Derivation and Validation of Parenteral Classification Strategy

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Disclaimer:

The views expressed in this presentation are those of the speaker and do not necessarily reflect the views of the US FDA.

This presentation should not be interpreted as FDA concurrence with the PQRI recommendations on parenteral drug products. FDA has not yet formally evaluated the proposals.
Safety Evaluation of Extractables & Leachables

- Approach for orally inhaled and nasal drug products (OINDP) was resource intensive for both industry and Division of Pulmonary, Allergy and Rheumatology Products (DPARP).
- The safety assessment of identified E&Ls from a container closure system is a complex process.
- Typically, the lists of chemicals identified are large (e.g., 50 for leachables and more for extractables for a metered dose inhaler).

**QUESTION:** Could application of a safety threshold(s) provide reasonable balance between patient safety and more efficient use of resources?
Initial DPARP threshold approach – mid-1990s

- Safety evaluation approach for OINDP considered systemic, local, genotoxic/carcinogenic, and sensitization/irritation potential

- Qualification threshold (QT) of 5 µg/day presented a negligible safety concern for non-carcinogenic effects
  - Based on evaluation of US Environmental Protection Agency (EPA) database for chemicals with inhalation data
  - Compounds with structural alert or identified concern for carcinogenicity required additional follow-up
PQRI OINDP Work Group confirms QT

- PQRI OINDP work group expanded the database to include Agency for Toxic Substances and Disease Registry (ATSDR) and California EPA data
  - Concluded that 5 µg/day QT was appropriate for non-carcinogenic effects for leachables derived from OINDP
Derivation of TTC/SCT

• History of derivation of Threshold of Toxicological Concern (TTC) described in previous presentation

• The Safety Concern Threshold (SCT) was first proposed by the PQRI OINDP Working Group

• For OINDP, the SCT is 0.15 μg/day
  • The SCT is the threshold below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and noncarcinogenic toxic effects

• Below the SCT, identification of leachables is unnecessary

Ball et al, 2007
Safe Human Inhalation Exposures for Different Toxicity Endpoints

PQRI OINDP Best Practices Recds

Carcinogenicity -- 10^{-6} Risk Specific Dose for CPDB Mutagens (N=276)
Acute Irritation -- Human Equivalent RD50/1000 (N=244)
Respiratory Toxicity -- Chronic Inhalation Reference Dose (N=57)
Systemic Toxicity -- Chronic Inhalation Reference Dose (N=98)

- SCT 0.15 µg/day
- QT 5.0 µg/day

Cumulative Percent of Compounds vs. Inhalation Dose (µg/day)
FDA Application of TTC/SCT Approach

• TTC applied by FDA CFSAN in evaluation of food packaging migrants, flavoring agents

• FDA/CDER applies SCT approach to OINDP
  • Originally applied SCT of 0.15 µg/day but, subsequent to ICH M7 finalization, now applies threshold of 1.5 µg/day in most cases
  • SCT of 0.15 µg/day currently serves as an identification threshold and supports calculation of Analytical Evaluation Threshold (AET)
FDA Application of TTC/SCT Approach

• Special cases - potent carcinogens in black rubber
  • Nitrosamines (permitted total of 0.04 ng/kg/day associated with a $10^{-5}$ risk level for cancer; derived from 2-year carcinogenicity rat study)
  • Polyaromatic hydrocarbons (Inhaled ADI can be identified in the literature)

• Other high potency carcinogens (aka, cohort of concern)
FDA/CDER values use of safety thresholds in evaluation of L&Es

- Use of thresholds allows resources to be applied to areas of more significant safety concern

- For OINDP:
  - SCT is 0.15 µg/day and used as an identification threshold
  - Genotoxic/carcinogenic threshold ≤ 1.5 µg/day (per ICH M7 Guidelines)
  - QT for other chemicals including irritants or sensitizers is 5 µg/day

- These thresholds have also been incorporated into review of other product types as a starting point
  - 1.5 µg/day for small volume parenterals
Parenteral Drug Product Classification

