



WRITTEN REQUEST – AMENDMENT #3

NDA 021518

Astellas Pharma Global Development, Inc.
Attention: Karen Oliver - Manager, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Ms. Oliver:

Please refer to your correspondence dated September 5 and October 10, 2014, requesting changes to FDA's July 27, 2012, Written Request for pediatric studies for solifenacin succinate.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on July 27, 2012, and as amended on April 17, 2014, remain the same. (Text added is underlined. Text deleted is strikethrough.)

- *Patients to be studied:*

Study 1: Pediatric pharmacokinetic study in NDO: A minimum of 12 male and female patients, 6 children (5 to less than 12 years of age) and 6 adolescents (aged 12 to less than 18 years of age).

Study 2: Pediatric safety and efficacy study in NDO: Approximately ~~74~~ 50 subjects in total (~~37~~ at least 20 adolescents aged 12 to less than 18 years and ~~37~~ at least 20 children aged 5 to less than 12 years).

- *Statistical information, including power of study(ies) and statistical assessments:*

Study 1: Pediatric pharmacokinetic study in NDO - A safety analysis population and a pharmacokinetic analysis set will be defined. Data will be analyzed separately for children and adolescents.

Individual solifenacin plasma concentrations and pharmacokinetic parameters will be summarized with descriptive statistics by age group and individual solifenacin concentrations will also be graphically displayed.

Adverse Events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of treatment-emergent adverse events will be summarized by relationship to study drug and overall.

Vital signs, ECG assessments, and safety laboratory evaluations (including urinalysis) will be summarized.

Study 2: Pediatric safety and efficacy study in NDO. Four analysis populations will be defined: the Safety Analysis Set (SAF), Full Analysis Set (FAS), Per Protocol Set (PPS), and Pharmacokinetic Analysis Set (PKAS) for pharmacokinetic population analysis. The FAS will consist of all subjects who receive at least one dose of study drug and have a baseline measurement and have at least one post-baseline measurement for the primary endpoint.

The null hypothesis is that the change from baseline in maximum cystometric capacity (MCC) is equal to 0 mL at Week 24. ~~Thirty-seven (37)~~Forty-four (44) patients will provide ~~at least 80%~~90% power ~~within each age group~~ to detect a change from baseline in MCC of 52 mL, assuming a standard deviation for the change from baseline of 103 mL, a Type I error rate of 5% (two-sided), and a dropout rate of 10%. The change from baseline of 52 mL is based on published reports for changes from baseline for other antimuscarinics, showing increases in MCC of approximately 52 to 98 mL.

The primary analysis will be a paired t-test for the change from baseline to Week 24 in MCC ~~within each age group~~ for both age groups combined for subjects included in the FAS. A 2-sided 95% confidence interval (CI) will be calculated for the mean change from baseline for both age groups combined ~~per age group and overall~~.

While the study will not be powered to detect a treatment effect in the separate adolescents (from 12 to less than 18 years of age) and children (from 5 to less than 12 years of age) cohorts, it will be powered to detect a treatment effect within the combined group.

As an additional analysis, the same method will also be used excluding those subjects who had no leakage up to the maximal 135% of age-related cystometric capacity at baseline (i.e. an analysis on those subjects for whom it is possible that an increase in MCC could be observed).

In addition to the test of the null hypothesis, an additional analysis will be conducted to assess whether the lower bound of the 2-sided 95% CI lies above 16.9 mL, based upon the assumed change from baseline of 52 mL, the assumed standard deviation of 103 mL, statistical power of ~~80%~~90%, and a two-sided significance of 0.05.

- *Timeframe for submitting reports of the studies:*

Reports of the above studies must be submitted to the Agency on or before **June 30, 2016** August 17, 2017. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated July 27, 2012, as amended by this letter and by the previous amendment dated April 17, 2014, must be submitted to the Agency on or before August 17, 2017, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission “**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**” in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (240-276-9327) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872>

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request “**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**” in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Health Project Manager, at 301-796-0875.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:

Complete Copy of Written Request as Amended



COPY OF THE AMENDED WRITTEN REQUEST

Reference is made to your March 23, 2012, Proposed Pediatric Study Request for VESicare® (solifenacin succinate) 5 mg and 10 mg tablets.

