CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203109Orig1s000

SUMMARY REVIEW

MEMORANDUM

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

DATE: May 11, 2012

FROM: Abraham Karkowsky, M.D., Ph.D. Group Leader, Division of Cardiovascular and Renal Products, HFD-110.

TO: Dr. Norman Stockbridge, M.D., Ph.D., Director, Division of Cardiovascular and Renal Products, HFD-110.

SUBJECT: Approval of new formulation sildenafil citrate powder for reconstitution of suspension (POS);
Complete response for use in a pediatric population.

The information which was incorporated into this review was derived from the following primary reviews:

- DSI audit by Xikui Chen, Ph.D., Bioequivalence Investigation Branch dated 4/27/12.
- Medical Officer Review by Maryann Gordon, M.D. dated 4/18/12.
- Statistical Review by John Lawrence, Ph.D. dated 4/29/12.
- Clinical Pharmacology Review by Satjit Brar, Pharm.D., Ph.D. dated 4/27/12.
- Pharmacology/Toxicology Review by Donald N. Jensen, DVM, MS dated 5/1/12.
- ONDQA Biopharmaceutic Review by Arzu Selen, Ph.D. dated 4/25/12.
- Chemistry Review by Mohan K. Sapru, Ph.D. dated 4/27/12.
- Initial Quality Assessment by Kasturi Srinivasachar, Ph.D. dated 1/18/12.
- Label and Labeling Review by Ray Ford, RPh dated 5/2/12.
- Safety memo by Mary Ross Southworth, PharmD., Deputy Director, Safety dated 4/20/12.
- Dissolution Telecon, Office of New Drug Quality Assessment signed by Teshara G. Bouie dated 5/1/12.

Background:

This submission (NDA 203,109) is the results of the pediatric development program for sildenafil citrate. The drug was initially approved on 3/27/98 (NDA 20,895) for erectile dysfunction as VIAGRA® and subsequently approved under NDA 21,845 for the treatment of pulmonary artery hypertension as REVATIO®. The initial indication for the pulmonary hypertension indication was "to improve exercise". A supplemental application approved in May 2009 added a "delay in clinical worsening" indication. A new formulation (NDA 22,473) was approved as a 0.8 mg/ml solution for injection as a TID regimen for those unable to take the oral formulation.

The evolution of the pediatric written request is documented in the Mr. Brum, the PM's review. The initial application for a written request was submitted on 12/17/2001 prior to the

approval for the adult indication in PAH patients. Once the adult application for REVATIO® was approved, a modified program was agreed upon that allowed for approval of a pediatric development program with the following studies: validating of the formulation, a short term parallel dose efficacy study and a long-term safety extension study. The initial efficacy endpoint was to be an increase in a measurement of performance by cycle ergometry.

Analyses done by the FDA (Dr. Satjit Brar), demonstrated, at least on a study cohort level that a change in either pulmonary vascular resistance index (PVRi) or mean pulmonary artery pressure (mPAP) was a good surrogate for increase in 6 minute walk distance (6MWD). An advisory committee was convened on July 29, 2010 to discuss the potential use of the hemodynamic measurements as primary endpoints for the efficacy portion of the pediatric development program, particularly for the younger population unable to easily exercise. The advisory committee indicated that a hemodynamic endpoint given the correlation of PVRi or mPAP and walk performance would be acceptable.

The primary clinical studies submitted on behalf of the amended written request were Study A1481131 (#31), a 16-week phase 3, placebo controlled dose ranging study in pediatric patients 1-17 years. The second pivotal study is study A1481156 (#56) a long-term randomized extension of study #31.

Recommendation:

This memo recommends that the drug sildenafil citrate (REVATIO®) powder for reconstitution as an oral solution (POS) not be approved for use in the pediatric population for the treatment of pulmonary artery hypertension. A complete response should be forwarded to the sponsor to indicate that in order for this application to be approved they would need to demonstrate safety of long-term use in pediatrics.

The formulation itself has been adequately characterized and is a reliable formulation so that it may be useful in an adult population who are unable to swallow pills and for whom the intravenous route is not convenient. The label will be modified (b) (4) long-term usage in children for the treatment of pulmonary artery hypertension.

The label should also indicate that the prevention of deterioration in the adult population is limited to a 16-week observation period. A PMR should be issued to establish that in a controlled dose-response study, no harm with long term use occurs in an adult PAH population.

Lastly, based on two lethal events and three additional serious non-lethal events, it appears necessary either to proscribe routine right heart catheterization or to severely limit this procedure to study sites which have demonstrated an expertise in the performance of this procedure in PAH population.

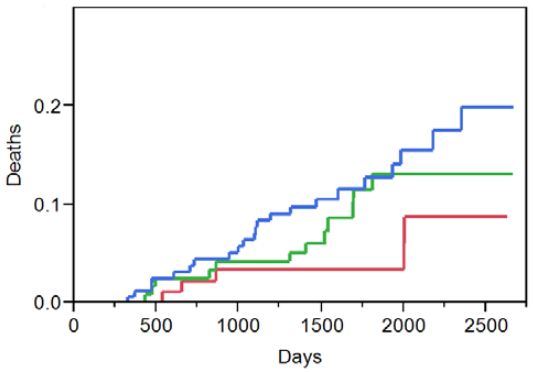
Review:

In the long term extension study of the sildenafil pediatric program, there was a strong suggestion of a dose-response effect for mortal outcomes, with the highest dose having the worst outcome. Doses, both in a short term (16 week), placebo-controlled, dose ranging study as well as in the long-term extension study were defined as low, medium and high. All doses were

administered TID. The specific dose was defined by the dose group and the subject's weight. The studies will be further described later.

