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APPLICATION NUMBER:

211970Orig1s000

OTHER ACTION LETTERS



NDA 211970

COMPLETE RESPONSE

Sarepta Therapeutics, Inc.
Attention: Patrick O'Malley
Executive Director, Regulatory Affairs
215 First Street, Suite 415
Cambridge, MA 02142

Dear Mr. O'Malley:

Please refer to your new drug application (NDA) dated December 19, 2018, received December 19, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic (FD&C) Act for Vyondys 53 (golodirsen) injection.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

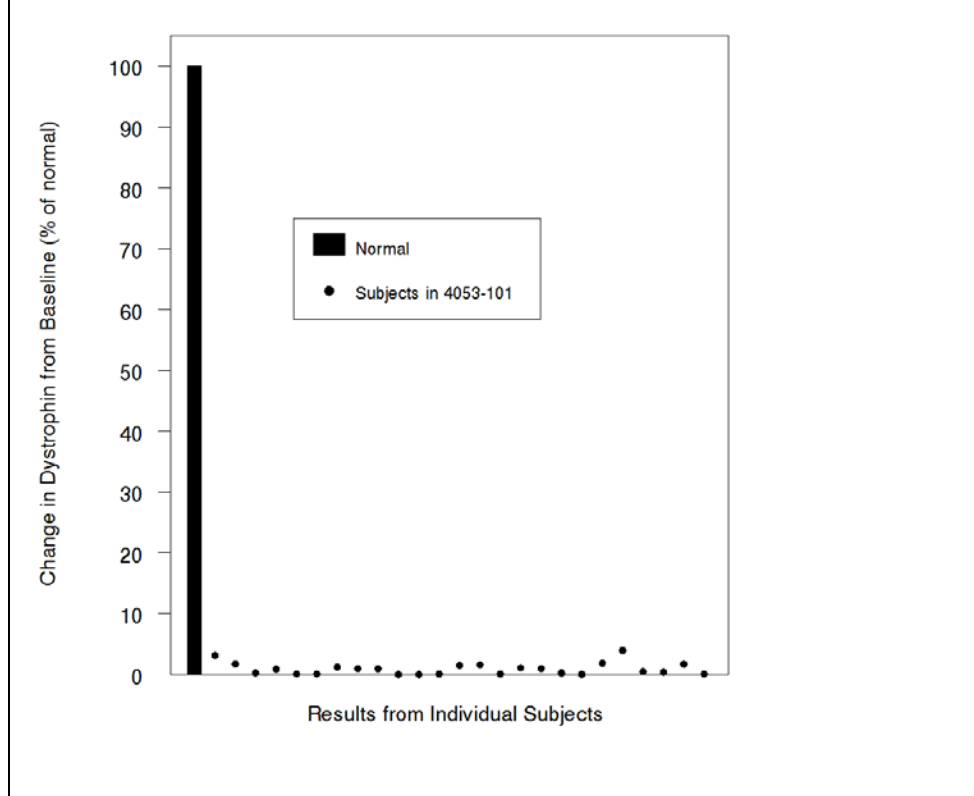
In support of golodirsen's approval, you submitted the results of Study 4053-101, demonstrating production of truncated dystrophin, a surrogate marker you consider "reasonably likely" to predict clinical benefit. Under the regulatory framework of section 506(c) of the FD&C Act and 21 CFR part 314, subpart H, you are seeking accelerated approval of golodirsen.

Benefits:

For the 25 evaluable patients in the study, the baseline mean dystrophin level assessed by Western blot was 0.10 ± 0.07 (percent of normal; mean \pm SD). At Week 48, the mean dystrophin level was 1.02 ± 1.03 (percent of normal; mean \pm SD), corresponding to a mean increase of 0.92 ± 1.01 percent of normal. The individual changes in dystrophin are shown below in Figure 1 using a normal (100%) scale to place the data in proper perspective and avoid exaggeration of the effect size. You note that the mean increases in truncated dystrophin are similar in response to golodirsen and eteplirsen in patients with mutations amenable to exon 53 and exon 51 skipping, respectively – with absolute mean increases of 0.9%, i.e., 9 parts in a thousand. We agree.

If one accepts the premise that a small increase in truncated dystrophin, on the order of 9 parts per thousand, is reasonably likely to predict clinical benefit, it seems reasonable to assume that the clinical benefit would be commensurately small.

Figure 1: Study 4053-101 – Change in Dystrophin Relative to Normal Levels



The 6-minute walk data from Study 4053-101 are not discussed herein, but they show progressive loss of physical function in essentially all boys. Moreover, there is no correlation between maintenance of physical performance and the magnitude of truncated dystrophin production, further suggesting that if there is indeed a clinical effect of golodirsen, the effect size is small.

