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APPLICATION NUMBER:

215252Orig1s000

NON-CLINICAL REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA 215252
Supporting document/s:	Orig-1 (12/30/2020), 09 (06/21/2021), 10 (07/28/2021), 11 (08/16/2021) and 12 (08/18/2021)
Applicant's letter date:	12/30/2020
CDER stamp date:	12/30/2020
Product:	Diltiazem Hydrochloride Injection
Indication:	Temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter and rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm.
Applicant:	Exela Pharma Sciences
Clinical Review Division:	Division of Cardiology and Nephrology (DCN)
Reviewer:	Srinivasa Raju Datla, Ph.D
Supervisor/Team Leader:	Jean Wu, MD, Ph.D
Division Director:	Norman Stockbridge, MD, PhD
Project Manager:	Sabry Soukehal

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1 Executive Summary

1.1 Introduction

The applicant is seeking approval of the proposed drug product, diltiazem hydrochloride (HCl) injection, for the treatment of temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter and rapid conversion of paroxysmal supraventricular tachycardias to sinus rhythm via a 505(b)(2) regulatory pathway. The proposed drug product is a premixed ready-to-use (RTU) product, which is to be supplied in 250 mL IV bags with a 125 mL or 250 mL fill volume. For the continuous iv infusion following the initial iv bolus dose, the infusion rate can be adjusted up to 15 mg/hr and the infusion may be maintained for up to 24 hrs, which results in a maximum infusion dose of 360 mg/24 hrs for this drug product. The proposed indication, route of administration, and rate of iv infusion for the proposed drug product are consistent with the reference listed drug (RLD), Cardizem injectable (diltiazem HCl injection, 5 mg/mL) (NDA 020027). As RLD, Cardizem, was withdrawn from the market, the applicant also used a reference standard drug (ANDA 075853).

This 505(b)(2) application relied on the FDA's previous findings of safety and effectiveness of the RLD. This nonclinical review mainly focused on the safety assessment of the extractable and leachable (E&L) compounds upon CMC's request. The maximum infusion dose of 360 mg/24hrs for the drug product is used as the maximum daily dose (MDD) for assessing safety of leachable compounds from IV bags in the review.

1.2 Brief Discussion of Nonclinical Findings

No nonclinical pharmacology or toxicology studies were submitted in support of this NDA application. This submission relied on FDA's findings of safety and effectiveness of the RLD for nonclinical evaluation.

There are no excipients/impurities/degradants identified that require nonclinical safety evaluation.

The applicant submitted extractable and leachable (E&L) studies to assess potential E&L compounds from two different container closure systems, (b) (4) and (b) (4) IV bags. A request from the CMC reviewer was received on 4/22/2021 for a safety evaluation of extractables and leachables based on the E&L studies. Extraction study was conducted on pulverized/reduced samples of primary container-closure system and manufacturing equipment components. The leachable study was conducted on twelve exhibit batches using (b) (4) and/or (b) (4) IV bags for up to 6 months at accelerated (25°C/40RH) conditions and up to 12 months at standard (5°C) conditions. It was understood that the analytical method (sensitivity and validation) and robustness of the test conditions are under CMC's purview.

The safety evaluation was referred to the initially submitted E&L study report, and the applicant responses to the Information Requests (IRs) from both CMC and Pharm/Tox teams.

For evaluation of elements in the leachables, 28 elements targeted from the extractable study were tested in the leachable study. Eighteen of them were not detectable or (b) (4) ppb (µg/L), hence, there is no need for further assessment. Ten out of 28 elements were detected at the levels (b) (4) ppb. Based on the acceptable limits listed in the ICH Q3D and additional justifications, the levels of these 10 elements are consider acceptable.

For organic leachable compounds, the analytical evaluation threshold (AET) was set as (b) (4) ppb (b) (4) µg/day for the MDD of the drug product) using a safety concern threshold (SCT) of (b) (4) µg/day, and is considered reasonable. A total of 30 organic leachable compounds were identified at levels above AET of (b) (4) ppb.

The potential mutagenic risks of the organic leachable compounds were assessed based on the threshold of toxicological concern (TTC) value of 120 µg/day ((b) (4) ppb) for a treatment duration <1 month (ICH M7). Among the 30 compounds, three leachable compounds, (b) (4), were found at the levels above the TTC (120 µg/day). However, they are not considered mutagenic according to the justifications per ICH (b) (4).

For potential non-mutagenic (general) toxicity risk assessment of organic leachable compounds, a qualification threshold (QT) of 5 µg/day is generally used and applied in this evaluation. Among 30 compounds, 6 compounds were at the level below the threshold of 5 µg/day and no justification was needed. For the remaining 24 compounds with levels above the threshold of 5 µg/day, justifications for potential general toxicity were provided. As a result, 8 out of the 24 leachables were justified by the established permitted daily exposures (PDEs) listed in ICH (b) (4) guidelines, 5 out of the 24 leachables were justified by the PDEs based on the published literature and 11 out of 24 leachables were justified using a read-across approach with appropriate surrogate compounds whenever limited or no toxicology information is available.

Overall, the leachable compounds identified in the E&L study, both elemental and organic, are considered adequately qualified at their detected levels and generate minimal concerns for the intended acute use of the drug product.