Solifenacin succinate is indicated for the treatment of overactive bladder (OAB), with symptoms of urinary frequency, urinary incontinence or urgency in adults. Solifenacin is a muscarinic-receptor antagonist.

This request is focused on the use of solifenacin in pediatric patients with neurogenic detrusor overactivity (NDO), not the use of solifenacin for idiopathic OAB. NDO is defined by the International Children's Continence Society (ICCS) as detrusor overactivity when there is a relevant neurologic condition. Overactive detrusor function is characterized by involuntary detrusor contractions during the filling phase, which may be spontaneous or provoked. NDO, unlike idiopathic OAB, is a urodynamic observation characterized by involuntary detrusor contractions that are spontaneous or provoked during the filling phase, involving a detrusor pressure increase of greater than 15 cm H₂O above baseline.

NDO can develop as a result of a lesion at any level in the nervous system, including the cerebral cortex, spinal cord, or peripheral nervous system. In children, the most prevalent cause of NDO is myelodysplasia, a group of developmental abnormalities that result from defects that occur during neural tube closure. Lesions may include myelomeningocele, meningocele, and occult spinal dysraphism (spina bifida occulta). Another congenital cause is total or partial sacral agenesis, with absence of part or all sacral vertebrae. The most common acquired cause for NDO is cerebral palsy. An injury in the perinatal period (e.g. perinatal infection, anoxia) can produce a neuromuscular disability or a specific cerebral dysfunction. Other acquired causes, such as spinal cord tumors, trauma, or sequelae of transverse myelitis, are less frequent.

The most common pharmacological treatment for NDO is with antimuscarinics which are administered to suppress detrusor overactivity. When coupled with clean intermittent catheterization, antimuscarinic treatment prevents both renal damage and secondary bladder-wall changes by preventing high-pressure detrusor contractions and reducing the bladder pressure during filling. To date, the vast majority (approximately 90%) of patients are treated successfully with the most commonly used antimuscarinic treatment of oxybutynin (oral or intravesical) coupled with clean intermittent self catheterization (CIC). Experience with compounds other than oxybutynin is still limited in children with NDO.

To obtain needed pediatric information on solifenacin succinate, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug

Administration Amendments Act of 2007, that you submit information from the studies described below.

- *Nonclinical study:*

No additional animal studies are required at this time to support the clinical studies described in this written request.

- *Clinical studies:*

Study 1: A Multicenter, Open-label, Single-dose Study to Evaluate Pharmacokinetics, Safety, and Tolerability of Solifenacin Succinate Suspension in Pediatric Patients from 5 to less than 18 years of Age with Neurogenic Detrusor Overactivity (NDO). This is a pediatric pharmacokinetic study in children and adolescents with NDO; the aim of this study is to confirm the comparability of the pharmacokinetic profiles in pediatric NDO and overactive bladder (OAB) patients.

Study 2: A Phase 3, Open-Label, Baseline-controlled, Multicenter, Sequential Dose Titration Study to Assess the Long-Term Efficacy and Safety, and the Pharmacokinetics of Solifenacin Succinate Suspension in Patients from 5 to less than 18 years of Age with Neurogenic Detrusor Overactivity (NDO). This is a long-term safety and efficacy study in children and adolescents with NDO.

These studies are necessary because efficacy in pediatric patients aged 5 to less than 18 years cannot be extrapolated and will be determined by the studies outlined in this Written Request.

- *Objective of each study:*

Study 1: The primary objective is to evaluate the pharmacokinetics of solifenacin succinate suspension after single-dose administration in children and adolescents with NDO and the secondary objective is to evaluate the safety and tolerability of solifenacin succinate suspension after single-dose administration in children and adolescents with NDO.

Study 2: To evaluate the long-term efficacy, safety, and pharmacokinetics of solifenacin succinate suspension after multiple dose administration.

- *Patients to be studied:*

Study 1: Pediatric pharmacokinetic study in NDO: A minimum of 12 male and female patients, 6 children (5 to less than 12 years of age) and 6 adolescents (aged 12 to less than 18 years of age).