Risks:

There are two important safety issues: 1) serious infections related to delivery of the drug; and 2) renal toxicity. Both are potentially life-threatening, and the latter is difficult or impossible to monitor.

Serious Infections:

Late in the review cycle I learned that reports of significant infections, bacteremia, sepsis, septic shock, and deaths have been submitted through quarterly Periodic Adverse Drug Experience Reports (PADERS) to the eteplirsen New Drug Application (NDA) file. Some cases have been reported spontaneously to FDA's Adverse Event Reporting System (FAERS). These cases, as summarized by the Division, are shown in Table 1. I found no mention or discussion of these cases in the golodirsen NDA.

Table 1: Eteplirsen’s Postmarketing Reports of Device Infections, Bacteremia, and Sepsis

FAERS#	Date	Medical History	Preferred Terms	Narrative	Comments
13122403	1/2017	Atrial fibrillation, Cachexia, Cardiomyopathy, Decubitus ulcer, Duchenne muscular dystrophy, Gastrostomy tube site complication, Muscle contracture, Respiratory failure, Tracheostomy, Vascular device user	Septic shock, Sepsis, Respiratory distress, Ischaemic hepatitis, Cardiac arrest	Patient with ventilator-dependence, g-tube, port. Also with chronic decubitus ulcers. Admitted to hospital with respiratory distress, cardiac arrest, sepsis. Death from cardiac arrest. Death was attributed to "end-stage DMD."	confounded by ventilator, decub ulcers
13268695	2/2017	Autism spectrum disorder, Colonoscopy, Dialysis, Duchenne muscular dystrophy, Joint contracture, Obesity, Respiratory failure, Scoliosis, Tenotomy, Tooth disorder, Tracheostomy, Ventricular dyssynchrony	Tachycardia, Pseudomonal bacteraemia, Pneumonia, Pain in extremity, Malaise, Hypertension, Chest pain, Anxiety	Patient with ventilator-dependence and port. Developed bilateral leg pain and chest pain after port de-accessed. Taken to ED for tachycardia and hypertension. Diagnosed with pneumonia and pseudomonas bacteremia. Port + for pseudomonas and removed. Exondys discontinued as family did not want port replaced.	confounded by ventilator
14077329	7/2017	Central venous catheterisation, Pericardial effusion	Pyrexia, Dehydration, Bacteraemia, Abdominal pain	Patient with port. The patient presented with a fever of 103F and abdominal pain and was hospitalised for dehydration and bacteremia. Bacterial culture grew Klebsiella and treatment included IV antibiotics.	port likely source of infection
14284355	11/2017	Not reported	Device related infection	Patient became ill, went to ED, treated with antibiotics for presumed port infection; port culture reported to be positive but organism not identified; (b) (6): admitted to hospital for "port issues."	port likely source of infection
14484983	1/2019	Not reported	Device related infection	Patient noticed discharge from port and went to hospital where port was removed.	port likely source of infection
14828296	3/2018	Abdominal pain, Central venous catheterisation, Chills, Gastrointestinal tube insertion, Leukopenia, Pyrexia, Thrombocytopenia	Sepsis, Respiratory failure, Gallbladder disorder	Patient taken to ED with fever and decreased oral intake, received IV fluids: (b) (6): taken to ED with septic shock (fever, abdominal pain, tachycardia, decreased urine) presumed secondary to line infection. Line culture with Strep pyogenes.	port likely source of infection
15143119	3/2018	Central venous catheterisation, Device related infection	Injection site infection, Infusion site swelling	Patient noticed port infection and went to ED where port was removed. Had Exondys infusion administered by peripheral IV on the same day and experienced swelling.	port likely source of infection
15182648	7/2018	Anaemia, Cardiomyopathy, Dependence on respirator, Gastrostomy, Inflammatory bowel disease, Muscle contracture, Respiratory failure	Sepsis, Oedema peripheral, Cardiac failure congestive	Patient with ventilator dependence, g-tube, port. (b) (6): patient hospitalized for peripheral edema and sepsis. (b) (6): patient died of "congestive heart failure."	death - multiple factors
15590967	UNK	Not reported	Sepsis	Patient went to ER for possible sepsis.	insufficient information
15699217	11/2018	Cardiomyopathy, Chronic respiratory failure, Depression, Hospitalisation, Hypotonia, Hypoxic-ischaemic encephalopathy, Implantable defibrillator insertion, Joint contracture, Mechanical ventilation, Obesity, Pneumonia, Seizure, Sinus arrest, Sleep apnoea syndrome, Spinal operation, Tracheostomy	Septic shock, Sepsis, Pneumonia, Multiple organ dysfunction syndrome, Cardio-respiratory arrest, Brain injury	Patient with pacemaker/AICD, ventilator, port. (b) (6) patient found pulseless at home; resuscitated for 10 minutes; cardiac arrest again in ED with 2 minutes of resuscitation; CT suggestive of aspiration pneumonia; diagnosed with septic shock secondary to pneumonia; patient comatose; CT head c/w diffuse anoxic injury. Removed from life support.	confounded by ventilator, aspiration pneumonia
16084969	UNK	Not reported	Sepsis	Patient's family member stated that the patient had sepsis on an unknown date.	insufficient information