In order to maintain blinding for the ongoing double-blind, placebo controlled-study the blinded dose-level was maintained into the extension study until the last individual completed the procedures planned during double-blind phase. The lowest dose carried into the extension had the fewest mortal events, the medium-dose had an intermediate number of events and the highest dose had the most mortal events. The graph below is the time to mortal events. The table on the right shows the specific numbers of patients who were at risk and who died.

Figure 1: Time to death study #56 and number of patients who died



Treatment	Total N	Event rate / year (95%CI)
High	20/100	4.9% (3.8 – 5.7%)
Medium	10/74	3.5% (2.1 – 4.8%)
Low	5/55	1.9 (0.4 – 3.4%)

With respect to the likelihood that the above finding is the result of the play of chance Dr. Lawrence the statistical reviewer notes.

> "In a proportional hazards model stratified by weight class assuming a linear relationship among the doses, the estimated hazard ratio of mortality comparing middle dose to low dose is 1.89 [p=0.008; confidence interval = (1.18, 3.03)]. Because of the assumed linear relationship, this is the same estimate of the hazard ratio for high dose compared to middle dose. The estimated hazard ratio of high dose compared to low dose is about 3.6. Note that this model assumes a linear relationship with dose level. Without assuming any model across doses and still stratifying by weight class, the estimated hazard ratio of high dose compared to medium dose (using only the data from these two doses) is approximately 2.0 (not statistically significant); the estimated hazard ratio of medium dose compared to low dose is also approximately 2.0 (not statistically significant); the estimated hazard ratio of high dose compared to low dose is approximately 3.5 (p=0.015)."

The mortality data, when the high dose is compared to the low dose or when a linear dose response relationship is presumed, indicates that the risk of the results being a play of chance is somewhere between 1in 67 (high dose versus low dose) or 1 in 125 (assuming dose response model).

There does not appear to be mitigating data to disregard the above mortality signal. This signal moreover, is likely an underestimate of the true size of the effect, since dosing changes were allowed during the latter portion of the extension study. Whether requiring the dose level to be maintained at the entry dose level would have increased the size of the mortality signal is not knowable.

The following information, if available, would have mitigated the overall concern regarding the current signal.

- Controlled long-term survival benefit in an alternative population with PAH (e.g., adults).

-Current controlled adult outcome data is limited to 16 week observation. Longer safety data is not available. There is open-label extension data for adults, but outcome cannot be assessed with respect to a randomized dosing regimens.

- Persistence of benefit such as performance, lack of deterioration or presence of improvement in the population with mortal effects.

-There is a single additional time (at 12-months therapy) when maximal O_2 consumption was measured during the pediatric development program. There was no evidence that the trend in increased exercise performance seen in the short term study persisted (see Table 6).

- Persistence of benefit in an alternate similar population (adults).

-No such data currently exists that any benefit of sildenafil persists for durations longer than 16 weeks.

- Similar drug class with different mortal outcome.

-To my knowledge, no such data exist for other drugs with PDE5 activity.

- Population with poor events differ substantially from the population as a whole i.e. those who died had etiology of their pulmonary hypertension which differs substantially from the adult population.

-While the majority of subjects in the pediatric study had their pulmonary hypertension as a consequence of congenital heart disease (67%), with only a fraction of the patients (33%) having the etiology of the pulmonary hypertension as a consequence of primary/idiopathic, the majority of the deaths 30/39, 77%) were in the idiopathic population (see Table 4 for the demographics of those who enrolled in study #31). The pediatric population who died was largely comprised of an idiopathic pulmonary artery hypertension population that is equivalent to the population for which performance benefit has been demonstrated in adults.

In summary, I find no mitigating data that casts doubt on the observed negative mortality outcomes during the extension study.

With regard to the dose-related mortality effects, the clinical pharmacology reviewer raised several issues regarding the internal consistency of mortality observed in study #56. Although I think some of the mitigating comments should be considered in assessing the credibility of the mortality effect; the strength of the mortality effect does not appear to be an artifact. Below are the clinical pharmacologist comments and my interpretation of the comments.

• Subjects who received placebo in the pivotal study and then went on to receive sildenafil in the long-term extension had better survival than those who received sildenafil from the start of the trial, suggesting that a 16 weeks delay in the start of sildenafil treatment is beneficial for survival. There is no physiologically plausible explanation as to why delay in treatment by 16 weeks would confer a long-term survival advantage.

- [CDTL] With respect to the mortality effects of those who were initially treated with placebo and then transferred to one of the doses of sildenafil the results of the mortality effect appear to show a similar dose response effect as the overall treatment effect (see right side of Table 1). The number of mortal events among those who were treated with placebo who were switched to active therapy is few and any conclusions are driven by data which is underpowered to allow for reasonable conclusions.

Table 1: Overall mortal events during study #56 and those that had mortal events that were treated with placebo during study #31

Dose #31	Dose #56	Mortality rate (%)		Placebo #31	Dose #56	Mortality rate (%)
Low	Low	5/42 (12%)		Placebo	Low	0/13 (0%)
Medium	Medium	9/55 (16.4%)		Placebo	Medium	1/19 (5.3%)
High	High	17/77 (22.1%)		Placebo	High	3/23 (13%)

• Evaluation of the mortality dose-response information during 5 years of the blinded-phase (start of Study A1481131 to June 2008, i.e., completion of 16 week double blind phase by the last subject) and 3 years of the open-label phase reveals a disproportionate number of subjects died in the open-label phase of the study (n=11 subjects during blinded period vs. n=24 subjects after). Importantly, the dose-response relationship for mortality is not evident during the controlled, blinded-phase of the trial, which lasted 5 years (3.6%, 5.4% and 5.0% mortality rate in the low, medium and high dose cohorts, respectively).