Study 2: Pediatric safety and efficacy study in NDO: Approximately 50 subjects in total (at least 20 adolescents aged 12 to less than 18 years and at least 20 children aged 5 to less than 12 years).

- *Representation of Ethnic and Racial Minorities:*

The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*

Study 1: Pediatric pharmacokinetic study in NDO:

Primary: Pharmacokinetic variables:

- 1) Maximum concentration (C_{\max})
- 2) Time to attain C_{\max} (t_{\max})
- 3) Area under the plasma concentration – time curve (AUC) from time of dosing until last measurable concentration (AUC_{last})
- 4) AUC extrapolated until time is infinity (AUC_{inf})
- 5) Apparent terminal elimination half-life ($t_{1/2}$)
- 6) Apparent Total Body Clearance (CL/F)
- 7) Apparent volume of distribution during the terminal phase (V_z/F)

Secondary: Safety variables:

Adverse events, clinical laboratory evaluations (hematology, biochemistry, urinalysis), vital signs, electrocardiograms (ECGs), and physical examination.

Study 2: Pediatric safety and efficacy study in NDO

Efficacy Variables

- The primary efficacy variable and primary endpoint will be the change from baseline in maximum cystometric capacity (MCC) after 24 weeks of treatment. The secondary efficacy variables based on urodynamics are change from baseline to the assessment for the last possible titration step (i.e. week 12 in current protocol, week 9 for subjects enrolled to protocol version 1.0 or 1.1) and/or Week 24:
 - 1) MCC (for last possible titration step only);
 - 2) Bladder compliance ($\Delta V/\Delta P_{\text{det}}$);
 - 3) Bladder volume until first detrusor contraction > 15 cm H₂O;
 - 4) Bladder volume at 30 cm H₂O detrusor pressure;

- 5) Bladder volume at 40 cm H₂O detrusor pressure;
- 6) Number of overactive detrusor contractions > 15 cm H₂O until leakage or maximum 135% of age-related bladder capacity;
- 7) Detrusor pressure at leakage or 135% of age-related cystometric capacity

In addition, there is an optional urodynamic investigation at Week 52. When this is performed, the urodynamic parameters listed above will be recorded and evaluated as secondary efficacy variables.

- The secondary efficacy variables based on diary will be:
 - 1) Change from baseline to each post-baseline visit (week 3 up to week 52) in:
 - Average catheterized volume per catheterization;
 - Maximum catheterized volume per day;
 - Mean number of incontinence episodes per 24 hours;
 - Number of dry (incontinence-free) days/7 days.
 - 2) Change from baseline to visit 8 (week 24) and visit 10 (week 52) in:
 - Quality of life.

Safety variables: The key safety variables which will be specifically monitored during the study are:

- Overall incidence and severity of adverse events,
- Change from baseline in vital signs (systolic and diastolic blood pressure, pulse rate and temperature) for visit 4 (week 3) to visit 10 (week 52)
- Change from baseline to visit 8 (week 24) and visit 10 (week 52) in safety laboratory parameters (hematology, chemistry, urinalysis);
- Change from baseline to visit 7 (week 12), visit 8 (week 24), and visit 10 (week 52) in ECG assessments
- Change from baseline to visit 10 (week 52) in creatinine clearance as an indicator for renal function
- Change from baseline to visit 10 (week 52) in renal ultrasound assessment to monitor structural changes in the urinary tract
- Change from baseline to visit 10 (week 52) in ocular accommodation testing;
- Change from baseline to visit 7 (week 12), visit 8 (week 24) and visit 10 (week 52) in cognitive function;
- Change from baseline to visit 7 (week 12), visit 8 (week 24) and visit 10 (week 52) in height and weight

Pharmacokinetic variables: Plasma concentrations of solifenacin succinate will be used to derive the following pharmacokinetic parameters: C_{max} , t_{max} , AUC_{tau} , C_{trough} , $t_{1/2}$, CL/F and V/F .

- *Known drug safety concerns and monitoring:*

Solifenacin succinate is contraindicated in patients with urinary retention, gastric retention, uncontrolled narrow-angle glaucoma, and patients who have demonstrated hypersensitivity to the drug.