1.3 Recommendations

1.3.1 Approvability

This application is approvable from the pharmacology/toxicology perspective.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

The applicant proposed labeling is to be in compliant with the Pregnancy and Lactation Labeling Rule (PLLR). As the labels of RLD and other approved diltiazem products have not been updated with the PLLR, the relevant nonclinical sections in the proposed labeling are based on the available limited animal data in the current RLD labeling. Minor revisions were suggested for clarity in Section 8.1. To be consistent with the RLD labeling, the “human oral antianginal therapeutic dose” was suggested in Section 8.1 where dose multiples were referred to a human oral dose.

Deletion of the proposed content (from literature search) in Section 8.3 was recommended by DPMH due to limited conflicting information.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional): 33286-22-5

Generic Name: Diltiazem hydrochloride

Code Name:

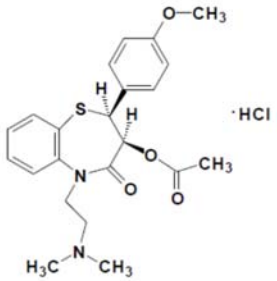
Chemical Name:

- 1,5-Benzothiazepin-4(5H)-one,3-(acetyl-oxy)-5-[2-(dimethylamino) ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride, (+)-cis-
- (+)-5-[2-(Dimethylamino) ethyl]-cis-2,3-di-hydro-3-hydroxy-2-(p-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one acetate (ester) monohydrochloride
- (2S,3S)-3-acetyloxy-5-[2-(dimethylamino)-ethyl]-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one hydrochloride

Molecular Formula/Molecular Weight: $C_{22}H_{26}N_2O_4S.HCl$ / 450.98 g/mol

Structure or Biochemical Description:

Figure 1



Pharmacologic Class: Non-dihydropyridine calcium channel blocker

2.2 Relevant INDs, NDAs, BLAs and DMFs

Pre-IND 141963: In the pre-IND response, Pharm/Tox agreed that no additional non-clinical studies are required.[1]

2.3 Drug Formulation

The applicant provided a side-by-side comparison of the formulation composition of the proposed drug product and the RLD (Table 1, excerpted from common technical document summaries / drug product summary). The proposed Exela's drug product is lacking in sorbitol, NF, but includes anhydrous dextrose USP and anhydrous citric acid USP.

Table 1: Quantitative Comparison of Exela's drug product with RLD:

Ingredients	Exela's Diltiazem HCl Injection (1 mg/mL) mg/ mL	RLD Product (Diltiazem HCl Injection 5 mg/mL) mg/mL
Diltiazem Hydrochloride, USP	1 mg	5 mg
Dextrose, Anhydrous, USP	50 mg	None
Sorbitol, (b) (4)	None	(b) (4)
Citric Acid, Monohydrate, USP	0.15 mg	None
Citric Acid, Anhydrous, USP	None	0.75 mg
Sodium Citrate, Dihydrate, USP	0.12 mg	0.65 mg
Sodium Hydroxide, NF	q.s to adjust pH to (b) (4)	q.s to adjust pH to 3.7 – 4.1
Hydrochloric Acid, NF	q.s to adjust pH to	q.s to adjust pH to 3.7 – 4.1
Water for Injection, USP	q.s to 1 mL	q.s to 1 mL

2.4 Comments on Novel Excipients

No novel excipients were proposed in the drug product. The amounts proposed for the excipients, including anhydrous dextrose, are within the limits of the other FDA approved drug products.

2.5 Comments on Impurities/Degradants of Concern

a. Drug Product Impurities and Qualification

Chemistry reviewer of this NDA requested Pharm/Tox to evaluate the safety and acceptability of the impurities in the drug product by posting the following question.[2]

"*The proposed acceptance criteria for impurity Desacetyl Diltiazem is NMT (b) (4)% and (b) (4) NMT 0.5 %. While the ICH limits for these (b) (4) impurities are 0.2 % as per ICH Q3B. The applicant mentioned that they (b) (4) and proposed these limits. Can you please check if these impurity limits are acceptable based on the toxicology data and it is present in safer level?*"

[1] PIND 141963 Meeting Request - Written Response Dated 01/23/2019
[2] Email communication on 04/26/2021

The applicant proposed a release and stability specification limit of NMT (b) (4)% for desacetyl diltiazem impurity (Table 2, excerpted from Justification of specifications document in Module 3.2.P.5.6), which is higher than the ICH Q3B QT limit of NMT 0.2%.[3]

Table 2: Degradant Impurity Acceptance Criteria at Release and on Stability

Impurity Name	IUPAC Chemical Name	Code#	MDD of Drug Product	Qualification Threshold (%) per Q3B Guidance	Qualification Threshold (TDI)	Proposed AC (%)	Justification if proposed AC (%) > Regulatory QT (%)
Desacetyl Diltiazem	5-[2-(dimethylamino)ethyl]-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4-one	42399-40-6	360 mg	0.2%	3 mg	NMT (b) (4)	(b) (4)

The applicant relied on a comparative analysis with reference standard (RS) or other approved diltiazem drug products, but not based on any toxicological justification. Upon communication with the CMC review team, it was agreed that CMC needs to review the comparative analysis and determine the acceptance of the proposed level of desacetyl diltiazem impurity. No Pharm/Tox evaluation of the impurities is necessary.

b. <u>Container Closure System Related Impurities and Qualification</u>

In addition, Chemistry reviewer requested the Pharm/Tox to evaluate the safety and acceptability of the leachables in the drug product by posting the following question.[2]

"The applicant provide extractables/leachables information in the pharmaceutical developments section for the container and closers. Their conclusion is the leachables are well below the PDE limits for volatile, semi volatile and nonvolatile impurities from container and closure. Can you please check to make sure it is within the safety levels?"

