PERMITTED DAILY EXPOSURE (PDE) FOR J.T.BAKER® CELL LYSIS SOLUTION

BACKGROUND

Permitted Daily Exposure (PDE), as defined in guidance by the European Medicines Agency, is a health-based exposure limit (HBEL), representing a dose or exposure by any route (e.g., oral, parenteral, dermal) that is unlikely to cause an adverse event if an individual is exposed, by that route, at or below the calculated dose, every day for a lifetime.[1] It is often used in the assessment of potential impurities in drug products.[2]

J.T.Baker® Cell Lysis Solution is a ready to use concentrated product, formulated using a blend of nonionic surfactants. As a critical component in Adeno-associated Virus (AAV) and recombinant protein processes, understanding and determining the PDE values for J.T.Baker® Cell Lysis Solution is essential for ensuring the safety and compliance of applications involving this product. To aid in this assessment, Permitted Daily Exposure (PDE) values were determined for each ingredient of the formulation by qualified Toxicologists[3] to evaluate the toxicity through different routes of exposure.

METHOD

To develop PDE values for J.T.Baker® Cell Lysis Solution, the Toxicologist reviewed safety data sheets for the raw materials as well as available and relevant pharmacokinetic, pharmacodynamic, clinical safety, and nonclinical toxicology data for the formulation to identify a point of departure (POD) for determining the no-observed-adverse-effect level (NOAEL) and/or lowest-observed-adverse-effect level (LOAEL). From these data, appropriate health-based endpoints on which to base the PDE values were identified and are presented in Table 1. A detailed summary of the available data, selection and justification of appropriate endpoints, and the calculation of the PDE value can be provided by request.

CALCULATION

The PDE is calculated as shown below:

PDE = NOAEL x Weight Adjustment/(F1 – F5 uncertainty factors)

- F1: A factor between 2 – 12 to account for extrapolation between species
- F2: A factor of 10 to account for variability between individuals.
- F3: A factor of 10 to account for repeat-dose toxicity studies of short duration.
- F4: A factor between 1 – 10 that may be applied in cases of severe toxicity, e.g., non-genotoxic carcinogenicity, neurotoxicity, or teratogenicity.
- F5: A variable factor applied if a no-effect level is not established.

Additional adjustment factors that may be considered include:

- Route-to-route adjustment factor (α) = adjusts for differences in bioavailability between different species and/or routes of exposure
- Accumulation factor (S) = adjusts for accumulation after repeated dosing when POD is not at steady state
- Modifying factor (MF) = accounts for residual uncertainties not covered by F1-5

PERMITTED DAILY EXPOSURE

Table 1: Health-based exposure limits for oral, parenteral, and ocular routes of administration[4]

Material	POD Description	Proposed oral PDE value		Proposed parenteral/ocular PDE value	
		(mg/day)	(mg/kg/day)*	(mg/day)	(mg/kg/day)*
Detergent A	NOAEL from the 2-year dietary study in rats	2,000	40	200	4
Detergent B	LOAEL from IV infusion dose of 10 mg/kg/hour in humans	10	0.2	25	0.5
Detergent C	NOAEL from an oral 90-day toxicity study in rats	15	0.3	10	0.2

*Adjusted to mg/kg/day by dividing by a 50 kg body weight adult as per regulatory guidance[1]

CONCLUSION

This technical note provides an evaluation of the toxicity risk from the detergents comprising Avantor J.T.Baker® Cell Lysis Solution, which is used as a critical component in Adeno-associated Virus (AAV) and recombinant protein processes. The values were based on a review of relevant data to identify a point of departure for determining the NOAEL for Detergents A and C and LOAEL for Detergent B. The information provided in this report can be used to determine margin of exposure[5] limits when conducting internal assessments for specific applications. A detailed summary of the available data, selection and justification of appropriate endpoints, calculation of the PDE value, and formulation can be provided by request under an active non-disclosure agreement (NDA).

References:

1. European Medicines Agency (2014) Guideline on Setting Health Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared facilities. Published November 2014. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/11/WC500177735.pdf.
2. International Society for Pharmaceutical Engineers (2010) Risk-Based Manufacture of Pharmaceutical Products. Volume 7: A Guide to Managing Risks Associated with Cross-Contamination. First Edition, September, 2010. Section 5.3 – Establishing Health-Based Exposure Limits. Available at: https://www.academia.edu/42064144/ISPE_Risk_MaPP.
3. SafeBridge® Regulatory & Life Sciences Group; a third-party consultancy firm contracted to evaluate the toxicity of J.T.Baker® Cell Lysis Solution. Toxicologist Curriculum Vitae may be provided by request.
4. Data extracted from Permitted Daily Exposure (PDE) Monographs for detergents; 2023, prepared by third-party consultancy firm for Avantor Performance Materials, LLC. Complete reports may be provided by request under an active mutual Non-disclosure agreement.
5. FDA Guidance for Industry M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals Questions and Answers(R2).; 2013. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm and/or http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

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