Validation of the toxicological threshold for E&L from the Single Use System

Akihiko Hirose

National Institute of Health Sciences, JAPAN
Contents

• Introduction

• General concepts for assessment of impurity

• Evaluation approach extractable and leachable

• Validation of the threshold value of QT and discussion

Disclaimer:
The contents in this presentation do not reflect any official NIHS or PMDA/ MHLW policy
International documents for qualification of SUS

**BPSA : Bio-Process Systems Alliance**


**BPOG : BioPhorum Operations Group**


**PDA : Parenteral Drug Association**

Application of Single-use System in Pharmaceutical Manufacturing

PDA technical report No 66 (2014)

**ASME : American Society of Mechanical Engineers**

Bioprocessing Equipment (2014)
White Paper:
Approaches to Quality Risk Management When Using Single Use Systems in the Manufacture of Biologics

1. Introduction
2. Scope
3. Basic Requirements
4. Risk Assessment
5. Risk Control Strategies
6. Lifecycle and Change Management
7. Conclusion
8. References
9. Glossary
RISK ASSESSMENT

An identified risk should be analyzed and compared to risk criteria to decide whether it is acceptable or should be mitigated.

Cf. Impact on the Quality of Biologics
- Residual Impurities
- Extractables and Leachables
- Insoluble Particulate Matter
- Insoluble Visible Matter (Visible Particle)
- Endotoxins and Microbes
- Deviation from the CQA control range

Points to consider in quality assurance of biotechnology product manufacturing by using single-use systems (in Japanese language)

4.1.1 Extractables and Leachables
refer the figure of risk assessment from the PQRI Leachables and Extractables WG document (2006)
Objective of the study

- As SUS is mostly made of plastic, any materials derived from the plastic may influence on the features, manufacturing, and product quality.
- Developing of the comprehensive risk management method for leachable chemicals would be important.
- However, we do not know the toxicity information for most of chemicals possibly leached from the plastics for medical use.
- We have to develop a threshold approach (such as TTC approach) for evaluating the health effects by the variety of chemicals exposure.
- PQRI developed the threshold approach for evaluating E&L of some drug products. The approach could be applicable for E&L from the SUS.
- The mutagenic threshold (SCT) same as the ICH M7 consensus value may be appropriate.
- Is the non-mutagenic TTC (QT) appropriate for E&L evaluation from SUS? => The QT proposed for PDP should be validate.
Safety Qualification Process

Is leachable greater than SCT?

No

Yes

No further action

Is leachable unusually toxic, a PNA, or a nitrosamine?

No

Yes

Reduce to not more than SCT?

No

Yes

Structure identified to extent that SAR and literature assessment can be performed?

No

Yes

No further action

Any known human relevant risks based on SAR and/or literature search?

No

Yes

Reduce to safe level?

No

Yes

Greater than QT?

No

Yes

Reduce to not more than QT?

No

Yes

Consider patient population and duration of use and consider conducting toxicity studies

Based on Assessment

Establish alternate acceptable level

Risk assessment based on SAR assessment, literature search, and other available regulatory limits

Lower thresholds may be appropriate. The thresholds will be dependent on the associated risk.

No further action

modified from the PQRI recommendation 2006
ASSESSMENT AND CONTROL OF DNA REACTIVE (MUTAGENIC) IMPURITIES IN PHARMACEUTICALS TO LIMIT POTENTIAL CARCINOGENIC RISK

Flow chart of qualification of mutagenic impurity in ICH M7

Is impurity greater than TTC level (or Acceptable level of each chemicals)?

Yes

Two QSRA assessment?

Positive either

Result of Ames study is positive

Reduction to lower than TTC, or conducting in vivo genotoxicity studies

No

No further action

For general toxicity, the qualification by Q3A/Q3B?