Diltiazem HCl injection (1.0 mg/mL) is proposed to supply in (b) (4) ready to use 250 mL IV bags with a fill volume of 125 mL and 250 mL. Two different types of 250 mL IV bags ((b) (4)) were proposed to use (Table 3, excerpted from the study report).

Table 3: Type of Container Closure Components used in the Extractable and Leachable Study.

Product Description	IV Bag Type	IV Bag Closure
Diltiazem Hydrochloride Injection (1 g/mL), 125 mL/250 mL bag and 250 mL/250 mL bag	250 mL IV Bag, (b) (4)	(b) (4) Port (b) (4)
Diltiazem Hydrochloride Injection (1 g/mL), 125 mL/250 mL bag and 250 mL/250 mL bag	250 mL IV Bag, (b) (4)	(b) (4) Port (b) (4)

The applicant conducted extractable and leachable studies to identify any potential leachables into the drug product.

[3] Module 3.2.P.5.6 Justification of Specification Drug Product Seq 0006 07May2021

Extractable study: Extraction study was conducted on primary container-closure system components and manufacturing equipment components. Individual components (listed below in Table 4, excerpted from the study report) of the container closer system were pulverized to increase surface area and refluxed in 25 mM NaH_2PO_4 at pH of 1.8 or 2, 6 or 12 for a minimum of 8 hrs.

Table 4: Materials Evaluated for Extractable Analysis

Exela Part #	Component Name	Supplier
2037	(b) (4)	
2088		
2422		
2091		
2231		

Leachable study: The potential migratable compounds; elemental and organic (volatile, semi-volatile, and non-volatile), were targeted in the stability testing of 12 lots of diltiazem HCl (Batch MBR-000715 and Batch MBR-000804). Leachables were analyzed at least three time points (Table 5, excerpted from the study report).[4] Out of 12 lots, six lots were tested for 3-months at standard (5˚C) and accelerated (25˚C/40RH) conditions using (b) (4) IV bags, and six lots were tested for 6-months at standard (5˚C) and accelerated (25˚C/40RH) conditions and for 12-months at standard (5˚C) conditions using (b) (4) IV bag.

Table 5: Drug Products Lots, IV Bags and Time Points Used in the Extractable Study.

Drug Product Lot #	IV Bag Type	Fill V (mL)	Time points and conditions analyzed				
			3 Months		6 Months		12 Months
			5˚C	25˚C/ 40RH	5˚C	25˚C/ 40RH	5˚C
X0000000A	(b) (4)	125	NT	NT	X	X	X
X0000000B		250	NT	NT	X	X	X
X0000001A		125	NT	NT	X	X	X
X0000001B		250	NT	NT	X	X	X
X0000002A		125	NT	NT	X	X	X
X0000002B		250	NT	NT	X	X	X
X0000091A		125	X	X	TBA	TBA	TBA
X0000091B		250	X	X	TBA	TBA	TBA
X0000092A		125	X	X	TBA	TBA	TBA
X0000092B		250	X	X	TBA	TBA	TBA
X0000093A		125	X	X	TBA	TBA	TBA
X0000093B		250	X	X	TBA	TBA	TBA
T0 Lab Batch Lot #: 2019-187/106 (filled in both (b) (4) IV Bags at 125 mL and 250 mL fill volumes).							

NT = Not Tested, TBA= To be analyzed, stability time point has not been pulled yet.

[4] \\CDSESUB1\evsprod\nda215252\0010\m3\32-body-data\32p-drug-prod\diltiazemhydrochlorideinjection-in\32p2-pharm-dev\pharmaceutical-development-ccs-dp.pdf

All elemental and organic (volatile, semi-volatile and non-volatile) compounds were analyzed using a sensitive detection limit of ~(b) (4)ppb. All the elements identified above this limit and organic leachables at the level above analytical evaluation threshold (AET) were evaluated for safety. AET determination is discussed below.

SCT and AET calculations: The applicant calculated the AET as (b) (4)ppb (Table 6, excerpted from the study report) using a safety concern threshold (SCT) of (b) (4) µg/day, which is considered acceptable. The applicant's calculation is also consistent with the reviewer's calculation of the AET for 250 mL bag (Table 7).

Table 6: Applicants SCT and AET Calculations for Diltiazem HCl injection.

