Assessment of Potential Leachables: Single-Use Systems for_site_name_ Manufacturing >_min_batch_size_L for_drug_product_ (_item_code_ parental_container)

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1. Introduction

The purpose of this document is to provide a human health risk assessment of the maximum potential leachables from the single-use items used in the manufacturing process. See Table below for assessment parameters. This risk assessment may be leveraged to support other _Molecule_ _Container_ manufacturing processes that use the same single use items, as needed.

Table 1. Assessment Parameters of Single Use Items1,2

Assessments Parametsrs	**Detail (Example)**
Molecule	Molecule *Donanemab*
LY#	LY# *LY3002813*
Applicable DS Site(s)	Site_Name_DS *Limerick*
Applicable DS Fill Lines (FL)/Building (B)	DS_Fill_Lines_Building *N/A*
Applicable DP Site(s)	Site_Name_DP *BSP (Contract manufacturing)*
Applicable DP Fill Lines (FL)/Building (B)	_DP_Fill_Lines_Building *FL16*
DP Minimum Batch Size (L)	DP_Min_batch_size *170*
Container Closure	Container *Syringe, vial, cartridge*

2 Assessment Strategy

The human health risk assessment strategy, material risk score, and single use item selection criteria for this assessment are detailed in LQP-230-8 . See Table below for a list of single use items assessed in this report.

Table 2. Process Contact Materials Assessed from DS Manufacturing

Single Use Item #	Manufacturer	Identification/Description PCM Type	Sterilization Method	Quantity Assessed	Total Product Contact Surface Area (cm^2)	Dilution Volume (mL)	SA:V (cm^2/mL)	Risk Level

1 LQP Reference
2 [Material List Reference(s) #] Reference Title

Table 3. Process Contact Materials Assessed from DP Manufacturing

Single Use Item #	Manufacturer	Identification/Description or Single use Category?	Sterilization Method	Quantity Assessed	Total Product Contact Surface Area (cm^2)	Dilution Volume (mL)	SA:V (cm^2/mL)	Risk Level

[Material List Reference(s) #] Reference Title

3 Analytical Evaluation Threshold for _drug_product_ Drug Product

Table 4. Analytical Evaluation Threshold (AET) Parameters

Assessment Parameter	Detail (Example)
Drug Product (DP)	Drug_Product *Donanemab*
Safety Concern Threshold (SCT)_	_Safety Concern Threshold (SCT)_ *9*
DP Concentration_ (mg/mL)	_DP_Concentration_ *17.5*
Maximum Dose (mg)	Maximum Dose (mg) *1400*
Maximum Dose Volume (mL/dose)	Max Dose Volume_ *80*
AET	_AET_ *0.1*

$$DP\ Dose\ (mL) =$$

$$AET\ \frac{\mu g}{mL} =$$

See Appendix for AET detailed description.

4 Extractables Studies

4.1 Extractables Study Description

An extractables study was performed to obtain an extractables profile (identity and estimated quantity) under anticipated “worst case” use conditions (see table below).

Table 5. Extractable Data Reference(s)

PCM Tested	Study Name	Study Reference

5 Potential Organic Leachables

5.1 Organic Extractables as Potential Leachables (to be repeated as needed)

Table 6: Extractables as Potential Leachables ≤AET for the _drug_product_ Drug Product[reference]

Component	Brand	Extract	Identification	CAS #	Max. Reported Extractable concentration (ug/cm2)	Potential Leachable Concentration (µg/mL)*

Potential Leachables are calculated by multiplying the Maximum reported extractables concentration (µg/cm2) by the vessel surface area (_vessel_surface_area cm2) and then diving by the minimum batch size (_min_batch_size_ mL).

Table Xsummarizes the SUV organic extractables with potential exposure concentrations above the AET (_AET_ mcg/mL) for the _drug_product_ product.

Table 7: Extractables as Potential Leachables >AET for the _drug_product_ Drug Product[reference]

Component	Brand	Extract	Identification	CAS #	Max. Reported Extractable concentration (ug/cm2)	Potential Leachable Concentration (µg/mL)a	Potential Exposure	ADI	MOS

* *Potential Leachables are calculated by multiplying the Maximum reported extractables concentration (µg/cm2) by the vessel surface area (_vessel_surface_area cm2) and then diving by the minimum batch size (min_batch_size mL).

5.2 Cumulative - Organic Extractables as Potential Leachables

Table 8: Potential Leachables >AET for the _drug_product_ Drug Product[reference]

Component	Brand	Extract	Identification	CAS #	Max. Reported Extractable concentration (ug/cm2)	Potential Leachable Concentration (µg/mL)a	Potential Exposure	ADI	MOS

* *Potential Leachables are calculated by multiplying the Maximum reported extractables concentration (µg/cm2) by the vessel surface area (_vessel_surface_area cm2) and then diving by the minimum batch size (min_batch_size mL).

6 Potential Elemental Impurities

6.1 Elemental Impurities as Potential Leachables

Table 9: Potential Leachables >AET for the _drug_product_ Drug Product[reference]

Brand	Extract	Identification	CAS #	Max. Reported Extractable concentration (ug/cm2)	Potential Leachable Concentration (µg/mL)a	Potential Exposure	ADI	MOS

* *Potential Leachables are calculated by multiplying the Maximum reported extractables concentration (µg/cm2) by the vessel surface area (_vessel_surface_area cm2) and then diving by the minimum batch size (min_batch_size mL).

