Advantages in Utilizing an Integrated *In Silico* Solution for ICH M7 Expert Review

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This session is an Exhibitor-Hosted Program. Although not an official part of the ACT Annual Meeting scientific program, its presentation is permitted by the college.
A total solution to ICH M7

developed through collaboration

ICH Harmonised Tripartite Guideline

Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk

M7

<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
<th>Proposed action for control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Known mutagenic carcinogens.</td>
<td>Control at or below compound specific acceptable limit.</td>
</tr>
<tr>
<td>2</td>
<td>Known mutagens with unknown carcinogenic potential (bacterial mutagenicity positive, no rodent carcinogenicity data).</td>
<td>Control at or below acceptable limits (generic or appropriate TTC).</td>
</tr>
<tr>
<td>3</td>
<td>Alert structure, unrelated to the structure of the drug substance, no mutagenicity data.</td>
<td>Control at or below acceptable limits (generic or appropriate TTC) or run bacterial mutagenicity assay; if non-mutagenic treat as Class 5. If mutagenic treat as Class 2.</td>
</tr>
<tr>
<td>4</td>
<td>Alerting structure, same alert in drug substance which have been tested and are non-mutagenic.</td>
<td>Treat as non-mutagenic impurity.</td>
</tr>
<tr>
<td>5</td>
<td>No structural data, or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity.</td>
<td>Treat as non-mutagenic impurity.</td>
</tr>
</tbody>
</table>
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ICH HARMONISED TRIPARTITE GUIDELINE

ASSESSMENT AND CONTROL OF DNA REACTIVE (MUTAGENIC) IMPURITIES IN PHARMACEUTICALS TO LIMIT POTENTIAL CARCINOGENIC RISK

M7

Impurity identification

ICH M7

Database searching

Expert prediction

Statistical prediction

Expert assessment

Purge mitigation

Classification

Reporting
Impurity identification

ICH Harmonised Tripartite Guideline

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M7

Observed impurities

Expected impurities

Synthesis-derived

Degradation-derived

- Starting material
- Reagent
- Catalyst / ligand
- Intermediates
- By-products

- Decomposition
- Reaction with
  - Packaging
  - Excipients
Identifying degradation-derived impurities

**Degradation Product:** A molecule resulting from a chemical change in the drug molecule brought about over time and/or by the action of light, temperature, pH, water, or by reaction with an excipient and/or the immediate container/closure system.

‘relevant stress conditions’
- Light
- Heat
- Humidity
- Acid/base hydrolysis
- Oxidation

...observed during manufacture or stability studies

“potential degradation pathways” including from interaction with excipients and/or packaging
Identifying degradation-derived impurities

‘relevant stress conditions’
- Light
- Heat
- Humidity
- Acid/base hydrolysis
- Oxidation

Expert review

Reaction type \( (n) \)
- Photochemical \( (38) \)
- Rearrangement \( (56) \)
- Elimination \( (32) \)
- Addition \( (90) \)
- Hydrolysis \( (87) \)
- Oxidation \( (143) \)

Zeneth includes predictions of reaction of the API under environmental conditions in the presence of excipients, solvents and degradants.
Publications on Zeneth for degradation prediction

- An expert system to predict the forced degradation of organic molecules
  - Parenty et al., *Mol. Pharmaceutics*, 2013, 10, 2962
- Forced degradation studies to assess the stability of drugs and products
- Mutagenic Impurities: Precompetitive/Competitive Collaborative and Data Sharing Initiatives
- Tools and workflow for structure elucidation of drug degradation products
- Strategies To Address Mutagenic Impurities Derived from Degradation in Drug Substances and Drug Products
  - Kleinman. *Org Process R & D*, 2015, 19, 1447
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Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk

ICH Harmonised Tripartite Guideline

- Database searching
- Expert prediction
- Statistical prediction
- Expert assessment
- Classification
- Reporting
- Purge mitigation
- Impurity identification
Undertaking a database search

Database searching

- Public data
- Proprietary data

Substructure / similarity search

Exact match

Class 1
- Mutagen
- Carcinogen

Class 2
- Mutagen
- Carcinogen

Class 5
- Non-Mutagen

ICH M7 classification

Further supporting information for expert review
Undertaking a database search

Vitic Nexus – an authoritative source of data

- Vitic contains raw, summary, and Lhasa overall call data + literature references
- Currently 400K records, 20K compounds across a wide range of tox endpoints
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Reporting
ICH M7 allows the use of *in silico* predictions