Table 1. Formulas and Calculations for the SCT and AET Values for Diltiazem Injection							
Max Daily Dose Diltiazem Hydrochloride=	360000	µg/day					
[Diltiazem Hydrochloride]-DP =	1000	µg/mL					
Dose Volume =	1000	mL/day					
Max Daily Dose Volume =	360	mL/day					
Duration of Treatment =	≤ 1	month					
Safety Concern Threshold (SCT) =	(b) (4)	µg/day	Qualification Threshold (QT)	5	µg/day	120†	µg/day
Analytical Evaluation Threshold (AET) =		ppb	Analytical Evaluation Threshold (AET)	(b) (4)	ppb	(b) (4)	ppb

Note: ppb for the AET are expressed in units of w/v with respect to maximum daily dose volume of the drug product.
† - ICH M7[1] limit for dosage durations of less than 30 days for a single mutagenic compound

Table 7: Reviewer SCT and AET Calculations for Diltiazem HCl injection.

MDD	360 mg/day
Max volume per bag	250 mL
Number of bags needed for MDD	360/250 = 1.44
SCT	(b) (4) µg/day
AET (container)	(b) (4) µg/day / 1.44 container/day = (b) (4) µg/container
AET (µg/L or ppb)	(b) (4) µg/container / 250 mL/container = (b) (4) µg/mL= (b) (4) µg/L (ppb)

Reviewer Comment: *Communications with the CMC review team were made during the review process. It was understood that the analytical method (sensitivity and validation) and robustness of the test conditions are under CMC's purview. The CMC reviewer was inquired whether the study conditions represent the typical storage conditions for diltiazem injections in a worst-case scenario, and the analytical methods are validated and sensitive to detect potential extractables/leachables. As indicated in the email dated 04/29/2021, it appeared there were no issues regarding these aspects. See the CMC review part for E&L study.*

The applicant's E&L studies and the justifications for the leachable compounds are evaluated below. Our safety assessment of the leachables are based on the initially

submitted E&L study report and the information provided in response to our Information Requests.

Leachables- Elemental Impurities: A total of 28 elemental impurities were tested and the maximum concentration observed in the extraction and leachable studies were provided below (Table 8, excerpted from the study report).

Out of the 28 elements tested (Table 8) in the leachable study, 14 elements could not be detected, and 4 elements were reported at level <(b) (4) ppb. No further justification is needed for these 18 elements. The remaining 10 elements at the detected levels ≥ (b) (4) ppb are evaluated below.

Table 8: List of Elemental Impurities Tested and their Levels.

Element	QL (ppb)	PDE (ppm/day)	AEC (ppb)	Maximum Concentration Observed in Extraction Studies (ppb)	Maximum Concentration Observed in Leachables Studies (ppb)
(b) (4)					

Review of Applicant's Justification for Elemental Impurities:

In Table 8 above, the applicant listed elemental impurities, their maximum concentrations observed in extraction and leachable studies with its associated PDEs and Allowable Elemental Concentration (AEC) values. The PDEs were referred to the ones established in USP Chapter <232>, EPA established Reference dose (RfD) values (with a (b) (4) safety factor) or CFR21 21(4); and AEC values were converted from the PDEs based on the maximum daily dose volume for diltiazem HCl injection of 360 mL. [*Reviewer's note: AECs may not be needed if the comparison was based on the PDEs*].

As shown in Table 8, in the leachable study, 10 elements were identified at the levels ≥(b) (4) ppb. For six of these elements, (b) (4), the levels are well below the ICH Q3D (R1) listed parenteral PDE values (Table 9); therefore, are acceptable.

Table 9: List of Elemental Impurities in ICH Q3D Guidelines.

Element	Maximum concentration (µg/L)* in leachable study	Maximum daily exposure# (µg/day)	ICH Q3D(R1) parenteral PDE (µg/day)$	MOE@
(b) (4)				

For other 4 elements, (b) (4), as the respective PDE values are not available in USP Chapter <232> or ICH guidelines, justifications based on the other sources are discussed below.

(b) (4) (maximum concentration observed =(b) (4) ppb or MDE of (b) (4) µg/day): In EPA IRIS chemical Assessment Summary, (b) (4), and compounds, a RfD value of (b) (4) mg/kg/day was determined based on human clinical studies.[5] This RfD is derived based on three principal studies and a total uncertainty factors of (b) (4) to account for variability in susceptibility in human population. Based on RfD and modification factor of (b) (4) for the route-route extrapolation (the oral absorption of (b) (4)), the PDE is determined as (b) (4) µg/day. As the level of (b) (4) in diltiazem HCl injection (MDE of (b) (4) µg/day) is below the PDE, it is considered acceptable.

(b) (4) (maximum concentration observed =(b) (4) ppb or MDE of (b) (4) µg/day): In EPA Provisional Peer Reviewed Toxicity Values for (b) (4) and Compounds Derivation of Sub

[5] EPA IRIS Chemical Assessment Summary, (b) (4)

chronic and Chronic Oral RfDs, a provisional RfD (p-RfD) of [redacted] mg/kg/day was determined based on human chronic oral toxicity data.[6] This p-RfD was determined based on LOAEL of 1 mg/kg/day and an uncertainty factors [redacted] for use of a minimal LOAEL, [redacted] for sensitivity individual, [redacted] for less than lifetime exposure, and [redacted] for an adequate data base. Based on RfD (p-RfD) of [redacted] mg/kg/day and an additional factor of [redacted] for the route-route extrapolation (the oral absorption of [redacted]), the PDE is determined as [redacted] µg/day. As the level of [redacted] in diltiazem HCl injection (MDE of [redacted] µg/day) is below the PDE level, it is considered acceptable.