Angioedema of the face, lips, tongue, and/or larynx have been reported with solifenacin. In some cases angioedema occurred after the first dose. Cases of angioedema have been reported to occur hours after the first dose or after multiple doses. Anaphylactic reactions have been reported rarely in patients treated with solifenacin succinate. Solifenacin succinate should not be used in patients with a known or suspected hypersensitivity to solifenacin succinate.

Solifenacin succinate, like other anticholinergic drugs, should be administered with caution to patients with:

- clinically significant bladder outflow obstruction because of the risk of urinary retention
- decreased gastrointestinal motility
- being treated for narrow-angle glaucoma
- hepatic impairment.
- renal impairment.

In a study of the effect of solifenacin on the QT interval in 76 healthy women the QT prolonging effect appeared less with solifenacin 10 mg than with 30 mg (three times the maximum recommended adult dose), and the effect of solifenacin 30 mg did not appear as large as that of the positive control moxifloxacin at its therapeutic dose. This observation should be considered in clinical decisions to prescribe solifenacin succinate for patients with a known history of QT prolongation or patients who are taking medications known to prolong the QT interval.

Specific safety monitoring to be conducted as part of Studies 1 and 2 are listed above and will include:

Study 1: Pediatric pharmacokinetic study in NDO: Safety assessments include recording and monitoring of vital signs, electrocardiograms (ECGs), physical examination, adverse events as reported by the subject and the investigator, monitoring of hematology and serum chemistry parameters, and urinalysis.

Study 2: Pediatric safety and efficacy study in NDO: Safety assessments include recording and monitoring of vital signs, ECGs, cognitive testing, ocular accommodation assessment, physical exams, height and weight, renal function and ultrasound of upper urinary tract, adverse events and quality of life as reported by the subject and/or the

subjects' parents/guardians and/or the investigator, monitoring of hematology and serum chemistry parameters, and urinalysis.

- *Extraordinary results:*

In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

- *dosage form:* Oral suspension formulation (1 mg/mL solifenacin succinate)
- *route of administration:* Oral
- *regimen:* Once daily

Study 1: Pediatric pharmacokinetic study in NDO

Weight-range based doses will be administered based on those used in a prior European study conducted in pediatric patients with idiopathic OAB. Doses were predicted to result in equivalent maximum plasma concentrations to 5 mg in adults at steady state. Table 1 shows the calculated pediatric equivalent dose per weight range, as predicted from the European study, and the actual dose to be administered in Study 1.

Table 1 Predicted Pediatric Doses Equivalent to 5 mg Once Daily in Adults at Steady State (PED5) and Corresponding Dose to be Administered as Single-dose[†], per Weight Range

Weight range (kg)	PED5 (mg)	Single-dose (mg[†])
14-20	1.32	4.0
21-31	2.00	6.0
32-50	3.00	9.0
51-70	4.47	13.4
> 70	5.00	15.0

[†] Single-dose expressed in mg. With suspension strength of 1 mg/mL, the amounts listed also apply for the volumes (mL) to be administered.

Study 2: Pediatric safety and efficacy study in NDO.

The initial dose administered in cohort 1 starts with the equivalent of 5 mg in adults and will be administered once a day orally via syringe. Doses will be calculated according to weight measured at the Baseline visit (visit 3) for visits 3 to 7 inclusive. At the Week 24

visit (visit 8) weight will be measured again. The volume of study medication will be adjusted if any change in weight places the subject within a new weight category. The current pediatric equivalent dose of study medication will remain unchanged, but a new volume may be assigned by the interactive response technology according to the subjects new weight category. This dose and volume will be assigned for visit 8 through visit 9 until the end of treatment at visit 10. The dose will be titrated up or down to the equivalent of the doses of 2.5, 7.5, and 10 mg in adults, according to the weight and titration criteria described in the study protocol.

The starting dose and titration steps for cohort 2 will be determined after review of the safety data from the first 10 subjects who have completed week 12 of cohort 1 by the data safety monitoring board (DSMB).

Dose selection for Study 2 will be confirmed with FDA once the results from Study 1 are available.