Both negative

No further action

No guidance for E/L in ICH

Out of scope: biological/biotechnological, peptide, oligonucleotide, radiopharmaceutical, fermentation products, herbal products, and crude products of animal or plant origin
Decision Tree for Identification and Qualification (partially modified from Q3A)

- **Is impurity greater than identification threshold?**
  - Yes: Structure identified?
    - Yes: Any known human relevant risks? (Mutagenic? More than PDE?)
      - Yes: Reduce to safe level
      - No: Consider patient population and duration of use and consider conducting toxicity studies
    - No: No further action
  - No: Reduce to not more than (≤) identification threshold?
    - Yes: No further action
    - No: Consider patient population and duration of use and consider conducting toxicity studies

- **No action**
Risk assessment frame work for chemical impurity
from the point of view of toxicological concern

1. Is a structure of the Impurity identified?
   - Yes
   - No

2. Is PDE or AL of the impurity officially established?
   - Yes
   - No

3. Assess exposure level comparing with mutagenic TTC level
   - Lower
   - Exceeded

   - Reduce the exposure level lower than the mutagenic TTC, (or replace to the substitute)

4. Assess exposure level comparing with PDE or AL
   - Lower
   - Exceeded

   - Reduce the exposure level lower than the PDE/AL, (or replace to the substitute)

5. Is mutagenicity of the impurity available?
   - Positive
   - Negative

   - Assess mutagenicity of the impurity

6. Is carcinogenicity Information available for deriving AL?
   - No
   - Yes

7. Is toxicological information available for deriving PDE/AL?
   - No
   - Yes

8. Confirm or reduce the exposure level lower than non-mutagenic TTC

9. Establish PDE/AL

10. No further action
Proposed Safety Classification of Extractables / Leachables for PODP by PQRI

(PDA Journal of Pharmaceutical Science and Technology September/October 2013 vol. 67 no. 5 430-447)

<table>
<thead>
<tr>
<th>Class</th>
<th>Threshold</th>
<th>Munro (1996)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>µg/day</td>
<td>µg/kg/day</td>
</tr>
<tr>
<td>Initial PQRI Classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (Cramer class I )</td>
<td>150</td>
<td>3</td>
</tr>
<tr>
<td>2 (Cramer class II )</td>
<td>50</td>
<td>1</td>
</tr>
<tr>
<td>3 (Cramer class III)</td>
<td>5</td>
<td>0.1</td>
</tr>
<tr>
<td>4 (genotoxicity)</td>
<td>0.15</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Additional safety factors to account for body weight (BW) and route of administration differences (oral vs parenteral) were considered to add orders of magnitude to the already conservative estimates established by Cramer and refined by Munro (1996).

**Qualification Threshold (QT)**: the threshold below which a given leachable is not considered for safety qualification (toxicological assessments) unless the leachable presents SAR concerns.
**Class I:** substances of simple chemical structure with known metabolic pathways and innocuous end products which suggest a low order of oral toxicity.

**Class II:** substances that are intermediate; not in Class I nor in Class III.

**Class III:** substances with chemical structures that permit no initial presumption of safety and may even suggest significant toxicity.

---

<table>
<thead>
<tr>
<th>Structural class I</th>
<th>5th Centile NOEL (mg/kg body weight/day)</th>
<th>Human exposure threshold (µg/person/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural class II</td>
<td>0.91</td>
<td>540</td>
</tr>
<tr>
<td>Structural class III</td>
<td>0.15</td>
<td>88</td>
</tr>
</tbody>
</table>

PQRI Toxicology Team Approach to Thresholds by using 600 chemicals

(PDA Journal of Pharmaceutical Science and Technology September/October 2013 vol. 67 no. 5 430-447)

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<td>5</td>
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<td></td>
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<tr>
<td>4 (genotoxicity)</td>
<td>0.15</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(2013) PQRI Classification proposal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (general toxicity, QT)</td>
<td>150</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>2 (sensitizers)</td>
<td>5</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>3 (genotoxicity, SCT)</td>
<td>1.5</td>
<td>0.03</td>
<td></td>
</tr>
</tbody>
</table>

- The degree of risk associated with a Class III chemical may not significantly differ from that for a Class I chemical, suggesting only one class instead of three classes for general toxicity were relevant.
Methods for our validation study of the QT

• The information about 218 substances/items in relation with extractables/leachables from the SUS were gathered from the below literatures.