[redacted] (maximum concentration observed = [redacted] ppb or MDE of [redacted] µg/day): In EPA drinking water health advisory for [redacted], a RfD of [redacted] mg/kg/day was determined based on human chronic oral toxicity data[7]. In this advisory, it is pointed out that the rodents are not good models for [redacted] toxicity studies as they do not exhibit the same neurological deficits observed followed by exposure in human and primates. Therefore, using a dietary information by WHO and NRC, EPA estimated that an intake of [redacted] mg/kg/day of [redacted] is considered safe for a lifetime of exposure. Considering the data is from human origin, an Uncertainty Factor (UF) of [redacted] was applied to estimate RfD of [redacted] mg/kg/day for [redacted]. Using an additional factor of [redacted] for the route-route extrapolation and considering the oral absorption of [redacted]%, the PDE is determined as [redacted] µg/day. As the level of [redacted] in diltiazem HCl injection (MDE of [redacted] µg/day) is below the PDE level, it is considered acceptable.

[redacted] (maximum concentration observed = [redacted] ppb or MDE of [redacted] µg/day) [redacted] It is also reported that patients with impaired kidney function, including premature neonates, who receive parenteral levels of [redacted] at greater than [redacted] µg/kg/day accumulate [redacted] at levels associated with toxicity in central nervous system and bone. Considering the required water [redacted], for 50 kg adult the minimal volume need [redacted] is equivalent to [redacted] µg/day of [redacted] for adults. As the level of [redacted] in diltiazem HCl injection (MDE of [redacted] µg/day) is below the allowable level, it is considered acceptable.

Leachables-Organic Compounds:
No unknown extractables and leachables were reported that are above the AET of [redacted] µg/day [redacted] ppb). Thirty leachable compounds (Table 10) above the AET were identified and their potential mutagenic and general toxicity risks were assessed below.

[redacted]

Review of Applicant's Justification for Organic Compounds:

Evaluation of Mutagenic potential for the compounds > (b) (4) µg/day (b) (4) ppb):
The proposed drug product, diltiazem HCl injection, is used for less than a month. Therefore, it is reasonable to apply ICH M7 threshold of toxicological concern (TTC) value of 120 µg/day ((b) (4) ppb) for potential mutagenic risk assessment.

Most compounds were identified at the levels below TTC, except three compounds; (b) (4) that are reported above the TTC limit of 120 µg/day (b) (4) ppb) and need mutagenicity evaluation. Per ICH (b) (4) are listed (b) (4) with a concentration limit of ppm or PDE value of (b) (4) mg/day, and a concentration limit of (b) (4) ppm or PDE value of (b) (4) mg/day, respectively. (b) (4) is listed (b) (4) with a concentration limit of (b) (4) ppm or PDE value of 50 mg/day. As these compounds up to their respective PDEs are listed as non-mutagenic and the level of each reported in the leachable study is lower than the correspondent PDE, they are not considered to have mutagenic potential.

Reviewer Note: *The applicant evaluated mutagenic potential using EPA T.E.S.T QSAR software. All compounds, except (b) (4), were reported negative for mutagenic potential. FDA DARS was consulted and determined that the T.E.S.T methods are not up to date, hence, is not acceptable.*

Evaluation of the general toxicity potential for the compounds with an MDE of >5 µg/day:
As per PQRI and general practice of OND Pharm/Tox, a QT of 5 µg/day is applied for general toxicity evaluation for parenteral products. All the compounds identified above (b) (4) ppb (5 µg/day) should be justified for the general toxicity. In response to the IR dated 6/7/2021,[11] the applicant provided additional justification for all the 24 compounds identified at levels ≥ 5 µg/day and clarified some justification with additional information.

Following the initial IR, three more IRs were requested. In the IR dated 7/23/2021, the applicant was asked to provide clarification on some compound's chemical identity and PDE calculation details due to multiple errors and/or missing information in the updated justification. In the IRs dated 08/12/2021 and 08/17/2021, the applicant was asked to clarify the chemical identity due to mistakes found in the provided chemical identity (names and structure) of the three leachable compounds, based on the DARS and CMC analysis.

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[9] As per ICH (b) (4) (b) (4)

[10] As per ICH (b) (4) (b) (4)

[11] Cover letter Exela Response Seq 0009 Seq 0009 18Jun2021

The evaluation below was based on the original[12] and revised version[13] of the extractable and leachable study reports and the responses[11,14,15,16] provided to our IRs listed above.

As listed in Table 10 below, six out of 30 leachables were identified at the levels below the QT limit of 5 µg/day ((b) (4) ppb), hence, there is no safety concern for these compounds.

For the remaining leachable compounds (24 out of 30) with MDE >5 µg/day, the justifications based on available information were evaluated in the following three categories.

1) Leachables (8 out of 24) with PDEs established in ICH (b) (4) guidelines;
2) Leachables (5 out of 24) with PDEs established based on published toxicological studies;
3) Leachables (11 out of 24) with limited or no toxicological data for which a surrogate compound is used in a read-across approach.

