months, with approximately 60% of patients developing the disease during the first year of life and 90% by the age of 5 years. For 10-30% of individuals, AD persists into adulthood. The prevalence is estimated to be approximately 2-3% in adults. Approximately one half of patients report moderate disease and one fifth report severe disease. **Comment:** Atopic dermatitis can have a significant impact on patients and their families due the cutaneous manifestations, accompanying pruritus, co-morbidities, and impairment of quality of life. Dupixent (dupilumab) is being developed for patients with moderate to severe disease who are not adequately controlled with topical therapies or for whom those therapies are unadvisable. Effective treatment for the signs and symptoms of atopic dermatitis will reduce the most bothersome symptoms of atopic dermatitis, pruritus in particular, and lead to significant improvements in quality of life.

Dimension	Evidence, Uncertainties and Conclusions
Current Treatment Options	Management of atopic dermatitis involves a multipronged approach, which includes elimination of exacerbating factors (i.e. heat and low humidity), hydration of the skin with emollients, treatment of skin infections, and reduction of stress and anxiety. Topically applied corticosteroids are typically first-line therapy for treatment of mild to moderate disease, with topical calcineurin inhibitors (TCIs) serving as a potential alternative, particularly for areas that cannot be treated with TCS, such as the face, and genital and intertriginous areas. Crisaborole, a topical phosphodiester-4 (PDE4) inhibitor, was recently approved. Potential adverse effects of topical corticosteroids include adrenal suppression, especially with use of high or super high potency preparations or application on large areas, skin atrophy, telangiectasias, dyspigmentation, folliculitis and contact dermatitis. Topical calcineurin inhibitors (TCI), such as tacrolimus and pimecrolimus, are nonsteroidal immunomodulating agents that do not cause skin atrophy or other corticosteroid adverse effects and are generally considered to be equivalent to medium potency steroids. TCIs carry a boxed warning regarding their long-term safety and potential increased risk of skin malignancies and lymphomas. While a causal relationship has not been established, rare cases of skin malignancy and lymphoma have been reported in patients treated with TCIs. Crisaborole is a topical PDE4 inhibitor approved in December 2016 for the treatment of mild to moderate atopic dermatitis. Adverse effects of topical crisaborole are mild and mainly limited to application site reactions (pain, paresthesia). Ultraviolet light therapy (phototherapy) with PUVA (psoralens plus ultraviolet A radiation), broadband UVA, broadband UVB, combined UVA and UVB, narrow-band UVB, or UVA1 is a treatment option for moderate to severe atopic dermatitis that is not adequately controlled with topical therapy. Common adverse reactions include actinic damage, local erythema, pruritus, burning/stinging, herpes simplex reactivation and folliculitis. Prolonged treatment

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	with phototherapy may lead to an increased risk of melanoma and non-melanoma skin cancer. Systemic therapy is indicated in patients with moderate to severe disease who fail or cannot use topical therapies. A few products have been evaluated in clinical trials for AD treatment and are currently recommended for use in treatment guidelines, but only systemic corticosteroids are approved in the US for treatment of moderate to severe AD. Additionally, only a few randomized, controlled trials have been conducted to compare currently used treatments, so comparative efficacy is not well elucidated. Despite FDA approval, the American Academy of Dermatology recommends avoiding use of systemic corticosteroids, because of their associated adverse reactions. Glaucoma, edema, weight gain, increased blood pressure, and mood swings are associated with short term use and cataracts, increased blood sugar, osteoporosis, thinning of the skin, and risk of infection are associated with long-term use. Short courses of systemic corticosteroids may lead to atopic flares when discontinued. Overall, the risk-benefit profile is generally considered to be unfavorable. Cyclosporin A (CSA) is a T-cell and interleukin-2 immunosuppressant is an unapproved systemic option. Potential adverse reactions include infection, nephrotoxicity, hypertension, tremor, hypertrichosis, headache, gingival hyperplasia, and increased risk of skin cancer and lymphoma. In general, once clearance or near-clearance is achieved and maintained, CSA should be tapered or discontinued, with maintenance of remission via emollients, topical agents, and/or phototherapy. Azathioprine (AZA) is a purine analog that inhibits DNA production, thus predominantly affecting cells such as B cells and T cells in high inflammatory states. It is recommended off-label for the treatment of refractory AD. Adverse reactions associated with use include GI symptoms, headache, hypersensitivity reactions, elevated liver enzymes and leukopenia. In