- [CDTL] The duration of exposure during this period of time i.e. the blinded phase was relatively short. The modal dose (most used dose for an individual) during entirety of the study largely reflects the randomized dose. The overall increase in mortality does not begin till approximately 2 years after randomization. The randomized dose likely reflects the best estimate dose with which to attribute the mortal events. The harm done by higher doses likely require longer durations of exposure.

• Exposure-response analysis indicates an exposure-dependent increase in mortality in the low and medium dose group but trends in the opposite direction for the high dose group. In the high dose group, the incidence proportion of death in patients with predicted steady-state exposure greater than median concentration of 129 ng/mL was ~0.15 compared to ~0.32 below the median.

- [CDTL] The pharmacokinetic evaluation was based on data for serum concentrations drawn at the end of the 16 week study. Deaths in the high dose group occurred at least 1-8 years later. I am hesitant to accept a single set of measurements distant in time as reflective of exposure in a growing and maturing population. The variance over time appears to be unknowable. So setting confidence intervals for the concentration in the high dose upper cohort is unlikely to be accurate.

• The 3-year survival rates obtained in this trial (87%, 88% and 80% for low, medium and high doses, respectively) are higher than reported in children with PAH prior to the availability of targeted PAH therapies (29-52%).

- [CDTL] The population of children enrolled in study #56 were likely fairly healthy. The comparison population is likely much more fragile than the population enrolled into this study. In study #31 the children were required to perform cycle exercise testing at baseline and therefore must have had a better exercise capability than a pooled unfiltered population. Mortal events in this study did not occur immediately but began approximately 2 years after the start of exposure. The lag time till mortal events began further suggests that the historic population was more advanced in their disease than the population in study #31 and #56.

• Baseline imbalances in specific covariates influenced the treatment comparisons with the survival data. Baseline etiology, pulmonary vascular resistance index and right atrial pressure were found to be most prognostic for survival. Accounting for these baseline risk factors, reduces the hazard ratio comparison between the dose groups.

- [CDTL] The process of randomization should have minimized differences between the groups eventually described as low, medium or high dose. I saw no analyses where mortality was related to baseline disease severity. In fact, based on hemodynamic measurements as well as WHO class, the severity of the disease appears somewhat worse in the low dose randomized group which had the better outcome than in the other treatment groups which had the worst mortal outcomes.

In summary, the strength of the signal of a dose-related increase in mortality in pediatric patients during the extension study cannot easily be disregarded.

With respect to other aspects of safety, there is a listing of events (labeled as sponsor's serious adverse events narrative table; p1775-1880) both mortal and non-mortal events which occurred during study A1481156 (#56). Of those with non-lethal events, there was an increased frequency of such events in the high dose group compared to the low dose group. I have just counted individuals once with the event listed as most likely related to the underlying PAH.

These events are shown in Table 2.

Table 2: Non-lethal events study #31 and #56, events were labeled as serious, lead to discontinuation of were of concern in this population. Events which were earliest or most related to disease are listed. Only one listing per subject is included.

	Sildenafil doses		
	Low	Medium	High
N=	4	14	18
Patients and nature of event (only 1 event/ patient)	-Syncope -SVT with dyspnea -Bronchitis -Worse PAH	-Seizures -Syncope -Surg repair A-V canal -Aspiration pneumonia -Removal of tonsils- hematemesis -Pneumonia -Pulm artery pressure increased -Pneumonia -PAT -Pneumonia -Heart failure -TIA -Cyanosis, syncope -Pneumonia	-Respiratory infection -Dyspnea, worse hemodynamics -Worse heart failure -Decrease O_2 sats post-surgery -Bronchopneumonia -Pneumonia -Worse PAH -Pneumonia -Worse HF -Worse WHO class -Syncope associated with anemia -Bronchitis -Pneumonia -Bronchitis -Pneumonia with dyspnea symptoms -Bronchitis -Bronchopneumonia -Pneumonia -Pneumonia

This table excludes those subjects who died any time during the extension study. There was a dose related increase in the number of children with non-lethal events during the long-term extension of the study. Most of the events appear to be disease-related.

With respect to efficacy, the efficacy information is derived from the placebo controlled parallel dose-ranging study (#31). The sildenafil doses were designated as low, medium and high with the specific dosing recommendations based on the subject's weight. The doses were chosen to target concentrations reflecting EC50 (low); the mid dose group was targeted to approximately 77% inhibition of PDE5 activity and the high dose group geared to concentrations at C_{max} which

would inhibit 90% of PDE5 activity in adults. The actual concentrations in children were somewhat less i.e. approximately 50% of those targeted (Figure 2).

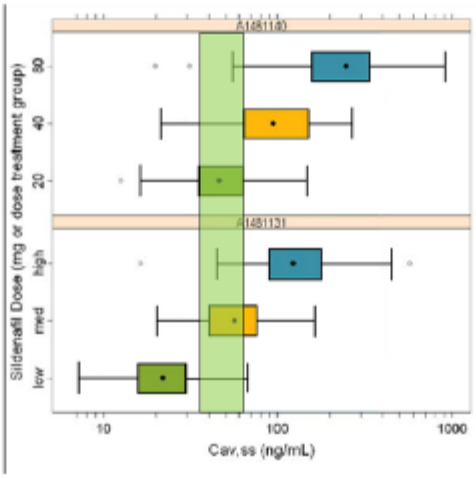
The specific dosing algorithm and the number of subjects for each weight group and dose level are shown in Table 3. For those in the low weight group randomization was in a 0:1:2:1 to low: medium: high: and placebo doses, respectively. For the other weight ranges the randomization scheme was in a 1:1:1:1 ratio. For those placebo patients who were enrolled into the long term extension phase, the doses were mirror images of the doses utilized the parallel dose range study. For the low weight group the randomization to low, medium and high was 0:1:2. For the other weight ranges the randomization to low medium and high was in a ratio of 1:1:1 ratio.