[12] Pharmaceutical Development Container Closure System DP Seq 0001
[13] Pharmaceutical Development Container Closure System DP Seq 0011
[14] Cover letter Exela Response Seq 0010 28Jul2021
[15] Cover letter Exela Response Seq 0011 16Aug2021
[16] Cover letter Exela Response Seq 0012 18 Aug2021

Table 10: List of Leachables observed at ≥ (b) (4) µg/day ((b) (4) ppb)

Compound	CAS #	Mutagenic	Carcinogenic	Systemic Toxicity Concerns	Maximum Concentration Observed in Extraction Studies (ppb)	Maximum Concentration Observed in Leachable Studies (ppb)	Dose Dep DP Limit (ppb)
(b) (4)							

Leachables with established PDEs in ICH (b) (4) guidelines: The following leachables (8 out of 30) listed in Table 11 have an established PDEs in ICH (b) (4) guideline[17]. Using these PDEs, we estimated the margin of exposure (MOE) for each leachable (Table 11). All the eight compounds listed below in Table 11 have adequate margin of exposure, when their MDEs were compared to the respective PDEs. Therefore, the levels of these eight leachable compounds are acceptable.

17 (b) (4)

Table 11: Leachables with Permitted Daily Exposures Established in ICH (b) (4) Guidelines.

Leachable compound	Highest level observed* (µg/L)	Maximum daily exposure# (µg/day)	PDE (µg/day)$	MOE@
(b) (4)				

Leachable compounds with PDEs established from published toxicological studies:

The following leachables (5 out of 24) listed in Table 12 have an established PDEs based on published toxicological studies.

In general, when a pivotal toxicity study was considered for estimating a PDE, various modification factors (F1 to F5) described in ICH (b) (4) guidelines are applied. In addition, modification factor, F6, for route-route extrapolation should also be taken into consideration based on available bioavailability information (e.g., F6 =100 if oral bioavailability <1%; F6=10 if oral bioavailability ≥1% and <50%; F6=2 if oral bioavailability ≥50% and <90%; F6=1 if oral bioavailability ≥90%). The modification factors F1-F6 used for each PDE estimation are listed in Table 12.

Table 12: Leachables with PDEs Established Based on Published Information.

Leachable compound	Highest level observed * (µg/L)	Max daily exposure # (µg/day)	NOAEL (mg/kg)	Modification Factors						PDE for 50 kg adult (µg/day)#	MOE @
				F1	F2	F3	F4	F5	F6		
(b) (4)											

(b) (4)

(b) (4) (maximum concentration observed = (b) (4) ppb or MDE of (b) (4) µg/day):
In a mouse study (13-week oral treatment in mice, 5 days/week[18]), a no observed adverse effect level (NOAEL) was determined as (b) (4) mg/kg/day (adjusted NOAEL based on a 5-day week dosing study, (b) (4) mg/kg/day). Based on this NOAEL and modification factors (F6 =2 for >50% oral bioavailability[19]), a PDE value was determined as (b) (4) mg/kg/day (b) (4) µg/day for a 50-kg adult). As shown in Table 12, the level of (b) (4) is lower (b) (4)) than the estimated PDE, hence, is considered justified.

(b) (4) (maximum concentration observed = (b) (4) ppb or MDE of (b) (4) µg/day):
In a rat toxicity study (2-generation reproductive/developmental toxicity, oral[20]), a NOAEL was determined as (b) (4) mg/kg/day. For the route-route extrapolation, the applicant provided a reference in which the oral absorption was predicted to be around 50% because of the number of (b) (4) present in the (b) (4); however, we considered that a conservative factor of 10 should be applied.[21] Based on the NOAEL and modification factors, a PDE was estimated as (b) (4) mg/kg/day ((b) (4) µg/day for a 50-kg adult). The level of (b) (4) is lower ((b) (4)) than the estimated PDE, and is considered justified.

(b) (4) (maximum concentration observed = (b) (4) ppb or MDE of (b) (4) µg/day):
In a rat study ((b) (4) for 4 -weeks), a NOAEL of (b) (4) mg/kg/day was determined (adjusted NOAEL for the (b) (4) mg/kg/day) because of the mortality and decrease in body weight at high-dose group.[22] We considered that route-route uncertainty factor of 10 is appropriate based on the observed toxicity after oral administration, which indicated more than 1% of bioavailability. Based on the NOAEL of (b) (4) mg/kg/day and modification factors, a PDE was determined as (b) (4) mg/kg/day ((b) (4) µg/day for a 50-kg adult). The level of (b) (4) is lower (b) (4)) than the estimated PDE, and is considered justified.

(b) (4)

(b) (4) (maximum concentration observed = (b) (4) ppb or MDE of (b) (4) µg/day):
In a rat 6-month oral toxicity study[23,24], a NOAEL of (b) (4) mg/kg/day was determined. Based on this NOAEL and modification factors (F6= 1 for >90% oral absorption[25]), a PDE value was estimated as (b) (4) mg/kg/day (b) (4) µg/day for a 50-kg adult). The level of (b) (4) is lower (b) (4) than the estimated PDE, and is considered justified.