(Slides 13-24 courtesy of Doug Ball or derived from PQRI PODP Working Group Recommendations document and represent FDA agreement)
### Examples of Packaging Concerns for Common Classes of Drug Products

<table>
<thead>
<tr>
<th>Degree of Concern Associated with the Route of Administration</th>
<th>Likelihood of Packaging Component-Dosage Form Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong></td>
<td><strong>High</strong></td>
</tr>
<tr>
<td>Inhalation Aerosols and Sprays</td>
<td>Injections and Injectable Suspensions; Inhalation Solutions</td>
</tr>
<tr>
<td>Transdermal Ointments and Patches</td>
<td>Ophthalmic Solutions and Suspensions; Nasal Aerosols and Sprays</td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td><strong>Low</strong></td>
</tr>
<tr>
<td>Topical Solutions and Suspensions; Topical and Lingual Aerosols; Oral Solutions and Suspensions</td>
<td>Oral Tablets and Oral (Hard and Soft Gelatin) Capsules; Topical Powders; Oral Powders</td>
</tr>
</tbody>
</table>

*a* While this table provides a convenient overview of the general level of regulatory concern with various dosage forms regarding leachables, it should not be inferred that “low-risk” dosage forms (e.g., oral tablets) by that definition carry no risk for leachables issues.
POPD WG proposed approach

- Given similar level of risk, WG hypothesized that best practices for OINDP could be applicable to PDP
  - The QT for OINDP was further evaluated and a Classification Strategy adapted from the Cramer Classification method was developed to identify and qualify L&Es in PDP
  - Extrapolation of threshold concepts with consideration of unique characteristics

- PQRI Chemistry sub-team prepared list of 613 chemicals representing various classes that are routinely observed

- WG evaluated the database using current toxicological qualification approaches
The PQRI Toxicology Team developed scientifically-justified thresholds for leachables in parenteral drug products by taking the following approach:

- Database of 613 chemicals that have been shown to potentially leach from container closure system materials
  - the database is representative of various chemical classes that have been observed in Controlled Extraction and/or Routine Leachable studies

- The database was analyzed using in silico methods, then sorted into classes using a modified Cramer approach (ToxTree) that includes a class for genotoxicants (DEREK)

- ~ 25 Class 3 (most toxic) leachables underwent an initial risk assessment to verify the classification
  - Based on this process a final classification scheme was developed
**POPD WG proposed approach**

- Based on general acceptance of Cramer classification strategy, PDP WG initially developed similar classification for PDP

<table>
<thead>
<tr>
<th>Class</th>
<th>Cramer/PQRI OINDP TDI (ug/day)</th>
<th>PQTI PDP TDI (ug/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (low toxicity)</td>
<td>1800 (Cramer)</td>
<td>150</td>
</tr>
<tr>
<td>2 (moderate toxicity)</td>
<td>540 (Cramer)</td>
<td>50</td>
</tr>
<tr>
<td>3 (marked toxicity)</td>
<td>90 (Cramer)</td>
<td>7.5</td>
</tr>
<tr>
<td>4 (sensitizers/irritants)</td>
<td>5 (PQRI OINDP)</td>
<td>5</td>
</tr>
<tr>
<td>5 (mutagenicity)</td>
<td>0.15 (PQRI OINDP)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

*Cramer class dose divided by factor of 10 and adjusted for 50 kg human body weight (vs 60 kg)*
Proposed parenteral classification strategy

5 tier strategy consolidated to 3 tier classification

Proposed Classification Based on ToxTree, DEREK, SARAH, and verification analysis:

<table>
<thead>
<tr>
<th></th>
<th>Class 1</th>
<th>Class 2</th>
<th>Class 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold Level</td>
<td>50*</td>
<td>5</td>
<td>1.5-120**</td>
</tr>
<tr>
<td>(ug/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Proposed Classification of Class 1 dose was determined from a literature based risk assessment of ~10% of the database to establish a chemical-specific ADI (mainly Class 2 and 3 Cramer sorted chemicals), statistical analysis, and comments received from the regulators (FDA, HC, MHRA) on validation strategy

