Regulation of Genotoxic and Carcinogenic Impurities in Pharmaceuticals

Impurities in Drugs: Monitoring, Safety and Regulation
The Israel Chapter of PDA

July, 15 – 16, 2008

David Jacobson-Kram, Ph.D. DABT
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Relevant guidelines, publications and promises on impurities

- ICH Q3A(R) Impurities in New Drug Substances, 2002
- ICH Q3B(R) Impurities in New Drug Products, 2003
- ICH Q3C Impurities: Guideline for Residual Solvents, 1997
- EMEA, Guideline on the Limits of Genotoxic Impurities, 2006
- EMEA, Questions and Answers on the CHMP Guideline on the limits of genotoxic impurities, 2008
- Establishment of Allowable Concentrations of Genotoxic Impurities in Drug Substance and Product, 2005, PhRMA position paper.
- FDA draft: Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches and Acceptable Limits
Mutations in Somatic Cells

- Cancer
- Heart disease
- Aging

Mutations in Germinal Cells

- Genetic diseases
  eg. achondroplasia

Food and Drug Administration (FDA)
Mechanisms of Activation/Inactivation of Cancer-Associated Genes

- Point Mutations
- Chromosomal Deletions
- Chromosomal Translocations
- Gene Amplification
Tests for qualifying impurities in drug substance

- Genotoxicity studies (point mutation, chromosomal aberration—Ames assay, in vitro cytogenetics or mouse lymphoma assay)
- General toxicity studies (one species, usually 14 to 90 days)
- Other specific toxicity endpoints as appropriate
What if impurity is found to be genotoxic and cannot be completely removed?

- ICH guidelines are not explicit in this regard
- Quantitative risk assessments for cancer are based on lifetime exposures of animals. What about drugs in clinical trials for relatively short periods? Should permissible levels of genotoxic impurities be higher?
Calculating thresholds for effects without thresholds—virtually safe doses, or TTCs

- Concept first proposed by CFSAN as a “threshold for regulation” of food contact materials.
- TTC refers to a dose of a material that does not pose a significant risk of cancer or other toxic effects.

*Fed. Regist. 60, 36582-36596, 1995*
Deals only with marketed products
EMEA guideline on limits of genotoxic impurities

Some genotoxic chemicals may have thresholds because of known mechanism of action, e.g. spindle poisons, topoisomerase inhibitors.

- Linear extrapolation may be not be justified for all DNA reactive chemicals.
EMEA guideline on limits of genotoxic impurities

- In most cases mechanistic data on impurity will not be available. May have structural alerts for genotoxicity and/or carcinogenicity.
- Applies a Threshold of Toxicological Concern (TTC)—exposure to an unstudied chemical that will not pose a significant risk of cancer or other toxic effect.
- TTC of 1.5 µg/person/day derived from a database of over 700 carcinogens (from the Carcinogenic Potency Data Base).
- Implies that daily exposure to this level of the average carcinogen increases the upper bound lifetime risk of contracting cancer by less than one in one million. Considered “virtually safe dose” and commonly used by EPA for environmental contaminants.
Distribution of estimated human $10^{-6}$ risk specific doses for 276 SAL-positive carcinogens from Carcinogen Potency Database (CPDB). From: Justification of Thresholds for Leachables in Orally Inhaled and Nasal Drug Products. Ball et al., In preparation.
Carcinogen Risk Assessment

Response (Tumor Data)

Dose

Impurity Exposure Levels of Interest

Point of Departure (POD)

Linear Default

LED\textsubscript{10} ED\textsubscript{10}

Lower 95% Confidence Limit on Dose

(Central Estimate)

Empirical Range of Observation

Range of Extrapolation
Risks from carcinogenic exposures

- Subset of highly potent carcinogens (generally those that are mutagens) suggest a lower TTC. These could be considered on a case-by-case basis.