(b) (4) (maximum concentration observed = (b) (4) ppb or MDE of (b) (4) µg/day):
In a rat toxicity study (13-week, inhalation), a NOAEL of (b) (4) mg/kg/day was derived. Using a bioavailability correction factor of 5, the applicant estimated a PDE of (b) (4) mg/kg/day ((b) (4) mg/day for a 70-kg adult). However, it is not clear how this NOAEL of (b) (4) mg/kg/day was determined. The applicant was requested (IR dated 06/07/2021) to provide appropriate reference for the study from which the NOAEL was determined.

In the response, the applicant did not provide any explanation about how its NOAEL was calculated, instead, provided new references[26,27] to a rat inhalation toxicology study (b) (4) ppm, 8 h/day, 3 days) and a mouse study ((b) (4) ppm, 30 min exposure). In the rat study, there were no dose-related effects on functional observation battery, body weight changes, clinical signs observed. Both of these new referenced animal studies were aimed to evaluate the CNS effects; no other standard general toxicology parameters were measured. Therefore, these studies were not considered appropriate for toxicology justification.

In search of additional information, this reviewer found a 13-week rat sub-chronic toxicity (b) (4) ppm, 6 hrs/day, 5 days/week, inhalation[28]) study for (b) (4) in which a no observed adverse effect concentration (NOAEC) of (b) (4) ppm was determined. This 13-week toxicity study is considered appropriate for justification based on the intended treatment duration of the proposed product.

The inhalation NOAEC can be converted to NOAEL (mg/kg) dose using the molecular weight of (b) (4) g/mol, and an ideal gas equation (n/v = P/RT). The calculations are presented below.

(b) (4)

Concentration used in the study (conversion from mg/L to mg/day)

n/v = (b) (4)

Rat respiratory volume = (b) (4)

(b) (4)

Actual exposure: Study exposure is 6 hrs per day, 5 days per week

(b) (4)

NOAEL Dose (conversion from mg/day to mg/kg):

(b) (4) mg/day / (b) (4) kg (Rat body weight) = (b) (4) mg/kg

Given the above converted NOAEL, PDE value is determined with the following modification factors.

F1 = 5; F2 = 10; F3 = 5; F4 = 1; F5 = 1 and F6 = 10 (conservative modification factor for inhalation to intravenous route)

PDE = NOAEL x 50 kg / (F1 x F2 x F3 x F4 x F5 x F6)

PDE = (b) (4) µg/day

The level of (b) (4) with a MDE of (b) (4) µg/day is lower (b) (4) than the estimated PDE, and is considered justified.

<u>Leachable compounds using surrogate compounds in a read-across approach</u>:

For 11 out of 24 leachable compounds, the applicant relied on a read-across approach by proposing surrogate molecules as there is limited or no toxicological information available for safety assessment. FDA DARS was consulted for the suitability of the selected surrogate compounds for the safety analysis. Based on the DARS analysis, the proposed surrogate could be rejected and a DARs suggested alternate surrogate compound may be used for the safety evaluation of the leachable compounds. If one surrogate is accepted for multiple leachables, the sum of all the leachable compounds MDEs should also be compared with the selected surrogate compound's PDE values in the safety evaluation.

The levels of leachable compounds and PDEs of their surrogate compounds are listed in Table 13 below.

Table 13: Leachable Compounds with Permitted Daily Exposures from Surrogate compounds

Leachable compound	Highest level observed* (µg/L or ppb)	Maximum daily exposure# (µg/day)	surrogate¶ compound	PDE of surrogate (µg/day)#	MOE@
[redacted] (b) (4)					

[redacted] (b) (4) (maximum concentration observed = [redacted] (b) (4) ppb or MDE of [redacted] (b) (4) µg/day):
In a read-across approach, the applicant proposed [redacted] (b) (4) as a surrogate compound, which was considered appropriate for the safety evaluation. As shown in Table 12, a PDE of [redacted] (b) (4) µg/day was determined for [redacted] (b) (4). [redacted] (b) (4) itself was identified as a leachable compound with an MDE of [redacted] (b) (4) µg/day. Either MDE of [redacted] (b) (4) alone or the sum of MDEs ([redacted] (b) (4) µg/day) of the two leachable compounds, [redacted] (b) (4), is much lower [redacted] (b) (4) than the estimated PDE, therefore, the level of [redacted] (b) (4) is considered justified.

[redacted] (b) (4): (maximum concentration observed = [redacted] (b) (4) and [redacted] (b) (4) ppb or MDE of [redacted] (b) (4) and [redacted] (b) (4) µg/day, respectively):
In a read-across approach, the applicant proposed [redacted] (b) (4) as surrogate compounds for [redacted] (b) (4), respectively, which were

considered appropriate for their respective leachable compounds. [(b) (4)] have an established PDEs of [(b) (4)] µg/day and [(b) (4)] µg/day, respectively, in ICH [(b) (4)] guidelines[17]. As the MDEs [(b) (4)] [(b) (4)] are lower than these respective PDEs, their levels are considered justified.

[(b) (4)]

The maximum concentrations of the 5 compounds listed above ranged [(b) (4)] ppb (MDEs of [(b) (4)] µg/day), in the leachable study.