** SCT=1.5 µg/day. Higher levels of a mutagenic leachable may be acceptable based on ICH M7 (2014) principles
Class 3 Verification

Primarily based on ICH M7 principles:

- 1.5 µg/day TTC-based Acceptable Intake
- Based on discussion with FDA, HC, and MHRA, parenteral DP is not expected to have the same level of concern as OINDP
- Mainly aqueous based formulations – fewer leachables than observed in MDIs
- ICH M7 principles allow for higher levels of a mutagenic leachable based on DP usage
Class 2 Verification

• PQRI recognizes there is no acceptable method to establish a threshold for sensitizers

• The proposed dose of 5 μg/day is considered a practical limit based on
  • 0.8 μg/cm² (0.01% in cosmetic products) on known fragrance allergens considered safe for the general population (SCCS, 2012). When converted to dose, 5 μg/day is ~2200-fold dose margin.

• FDA CFSAN threshold working group – using penicillin as an example, 3.5 μg/day would be considered a safe daily exposure in foods

• PQRI OINDP QT level – no reported instances of paradoxical bronchoconstriction or sensitization responses in pulmonary DP
Class 1 Verification

• ~10% of the L&E database (n=60) were used to calculate a chemical specific acceptable daily intake (ADI)
  • Mainly Class 2 and 3 chemicals (intermediate and high toxicity) from the Cramer sort

• Employed ICH Q3C/Q3D methods to calculate ADI
  • Added F6 (10x) to account for oral to parenteral route differences

• Statistical analysis of the output to determine acceptable ADI
## Examples of Class 1 ADI Calculations

<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>Mutagenic (Yes/No)</th>
<th>Sensitizer (Yes/No)</th>
<th>ADI (µg/day)/Margin*</th>
<th>Pass/Fail (Comments)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distearyl pentaerythritol diposphite</td>
<td>No</td>
<td>Unknown</td>
<td>100000/2000 (Based on NOAEL of 1000 mg/kg/day in a 2 year rat study)</td>
<td>PASS</td>
</tr>
<tr>
<td>Tri(nonylphenyl)phosphite</td>
<td>No</td>
<td>Unknown</td>
<td>16700/334 (Based on NOAEL of 167 mg/kg/day in a 2 year rat study)</td>
<td>PASS</td>
</tr>
<tr>
<td>Cyasorb-UV-1164</td>
<td>No</td>
<td>Unknown</td>
<td>10000/200 (Based on NOEL of 1000 mg/kg/day in a 28 day rat study)</td>
<td>PASS</td>
</tr>
<tr>
<td>Bis(3,4-dimethylbenzyldiene) sorbitol</td>
<td>No</td>
<td>No</td>
<td>2460/49.2 (Based on 13-week rat NOEL)</td>
<td>PASS</td>
</tr>
<tr>
<td>3,5-di-tertbutyl-4-hydroxyanisole</td>
<td>Unknown</td>
<td>Unknown</td>
<td>2120/42.4 (Based on NOEL of 106 mg/kg/day in a 90 day rat study)</td>
<td>PASS</td>
</tr>
<tr>
<td>Cyasorb UV-3346</td>
<td>No</td>
<td>Unknown</td>
<td>2000/40 (Based on a NOEL of 100 mg/kg/day in a 90-day rat study)</td>
<td>PASS</td>
</tr>
<tr>
<td>Cyasorb UV-24</td>
<td>No</td>
<td>Unknown</td>
<td>1850/37 (Based on NOAEL of 185 mg/kg/day in a 36 day rat study)</td>
<td>PASS</td>
</tr>
<tr>
<td>1,1,1-Trimethylsilanol</td>
<td>No</td>
<td>Unknown</td>
<td>1600/32 (Based on NOAEL of 160 mg/kg/day in a repeat dose day rat study)</td>
<td>PASS</td>
</tr>
<tr>
<td>Chimassorb 81</td>
<td>No</td>
<td>Unknown</td>
<td>1800/56 (Based on a NOEL of 900 mg/kg/day in a 3 month rat study)</td>
<td>PASS</td>
</tr>
<tr>
<td>Bisphenol A bis(2,3-dihydroxypropyl) ether</td>
<td>No</td>
<td>No</td>
<td>1500/30 (based on 2 year rat study data)</td>
<td>PASS</td>
</tr>
<tr>
<td>Diphenylamine</td>
<td>No</td>
<td>Unknown</td>
<td>670/13.4 (Based on a NOAEL of 6.7 mg/kg/day in a 2 year rat study)</td>
<td>PASS</td>
</tr>
</tbody>
</table>
5 Chemicals with Dose Margin < 1 (FAIL)