Use an age-appropriate formulation in the studies described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), if

- 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
- 2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
- 3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice indicating you have not marketed the new pediatric formulation

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Statistical information, including power of study(ies) and statistical assessments:*

Study 1: Pediatric pharmacokinetic study in NDO - A safety analysis population and a pharmacokinetic analysis set will be defined. Data will be analyzed separately for children and adolescents.

Individual solifenacin plasma concentrations and pharmacokinetic parameters will be summarized with descriptive statistics by age group and individual solifenacin concentrations will also be graphically displayed.

Adverse Events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of treatment-emergent adverse events will be summarized by relationship to study drug and overall.

Vital signs, ECG assessments, and safety laboratory evaluations (including urinalysis) will be summarized.

Study 2: Pediatric safety and efficacy study in NDO. Four analysis populations will be defined: the Safety Analysis Set (SAF), Full Analysis Set (FAS), Per Protocol Set (PPS), and Pharmacokinetic Analysis Set (PKAS) for pharmacokinetic population analysis. The FAS will consist of all subjects who receive at least one dose of study drug and have a baseline measurement and have at least one post-baseline measurement for the primary endpoint.

The null hypothesis is that the change from baseline in maximum cystometric capacity (MCC) is equal to 0 mL at Week 24. Forty-four (44) patients will provide 90% power to detect a change from baseline in MCC of 52 mL, assuming a standard deviation for the change from baseline of 103 mL, a Type I error rate of 5% (two-sided), and a dropout rate of 10%. The change from baseline of 52 mL is based on published reports for changes from baseline for other antimuscarinics, showing increases in MCC of approximately 52 to 98 mL.

The primary analysis will be a paired t-test for the change from baseline to Week 24 in MCC for both age groups combined for subjects included in the FAS. A 2-sided 95% confidence interval (CI) will be calculated for the mean change from baseline for both age groups combined.

While the study will not be powered to detect a treatment effect in the separate adolescents (from 12 to less than 18 years of age) and children (from 5 to less than 12 years of age) cohorts, it will be powered to detect a treatment effect within the combined group.

As an additional analysis, the same method will also be used excluding those subjects who had no leakage up to the maximal 135% of age-related cystometric capacity at baseline (i.e. an analysis on those subjects for whom it is possible that an increase in MCC could be observed).

In addition to the test of the null hypothesis, an additional analysis will be conducted to assess whether the lower bound of the 2-sided 95% CI lies above 16.9 mL, based upon the assumed change from baseline of 52 mL, the assumed standard deviation of 103 mL, statistical power of 90%, and a two-sided significance of 0.05.

The mean change from baseline at week 9, week 24 (and week 52) in MCC and its variability will be qualitatively compared with published historical data. The relevant historical control data will come from treatment with another antimuscarinic drug (oxybutynin treatment; Franco et al, 2005).

The results of variables derived from the micturition/catheterization and incontinence diary and also the quality of life data will be compared with the results (including 2-sided 95% CI) collected for the same subjects at the start of the washout of their previous OAB treatment and also with published data from other studies.

Safety endpoints will be summarized for the Safety Analysis Set using descriptive statistics and also 2-sided 95% CIs for some selected parameters. Mean change from baseline (with 2-sided 95% CI) in cognitive function will be compared with data from published studies.

Other analyses: Descriptive statistics will be used to explore whether there is an association between certain subject characteristics (like medical history) and the final titrated solifenacin succinate doses. Collected data on compliance rates and maintenance of treatment will be analyzed using descriptive statistics.

Other secondary efficacy variables will be analyzed analogously.

- *Labeling that may result from the studies:*

Appropriate sections of the labeling may be changed to incorporate the findings of these studies. You must submit proposed pediatric labeling to incorporate the findings of the studies. Under section 505A(j) of the Act, regardless of whether the studies demonstrate that solifenacin succinate is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the studies. Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the studies.

- *Format and types of reports to be submitted:*

You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document “Study Data Specifications,” which is posted on the FDA website at <http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf> and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072349.pdf>.

- *Timeframe for submitting reports of the studies:*

Reports of the above studies must be submitted to the Agency on or before August 17, 2017. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:*

Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the studies. If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the studies, but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, complete response); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872>

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST**"

FOR PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

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

/s/

JULIE G BEITZ
12/12/2014