In a read-across approach, the applicant proposed [(b) (4)] as a surrogate compound for all these 5 leachable compounds, which is considered appropriate. A PDE for this surrogate compound was determined and used for comparison.

In a rat toxicology study (28 day, oral), a NOAEL of [(b) (4)] mg/kg/day was determined for the surrogate, [(b) (4)]. Based on this NOAEL and modification factors (F1=5, F2=10, F3=10, F4=1, F5=1, F6=10 (a conservative route-route bioavailability correction factor)), a PDE was determined as [(b) (4)] mg/kg/day ([(b) (4)] µg/day for a 50 kg adult).[29,30, 31] As the individual MDE or sum of all the five leachable compounds MDEs ([(b) (4)] µg/day) are lower than the estimated PDE for the surrogate, the levels of all the five leachables are considered justified.

[(b) (4)] [(b) (4)] (maximum concentration observed = [(b) (4)] and [(b) (4)] ppb or MDE of [(b) (4)] or [(b) (4)] µg/day, respectively):

Using a read-across approach, the applicant proposed [(b) (4)] [(b) (4)] as a surrogate compound. Based on the FDA DARS analysis, the proposed surrogate is deemed inappropriate to support safety evaluation of both leachable compounds. As explained in detail, the proposed surrogate compound contains [(b) (4)] while the leachable compounds contains [(b) (4)], and this difference is expected to affect the solubility and overall toxicity.

In the consultation with DARS, it was noted that the chemical structures provided by the applicant doesn't match with the names provided. For example, the chemical structure [(b) (4)]

[29] Parris, et.al., RegulatoryToxicolandPharmacol, 2020, 118 104802 – Considerations when deriving compoundspecificlimits for extractables and leachable from pharmaceutical products: Four case studies

[30] [(b) (4)]

[31] [(b) (4)]

(b) (4) and the PubChem chemical ID (b) (4) provided (b) (4) (b) (4) does not match with the chemical name provided. This inconsistency was further confirmed by the CMC reviewer. IRs from both CMC and Pharm/Toxicology teams, dated 08/12/2021 and 08/18/2021, were sent for the applicant to resolve the inconsistency. In the responses, the applicant provided the final structures as below in Table 14 that are consistent with the chemical names provided.

The corrected structures of the leachable compounds did not change the DARS position for the proposed surrogate that was not appropriate for safety evaluation of the identified leachable compounds. Upon further discussion with DARS, (b) (4) was recommended as an appropriate surrogate compound for the safety evaluation of these two leachable compounds. In a rat (b) (4) oral toxicology study[32] for (b) (4), a NOAEL of (b) (4) mg/kg was determined given a slight reduction in body weight at high dose level. Using an appropriate uncertainty factors (F1=5, F2=10, F3=1, F4=1, F5=1 and F6=10), a PDE for (b) (4) was determined as (b) (4) mg/kg/day ((b) (4) µg/day for a 50-kg adult). As the sum of the two leachable compounds MDEs (b) (4) µg/day) is lower than the estimated PDEs, their levels are considered acceptable.

(b) (4) (maximum concentration observed = (b) (4) ppb or MDE of (b) (4) µg/day):
In a read-across approach, the applicant proposed (b) (4) as a surrogate, which is appropriate for evaluation of the (b) (4) (b) (4)

In a rat toxicity study[33] (90-day, oral) for the surrogate, a NOAEL of (b) (4) mg/kg was determined. Based on this NOAEL and modification factors (F1=5, F2=10, F3=5, F4=1,

32 (b) (4)
33 (b) (4). (b) (4)

F5=1 and F6=10), a PDE value was estimated as (b) (4) mg/kg/day ((b) (4) µg/day for a 50 kg adult). The level of (b) (4) is lower (b) (4) than the estimated PDE of the surrogate, hence, is considered justified.

3 Studies Submitted

No nonclinical studies were submitted. For container closure system, E&L study report was submitted in Seq 0001, and additional information was provided in response to various IRs that includes the updated E&L study report in Seq 0010 and Seq 0011, as listed below.

Table 15: List of E&L Studies Reports and IR Responses

Sequence	Study Report	IR response	Submission Date
0001	3.2.P.2 Pharmaceutical Development: Pharmaceutical Development container Closure System DP Seq 0001		12/30/2020
0009	3.2.P.2 Pharmaceutical Development: Pharmaceutical Development container Closure System DP Seq 0009	1.2 Cover Letters: Cover Letter Exela Response Seq 009	06/21/2021
0010	3.2.P.2 Pharmaceutical Development: Pharmaceutical Development container Closure System DP Seq 0010	1.2 Cover Letters: Cover Letter Exela Response Seq 0010	07/28/2021
0011	3.2.P.2 Pharmaceutical Development: Pharmaceutical Development CCS Seq 0011	1.2 Cover Letters: Cover Letter Exela Response Seq 0011	08/16/2021
0012		1.2 Cover Letters: Cover Letter Exela Response Seq 0012	08/18/2021

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/

SRINIVASA RAJU DATLA
09/21/2021 03:13:36 PM

JEAN Q WU
09/21/2021 05:03:13 PM