- ICH M7 allows the use of two complimentary QSAR systems (one expert-rule based, one statistical based) to predict the outcome of *in vitro* mutagenesis for a given impurity:

  “The *absence of structural alerts* from two complementary (Q)SAR methodologies (expert rule-based and statistical) is sufficient to conclude that the impurity is of *no mutagenic concern*”

  “If warranted, the outcome of any computer system-based analysis can be reviewed with the use of expert knowledge in order to provide… a *rationale to support the final conclusion*”

- “To facilitate the consideration of a (Q)SAR model for regulatory purposes, it should be associated with the following information:

  1. a defined endpoint;
  2. an unambiguous algorithm
  3. a defined domain of applicability;
  4. appropriate measures of goodness-of-fit, robustness and predictivity;
  5. a mechanistic interpretation, if possible.”
In silico predictions should also...

- Make predictions and have good accuracy
  - Within your chemical space
- Provide some meaningful measure of confidence
- Be regularly updated with new knowledge
- Ideally be well understood by regulatory authorities
- Be transparent and highlight areas of uncertainty
  - To support expert review
- Make predictions that you understand and can support or overturn
How independent are statistical and expert systems?

- ICH M7 doesn’t prescribe how to build the 2 systems but the expectation is that they are independent...

```
Expert pre-define fragments used by statistical system to learn weightings

Fragmentation rules enable statistical system to independently discover both fragments and their significance

Proprietary datasets not seen by statistical system

Statistically found fragments imported into expert system

Range of techniques used to discover relevant fragments. Expert only adds them when supported by a clear scientific rationale, mechanism, literature...
```
Derek Nexus - an expert *in silico* prediction system

- 72 unique toxicity endpoints
- Over 850 alerts
- Nearly 3000 patterns
Derek Nexus - an expert *in silico* prediction system

**Query**

Alert fired?

Y → **Active**

---

354: Aromatic amine or amide

- Alert Matches
- Description Image
- Comments

**Mutagenicity: Ames test, transgenic rodent mutation assay**

This alert describes the mutagenicity of aromatic amines (I), including their N-protonated forms, and aromatic amides (II). Aromatic amines or amides which contain more than 25 non-hydrogen atoms are excluded from this alert as such compounds in the Ames test. In addition, the following structural restrictions also apply:

1. Sulphonic acid or sulphonate groups are not permitted on the aromatic ring which directly bears the amine or amide group.
2. For aromatic amides, the amide group may not lie alpha to a point of diaryl ring fusion.
3. Aromatic amines are excluded where the amine group lies alpha to a point of diaryl ring fusion on a 6-membered aryl ring.
It’s difficult, but important, to make negative predictions
Williams et al., *Reg. Tox. and Pharmacol.* 2016, 76, 79
Establishing best practise in the application of expert review of mutagenicity under ICH M7
Barber et al., *Reg. Tox. and Pharmacol.* 2015, 73, 367
Inactive with unclassified features

**Inactive with unclassified**

Is a negative prediction

Highlights fragments in contexts not seen in public data
- May be present in confidential data
- Could be innocuous

Expert review recommended

*It's difficult, but important, to make negative predictions*
Williams et al., *Reg. Tox. and Pharmacol.* 2016, 76, 79

*Establishing best practise in the application of expert review of mutagenicity under ICH M7*
Barber et al., *Reg. Tox. and Pharmacol.* 2015, 73, 367
Reviewing an inactive with misclassified features

**Inactive with misclassified**

Is a negative prediction

Highlights fragments seen in false positives

Many possible reasons for activity...
- ‘Innocent spectator’
- Inconsistent data
- Alert refinement

Expert review recommended

It’s difficult, but important, to make negative predictions
Williams et al., *Reg. Tox. and Pharmacol.* 2016, 76, 79
Establishing best practice in the application of expert review of mutagenicity under ICH M7
Barber et al., *Reg. Tox. and Pharmacol.* 2015, 73, 367
Expert review – reconsider the source data...
Reviewing negative predictions from Derek

Performance of mutagenicity negative predictions:

What percentage of chemicals fall in each category?