Table 3: Dose and number randomized for study #31.

Body weight	Low	Medium	High	Placebo
≥ 8 to 20 Kg	Not treated	10 mg TID (n=15)	20 mg TID (n=35)	PBO TID (n=18)
>20-45 Kg	10 mg TID (n=31)	20 mg TID (n=30)	40 mg TID (n=31)	PBO TID (n=32)
>45 Kg	10 mg TID (n=11)	40 mg TID (n=10)	80 mg TID (n=11)	PBO TID (n=10)

Figure 2: Comparisons of concentrations in adult and pediatric studies.

Figure 8. Boxplot of predicted average steady state sildenafil concentrations for adults (Study A1481140: 20, 40 and 80 mg TID) and pediatrics >45 kg, >20 to <45kg and 8 to 20 kg weight groups that were randomized to a high (blue), medium (yellow) or low (green) dose.



* Black symbol represents median. Green shaded bar represents interquartile range of the steady state concentration for the approved adult dosing regimen of 20 mg TID.

The demographics of those who enrolled in study #31 are shown below.

Table 4: Demographics among those entering study #31.

Parameter	Low dose	Medium dose	High dose	Combined doses	Placebo
Number	42	55	77	174	60
Age range					
1-4	0	9 (16%)	19 (25%)	28 (16%)	7 (12%)
5-12	25(60%)	28(51%)	36 (47%)	89 (51%)	37 (62%)
13-17	17(40%)	18(33%)	22(29%)	57(33%)	16 (27%)
≥ 18	0	0	0	0	0
Race					
White	19 (45%)	26 (47%)	28 (36%)	73 (42%)	24 (40%)
Black	1 (2%)	1 (2%)	1 (1%)	3 (2%)	2 (3%)
Asian	6 (14%)	13 (24%)	15 (19%)	34 (20%)	7 (12%)
Other	18 (38%)	15 (27%)	33 (43%)	64 (37%)	27 (45%)
Region					
America (USA Canada, Mexico)	10 (24%)	11 (20%)	16 (21%)	37 (21%)	17 (28%)
Asia	6 (14%)	13 (24%)	15 (19%)	34 (20%)	7 (12%)
Europe	16 (38%)	18 (33%)	22 (29%)	56 (32%)	16 (27%)
South America	10 (24%)	13 (24%)	24 (31%)	47 (27%)	20 (33%)
Etiology					
Primary pulmonary hypertension	12 (29%)	19 (35%)	26 (34%)	57 (33%)	21(51%)
Secondary pulmonary hypertension	30 (71%)	36 (65%)	51 (64%)	117 (67%)	39 (49%)

Given the modest number of subjects randomized in the study, the results are reasonably well balanced. A greater fraction of those randomized to placebo had their etiology as primary pulmonary hypertension compared to the sildenafil treated groups.

The initial metric of efficacy was CPET (Cardio-pulmonary exercise testing) related to the maximal amount of oxygen consumed (PVO_2) during exercise. CPET was performed at screening and at baseline as well as on therapy at week 8 at peak and week 16 end of dose ranging study. It was also performed in a large subgroup of subjects at 1 year during the long term extension. The ergometry protocol imposed a progressively increasing workload until the subject claimed they could no longer perform the test. Ergometry testing was performed at a fixed 50-60 revolution /minute exercise speed. The maximum amount of O_2 consumed during the test was the metric of interest. There were too few individuals who performed week 8 ergometry and I have not included the data here.

Table 5: Peak volume of O_2 consumed (in ml/kg/min) baseline and 16 weeks; Values are mean ± SD

	Low	Medium	High	Combined	Placebo
N=	24	26	27	77	29
Baseline	17.4 ±4.4	18.0 ± 4.7	17.4 ±3.7	17.6 ± 4.2	20.0 ± 3.8
Week 16	18.4 ± 5.6	20.4 ±6.2	19.0 ± 3.6	19.3 ±5.2	20.0 ± 4.4
Change	1.0 ± 3.4	2.4 ± 3.4	1.6 ± 2.6	1.7 ± 3.1	-0.1 ± 3.3
% change	6.4 ± 20.2	13.4 ± 19.5	10.6 ± 15.5	10.2 ± 18.4	0.5 ± 15.9

- Baseline was defined as measurements (including screening and baseline)
- Analyses were performed using analysis of covariance with etiology, weight and baseline VO2 as the covariates.

The results were borderline but not statistically significant. Of note, the placebo group appeared the healthiest. Based on baseline PVO_2, there did not seem to be a major difference in PVO_2, consumed at baseline among the treatment groups. The change in baseline was least in the placebo group and greatest in the mid dose group. The high dose group had somewhat less effect than that of the medium dose group.

There was a follow-up measurement of PVO_2, at 1 year (Table 6). The results do not indicate a persistence of a positive effect in the high dose group. In fact the maximal effect was inversely dose-related. The best effect was observed in the low dose group but was not significantly different than the high dose group (P=0.1). In the high dose group there was virtually no change from baseline (prior to study #31) measurements.

Table 6: PVO_2 effects at 1 year.

	Sildenafil Low Dose (N=33)	Sildenafil Medium Dose (N=32)	Sildenafil High Dose (N=35)
Baseline			
Mean (SD)	18.30 (4.54)	18.11 (4.44)	17.78 (3.65)
Year 1			
Mean (SD)	19.97 (5.17)	18.69 (5.92)	17.93 (4.02)
Mean (SD) Change from Baseline	1.67 (3.64)	0.58 (5.22)	0.15 (3.44)
Mean (SD) % Change from Baseline	11.19 (22.98)	5.37 (31.62)	2.56 (21.46)
Comparison with Low Dose:			
Mean Difference (SE)		-7.02 (6.10)	-9.84 (5.92)
95% Confidence Interval		-19.13, 5.09	-21.60, 1.93
p-value		0.253	0.100
Comparison with Medium Dose:			
Mean Difference (SE)			-2.82 (6.01)
95% Confidence Interval			-14.75, 9.11
p-value			0.640

Derived from Table 3 of Dr. Lawrence's review

With respect to other metrics of interest, the Division has concluded that both PVRi as well as mPAP appear to correlate with 6- minute walk distance in adults on a group level but not necessarily on a patient level (as per our statistician Dr. John Lawrence). The results of PVRi (Table 7), mPAP (Table 8), cardiac index (Table 9) and change in WHO class (Table 10) in the pediatric study are shown below.