6.2 Cumulative – Elemental Impurities as Potential Leachables

Table 10: Potential Leachables >AET for the _drug_product_ Drug Product[reference]

Component	Brand	Extract	Identification	Max. Reported Extractable concentration (ug/cm2)	Potential Leachable Concentration (µg/mL)a	Potential Exposure	ADI	MOS

* *Potential Leachables are calculated by multiplying the Maximum reported extractables concentration (µg/cm2) by the vessel surface area (_vessel_surface_area cm2) and then diving by the minimum batch size (min_batch_size mL).

7 Human Health Assessment Conclusion

Option 1: All compounds below AET.
As shown in x all the potential leachables from the single-use components with projected exposure concentrations less than the AET and all elemental impurities were determined to have a high margin of safety greater than one. Therefore, none of the extractables were present at concentrations of toxicological concern. Based on the assessment of extractables as potential leachables in drug product, leachables studies for the single use components in the DS and DP manufacturing processes are not required to demonstrate safety.

Option 2: Some compounds above AET with MOS>1.
There were several potential leachables from the single-use components with projected exposure concentrations greater than the AET with margins of safety greater than 1; and all elemental impurities were determined to have a high margin of safety greater than one Therefore, the extractables were not present at concentrations of toxicological concern. Based on the assessment of extractables as potential leachables in drug product, further assessment of the single use components in the DS and DP manufacturing processes are required to demonstrate safety

Option 3: Some compounds above AET without MOS>1.
There were several potential leachables from the single-use components with projected exposure concentrations greater than the AET with margins of safety less than one. Therefore, the extractables were present at concentrations of toxicological concern. Based on the assessment of extractables as potential leachables in drug product, further assessment of the single use components in the DS and DP manufacturing processes are required to demonstrate safety.

8 Appendix

- Full Tables of results (as opposed to concise tables in body of report)
- Toxicologist opinion

AET Description

The analytical evaluation threshold (AET) for organic chemical entities is defined as the concentration above which peaks (extractables) need to be identified, quantified, and toxicologically assessed. The AET is derived by a toxicologist from the safety concern threshold (SCT) which is the threshold at or below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and non-carcinogenic toxic effects. The AET is derived using an appropriate SCT, that is based on the route of administration, dosing volume, dosing regimen, and treatment indication. The current regimen for _drug_product_ is a subcutaneous weekly dose, which is the same regime (weekly dose) that is planned to be applied for the _drug_product_ injection.

For a parenteral product dosed weekly, an SCT of _SCT_ in the AET calculation is appropriate. A _SCT_ was derived to protect for potential carcinogenic and non-carcinogenic effects as described below.

ICH M7 guidance on DNA reactive impurities maintains that cancer risk of a continuous low dose over a lifetime would be equivalent to the cancer risk associated with an identical cumulative exposure averaged over a shorter duration. ICH M7 supports a 10 µg/dose limit for less-than-lifetime (LTL) exposures up to a cumulative duration of ten years as it maintains an excess cancer risk of less than 1 in 100,000. For a once weekly or less frequent dosing interval over the course of 70 years, the cumulative number of days of dosing would be no more than 3640 (i.e., 52 weeks/year x 70 years) or 9.97 years of daily dosing. Therefore, the intermittent dosing regimens fall into the cumulative >1 year – 10 years category as described in Table 2, Section 7.3 of ICH M7.

The derived _SCT_ was also based on a published oral acceptable daily intake (ADI) of 90 µg/day for Cramer Class III structures, or "substances of a chemical structure that permit no strong initial presumptions of safety or may even suggest significant toxicity". The Cramer Class III oral ADI was derived by applying a 100-fold uncertainty factor to the 5th percentile no-observed adverse effect levels of repeat-dose oral toxicity data for the Class III structure chemicals. An assumption of 10% oral bioavailability (applied to adjust the Cramer Class III oral ADI for route of exposure) results in a parenteral ADI of _SCT_. This would be considered conservative for a weekly dosing regimen, but _SCT_ was chosen as the SCT to mitigate the potential for induction of sensitization response due to potential leachables.

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4 RPT-245606: Development Process Flow Document LY3298176 Injection at 200L and 400L scale
5 ICH M7 (R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, Step 4 dated 31March2017. https://database.ich.org/sites/default/files/M7_R1_Guideline.pdf.
6 Kim Li et al (2015). Creating a Holistic Extractables and Leachables (E&L) Program for Biotechnology Products. PDA J Pharm Sci and Tech 69: 590-619. doi:10.5731/pdajpst.2015.01073
7 Kimber I, Gerberick GF, Basketter DA. Thresholds in contact sensitization: theoretical and practical considerations. Food Chem Toxicol. 1999;37(5):553-560. doi:10.1016/s0278-6915(99)00048-4.

An SCT of _SCT_ µg/dose is appropriate to protect for potential mutagenicity, target organ toxicity, and sensitization based on guidance in ICH M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, Cramer structural classification thresholds, and a PQRI publication on parenteral and ophthalmic drug products which includes Cramer structural classification thresholds and other considerations, respectively. , The maximum dose is _max_dose_ mg.1 The DP concentration is _dp_concentration_ mg/mL. The maximum dose is outlined in the equation below:

8 ICH M7 (R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, Step 4 dated 31March2017. https://database.ich.org/sites/default/files/M7_R1_Guideline.pdf;
9 Paskiet D et al. The Product Quality Research Institute (PQRI) Leachables Extractables Working Group Initiatives for Parenteral and and Ophthalmic Drug Product (PODP), PDA J Pharm Sci and Tech. 67: 430-447. doi:10.5731/pdajpst.2013.00936.