The most recent PADER (7/18/2019) submitted to the eteplirsen NDA states that a total of 469 patients have been exposed to commercial eteplirsen through 3/18/2019. Thus, we are aware of some 11 cases reported with 469 patients exposed – a frequency of 2.3%. Because reporting in FAERS is voluntary for health care professionals, patients, and their advocates, we recognize that substantial underreporting is possible (conversely, the raw data may contain duplicate reports). In any case, it seems likely that the rate of serious infusion device-related infections with eteplirsen has been *at least 2.3%*.

Some may characterize these infections as device-related rather than drug-related and downplay their importance. This is a weak argument: these individuals would have had no reason for implantation of a central intravenous infusion port other than to receive eteplirsen; many of these infections would not have occurred if the patients had not been receiving eteplirsen. *If these devices are necessary to deliver the drug, then these infections must be construed to be drug-related.*

Although the aforementioned information was obtained from the eteplirsen postmarketing experience, such information is directly applicable to the potential marketing of golodirsen, which too would be administered through implanted infusion ports in many patients.

In the golodirsen clinical development program, study drugs were administered via a central venous access port in approximately half of the patients (~30 of 60). Approximately 30% of such patients (i.e., ~9) had device-related adverse events. These were generally procedural pain, catheter site pain, catheter site bruises, and rash, and did not lead to discontinuation or interruption of the investigational product. There were no serious or severe adverse events of infection in the adae.xpt database, and no reports of bacteremia or sepsis in the Summary of Clinical Safety.

You may consider the lack of device-related infections in the golodirsen development program to be reassuring. Importantly however, only ~30 patients have received the drug through a central venous access port, and such patients were enrolled at highly specialized centers. With no infections reported in ~30 patients with infusion ports through a median exposure of ~1.5 years, based on the rule of 3, the estimated upper limit of the 95% confidence interval for the risk of a serious infection through 1.5 years is $1/(30/3)$ or approximately 10%.

We well recognize that, no matter the level of expertise of healthcare providers involved in inserting and managing central access ports, infections *will occur*, and the risk in the Duchenne muscular dystrophy (DMD) patient population is increased in light of the chronic corticosteroid use and generally debilitated condition in many of the patients. Thus, the 2.3% or greater risk of serious infections reported in the eteplirsen postmarketing period is directly applicable to future patients who might receive commercially available golodirsen. Ignoring the applicability of these infections to boys

who would receive golodirsen is irresponsible, as this puts vulnerable boys at even greater risk of complications and death.

Renal Toxicity:

As you know, renal toxicity, including potentially fatal glomerulonephritis, has occurred with administration of other antisense oligonucleotides. The nonclinical studies for golodirsen showed evidence of significant renal toxicity. Chronic golodirsen exposure was found to cause severe renal impairment, and there was evidence of irreversible renal damage in juvenile animals with only a small safety margin. Some animals had signs of renal failure leading to death.

Importantly, the potential for clinical renal toxicity is magnified by two factors:

- 1) Golodirsen is excreted mostly unchanged in the urine; therefore, renal dysfunction increases golodirsen exposure. In subjects with reduced creatinine clearance (between 30 and 60 mL/min/1.73/m²), exposure (area under the concentration-time curve) increased approximately 2-fold. Thus, renal toxicity leading to a decrease in renal function could be self-perpetuating, with the potential to occur rapidly.
- 2) Because patients with DMD have reduced muscle mass with attenuated creatinine production, serum creatinine cannot be used as the basis to monitor renal function or to adjust the dose of medications. Monitoring changes in renal function in patients with DMD is an issue that needs further research. Cystatin C, kidney injury molecule-1 (KIM-1), and the urinary protein/creatinine ratio have been mentioned as monitorable parameters; however, none of the details have been worked out, and, accordingly, no practicable proposals for renal monitoring have been proposed.

