CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214952Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Memo
PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	214952
Supporting document/s:	0000, 0010, and 0011
Applicant's letter date:	10/03/2020, 03/19/2021, and 04/14/2021
CDER stamp date:	10/03/2020, 03/19/2021, and 04/14/2021
Product:	Liqrev® (Sildenafil Oral Suspension)
Indication:	Pulmonary Arterial Hypertension (PAH)
Applicant:	CMP Development LLC (CMP)
Clinical Review Division:	Division of Cardiology and Nephrology
Pharm/Tox Division:	Division of Pharmacology and Toxicology/ Office of Cardiology, Hematology, Endocrinology, Nephrology
Reviewer:	Xi Yang, PhD, DABT
Supervisor/Team Leader:	Jean Wu, MD, PhD
Clinical Division Director:	Norman Stockbridge, MD, PhD
Project Manager:	Christine (Tina) Sadr, MS

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1 Executive Summary

1.1 Introduction

The applicant, CMP Development LLC, seeks approval of sildenafil oral suspension, 10 mg/mL (proposed tradename Liqrev®) for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability.

Sildenafil is a phosphodiesterase 5 (PDE5) inhibitor, and it protects cyclic guanosine monophosphate (cGMP) from degradation by PDE5. The applicant's product is an oral suspension, which could be used as an alternative dosage for patients preferring ready-to-use liquid formulation, and the reference listed drug (RLD), Revatio®, is available as tablets.

This is a 505(b)(2) application relying on the FDA's previous findings of safety and effectiveness of the listed drug Revatio® (NDA 021845), which was initially approved in 1998. The proposed indication is same as the RLD. No additional nonclinical studies have been submitted to the current application.

1.2 Brief Discussion of Nonclinical Findings

No additional nonclinical studies were submitted to the current application. This submission relied on FDA's previous findings of safety of the RLD (Revatio®) for nonclinical evaluation.

All excipients used in the formulation are compendial. The flavoring substances used in the strawberry flavor are considered generally recognized as safe (GRAS), have Joint Expert Committee on Food Additives (JECFA) status, and are present below (b) (4)%. The amounts of other excipients present in sildenafil oral suspension are below the maximum daily intake listed in Inactive Ingredient Report (IIR) for chronic oral administration. Overall, there are no safety concerns regarding the amount of the excipients in the proposed formulation for the intended use.

On March 22 2021, a request from CMC reviewer was received for safety evaluation of extractable and leachable (E&L) based on the E&L studies submitted on March 19, 2021, which were conducted to assess potential E&L chemicals from the container closure system. It is understood that the analytical method (sensitivity and validation) and robustness of the extraction conditions in the study are under CMC's purview. During the review process, CMC team was contacted for clarification of the calculation of Maximum Daily Intake (MDI) of the E&L that were related to the reported concentrations in the leachable study report (Study 2, LGC 331225/supporting document #0010). Following discussions with the CMC team through emails and internal meeting, an Information Request (IR) initiated by the CMC team with Pharm/Tox inputs were sent to the sponsor (as shown below in italic).

"Regarding the leachable study, provide: (a) clarification how the estimated concentrations for all leachables and the analytical evaluation thresholds (AET, µg/ mL) for the drug product were

calculated, and (b) maximum daily intake (MDI) of all the leachables that exceed the AET and a description of how the MDI is derived. Please note that any leachable that is detected above the AET should be identified and qualified for safety with a risk assessment. Therefore, provide an adequate risk assessment for any compounds that exceed the AET and/or explain why no further safety assessment is needed for these leachables." (IR dated April 06, 2021)

In the response to the IR received on April 14, 2021, the applicant provided further clarification on E&L, and the response to CMC question is acceptable as assessed by Dr. Ali Mohamadi. Regarding to leachables detected above AET, the risk assessment of E&L was provided by the applicant and is reviewed below.

According to the applicant, a total of five separate batches (inverted stress condition) was assessed for the potential presence of leachables. The evaluation of individual leachable was based on data presented in the leachable study report (Study 2, LGC 331225/sample reference number 20J0596).

The applicant calculated the AET based on the threshold of toxicological concern (TTC) of (b) (4) mcg/day for potential genotoxic risk. As the recommended maximum daily doses for sildenafil is 60 mg/day and the total volume is (b) (4) mL for the 10 mg/mL oral suspension, the AET based on TTC would be (b) (4) the highest volume to be administered) mcg/mL. the applicant applied an additional uncertain factor of (b) (4) which resulted in a final conservative AET as (b) (4) mcg/mL.