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	other patient populations, an increased risk of infection, lymphoma and non-melanoma skin cancers has been observed in some patients. Methotrexate is an anti-folate metabolite used off-label to treat refractory AD. GI symptoms, bone-marrow suppression, pulmonary fibrosis and hepatic toxicity are among the potential adverse reactions. **Comment:** Currently used treatments for moderate to severe AD not adequately treated with topical therapies are associated with significant risk of potentially serious adverse reactions and, for the most part, are not well studied. The optimal dose and duration of these treatments are not well known. Safer, adequately characterized and more efficacious treatments are clearly needed for moderate to severe AD.
Benefit	The efficacy of dupilumab was established in three pivotal Phase 3 trials (Trials 1224, 1334, and 1416). All trials evaluated two dose frequencies, 300 mg every 2 weeks (Q2W), and 300 mg weekly (QW), versus placebo. Trial 1224 was an adjunctive therapy trial that allowed the use of topical corticosteroid (TCS) and Trials 1334 and 1416 were monotherapy trials. All trials enrolled men and women, 18 years of age or older, with chronic AD that had been present for at least 3 years before screening with; an Eczema Area and Severity Index (EASI) $\geq$ 16; Investigator's Global Assessment (IGA) $\geq$3; body surface area (BSA) involvement $\geq$10%; baseline pruritus numeric rating scale (NRS) average for maximum itch intensity $\geq$3; and a documented history within 6 months of inadequate response to treatment with topical medications or for whom topical treatments were medically inadvisable. In all three trials, subjects received an initial dose of 600 mg dupilumab on Day 1, followed by 300 mg QW or 300 mg Q2W, or matching placebo. In the monotherapy trials, subjects were required to apply moisturizers twice daily for at least 7 days after the baseline visit. In the combination trial, they

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	were required to apply moisturizers throughout the study; however, only about one-third of subjects complied with the requirement. In the monotherapy trials, subjects were permitted to receive rescue treatment (TCS) to control intolerable symptoms; those subjects who received rescue treatment after Week 2 were considered as non-responders for the efficacy analyses done by the sponsor. The baseline demographics were generally balanced across the treatment arms within each trial. Approximately 59% of the subjects were male, 67% were Caucasians, and 96% of subjects were <65 years of age. Relevant comorbid medical conditions reported by trial subjects included asthma (48%), allergic rhinitis (49%), food allergy (37%) and allergic conjunctivitis (27%). For all Phase 3 trials, about 52% of the subjects had IGA scores 3 (moderate) at baseline, and about 94% of the subjects had a weekly average peak pruritus NRS score of at least 4 at baseline. In the monotherapy trials, about 33% had previously used systemic corticosteroids and about 31% had used cyclosporine. In all three trials, both dupilumab 300 mg QW and 300 mg Q2W regimens were superior to placebo at Week 16 for the primary endpoint of IGA success defined as a score of 0 or 1. The proportion of subjects receiving dupilumab 300 mg Q2W who achieved IGA success in the two monotherapy trials was 37% as compared to 9% of placebo-treated subjects. In the combination trial in which concomitant TCS use was allowed, 39% of dupilumab-treated subjects as compared to 12% of placebo-treated subjects achieved IGA success. The weekly dosing strategy was not found to be more efficacious than the biweekly dosing strategy; therefore, the biweekly dosing strategy was selected as the to-be-marketed dose. The majority of subjects enrolled were Caucasian and under the age of 65 years, so any differences for non-Caucasians and older subjects would be difficult to detect. In all three trials, females generally had higher IGA response rates than those of the males; however, the majority of the subjects (59%) in the trials were male subjects.

Dimension	Evidence, Uncertainties and Conclusions
	Comment: The applicant provided substantial evidence of the effectiveness of dupilumab for the treatment of moderate-to-severe atopic dermatitis in three randomized, controlled clinical trials. Efficacy was established both as monotherapy and in combination with TCS. A maintenance trial that enrolled Week 16 responders from the monotherapy trials is currently being conducted to evaluate the optimal dose for maintenance of response.
Risk	The safety database for dupilumab was comprised of 2526 subjects with atopic dermatitis who were exposed to various doses of dupilumab in 11 clinical trials. At the time of datalock for this application, 739 subjects had received dupilumab for at least one year, 309 subjects had received dupilumab for at least 1.5 years and 160 subjects had received dupilumab for at least 2 years. The numbers of subjects who received dupilumab at or above the proposed to-be-marketed dose exceed those recommended in the ICH E1A treatment guidelines. Pooled data from the 16-week treatment period of the two monotherapy Trials 1334 and 1416, and relevant treatment arms from the Phase 2 dose-ranging trial R668-AD-102 comprised the primary safety database for dupilumab monotherapy. This primary safety pool included 1,564 subjects. Fifty-two week data from Trial 1224 that evaluated use of dupilumab in combination with TCS provided safety data for long-term treatment (52 weeks). In addition to these clinical trials, a 164-week, open-label extension study, Trial 1225, enrolled subjects who had either participated in Phase 2/3 trials or were screened for Phase 3 trials but could not be randomized because of randomization closure. A total of 1491 subjects were enrolled in Trial 1225. As previously noted, two doses were evaluated in Phase 3 clinical trials, 300 mg QW and 300 mg Q2W. During the first 16 weeks of treatment, adverse drug reactions (ADRs) that occurred with a