<table>
<thead>
<tr>
<th>Data Set</th>
<th>Inactive</th>
<th>Inactive with misclassified features</th>
<th>Inactive with unclassified features</th>
<th>Inactive with unclassified &amp; misclassified features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Private data 1</td>
<td>86%</td>
<td>9%</td>
<td>5%</td>
<td>-</td>
</tr>
<tr>
<td>(n = 325)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private data 2</td>
<td>89%</td>
<td>7%</td>
<td>3%</td>
<td>-</td>
</tr>
<tr>
<td>(n = 416)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private data 3</td>
<td>90%</td>
<td>7%</td>
<td>3%</td>
<td>-</td>
</tr>
<tr>
<td>(n = 1669)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Reviewing negative predictions from Derek

Performance of mutagenicity negative predictions:

What percentage of **non-mutagens** fall in each category?

<table>
<thead>
<tr>
<th>Private data 1 (n = 325)</th>
<th>Inactive</th>
<th>Inactive with misclassified features</th>
<th>Inactive with unclassified features</th>
<th>Inactive with unclassified &amp; misclassified features</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>94%</td>
<td>86%</td>
<td>86%</td>
<td>-</td>
</tr>
<tr>
<td>Private data 2 (n = 416)</td>
<td>87%</td>
<td>86%</td>
<td>94%</td>
<td>-</td>
</tr>
<tr>
<td>Private data 3 (n = 1669)</td>
<td>91%</td>
<td>93%</td>
<td>95%</td>
<td>-</td>
</tr>
</tbody>
</table>
A total solution to ICH M7

developed through collaboration

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Database searching

Expert prediction

Statistical prediction

Expert assessment

Classification

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Impurity identification

Purge mitigation
Sarah Nexus – a statistical model for mutagenicity

- Supplied with model built with Lhasa-curated public data
- Optimised to learn mutagenicity:
  - Fragmentation designed for reactivity-driven endpoints
  - Self-organising Hierarchical Network to maximise information gain
  - Decision-tree to reduce the chance of coincidence
- Explicit applicability domain
- Confidence score is provided for each prediction
- Predictions are transparent and therefore interpretable
A self-organising hypothesis network produces transparent predictions.
A self-organising hypothesis network produces transparent predictions

• Allows the most specific hypothesis to be applied
• Links back to training set
Possible outcomes from Sarah Nexus

For the 'Mutagenicity in vitro' endpoint the prediction is:

**NEGATIVE**

with 42% confidence

For the 'Mutagenicity in vitro' endpoint the prediction is:

**EQUIVOCAL**

For the 'Mutagenicity in vitro' endpoint the prediction is:

**POSITIVE**

with 100% confidence

**OUTSIDE DOMAIN**

Displaying 'outside domain features', click above to view the original structure
Reviewing a prediction from Sarah Nexus
Model building allows you to import your own data – appending or replacing the default data set.
Internal Cross-Validation using Sarah Nexus
External Validation using Sarah Nexus
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**ICH Harmonised Tripartite Guideline**

**Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk**

ICH M7

- Impurity identification
- Database searching
- Expert prediction
- Statistical prediction
- Expert assessment
- Purge mitigation
- Classification
- Reporting
Expert review – the M7 Decision Matrix

Performance of Sarah and Derek...

Probability of being positive (%)

<table>
<thead>
<tr>
<th></th>
<th>OOD</th>
<th>+</th>
<th>Equiv.</th>
<th>-</th>
<th>Equiv.</th>
<th>+</th>
</tr>
</thead>
<tbody>
<tr>
<td>OOD</td>
<td>29</td>
<td>30</td>
<td>23</td>
<td>8</td>
<td>-</td>
<td>62</td>
</tr>
<tr>
<td>+</td>
<td>-*</td>
<td>-*</td>
<td></td>
<td>15</td>
<td></td>
<td>70</td>
</tr>
<tr>
<td>Equiv.</td>
<td>-</td>
<td>-</td>
<td>51</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td></td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td>34</td>
</tr>
</tbody>
</table>

- * = no occurrences of specific combination in data set

Lhasa data sharing consortium group (n = 777; 32% positive)
Expert review of *in silico* predictions

- M7 guidelines
  - “If warranted, the outcome of any computer system-based analysis can be reviewed with the use of expert knowledge.”