<Reviewed references>
BioProcess International 7(5), 46-51, 2009
BioProcess International 8(11), 52-59, 2010

The 168 chemical structures were identified among the 218 substances, and used them for further evaluation.
The structure variety of the chemicals between the PQRI study and our study were evaluated according with the Crammer classification

**PQRI Toxicology Team Approach to Thresholds**

*About 600 chemicals of extractables/leachables from the container/closure systems in parenteral products*

- Cramer Class I: 53%
- Cramer Class II: 9%
- Cramer Class III: 38%

Positive prediction for mutagenicity by DEREK: 11% (class III: 83%)

**Our validation study**

*168 chemicals of extractables/leachables from the SUS*

- Cramer Class I: 62% (104 chemicals)
- Cramer Class II: 9% (16 chemicals)
- Cramer Class III: 29% (48 chemicals)

Positive prediction for mutagenicity by DEREK/CASE Ultra: 11% (7 chemicals)

(class III: 86% (6 chemicals))
## Chemicals for positive (Q)SAR prediction of genotoxicity

<table>
<thead>
<tr>
<th>(Q)SAR software</th>
<th>Chemical predicted as positive</th>
<th>Actual information of test results (genotoxicity and carcinogenicity)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Derek Nexus</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthracene</td>
<td><em>in vitro</em> inconclusive; <em>in vivo</em> negative; IARC 3, USEPA D</td>
<td></td>
</tr>
<tr>
<td>Epoxidized soybean oil (ESBO)</td>
<td><em>in vitro</em> negative, no indication of carcinogenicity</td>
<td></td>
</tr>
<tr>
<td>Furfural</td>
<td><em>in vitro</em> inconclusive; <em>in vivo</em> negative</td>
<td></td>
</tr>
<tr>
<td>Stearic acid, 9,10-epoxy-isopropyl ester</td>
<td>No information</td>
<td></td>
</tr>
<tr>
<td><strong>CASE Ultra</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthracene</td>
<td><em>in vitro</em> inconclusive; <em>in vivo</em> negative; IARC 3, USEPA D</td>
<td></td>
</tr>
<tr>
<td>Butyl cyclohexanecarboxylate</td>
<td><em>in vitro, in vivo</em> inconclusive</td>
<td></td>
</tr>
<tr>
<td>2,3-Dihydrofuran</td>
<td>No information</td>
<td></td>
</tr>
<tr>
<td>2-Phenylphenol</td>
<td><em>in vitro</em> inconclusive; <em>in vivo</em> negative; IARC 3</td>
<td></td>
</tr>
</tbody>
</table>

As for a genotoxicity evaluation, these chemicals were evaluated by different types of (Q)SAR software (Derek Nexus, CASE Ultra).
Estimation of the PDEs of extractables/leachables

- Reference doses (TDI, ADI, RfD, NOAEL, LOAEL, etc.) of non-carcinogenic endpoints for 57 out of 168 chemicals were obtained from information published by organizations or assessment reports listed in the below.