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	≥1% overall incidence rate in the dupilumab group (with or without TCS) and that occurred more frequently than in the placebo group were injection site reactions, conjunctivitis, blepharitis, oral herpes infections, keratitis, eye pruritus, other herpes infections, and dry eye. The safety profile of dupilumab in combination with TCS through Week 52 was generally consistent with the safety profile observed at Week 16. During the initial 16-week treatment period, serious adverse events (SAEs) were reported in 5% of placebo subjects and 2.3% of dupilumab-treated subjects. One subject developed a serum-sickness like reaction that resulted in permanent discontinuation of dupilumab. One subject developed serum sickness that resulted in hospitalization and permanent discontinuation of dupilumab. Both of these events were considered related to dupilumab. **Comment:** The product label will contain a warning about hypersensitivity reactions, including serum sickness or serum sickness-like reactions. Additionally, five SAEs reported in dupilumab-treated subjects were infections (sweat gland abscess, cellulitis, erysipelas, kidney infection, and viral infection), 4 SAEs were atopic dermatitis, and 2 SAEs were myocardial infarctions. No other SAEs were reported in more than one subject. Overall, the incidence of SAEs during the initial treatment period appeared low, and with the exception of hypersensitivity reactions, unrelated to dupilumab. During the initial 16-week treatment period, the proportion of subjects who experienced treatment-emergent adverse events (TEAEs) leading to discontinuation was low overall and generally comparable across treatment arms. Of the adverse events that occurred at a higher frequency in the dupilumab treatment groups, one event of allergic conjunctivitis and one event of diarrhea led to permanent study drug discontinuation. About 1% of subjects receiving dupilumab and 1% of subjects receiving placebo discontinued for worsening of atopic

Dimension	Evidence, Uncertainties and Conclusions
	dermatitis. During the 52-week period of Trial 1224, notable TEAEs that led to discontinuation included 2 cases of injections site reactions, and one case each of allergic keratitis, eye pruritus, cystoid macular edema and hypersensitivity. **Comment:** The product label will contain a warning about risk of conjunctivitis and keratitis. Three deaths were reported in the development program for AD; all three were considered unrelated to dupilumab by study investigators. One subject died from complications of asthma; she was a 49 year old female taking salbutamol, valproic acid and citalopram who received her last study treatment on Day 105. She began experiencing cough on Day 165 and experienced extreme dyspnea and loss of consciousness on Day 170, one day after being seen by her primary care physician. She expired on Day 189 from severe hypoxic ischemic encephalopathy, asthma, and respiratory failure. **Comment:** Based on review of this death, the primary reviewer agreed with the investigator that the subject's death does not appear to be related to discontinuation of dupilumab. None-the-less, because dupilumab is under development for the treatment of asthma, but not yet approved for this use, the product label will state, "Safety and efficacy of DUPIXENT have not been established in the treatment of asthma. Advise patients with comorbid asthma not to adjust or stop their asthma treatments without consultation with their physicians." Additionally, because subjects with helminth infections were excluded from clinical trials, the product label will contain a warning that it is unknown if Dupixent (dupilumab) will influence the immune response against helminth infections. **Comment**: The safety profile of Dupixent (dupilumab) has been adequately characterized for use in adult patients with moderate to severe atopic dermatitis.

Dimension	Evidence, Uncertainties and Conclusions
	There are no human data with Dupixent (dupilumab) use in pregnant women to inform a drug-associated risk. There are no data on the presence of dupilumab in human or animal milk, the effects on the breast-fed infant, or the effects on milk production. The safety of Dupixent (dupilumab) in patients less than 18 years of age has not been established.
Risk Management	**Labeling** – Product labeling will include warnings about hypersensitivity reactions, conjunctivitis and keratitis, comorbid asthma, and helminth infections. **Risk Mitigation** - A Risk Evaluation and Mitigation Strategy (REMS) will not be required for Dupixent (dupilumab). **Postmarketing Required Studies** **Pediatric Research Equity Act (PREA)** - The Applicant has an Agreed initial Pediatric Study Plan (iPSP) which covers cohorts down to 6 months of age. These pediatric studies are deferred because the adult studies are ready for approval. Studies are waived for subjects younger than 6 months because study of these subjects would be impossible or highly impractical to conduct. Since dupilumab is being developed for the treatment of moderate to severe atopic dermatitis in pediatric patients who are not adequately controlled with, or who are intolerant to topical (TCS) medications, it will be impractical to enroll patients younger than 6 months of age. **Postmarketing Requirements (PMRs)** – Because pregnant and breastfeeding women, and women planning to become pregnant and breastfeed during the clinical trial period were excluded from participation in the studies, the sponsor has the following PMRs. 1. Conduct a prospective, registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to dupilumab during pregnancy to an unexposed control population. The registry will detect and record major

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	and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age births, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life. 2. Conduct a retrospective cohort study using administrative databases to identify pregnancy outcomes in a cohort of women exposed to dupilumab and a non-dupilumab systemic medication or phototherapy exposure cohort. The outcomes will include major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age births. This study may use multiple data sources in order to obtain a sufficient sample size as women with atopic dermatitis are counseled to avoid systemic treatments while trying to conceive and during the course of pregnancy.

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/s/

KENDALL A MARCUS
03/27/2017

JULIE G BEITZ
03/27/2017
I concur with the recommendation to approve this application.