Table 7: Effects of dose and PVRi during study #31.

	Sildenafil				
	Low	Medium	High	Combined	Placebo
N=	36	49	67	152	50
PVRi Woods units/m2 Mean ± SD (LOCF analysis)					
Baseline	23.5 ± 15.2	19.0 ± 13.8	20.9 ±19.0	20.9 ±16.6	16.1 ±12.0
Week 16	23.6 ± 16	16.0 ± 11.0	15.8 ± 13.5	17.7 ± 13.7	17.7 ± 13.8
Change of baseline	0.1 ± 10.9	-2.9 ± 11.5	-5.1 ± 14.7	-3.2 ± 13.0	1.6 ± 9.2
Change versus PBO, Mean ± SE [95% CI]	-0.6 ± 2.7 [-5.9, 4.7]	-4.5 ± 2.4 [-9.3, 0.2]	-7.2 ±2.3 [-11.7, -2.7]	-4.1 ±2.0 [-8.0, -0.2]	NA NA
P-value				0.041	

With respect to PVRi, the placebo group has the lowest value at baseline. The low dose group had the highest measurement at baseline. There appears to be a dose related decrease in PVRi with a comparison to placebo nominally significant. The p-value is very sensitive to a small number of changes in the delta PVRi.

In a scatter plot of pretreatment measurements and post treatment measurements for PVRi (prepared by Dr. John Lawrence), there were 4 subjects who had very high baseline measurements between approximately 65-85 woods units (I am not sure these are credible) whose post treatment

values were in the 18-30 Woods unit range (circled group). Of these 4 subjects 3 were in the high dose group and one in the medium dose group. Excluding these subjects removes the statistical effect.

Figure 3: Scatter plot of PVRi baseline versus PVRi end of therapy. Circled values are those with very high baseline values which normalized at end of therapy

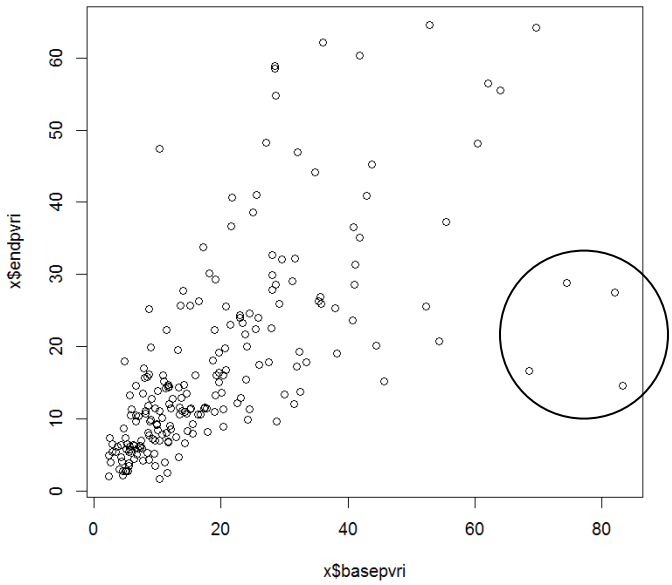


Table 8: Changes in mPAP by dose and in the combined treated group versus placebo study #31

	Sildenafil				
	Low	Medium	High	Combined	Placebo
N=	39	55	71	165	56
mPAP (mm Hg) Mean ± SD (LOCF analysis)					
Baseline	66.3 ± 22.2	61.9 ± 18.1	61.6 ±23.9	62.8 ±21.7	59.4 ±21.6
Week 16	67.1 ± 24.4	57.9 ± 19.4	54.2 ± 20.6	58.5 ± 21.6	59.0 ± 20.3
Change of baseline	0.9 ± 12.3	-3.9 ± 12.0	-7.4 ± 15.4	-3.1 ± 12.2	-0.4 ± 15.9
Change versus PBO, Mean ± SE [95% CI]	1.6 ± 3.1 [-4.5, 7.6]	-3.5 ± 2.7 [-8.9, 1.9]	-7.3 ±2.6 [-12.4, -2.1]	-7.5 ±1.3 [-7.5, 1.3]	NA NA
				P=0.17, NS	

With respect to mPAP, the baseline measurements suggest that the placebo group had the lowest pressures. The low dose group had the highest pressures. The change in pressures seemed to not be meaningfully changed during the course of the 16 week study.

Table 9: Changes in cardiac index by dose and in the combined treated group versus placebo study #31

	Sildenafil				
	Low	Medium	High	Combined	Placebo
N=	37	51	69	157	55
Cardiac Index (L/min/M2) Mean ± SD (LOCF analysis)					
Baseline	3.1 ± 1.1	3.3 ± 1.4	3.4 ±1.7	3.3 ±1.5	4.0 ±2.1
Week 16	3.4 ± 1.3	3.3 ± 1.5	3.7 ± 1.7	3.5 ± 1.6	3.4 ± 1.0
Change of baseline	0.3 ± 1.1	0.1 ± 1.4	0.3 ± 2.1	0.2 ± 1.7	-0.6 ± 2.0
Ratio comparison to PBO	1.1	1.04	1.15	1.1	NA
95% CI	[0.97, 1.3]	[0.93, 1.2]	[1.03, 1.29]	[0.99, 1.21]	NA
P-value				P=0.66; NS	

With respect to cardiac index, the placebo group had the highest cardiac output at baseline. The lowest dose had the lowest cardiac output. The change comparing the pooled effect to placebo was essentially unchanged.