Ordinarily, where harm is anticipated, there are adequate means available to monitor patients to avoid risk, and appropriate advice can be recommended in labeling. The present situation is unique, however, in that standard monitoring of serum creatinine would not be sufficient for these patients. Because there is no established way to monitor renal function in this patient population, practitioners could be blind to worsening renal function, leaving these patients vulnerable. At this juncture, therefore, there is no way to provide adequate instructions for use in labeling.

Although there was no clear evidence of renal toxicity in the clinical development program, the size of the exposed patient population was quite small, and the development program would be unlikely to detect adverse events that occur infrequently.

Disparate Risks of Golodirsén and Eteplirsén (at the Time of Its Approval):Infections:

When eteplirsén was approved in 2016, the theoretical possibility of infections related to indwelling ports was raised; however, no serious infections had been reported in the development program. *Importantly, therefore, the possibility of infections did not figure into eteplirsén's risk-benefit calculus at the time of its approval.*

Three years later, with 469 patients exposed to commercial eteplirsén, we have incontrovertible evidence of a significant likelihood of serious infections, including sepsis, septic shock, and possibly death. Thus, the risk of serious and life-threatening infections is no longer theoretical. Moreover, the infection risk is a function of the patient population and the delivery system – not the drug. Accordingly, the risk is fully applicable to golodirsén, and the 2.3% frequency from eteplirsén's voluntary postmarketing reporting probably represents a conservative estimate of the risk, given the typical under-reporting of spontaneous adverse events.

Renal toxicity:

As noted above, based on nonclinical studies, golodirsén has a greater risk for renal toxicity than does eteplirsén; renal failure leading to death was observed in the golodirsén juvenile rat study, but not in a similar eteplirsén juvenile rat study. And again, because there is no proven way to monitor renal function in these patients, we are not aware of a mechanism to provide adequate instructions for use in labeling for golodirsén.

When eteplirsén was granted accelerated approval in 2016, you were required to perform a postmarketing study to verify eteplirsén's clinical benefit. Patients were to be randomized to the approved dosage of eteplirsén (30 mg/kg weekly) or to a dose 7-fold higher, e.g., 30 mg/kg daily. We thought that the considerable increase in dose was acceptable because we were not aware of any significant toxicity related to eteplirsén. The same cannot be said of golodirsén, where nonclinical data have demonstrated considerable risk of renal toxicity.

In summary, therefore, at the time of eteplirsén's approval, there were no adverse events of note in the clinical data, and no nonclinical concerns. Although we recognized that the clinical database was limited, the drug had no known toxicities, which enabled us to require a confirmatory trial to study a dose that was 7-fold higher than the to-be-marketed dose. The risk of serious and life-threatening infections, including sepsis, was not known in 2016 when eteplirsén gained accelerated approval. In essence, the small potential benefit of eteplirsén was weighed against essentially zero risk.

With golodirsén, on the other hand, there are concerns with respect to renal toxicity, with no proven way to monitor patients to recognize toxicity early when it might be

reversible. We are not aware of a way to write adequate directions for use. We now have evidence that patients with DMD who undergo implantation of intravenous infusion ports will have serious and life-threatening infections, with the risk exacerbated by chronic corticosteroid use and general debilitation. Neither of these risks were considerations in the approval of eteplirsen: the renal risk did not exist, and the risk of infections was only theoretical.

DECISION

In the Commissioner's September 16, 2016, decision with respect to "Scientific Dispute Regarding Accelerated Approval of Sarepta Therapeutics' Eteplirsen (NDA 206488),"¹ under "Opportunities for Process Improvement," it was explicitly noted (in bold lettering):

"Thus, I am confident that this unique situation will not set a general precedent for drug approvals under the accelerated approval pathway, as the statute and regulations are clear that each situation must be evaluated on its own merits based on the totality of data and information."

The Commissioner's opinion was prescient, given the present circumstances. Golodirsen must be evaluated on its own merits based on the totality of the data and available information.

First, considering the Center Director's 2016 decision on the accelerated approval of eteplirsen, there would have been support for granting accelerated approval to golodirsen – assuming other important aspects of the two drugs were equal. Unfortunately, golodirsen's risk profile differs considerably from the risk profile of eteplirsen as it was known at the time of approval. At the time eteplirsen was approved, essentially no risks had been identified, albeit there was limited clinical experience. **Importantly therefore, eteplirsen's benefit – no matter how tiny and unverified – was weighed against essentially no risk.** In contrast, golodirsen's risk of renal toxicity poses a significant concern, for which a warning has been placed in the draft labeling. As noted above, the renal risk could be self-perpetuating because the drug is primarily eliminated through renal excretion. Moreover, because serum creatinine cannot be used to monitor renal function in patients with DMD, there is no practicable and proven paradigm for renal monitoring for this drug in this patient population. The problem is laid bare by statements in section 5.2 of the draft labeling that has been under negotiation. With respect to renal monitoring; these statements are neither comprehensible nor actionable:

"Renal function should be monitored in patients taking VYONDYS 53. Because of the effect of reduced skeletal muscle mass on creatinine measurements, creatinine may not be a reliable measure of renal function in DMD patients."

