Safety Thresholds and Best Practices for Extractables & Leachables in OINDP: A PQRI Success Story

Daniel L. Norwood* and Lee M. Nagao†

INTRODUCTION

The PQRI Leachables and Extractables Working Group was established in 2001, through a proposal submitted to PQRI by the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS). The objectives of the Working Group were to:

- Develop science-based safety thresholds for leachables and extractables in orally inhaled and nasal drug products (OINDP);
- Develop an approach to establishing an analytical evaluation threshold based on a safety threshold; and
- Establish best practices for evaluation of extractables and leachables in OINDP.

The Working Group is lead by IPAC-RS and includes participants from PDA, academia, AAPS, and PhRMA.

ACCOMPLISHMENTS

The Group's work and recommendations are contained in *Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products* (1), submitted to the FDA in 2006. **The Recommendations are being used widely throughout the OINDP industry and its supply chain, and by FDA and other international regulatory agencies.**

The Working Group:

- Used publicly available data and information to establish a Safety Concern Threshold (SCT) and a Qualification Threshold (QT)
- Developed a process for establishing an Analytical Evaluation Threshold (AET) based on the SCT
- Developed protocols and conducted controlled extraction studies and simulated leachables studies, generating data to establish analytical best practices

After completing the Recommendations, the Group:

- Held a 2005 workshop to introduce and discuss the Recommendations to the public
- Held 5 training courses in Washington, DC, Chicago, Basel, La Jolla, and to Health Canada in Ottowa
- Published the development of the safety thresholds in *Toxicological Sciences* (2)
- Published the best practices in *Pharmaceutical Research* (3)
- Is contributing to a book on L&E safety thresholds and best practices

SAFETY THRESHOLDS

The SCT is 0.15 µg/day (~ 0.14 – 0.36 µg/g). The SCT is the threshold below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and non-carcinogenic effects.

The QT is 5 µg/day (~ 4.7 – 11.9 µg/g). The QT is a threshold below which a given non-carcinogenic leachable is not considered for safety qualification unless it presents structure-activity relationship concerns.

The SCT is derived from :

- Risk Specific Doses from Salmonella (SAL) positive (genotoxic carcinogen) results from the Carcinogenic Potency Database (4)
- Incorporation of 10^{-6} excess cancer risk
- 50 kg default human body weight
- Geometric mean of potencies from rats and mice

The QT is developed from:

- Evaluation of the California EPA, US EPA and ATSDR database inhalation reference values
- Consideration of irritant thresholds
- Consideration of ambient air particulate matter thresholds
- Consideration of effects on children

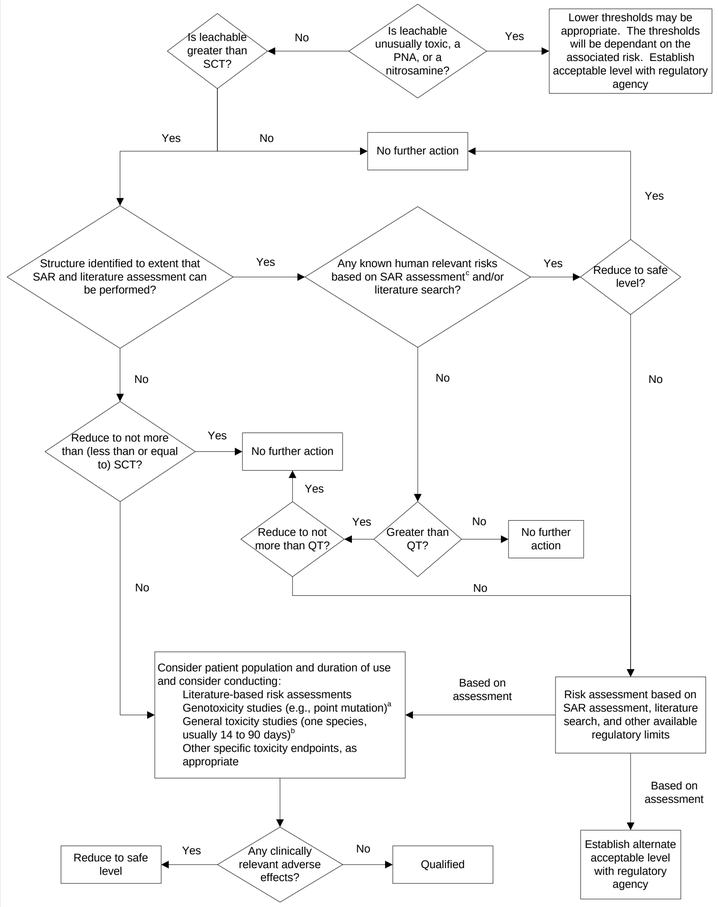

Figure 1. *Decision tree for identification and safety qualification of leachables. (a) if needed, a minimum screen should be conducted; (b) if general tox studies are needed, one or more studies should be designed to allow comparison of unqualifed to qualified material; (c) e.g., do known safety data for leachable or structureal class preclude human exposure at the present concentration*