- We recommend that you always do some review….
  - Be guided by the software and your knowledge…
    - Use confidence measures if they are proven to indicate accuracy
    - Use software that is transparent and highlights areas of concern
    - Use the expert commentary, mechanism and references
    - Look at relevant close examples from the models & databases

- Depth of your analysis and the detail you report will vary
  - …from a cursory analysis to a well-supported argument
Likely to conclude positive
Very strong evidence would be needed to overturn both predictions

Likely to conclude positive
Lack of a second prediction suggests insufficient evidence to draw any other conclusion

Uncertain
Likely to conclude positive without strong evidence to overturn a positive prediction

**In silico prediction 1**

<table>
<thead>
<tr>
<th>Positive</th>
<th>Positive</th>
<th>Positive</th>
<th>Negative</th>
<th>Negative</th>
</tr>
</thead>
</table>

**In silico prediction 2**

<table>
<thead>
<tr>
<th>Positive</th>
<th>Positive</th>
<th>O.O.D. or equivocal</th>
<th>Negative</th>
<th>O.O.D. or equivocal</th>
<th>Negative</th>
</tr>
</thead>
</table>

O.O.D. = out of domain

Uncertain
Conservatively could assign as positive. May conclude negative with strong evidence showing feature driving a ‘no prediction’ is present in the same context in known negative examples (without deactivating features)

Establishing best practice in the application of expert review of mutagenicity under ICH M7
Barber et al., Reg. Tox. and Pharmacol. 2015, 73, 367
Expert review of *in silico* predictions

- There are publications describing expert analysis for M7
  - *In silico* methods combined with expert knowledge rule out mutagenic potential of pharmaceutical impurities: an industry survey
  - (Q)SAR assessments of potentially mutagenic impurities: A regulatory perspective on the utility of expert knowledge and data submission
  - Establishing best practise in the application of expert review of mutagenicity under ICH M7
    - Barber *et al.*, Reg. Toxicol. Pharmacol. 2015, 73, 367
  - Principles and procedures for implementation of ICH M7 recommended (Q)SAR analyses
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Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk

- Database searching
- Expert prediction
- Statistical prediction
- Expert assessment

Impurity identification

Purge mitigation

Classification

Reporting
M7 Classification

- M7 classification helps define how to control impurities…

Batch process against M7 settings

- User can add additional data
- Searches for carc’ and mut’ data from Lhasa and custom database

### API Structure

<table>
<thead>
<tr>
<th>API Structure</th>
<th>Name</th>
<th>Mutagenicity Mapping</th>
<th>Carcinogenicity Mapping</th>
<th>Alerts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ranitidine</td>
<td>Negative</td>
<td>No Results</td>
<td>PLAUSIBLE: Arenal12 - Aliphatic nitro compound</td>
</tr>
</tbody>
</table>

### Results

<table>
<thead>
<tr>
<th>Status</th>
<th>Structure</th>
<th>Name</th>
<th>CAS No.</th>
<th>Derek Prediction</th>
<th>Sarah Prediction</th>
<th>OSAR Prediction</th>
<th>Similarity to API</th>
<th>Overall Carc.</th>
<th>Overall Ames</th>
<th>ICH M7 Class</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>✔</td>
<td>Impurity 1</td>
<td></td>
<td></td>
<td>INACTIVE: No misclassified or unclassified features</td>
<td>POSITIVE - 1%</td>
<td>No Derek Alerts found</td>
<td>Active</td>
<td>Conflicted</td>
<td>Class 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>✔</td>
<td>Impurity 2</td>
<td></td>
<td></td>
<td>INACTIVE: No misclassified or unclassified features</td>
<td>NEGATIVE - 41%</td>
<td>No Derek Alerts found</td>
<td>Unspecified</td>
<td>Unspecified</td>
<td>Class 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>✔</td>
<td>Impurity 3</td>
<td></td>
<td></td>
<td>INACTIVE: No misclassified or unclassified features</td>
<td>EQUIVOCAL - -</td>
<td>No Derek Alerts found</td>
<td>Unspecified</td>
<td>Unspecified</td>
<td>Inconclusive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>✔</td>
<td>Impurity 4</td>
<td></td>
<td></td>
<td>PLAUSIBLE: Arenal12 - Aliphatic nitro compound</td>
<td>OUTSIDE DOMAIN - -</td>
<td>All Alerts found in API</td>
<td>Unspecified</td>
<td>Unspecified</td>
<td>Class 4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ICH M7 class generated and report produced

Each impurity is classified according to whether there is Ames or Carcinogenicity information in addition to the Derek Prediction.