<Information sources>

CANADA: Health Canada;
IPCS: Concise International Chemical Assessment Document (CICAD);
OECD: OECD SIAM assessment reports;
USEPA: Integrated Risk Information System (IRIS) by the US Environmental Protection Agency (USA);
NTP: US National Toxicology Program test reports (USA);
NSF: National Sanitation Foundation International (USA);
RIVM: National Institute of Public Health and the Environment, (the Netherlands);
MHLW: Existing chemicals test reports by Ministry of Health, Labour and Welfare (Japan);
MOE: Initial assessment reports by the Ministry of Environment (Japan);
NITE: Initial assessment reports by the National Institute of Technology and Evaluation (Japan);
<table>
<thead>
<tr>
<th>CAS</th>
<th>Chemical name</th>
<th>Structure</th>
<th>Crammer</th>
<th>Proposed TDI for oral dose (ug/kg/day)</th>
<th>Proposed PDE for oral dose (ug/day)</th>
<th>Oral absorption rate (%)</th>
<th>Proposed PDE for i.v. route (ug/day)</th>
<th>Reference</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>576-26-1</td>
<td>2,6-Dimethylbutylphenol</td>
<td>Low (Class I)</td>
<td>0.6</td>
<td>30</td>
<td>100</td>
<td>30</td>
<td></td>
<td>USEPA</td>
<td>1988</td>
</tr>
<tr>
<td>117-81-7</td>
<td>Di-2-ethylhexyl phthalate (DEHP) : Diocyl phthalate</td>
<td>Low (Class I)</td>
<td>4</td>
<td>200</td>
<td>50</td>
<td>100</td>
<td></td>
<td>RIVM</td>
<td>2000</td>
</tr>
<tr>
<td>591-78-6</td>
<td>2-Hexanone</td>
<td>Intermediate (Class II)</td>
<td>5</td>
<td>250</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>USEPA</td>
<td>2009</td>
</tr>
<tr>
<td>127-19-5</td>
<td>N,N-dimethylacetamide</td>
<td>High (Class III)</td>
<td>5</td>
<td>250</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>MOE</td>
<td>2010</td>
</tr>
<tr>
<td>96-76-4</td>
<td>2,4-Diterbutylphenol (2,4-DTBP)</td>
<td>Low (Class I)</td>
<td>5</td>
<td>250</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>MOE</td>
<td>2011</td>
</tr>
<tr>
<td>123-72-8</td>
<td>Butanal</td>
<td>Low (Class I)</td>
<td>5.4</td>
<td>270</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>MOE</td>
<td>2010</td>
</tr>
<tr>
<td>124-07-2</td>
<td>Caprylic acid : Octanoic acid</td>
<td>Low (Class I)</td>
<td>6.25</td>
<td>312.5</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>MHLW</td>
<td>2011</td>
</tr>
<tr>
<td>62-53-3</td>
<td>Aniline : Phenylamine</td>
<td>High (Class III)</td>
<td>7</td>
<td>350</td>
<td>95</td>
<td>332.5</td>
<td></td>
<td>CANADA</td>
<td>1993</td>
</tr>
<tr>
<td>540-97-6</td>
<td>Dodecamethyl-cyclohexasiloxane</td>
<td>High (Class III)</td>
<td>10</td>
<td>500</td>
<td>10</td>
<td>50</td>
<td></td>
<td>OECD</td>
<td>2002</td>
</tr>
<tr>
<td>527-60-6</td>
<td>2,4,6-Trimethylphenol</td>
<td>Low (Class I)</td>
<td>10</td>
<td>500</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>NITE</td>
<td>2007</td>
</tr>
<tr>
<td>98-01-1</td>
<td>Furfural</td>
<td>High (Class III)</td>
<td>10</td>
<td>500</td>
<td>90</td>
<td>450</td>
<td></td>
<td>USEPA</td>
<td>2010</td>
</tr>
<tr>
<td>70-55-3</td>
<td>p-Toluenesulfonamide(PTS)</td>
<td>High (Class III)</td>
<td>12</td>
<td>600</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>MHLW</td>
<td>1992</td>
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- If value of tolerable intake (e.g. TDI, ADI, RfD) were evaluated by the assessment organization, the value was directly used for oral PDE derivation.

- If NOAEL from short term study is available, proposed TDI was calculated by using uncertainty factor of 1000.

- If only LOAEL from short term study is available, proposed TDI was calculated by using uncertainty factor of 10000.
Methods of estimation of absorption rate
for calculating the PDE of i.v. route exposure

• Primary information of oral absorption rate was derived from the section for kinetics in the assessment reports or monographs of chemicals with TDI/NOAELs which we used for PDE derivation.
  
  If concrete numbers of absorption rate are available, smaller value was selected. If the document stated “the chemicals is easily absorbed by oral route”, the absorption rate of 100% was assigned as absorption rate.

• If no clear information about oral absorption rate in the document was available, some absorption values were estimated from the kinetics study results.
  
  if some portion of the labeled chemicals orally absorbed was recovered from urine, the percentage for systemic absorption would be estimated as same as the percentage of recovery from urine.

• If we could not get any kinds of in vivo absorption information, we did not calculate the i.v. PDE.
  