- What is “virtually safe dose”
  - EPA generally uses $10^{-6}$ lifetime risk for cancer
  - State of California uses $10^{-5}$ lifetime as their “no significant risk level.”
  - EMEA proposes $10^{-5}$ lifetime risk for cancer for pharmaceuticals since unlike environmental contaminants, they provide benefit
  - ICH Q3C uses $10^{-5}$ lifetime risk for cancer as the criterion for setting acceptable levels of solvents in marketed drug products
CHMP SAFETY WORKING PARTY (SWP)

Question & Answers on the CHMP Guideline on the Limits of Genotoxic Impurities
Major points in EMEA’s June 2008 Q&A

- Guideline is NOT applied retrospectively unless there “cause for concern” e.g. mesylate salt drugs.
- If the level of a mutagenic impurity is below TTC (<1.5 µg/day) it is not necessary to apply ALARP (as low as reasonably possible) unless structure is of high concern, e.g. N-nitroso or azoxy compounds.
- Negative result in an Ames assay qualifies an impurity with a structural alert.
- Absence of structural alerts is sufficient to regard impurity a “not genotoxic.”
- It is sufficient to reduce impurities with structural alerts to TTC levels without an actual test (assume it’s positive).
Major points in EMEA’s June 2008 Q&A

- No action is required for a new unidentified impurity found at levels below the ICH identification threshold.

- When an impurity is found above the ICH identification threshold, but below the qualification threshold and it has a structural alert, this can be qualified with an Ames test on the API containing the impurity as long as the impurity is tested up to 250 µg/plate.

- EMEA accepts the notion of a “staged TTC.”
When more than one genotoxic impurity is present in the drug substance, the TTC value of 1.5 µg/day can be applied to each impurity if they are structurally unrelated. If structurally similar, MOA expected to be the same and they are summed.

May not always be achievable:
- Maximum daily dose of API
- Indication
- Step of synthesis at which impurity arises
- Capability to eliminate by purification
- Capability of analytical procedures
Risk assessment of peak exposure to genotoxic carcinogens: a pragmatic approach

Peter M. J. Bos, Bert-Jan Baars and Marcel T. M. van Raaij
Toxicology Letters 151: 43 – 50, 2004
## Staged TTC during drug development

*From EMEA Q & A, June 2008*

<table>
<thead>
<tr>
<th>Allowable Daily Intake (µg/day)</th>
<th>Single dose</th>
<th>≤1 mo.</th>
<th>≤3 mo.</th>
<th>≤6 mo.</th>
<th>&gt; 12 mo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>120</td>
<td>60</td>
<td>20</td>
<td>10</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>
Acceptable limits in ug/day based on Allowable Daily Intake calculations using a staged TTC approach*


<table>
<thead>
<tr>
<th>Duration of Exposure</th>
<th>≤1 mo.</th>
<th>&gt;1-3 mo.</th>
<th>&gt;3-6 mo.</th>
<th>&gt;6-12 mo.</th>
<th>&gt; 12 mo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proposed Allowable Daily Intake (µg/day) for all Phases of development</td>
<td>120</td>
<td>40</td>
<td>20</td>
<td>10</td>
<td>1.5</td>
</tr>
<tr>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td></td>
</tr>
<tr>
<td>Alternative maximum based on percentage of impurity in API</td>
<td>0.5%</td>
<td>0.5%</td>
<td>0.5%</td>
<td>0.5%</td>
<td></td>
</tr>
</tbody>
</table>

- $10^{-6}$ cancer risk – extra conservatism during shorter duration trials (e.g. for volunteers)
- $10^{-5}$ cancer risk – risk used by ICH for carcinogenic residual solvents and CHMP draft for genotoxic impurities

Food and Drug Administration (FDA)
A few typical daily exposures to carcinogens

<table>
<thead>
<tr>
<th>Source of carcinogen</th>
<th>Carcinogen</th>
<th>Average daily human exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indoor air</td>
<td>Formaldehyde</td>
<td>598 µg</td>
</tr>
<tr>
<td></td>
<td>Benzene</td>
<td>155 µg</td>
</tr>
<tr>
<td>Tap water</td>
<td>Bromodichloromethane</td>
<td>13 µg</td>
</tr>
<tr>
<td></td>
<td>chloroform</td>
<td>17 µg</td>
</tr>
<tr>
<td>Celery</td>
<td>8-methoxy psoralen</td>
<td>4.9 µg</td>
</tr>
<tr>
<td>Coffee</td>
<td>Catechol</td>
<td>1.3 mg</td>
</tr>
<tr>
<td></td>
<td>Hydroquinone</td>
<td>333 µg</td>
</tr>
<tr>
<td></td>
<td>Caffeic acid</td>
<td>23.9 mg</td>
</tr>
<tr>
<td>Lettuce</td>
<td>Caffeic acid</td>
<td>7.9 mg</td>
</tr>
<tr>
<td>Brown mustard</td>
<td>Allyl isothiocyanate</td>
<td>62.9 µg</td>
</tr>
</tbody>
</table>

Food and Drug Administration