The functional class at baseline is shown below. The placebo group had the highest percentage of functional class I patients at baseline and the lowest fraction of class III patients. The lowest dose group was on the other end with the fewest Class I and greatest Class III patients. With respect to change in WHO status, the highest and medium dose group had the greatest improvement in status.

Table 10: WHO functional class at baseline and change in WHO class after therapy, study # 31.

	Sildenafil				
	Low	Medium	High	Combined	Placebo
Class n (%)					
I	9 (22.5%)	20 (37%)	21 (28%)	50 (29%)	25 (42%)
II	22 (55%)	25 (46%)	43 (57%)	90 (53%)	29 (48%)
III	9 (22.5%)	8 (15%)	12 (16%)	29 (17%)	6 (10%)
IV	0	1 (2%)	0	1 (1%)	0
Missing	2	1	1	4	0
Improvement from baseline in WHO functional status (class II-IV					
N	31	34	55	120	35
No change	25 (81%)	24 (71%)	38 (69%)	84 (70%)	31 (89%)
Improved by 1 classes	6 (19%)	10 (29%)	16 (29%)	32 (27%)	41 (11%)
Improved by 2 classes	0	0	1(2%)	1 (1%)	0

In summary, there was a trend to a benefit in considering PVO_2 at 16 weeks but not at one year. There was a small dose-response relationship to PVRi which appears to be largely driven by a small number of individuals. Overall, the potential clinical benefit is small and when compared to the mortality and adverse event profile does not suggest a reasonable benefit: risk profile.

A complete response should be sent to the sponsor recommending that the application may be approved if there was convincing data that the drug when used in a pediatric population for an extended period of time and at a dose which has demonstrated benefit is not harmful or lethal.

Is there adequate duration safety data in adults?

The results of this study raise three additional concerns. The first of these concerns is whether there is adequate long-term data in adults to assure no harm with life-long durations of treatment?

Currently, the Indication for REVATIO® in adults is:

Indicated for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability and delay clinical worsening. The delay in clinical worsening was demonstrated when REVATIO® was added to background epoprostenol therapy.

Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-III symptoms and etiologies of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%).

Limitation of use:

The efficacy of REVATIO® has not been adequately evaluated in patients taking bosentan concurrently.

The indication for REVATIO® includes an increase in exercise capability. This parameter was generally measured after 16 weeks of therapy. The indication also contains a prevention of deterioration claim (in a population concurrently treated with epoprostenol). This claim was based on data limited to 112 days of therapy (16 weeks). There is as far as I know no comparative outcome data for longer than 16 weeks. The outcome data defining benefit for REVATIO® in an adult pulmonary artery hypertension is taken from the package insert and is shown below.

Table 11 REVATIO® label table regarding worsening status

	Placebo (N = 131)		REVATIO (N = 134)	
Number of subjects with clinical worsening event n (%)	23 (17.6)		8 (6.0)	
Incidence of Clinical Worsening Events	**First Event**	**All Events**	**First Event**	**All Events**
Death	3	4	0	0
Lung Transplantation	1	1	0	0
Hospitalization due to PAH	9	11	8	8
Clinical deterioration resulting in:				
Change of Epoprostenol Dose	9	16	0	2
Initiation of Bosentan Therapy	1	1	0	0
Proportion Worsened	0.187		0.062	
95% Confidence Intervals	(0.12 - 0.26)		(0.02 - 0.10)	

Although mortality definitely trends favorably in this 16 week study, the prevention in deterioration effect is largely driven by increase in the need for a higher dose of epoprostenol. In the pediatric long-term outcome studies, the Kaplan-Meier curves did not have any events till at least 1 1/2 to 2 years. The 16 week outcome data in adults is dwarfed by the duration of follow up in the pediatric population. Of interest, is that the vast majority of the mortal events as observed in the pediatric study are individuals with primary pulmonary hypertension, precisely the most common etiology in the adult population. Since the duration of therapy for which harmful outcomes in children were observed and since the population where harm was observed is similar in etiology to the adult population the prevention of deterioration claim should it make it clear that the data is limited to 16-weeks.

In order to assess whether long-term harm occurs in an adult population treated with REVATIO®, a PMR requiring additional controlled safety data in an adult population seems necessary.

Is right heart catheterization safe as a metric for drug effect?

Is the safety and consequently, the ethics, of performing hemodynamic assessments in children, if not directly needed for the care of the child an appropriate procedure. In the performance of this WR, there were two subjects who died pre-randomization due to complications of the hemodynamic measurements. There were two additional subjects who had serious adverse events as a consequence of pre-randomization hemodynamic assessments. Furthermore, there was one additional subject who sustained a serious adverse event with end of study assessment of hemodynamics. The specific events are described in Table 12.

Was the information gained by these assessments worth the risk to the children? Although experienced sites which perform right heart catheterizations may have better safety outcomes, there is still risk to the child. Is the outcome data from hemodynamics sufficiently predictive of outcome to warrant the attendant risk?