¹ Downloaded 8/12/2019 from https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488Orig1s000SumR.pdf

Having recently become aware of postmarketing reports of serious and life-threatening infections with eteplirsen, we now recognize that administration of both drugs via implanted intravenous ports poses considerable risk of serious and life-threatening infections. Though we well recognize that the risk is similar for both drugs, the risk was only theoretical when eteplirsen was approved in 2016; *the risk was not considered in the Center's approval of eteplirsen*. For the present evaluation of golodirsen, we are acutely aware of this risk, and it must be weighed when considering accelerated approval. The important point here is that the benefit-risk balance with golodirsen differs from the benefit-risk balance that was known for eteplirsen at the time of its accelerated approval.

As noted, if a mean increase in dystrophin of 9 parts per thousand is construed to be reasonably likely to predict clinical benefit, the clinical benefit would surely be, at most, very small. **I have reached the conclusion that this small benefit, which has not yet been verified, does not outweigh its risks.** One risk (serious and life-threatening infections) is proven; the other (renal toxicity) has been identified in nonclinical studies, and significant glomerulonephritis has occurred with other antisense oligonucleotides. Though renal toxicity has not been detected in the small number of patients exposed in the golodirsen development program, the risk is nevertheless concerning and unmonitorable. The risk-benefit profile for eteplirsen was quite different when it was given accelerated approval in 2016, as no risks were evident.

Confirming the Clinical Benefit of Small Changes in Truncated Dystrophin:

As noted above, you were to have begun your confirmatory trial for eteplirsen some time ago – ideally at the time of its 2016 approval or soon thereafter. As of today, exactly 2 years and 11 months after approval, you have not *initiated* the required confirmatory trial. Given that you have established a standard paradigm and design for these types of studies, given that you have relationships with a number of DMD referral centers, and given that some 469 patients have received commercial eteplirsen, it is necessary to ask why you have not initiated your required confirmatory study with due diligence. We possess no more knowledge than we did three years ago in terms of the likelihood that small amounts of truncated dystrophin will lead to clinical benefit. Such information, if available now, could have informed our decision-making for golodirsen. And for eteplirsen, patients are being subjected to the risk of serious and life-threatening infections. One could even argue that eteplirsen's benefit-risk profile has changed in light of new information regarding the risk of serious infections and the uncertainty of its benefit. **Please understand that your failure to initiate eteplirsen's confirmatory study with due diligence is very concerning to FDA and is of concern to the public.**

PATH FORWARD:

Because of the risks of serious infections and renal toxicity, the most expeditious route to approval would be to provide substantial evidence of a clinical benefit on physical

function/performance (e.g., North Star Ambulatory Assessment, 6-minute walk distance, other measures of physical performance) through completion of the placebo-controlled study. It would also be necessary to develop a practicable renal monitoring paradigm to allow mitigation of the renal risk. Finally, if the drug could be administered without implantation of an indwelling port, the benefit-risk profile could be improved.

ADDITIONAL COMMENT:

You have continued to perform open muscle biopsies on patients to obtain immunohistochemistry data. Such information can be useful to show the localization of dystrophin in skeletal muscle samples, however, samples from a small number of patients would suffice for this purpose. The immunohistochemistry data are not quantitative; they can be, in fact, quite deceptive. We continue to discourage you from pursuing open muscle biopsies in these patients, which can be painful and invasive. Adequate tissue can be collected for Western blot using less invasive needle biopsy methods.

PRESCRIBING INFORMATION

- (1) We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information² and Pregnancy and Lactation Labeling Final Rule³ websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.⁴

CARTON AND CONTAINER LABELING

- (2) Submit draft carton and container labeling based on your proposed revisions dated April 15, 2019.

² <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>

³ <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>

⁴ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

PROPRIETARY NAME

- (3) Please refer to our correspondence dated May 31, 2019, which addresses the proposed proprietary name, Vyondys 53. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

- (1) Describe in detail any significant changes or findings in the safety profile.
- (2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
 - Present tabulations of the new safety data combined with the original application data.
 - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
- (3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
- (4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
- (5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.
- (6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

- (7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
- (8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Fannie Choy, Regulatory Project Manager, by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ELLIS F UNGER
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