- Flourene
- Chimasorb 119
- Tinuvin 320
- Tinuvin 144
- Tinuvin 770

12 chemicals evaluated as “Unknown” due to lack of data
### Statistical Evaluation for Class 1

<table>
<thead>
<tr>
<th>Dose (µg/day)</th>
<th>Pass (%) (Dose Margin ≥1)</th>
<th>90 % Confidence Interval</th>
<th>95% Confidence Interval</th>
<th>99% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower Bound</td>
<td>Upper Bound</td>
<td>Lower Bound</td>
</tr>
<tr>
<td>50</td>
<td>55/60 (91.7)</td>
<td>82.8</td>
<td>96.4</td>
<td>80.9</td>
</tr>
<tr>
<td>150</td>
<td>48/60 (80.0)</td>
<td>69.4</td>
<td>87.8</td>
<td>67.3</td>
</tr>
</tbody>
</table>

Based on this analysis, a Class 1 dose of 50 µg/day provides a greater degree of confidence than 150 µg/day. The level of confidence at 50 µg/day support that leachables that are identified at or below 50 µg/day would be considered qualified for systemic risk unless individual chemical data warrant a lower acceptable daily intake.

Class 1 dose of 50 µg/day provides greater degree of confidence compared to 150 µg/day that leachables would be qualified for systemic risk unless individual chemical data warrant a lower ADI.
Class 1 Threshold vs ICH Q3B(R2)

• Results of verification process demonstrated that a level of 50 µg/day is comparable to the most conservative qualification threshold for degradation products in new drug products
Routine Leachable Study
Identify chemicals for safety assessment
Based on AET derived from SCT

Genotoxic concern?
Yes – qualify (based on ICH M7)
No – S/I potential?

S/I concern?
Yes – qualify
No – systemic tox

Systemic Tox concern?
Yes – qualify
No – DP CCS qualified
Safe Human Inhalation Exposures for Different Toxicity Endpoints

- **Carcinogenicity**
  - **Acute Irritation**
  - **Respiratory Toxicity**
  - **Systemic Toxicity**

**Inhalation Dose (µg/day)**

- **Carcinogenicity** — $10^{-6}$ Risk Specific Dose for CPDB Mutagens (N=276)
- **Acute Irritation** — Human Equivalent RD50/1000 (N=244)
- **Respiratory Toxicity** — Chronic Inhalation Reference Dose (N=57)
- **Systemic Toxicity** — Chronic Inhalation Reference Dose (N=98)

Cumulative Percent of Compounds

- **SCT** 0.15 µg/day
- **QT** 5.0 µg/day

PQRI OINDP Best Practices Recds
Conclusions

- Application of safety thresholds for OINDP considers systemic, local, genotoxic/carcinogenic, and sensitization/irritation potential
  - OINDP thresholds based primarily on inhalation data and conservative assumptions

- Safety thresholds can be an effective approach to balance patient safety and efficient use of resources

- Application of these general approaches to parenteral products appears reasonable

- FDA is currently evaluating the PQRI WG proposed safety thresholds
Thank You