The specific serious adverse events associated with the catheterization procedure are shown below:

Table 12 Lethal or serious adverse events associated with right heart catheterization

Deaths	
1026S8034	14 month old male in Poland had a cardiac arrest associated with general anesthesia for right heart catheterization. The subject died. An autopsy performed showed the patient was status-post repair of transposition of great arteries. And status post excision of intra-atrial septum. The autopsy diagnosis was consistent with pulmonary hypertension as the cause of death.
1029S8174	5 year old female who was pretreated for catheterization with ketamine and midazolam. Post-procedure the child developed bradycardia and hypotension which temporarily responded to resuscitation. The subject however arrested in the ICU and died. It is unclear if an autopsy was performed.
Serious Adverse events pre-randomization	
1027S8191	4 year old Polish female developed complete A-V block during pre-randomization catheterization. She was treated with isoproteranol and the blockade resolved.
1027S8072	4 year old Polish male, developed right ventricular insufficiency and edema during catheterization. The child was treated with oxygen, diuretics and dopamine. Chest X-ray showed cardiomegaly and decreased vascular markings. The subject was discharged after 9 days.
Serious Adverse events end of 16-week study	
102910427	This was a 3 year old Asian male who in preparation for end of double-blind study right heart catheterization received midazolam and ketamine. The subjected desaturated, developed bronchospasm, respiratory distress and bradycardia. He was treated with oxygen, steroids, and B_2 agonists, as well as received bag and mask ventilation. The bronchospasm, respiratory distress and bradycardia resolved after 3 days.

Are younger and older children equivalently responsive to sildenafil based on hemodynamics?

There is an underlying assumption that any parameter changes and benefit can be assigned to both age sets of patients; those able to exercise and those too young to exercise. The results from study #31 for hemodynamic measurements raise some issues.

Table 13: Comparison of hemodynamics and change in hemodynamics comparing those < 7 years old and those ≥ 7 years old

	< 7 years old	≥ 7 years old		< 7 years old	≥ 7 years old
	N=63	N=171			
PVRi (Woods units* M2 (Ratio to placebo)	12 [8.0-58]	21 [15-164]	Low Medium High	0.97 [0.5 to 2.0] N=2 0.77 [0.5 to 1.1] N=14 0.7 [0.5 to 1.0] N=23	0.97 [0.8 to1.2] N=35 0.8 [0.7 to 1.0] N=37 0.7 [0.6 to 0.9] N=45
mPAP (mm Hg) Difference from placebo	4.2 [2-58]	3.2[1.6-168]	Low Medium High	-3.3 [-26 to 20] N=2 -1.7 [-12.5 to 9.2] N=14 -0.8 [-10.7 to 1.4] N=23	0.5 [-5.7 to 6.8] N=35 -4.2 [-10.4 to 2.0] N=38 -9.2 [-15.7 to -3.9] N=45
Cardiac Index (L/min/m2) (Ratio to placebo)	54 [21-61]	65 [22-170]	Low Medium High	1.0 [0.6 to 1.6] N=2 1.1 [0.8 to 1.3] N=14 1.2 [0.9 to 1.4] N=23	1.1 [1.0 to 1.3] N=35 1.0 [0.9 to 1.2] N=37 1.2 [1.0 to 1.3] N=45

Table 13 above compared baseline for those less than and greater than 7 years old. The right side of the table has the effect of treatment and the end of study for the two age ranges. For PVRi and cardiac index the value is a ratio compared to placebo. For mPAP the number is a difference when compared to placebo. There are too few subjects in the low dose group for the < 7 years old group that comparisons are not useful. For the mPAP the magnitude of decrease was greater for the ≥ 7 year old group than for the < 7 year old group. PVRi effects seem similar in both age ranges.

Aside from the likelihood that some of the values are not credible (e.g. cardiac index of 170 l/min), the results seem to suggest differences limited to changes in mPAP, particularly in the high dose group comparing the ≥ 7 years old to the < 7 years old cohorts.

Pharmacology:

There were no new pharmacology-toxicology studies that were performed by Pfizer Pharmaceuticals for this application. Most safety information was submitted in conjunction with NDA 20895 (treatment of erectile dysfunction) or NDA 21845 (treatment of pulmonary hypertension). Dr. Jensen further explored whether there was any preclinical information which could shed light on the apparent dose response to mortality in the pediatric population. Based on the reviewed literature it appears that in a hypertrophied heart, PDE5 is upregulated[1]. Moreover, in rat animal model systems whose right ventricle is hypertrophied by either monocrotaline injection or banding the right ventricle has an increased response to PDE5 agonists[2]. Sildenafil in the presence of a hypertrophied right ventricle would provoke an inotropic response. As an analogy to similar drugs which similarly increase cAMP in the left ventricle, the right ventricular increased cAMP could provoke premature mortality.

[1] E.g., Nagendranj, et al., Circulation 2007,; 116 (3):238-48.
[2] E.g., AndersenA, et al., Eur J. Heart Fail 2008; 10 (12) 1158-65

Dr. Jensen also suggests that PDE5 inhibition may alter oxygenation by intrapulmonary shunting. This may be tangentially important if blood is shunted into poorly perfused areas such as during pneumonia.

CMC/Biopharm:

The CMC and Biopharm reviewer considered the application approvable. The only issue reflected in the review was related to the dissolution specifications. The reviewer recommended tentatively accepting the proposed dissolution specifications but more data was requested. These new assessments of dissolution from the reconstituted powder have been submitted and are pending review.