Users can also input experimental results for mutagenicity or carcinogenicity which updates the ICH M7 Class.
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- Database searching
- Expert prediction
- Statistical prediction
- Expert assessment
- Classification
- Reporting
- Impurity identification
- Purge mitigation

..developed through collaboration
Mirabilis - A Tool for Purge Factor Calculation

Background

• The threat posed by mutagenic impurities (MI) in drug substances generally arises from the use of electrophilic agents within the synthesis - these are ubiquitous in the build-up of molecular structure, therefore any synthetic drug poses a latent MI-related risk.

• Original approach was to test for all impurities
  • Very simplistic
  • Doesn’t take reactive nature of impurity into account

https://www.lhasalimited.org/Public/Library/2014/Explaining%20and%20demonstrating%20successful%20use%20of%20purging%20to%20control%20mutagenic%20impurities.pdf
Mirabilis - A Tool for Purge Factor Calculation

Background

• ICH M7 - Section 8 - CONTROL

  • Allows options other than just testing for impurity in final API

<table>
<thead>
<tr>
<th>Option 1</th>
<th>Option 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>Test in starting material or intermediate at permitted level</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Option 3</th>
<th>Option 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test at intermediate stage with higher limit and understanding of process capacity</td>
<td>No testing required - MI too reactive</td>
</tr>
</tbody>
</table>

• Purge of MI can be assessed using physicochemical/process based arguments

https://www.lhasalimited.org/Public/Library/2014/Explaining%20and%20demonstrating%20successful%20use%20of%20purging%20to%20control%20mutagenic%20impurities.pdf
Mirabilis - A Tool for Purge Factor Calculation

Background

• Relating the physicochemical properties of a MI to the chemical process is defined in the concept of purge factor calculations

  • Key factors defined
    • Assesses carry-over of MI (e.g. reactivity, volatility, ionisability, chromatography)
    • Score assigned on the basis of the physicochemical properties of the MI relative to the process conditions
  • Overall purge factor is a multiple of the factors for individual stages

https://www.lhasalimited.org/Public/Library/2014/Explaining%20and%20demonstrating%20successful%20use%20of%20purging%20to%20control%20mutagenic%20impurities.pdf
### A theoretical approach to estimating purge factors

<table>
<thead>
<tr>
<th>Physicochemical Parameters</th>
<th>Purge Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reactivity</strong></td>
<td></td>
</tr>
<tr>
<td>Highly Reactive = 100</td>
<td></td>
</tr>
<tr>
<td>Moderately reactive = 10</td>
<td></td>
</tr>
<tr>
<td>Low Reactivity / un-reactive = 1</td>
<td></td>
</tr>
<tr>
<td><strong>Solubility</strong></td>
<td></td>
</tr>
<tr>
<td>Freely Soluble = 10</td>
<td></td>
</tr>
<tr>
<td>Moderately soluble = 3</td>
<td></td>
</tr>
<tr>
<td>Sparingly Soluble = 1</td>
<td></td>
</tr>
<tr>
<td><strong>Volutility</strong></td>
<td></td>
</tr>
<tr>
<td>Boiling point &gt;20°C below that of the reaction/process solvent = 10</td>
<td></td>
</tr>
<tr>
<td>Boiling point +/- 10°C that of the reaction/process solvent = 3</td>
<td></td>
</tr>
<tr>
<td>Boiling point &gt;20°C above that of the reaction/process solvent = 1</td>
<td></td>
</tr>
<tr>
<td><strong>Ionisability</strong></td>
<td></td>
</tr>
<tr>
<td>Ionisation potential of GI significantly different to that of the desired product</td>
<td></td>
</tr>
<tr>
<td><strong>Physical Processes – chromatography</strong></td>
<td></td>
</tr>
<tr>
<td>Chromatography – GI elutes prior to desired product = 100</td>
<td></td>
</tr>
<tr>
<td>Chromatography – GI elutes after desired product = 10</td>
<td></td>
</tr>
<tr>
<td>Others evaluated on an individual basis</td>
<td></td>
</tr>
</tbody>
</table>