  < In future, the information from in vitro/in silico studies may be applicable. >
## Summary table of the 57 chemicals with provisional PDEs

<table>
<thead>
<tr>
<th>CAS</th>
<th>Chemical name</th>
<th>Structure</th>
<th>Cramer</th>
<th>Proposed TDI for oral dose (ug/kg/day)</th>
<th>Proposed PDE for oral dose (ug/day)</th>
<th>Oral absorption rate (%)</th>
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- If only LOAEL from short term study is available, proposed TDI was calculated by using uncertainty factor of 10000.
Distribution of PDE values

- Blue dots: Oral (39)
- Orange dots: Parenteral (39)
- Gray dots: oral_all (59)

The graph shows the distribution of PDE values in ug/day, with a focus on the 30–50 ug/day range.
## Chemical list predicted as having potent of protein binding

<table>
<thead>
<tr>
<th>Chemical name</th>
<th>by OECD QSAR application toolbox</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butanal</td>
<td>Schiff Base Formers</td>
</tr>
<tr>
<td>2-(5-Chloro-2-benzotriazolyl)- 6-tert-butyl-p-cresol</td>
<td>Michael addition</td>
</tr>
<tr>
<td>Caprolactam oxohexamethyleneimine</td>
<td>Acylation</td>
</tr>
<tr>
<td>Lauryl acrylate</td>
<td>Michael addition</td>
</tr>
<tr>
<td>Phthalic anhydride 2-Benzofuran-1,3-dione</td>
<td>Acylation</td>
</tr>
</tbody>
</table>

## Chemical list of lower absorption rate to exposure dose (less than 10%)

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<tr>
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<th>Structure</th>
<th>Cramer</th>
<th>Proposed TDI for oral dose (ug/kg/day)</th>
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<th>Oral absorption rate (%)</th>
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</thead>
<tbody>
<tr>
<td>Dodecamethyl-cyclohexasiloxane</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>High (Class III)</td>
<td>10</td>
<td>500</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>Methanetetritetramethyl tetrakis[3-(3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl)propanoate]</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>Intermediate (Class II)</td>
<td>135</td>
<td>6750</td>
<td>2</td>
<td>135</td>
</tr>
<tr>
<td>Tris[2,4-bis(1,1dimethylethyl)phenyl phosphite</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>High (Class III)</td>
<td>1000</td>
<td>50000</td>
<td>1</td>
<td>500</td>
</tr>
</tbody>
</table>
Summary and points of consideration

Assessment of exposure level comparing with SCT of 1.5 ug/day

• If the impurity is mutagenic or not determined, the exposure level should be lower than SCT.

If not,
Are there any toxicological information to establish PDE or AL?
  Yes: The exposure level should be lower than PDE/AL.
  No: The exposure level should be lower than QT (of 30-50 ug/day).

• But, assessment of possibility for sensitization or chemical reactivity would be needed.
• And possibility of accumulation or persistency to specific tissues should be assessed, if the absorption rate by oral exposure is very low, because of concerns for possible toxicity by long-term internal exposure. (non-biodegradable and higher molecular weight, higher lipophilic etc.,)
Risk assessment framework for chemical impurity
from the point of view of toxicological concern

Is a structure of the Impurity identified? (Yes/No)

If Yes:
- Is PDE or AL of the impurity officially established? (Yes/No)
  - Yes: Assess exposure level comparing with PDE or AL
  - No: Assess exposure level comparing with mutagenic TTC level

If No (of the impurity):
- Assess mutagenicity of the impurity (Positive/Negative)
  - Positive: Reduce the exposure level lower than the mutagenic TTC, (or replace to the substitute)
  - Negative: No further action

- Is carcionogenicity Information available for deriving AL? (Yes/No)
  - Yes: Assess exposure level comparing with mutagenic TTC level
  - No: Assess mutagenic level comparing with mutagenic TTC level

- Is toxicological information available for deriving PDE/AL? (Yes/No)
  - Yes: Establish PDE/AL
  - No: No further action

- Confirm or reduce the exposure level lower than non-mutagenic TTC

*: assess the potency of sensitization and bioaccumulation or biopersistency
Thank you for your attention