Label and Labeling Review:

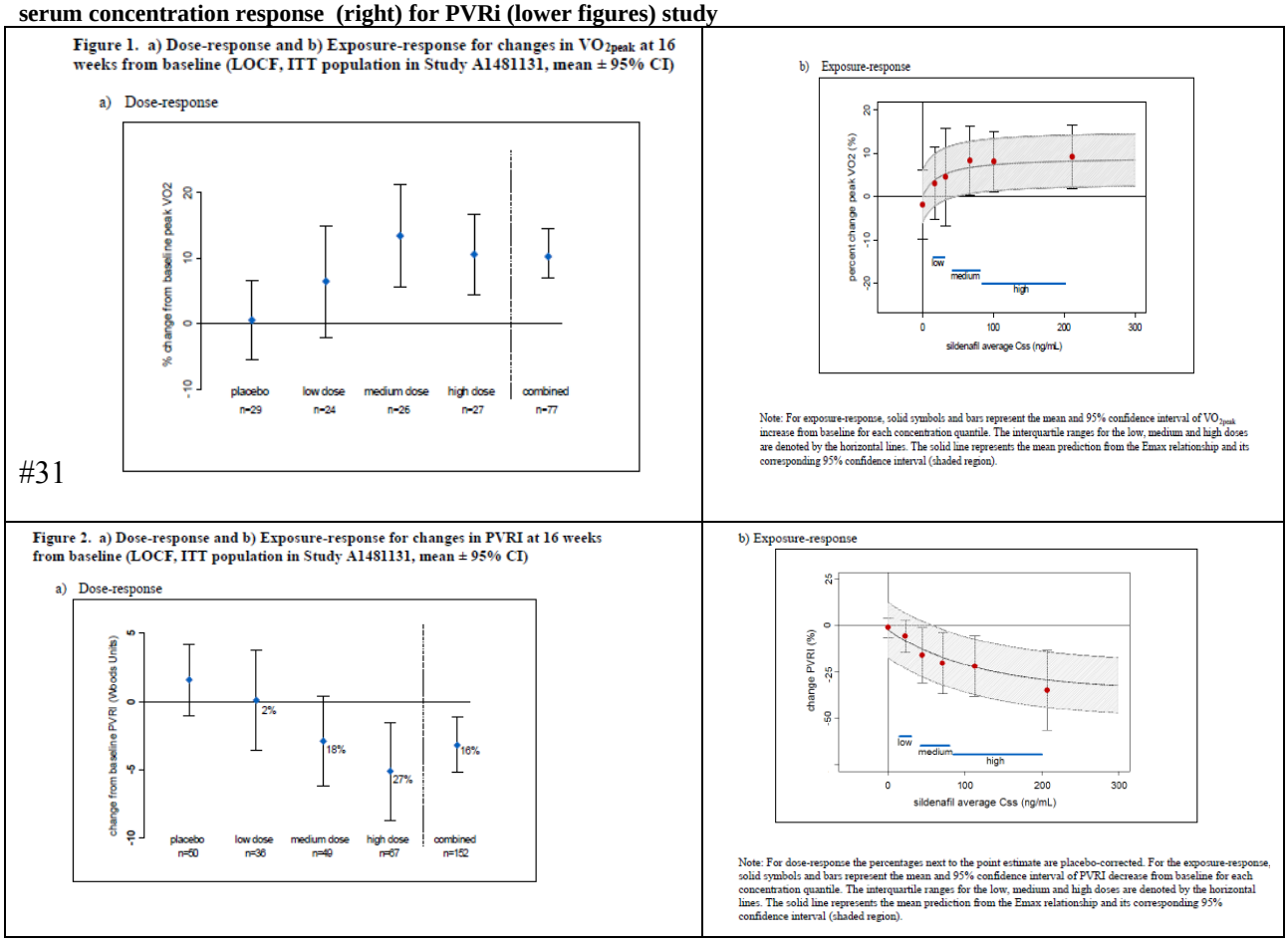
DMEPA was concerned that the [redacted] (b) (4) They recommended omission [redacted] (b) (4) since the formulation will formulated by a pharmacist. Their recommendation is reasonable.

Other recommendations by DMEPA regarding the oral syringe, the carton label, container label and insert label will be transmitted to the sponsor if appropriate.

Clinical pharmacology:

Dr. Brar recommended that sildenafil be approved for use in children with a dose for those [redacted] (b) (4) This recommendation was based on several analyses from the short term, placebo-controlled, dose ranging study. The specific metrics and the relationship of these metrics to dose are shown below.

Figure 4: Dose response (left) and serum concentration response (right) to PVO_2 upper figures. Dose response (left) and serum concentration response (right) for PVRi (lower figures) study



Although the 16-week study and the pharmacokinetic study show a trend to benefit, the overwhelming safety concern makes the CDTL review recommend not approval. Should you not think that the long-term safety is real, then based on concentration-response relationships, higher doses appear to have greater effects and all doses should be approved.

Formulations:

The formulation utilized in the clinical trial was an extemporaneously formulated product derived from the REVATIO® tablets. The proposed to-be-marketed formulation is a powder for reconstitution. Both the extemporaneously produced and the to-be-marketed formulation are nominally bioequivalent to the marketed tablets. The results of the PK parameters are shown below. Although the CI for $AUC_{0-\infty}$ comparing suspension to tablets is within the 80-125% confidence intervals, the UCL for $AUC_{0-\infty}$ does not cross 1.0. As such the exposure is likely to be somewhat less than that observed with the tablets.

Table 14 Pharmacokinetic parameters for the comparison of the sidenafil (POS) formulation to REVATIO® tablets

Parameter	N	Suspension (S)		N	Tablet (T)	Ratio S/T	Lower 90% CI	Upper 90% CI
$AUC_{0-\infty}$ ng* h/ml	42	166.6		42	184.0	90.6	85.5	95.9
C_{max} ng/mL	42	71.9		42	75.7	94.9	85.5	105.5

Considering the formulation utilized in the clinical trials, the formulation appears to be bioequivalent to the to-be marketed formulation.

Table 15 Comparison of the extemporaneously compounded formulation to the sildenafil (POS) formulation

Parameter	N	Suspension (S)		N	Tablet (T)	Ratio S/T	Lower 90% CI	Upper 90% CI
$AUC_{0-\infty}$ ng* h/ml	18	207.9		18	199.5	104.2	97.3	111.8
C_{max} ng/mL	18	79.6		18	93.4	85.2	76.1	95.4

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/s/

ABRAHAM M KARKOWSKY
05/15/2012