Reviewer's comments: The TTC of (b) (4) mcg/day is typically applied when dealing with potential mutagenicity of an impurity for a life-time exposure. Applying a factor of (b) (4) to lower the threshold provides a more conserved AET. Therefore, the approach to set the AET is considered acceptable.

(b) (4) were detected at levels higher than the AET of (b) (4) mcg/mL (Table 1, adapted from the applicant's table 6 in the risk assessment report).

Table 1 Leachable Chemicals at Levels Higher than (b) (4) mcg/mL

Leachable	CAS #	Estimated concentration identified in leachable study (mcg/mL)#	Daily exposure to leachable chemicals (mcg/day)*
(b) (4)			

Note: #, The concentrations were originally reported as µg/g. However, for the purpose of calculation of patient exposure, it was assumed that µg/g is equivalent to µg/mL. *, the

highest volume to be administered was estimated as [(b) (4)]mL at the recommended maximum daily dose (60 mg for sildenafil).

As shown in Table 1, the daily exposure of [(b) (4)] based on the detected level is below the TTC of [(b) (4)]mcg, which did not generate safety concern for the intended use of the drug product. In addition, [(b) (4)] and [(b) (4)] are commonly used [(b) (4)] frequently observed as extractable substances, and have a comprehensive set of toxicity studies as reviewed in a recent publication by a cross-industry [(b) (4)] [(b) (4)] No evidence of mutagenicity or carcinogenicity was found based on the published literatures. No significant reproductive or developmental findings was observed in the published literature.

[(b) (4)] also known as [(b) (4)] is a naturally occurring [(b) (4)] [(b) (4)] [(b) (4)] is in the human diet with an estimated daily intake of [(b) (4)]mg/day, which is higher than the maximum daily exposure from the proposed product as [(b) (4)] mcg/day (see Table 1) via oral administration. The FDA granted GRAS status to [(b) (4)] as a [(b) (4)] and [(b) (4)] in foods [(b) (4)] [(b) (4)] which also has JECFA status [(b) (4)] as a [(b) (4)] [(b) (4)] In addition, the amount of [(b) (4)] potentially presented in sildenafil oral suspension is below the maximum daily intake (up to [(b) (4)] mg/day) in the approved products listed in IIR for chronic oral administration. Therefore, the daily exposure of [(b) (4)] at the current detected level do not represent a safety concern for the proposed use of the drug product.

Given the role as a [(b) (4)] more information about [(b) (4)] is available in public domain. Chronic exposure to [(b) (4)] (up to [(b) (4)] mg/kg/day) was found to cause [(b) (4)] and was [(b) (4)] (as cited in [(b) (4)] . [(b) (4)] was negative for mutagenic potential in an Ames assay [(b) (4)] [(b) (4)] In the oral rat carcinogenicity study, reversible [(b) (4)] which were attributed to general dietary imbalance as opposed to [(b) (4)] were observed [(b) (4)] No studies of reproductive or developmental toxicity studies with [(b) (4)] were identified in the literature. Most available repeat-dose toxicity studies for [(b) (4)] in the literature are dietary oral administration studies and are relatively old (before 1970s). As previously reviewed by [(b) (4)], these studies cannot be viewed as standard chronic toxicity studies because the proper endpoints of a general toxicology study were not included, and a NOAEL was not determined in these studies. Accordingly, no Permitted Daily Exposure (PDE) for [(b) (4)] was determined.

In addition, the applicant attempted to calculate PDE based on a structurally similar [(b) (4)] [(b) (4)] because there were no definitive toxicology studies for [(b) (4)] Although using a surrogate compound for PDE might be supportive in some cases, it may not be applicable for this case, considering there are available public information and scientific review of [(b) (4)]

Overall, at the detected level, the exposure of the questioned leachables (b) (4) (b) (4) and (b) (4) generates no concerns for the intended use of the drug product.

There are no issues for impurities that require nonclinical safety evaluation.

1.3 Recommendations

1.3.1 Approvability

The application is approvable from a nonclinical perspective.

1.3.2 Additional Non-Clinical Recommendations

None

1.3.3 Labeling

In the sections relevant to nonclinical information, the sponsor proposed labeling is consistent with the current FDA-approved Revatio® (NDA 021845) Prescribing Information (Revised: 02/2020) which is compliant with the Pregnancy and Lactation Labeling Rule (PLLR). This reviewer does not recommend any additional labeling changes.

References

(b) (4)

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/s/

XI YANG
06/30/2021 05:38:18 PM

JEAN Q WU
06/30/2021 08:22:18 PM