Classification of Leachables and Extractables for Parenteral Drug Products: Update on the Validation and Revisions to the Proposed Classification

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Introduction

In many cases, extractables and leachables from container closure system materials have no in vitro and/or in vivo studies and/or human exposure data to utilize for risk assessment and qualification. In these cases, there appears to be precedented approaches that have been developed for the application of *in silico* methodologies to establish classification levels associated with exposure to chemicals for which no toxicological data are available. The Product Quality Research Institute (PQRI) Parenteral and Ophthalmic Drug Product (PODP) Leachable and Extractable team proposed a Classification Strategy based on a 606 chemical database using *in silico* software (Toxtree, EC JRC IHCP) based on chemical classification approaches developed by Cramer[1] and later refined by Munro[2]. Neither of these approaches nor Toxtree took into account a carcinogenic endpoint; therefore the PODP team also evaluated the 606 chemical database using Deductive Estimation of Risk from Existing Knowledge software (DEREK, Lhasa, Ltd). The combination of Toxtree and DEREK evaluation led the PQRI team to develop an initial approach consisting 5 Classes: Classes I-III for systemic toxicity; Class IV for sensitizers/irritants, and Class V for genotoxicants/carcinogens/mutagens. The initial scheme was modified to 3 Classes: Class I for systemic toxicity; Class II for sensitizers/irritants, and Class III for genotoxicants/carcinogens/mutagens.

Ongoing validation of the modified classification scheme is in progress and the results (to date) are presented.

Classification Strategy

The initial PQRI Classification for Classes I-III was based modifications of Cramer[1] and Munro[2] that adjusted human body weight from 60 kg to 50 kg and added an uncertainty factor (UF) of 10 to account exposure differences from oral to parenteral administration. Utilizing the PQRI Orally inhaled and Nasal DP recommendations Classes IV and V were added for sensitizers/irritants and genotoxicants (Table 1).

Table 1: Initial PQRI Classification Table

	Class I	Class II	Class III	Class IV	Class V
Level (µg/day)	**150**	**45**	**7.5**	**5**	**0.15**

Based on an initial review of the data, the team determined that it may be possible to have a single class for systemic toxicity, retain the sensitizer/irritant class and based on FDA feedback adjust Class V to align with current proposals being developed by the International Conference for Harminisation (ICH) Expert Working Group on genotoxic impurities (ICH M7)[3]. The modified Classification Table is presented in Table 2.

Table 2: Modified PQRI Classification Table

	Class I	Class II	Class III
Level (µg/day)	**150**	**5**	**1.5**

Validation of Class I is ongoing and is conducted as follows

- Identify chemicals from initial class III (7.5 µg/day) with reliable NO(A)EL data from an animal study
- Use ICH Q3C[4] method to develop an ADI (µg/day)
  - ADI = NO(A)EL x BW/F1 x F2 x F3 x F4 x F5
- Use an additional UF of 10 (F6) to account for exposure differences from oral to parenteral exposure
- Determine exposure multiple and compare to Modified PQRI Class I (150 µg/day)

Results

Thirty-three (33) chemical assessments have been completed. Several examples of calculated ADIs are presented in Table 3.

Chemical (CAS No.)	NO(A)EL (mg/kg/day)	Calculated ADI (µg/day = NO(A)EL x BW/F1-F6)	Exposure Multiple from 150 µg/day
Distearyl pentaerythritol diphosphite (3806-34-6)	1000 mg/kg/day (from a 2 year rat study)	100000	667
Tri(nonylphenyl)phosphate (26523-78-4)	167 mg/kg/day (from a 2 year rat study)	1670	11
Diphenylamine (122-39-4)	6.7 mg/kg/day (from a 2 year rat study)	670	4.5
4,4'-Thiobis(6-tert-butyl-m-cresol) (96-69-5)	0.2 mg/kg/day (from an embryo fetal development rabbit study)	8	0.05

16 of the 33 chemicals were removed from the overall summary because:

- Only had LD50 data which was considered unacceptable to develop an ADI
- Published reports that the chemical was a sensitizer/irritant
- Published reports that the chemical was a genotoxicant

A summary of 17 of the 33 chemicals that resulted in exposure margins greater than or less than 1 when compared to 150 µg/day is presented in Table 4.

Exposure Multiple ≥1	Exposure Multiple <1
12/17 = 71%	5/17 = 29%

Discussion

Validation of the proposed PQRI classification strategy will require validation for use as a best practice used in the qualification of extractables and leachables in parenteral drug products. The validation approaches for each Class are summarizied below:

Class I
Any risk assessment is inherently associated with a degree uncertainty. The PQRI team has employed established UF methods to develop a chemical specific ADI. To deal with an additional uncertainty, the PQRI team included F6 (10x) to account for exposure differences from oral and parenteral routes of administration. Application of 6 levels of uncertainty will provide a conservative calculation of a chemical specific ADI to use in validation of the PQRI Classification level of 150 µg/day for systemic toxicity.

Class II
The Classification level of 5 µg/day was previously accepted as a qualification threshold for leachables and extractables in Orally Inhaled and Nasal Drug Products (OINDP)[5]. The PQRI team plans to utilize the sensitization/irritation data provided to establish the Qualification Threshold for OINDP to support 5 µg/day for parenteral DP.

Class III
The PQRI OINDP best practices developed a safety concern threshold (SCT; 0.15 µg/day) based on a level that below which would have a negligible carcinogenic risk of 1:1000000[5]. This level was based on the knowledge that many compounds of concern (eg, PNAs, NAs and MBT) were present at detectable levels in metered dose inhaler drug products. In contrast, compounds of concern are rarely indentified in parenteral DP. Based on initial discussions with the FDA, the PQRI team received guidance to move the SCT (Class III) level to 1.5 µg/day which is in line with current proposals being developed by the ICH M7 EWG[3] and will provide a carcinogenic risk level of 1:100000.

Recommendations / Conclusions

Based on the initial results, the PQRI team is confident that the proposed Classification strategy can be utilized as a valid alternative to the need to conduct animal toxicology studies in order to qualify identified leachables and extractables that have no toxicological data to develop a chemical specific risk assessment.

Next steps for the PQRI Team:

- Engage a statistician to determine if additional chemical assessments may be required to validate Class I
- Present initial findings to regulatory authorities (FDA, EMA, and HC) for review/comment
- Modify approach based on Regulatory feedback
- Gain regulatory acceptance for a final classification approach
- Publish Final Classification Strategy as a PQRI best practice

References

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Acknowledgments

The PQRI team acknowledges Russell Naven (Pfizer, Inc) for providing the *in silico* assessment of the PQRI database. We also want to acknowledge the ongoing regulatory guidance and perspectives from Tim Robison, Abby Jacobs (FDA), Alisa Vespa (HC), and David Jones (MHRA).

All research work is supported under the direction of PQRI.

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