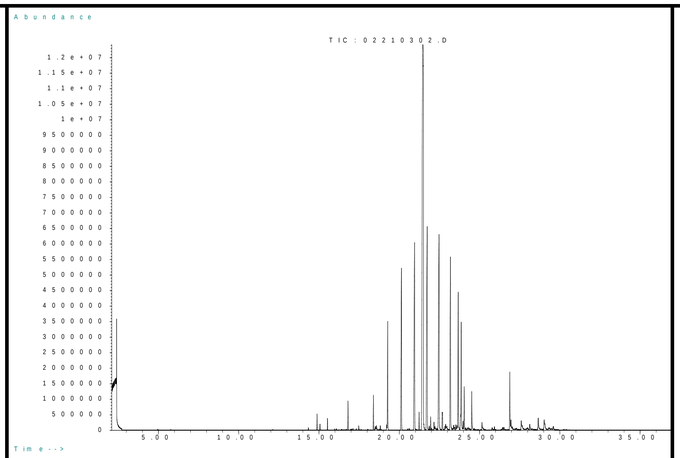

Figure 2. *GC/MS extractables profile of the sulfur-cured elastomer test article, methylene chloride reflux extract*

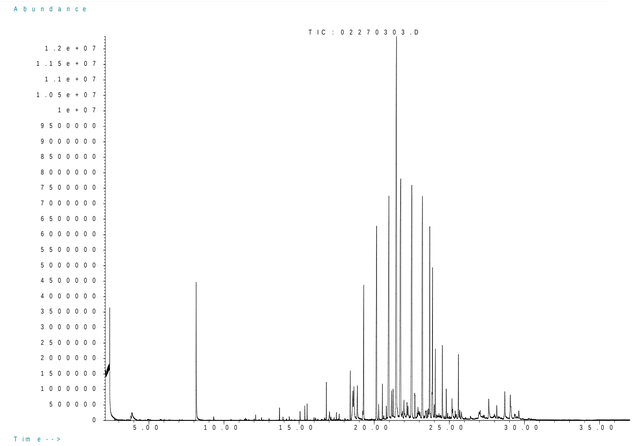

Figure 3. *GC/MS extractables profile of the sulfur-cured elastomer test article, 2-propanol reflux extract.*

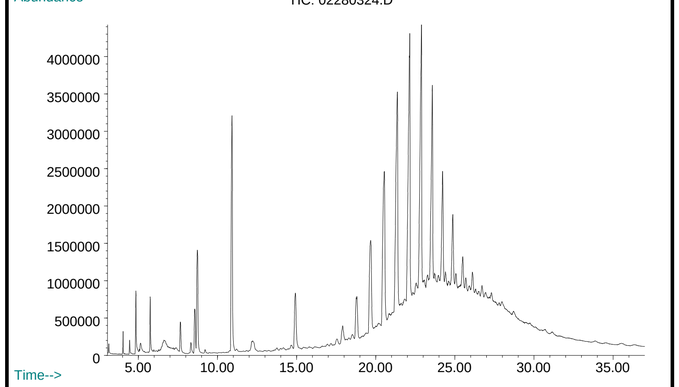

Figure 4. *GC/MS extractables profile of peroxide-cured elastomer test article, 2-propanol reflux extract.*

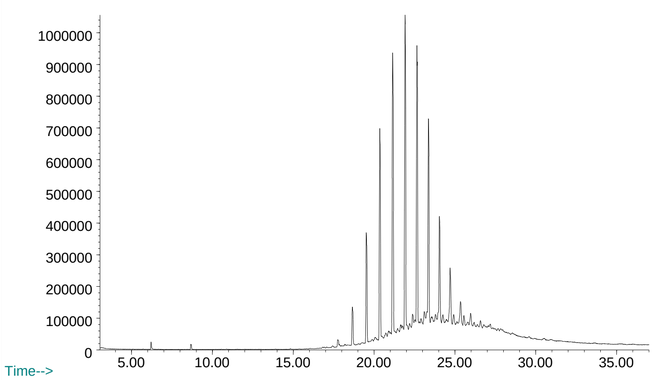

Figure 5. *GC/MS extractables profile of peroxide-cured elastomer test article, 2-propanol sonication extract*

AET AND BEST PRACTICES

The AET is the threshold at or above which an OINDP pharmaceutical development team should identify and quantify a particular extractable and/or leachable and report it for potential toxicological assessment.

The AET is based on the SCT and is generally reported in units of amount per unit container (e.g., µg/blister, µg/canister). The SCT is converted to the AET using the individual drug product configuration values – actuations/doses per day, doses per blister, etc.

The best practices include the following recommendations:

- Obtain from suppliers, extractables data and, if possible, formulation information (e.g., relative amounts of ingredients/additives) on container closure system/device components. Consider early safety risk analysis on extractables
- Conduct thorough controlled extractables studies on "critical components" using multiple solvents, extraction techniques, and analytical methods **(See Figures 2-5),** optimization and systematic identification
- Conduct leachables studies and establish a correlation between the extractables and leachables profiles

ACKNOWLEDGEMENTS AND REFERENCES

The authors thank the:

- PQRI L&E Working Group: Doug Ball, James Blanchard, Lidiette Celado, T.J. Deng, Fran DeGrazio, Bill Doub, Thomas Feinberg, Alan Hendricker, Jeff Hrkach, Roger McClellan, Tim McGovern, Diane Paskiet, David Porter, Michael Ruberto, Alan Schroeder, Mark Vogel, Qinxi Wang, Ronald Wolff, and Guirag Poochikian (PQRI DPTC).
- PQRI Steering Committee
- IPAC-RS Board of Directors

1. http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf
2. *Toxicological Sciences.* Vol 97, No 2, pp. 226–236 (2007)
3. *Pharmaceutical Research*, 25(4), 727-739 (2008)
4. http://potency.berkeley.edu/

*Boehringer Ingelheim Pharmaceuticals, Inc. † Drinker Biddle and Reath, LLP