---

The need was recognised for a software tool to:

- Build on the success and simplicity of the paper-based approach.
- Assist in the presentation of consistent and standardised purge factor arguments for regulatory submissions across industry.
- Provide transparent supporting scientific rationale for purge arguments.
- Provide a record of purge factor calculations and decisions.
- Generate a report suitable for inclusion in a regulatory submission.
- Facilitate knowledge and data sharing across industry.
<table>
<thead>
<tr>
<th>Stage</th>
<th>Impurity 1</th>
<th>Impurity 2</th>
<th>Impurity 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction</td>
<td>Reactivity</td>
<td>Solubility</td>
<td>Volatility</td>
</tr>
<tr>
<td>Work-up - Liquid-Liquid Extraction</td>
<td>100</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Mirabilis – supporting expert assessment of purge

- Concept is part of the M7 guidelines

- Risk of potential mutagenic impurity
  - Ames or 2 in silico models...
    - -ve
    - +ve
  - Treat as a non-mutagen
  - Control & monitor in final API
    - Present a purge argument for absence...
      - ✓
      - ≠
    - Risk mitigated


Mirabilis – supporting expert assessment of purge

• 6 companies originally established an industry consortium
• 16 companies are currently sponsoring development
  • **Software**
    • To apply methodology agreed by industry and regulators
    • To facilitate efficient internal decision-making and reporting
    • will support estimating & expert-review of purge values
      • **Web-based** to support **collaborative** (internal) use
      • Support a **consistent industry-standardised** approach
      • Provide supporting commentary and data for **expert review**
      • Generate **reports** suitable for **regulatory submission**
  • **Science**
    • Support capture of expert-driven knowledge
    • Undertake analytical studies to
      • fill in knowledge gaps
      • test performance
A total solution to ICH M7

ICH Harmonised Tripartite Guideline

Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk

M7

Database searching
Expert prediction
Statistical prediction
Expert assessment
Classification
Reporting

Impurity identification
Purge mitigation

developed through collaboration
Summary

- Lhasa has produced a suite of integrated tools to address M7 with the support of members and regulators
  - Developing scientifically robust, transparent and trusted tools to meet our charitable purpose
    - “advance scientific knowledge and understanding through the use of computer-aided reasoning in chemistry and the life sciences”

- Acknowledgements
  - All the members involved in pre-competitive Lhasa collaborations
  - Dedicated staff at Lhasa
Lhasa Limited is a not-for-profit organisation and educational charity that facilitates collaborative data sharing projects in the pharmaceutical, cosmetics and chemistry-related industries.
What type of data was used to build the model?

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<th>-ve</th>
<th>Total</th>
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Sarah’s confidence score correlates with accuracy

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<th>Confidence Score</th>
<th>0-20%</th>
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<th>40-60%</th>
<th>60-80%</th>
<th>80-100%</th>
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<td>74%</td>
<td>85%</td>
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<td>92%</td>
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<tr>
<td>NPV</td>
<td>62%</td>
<td>80%</td>
<td>95%</td>
<td>96%</td>
<td>97%</td>
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</tbody>
</table>

• Less confident predictions deserve greater scrutiny
• Default settings optimum for regulatory submissions

ESTABLISHING BEST PRACTICE FOR THE APPLICATION OF A NOVEL STATISTICAL-BASED MODEL TO EVALUATE POTENTIAL MUTAGENIC IMPURITIES UNDER ICH M7

Sarah vs. external dataset of confidential data from Lhasa members
Expert review improves prediction accuracy.

It’s difficult, but important, to make negative predictions.

Williams... *Reg. Tox. and Pharmacol.* 2016, 76, 79

# M7 Classification (Muller)

<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
<th>Proposed action for control (details in Section 7 and 8)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Known mutagenic carcinogens</td>
<td>Control at or below compound-specific acceptable limit</td>
</tr>
<tr>
<td>2</td>
<td>Known mutagens with unknown carcinogenic potential (bacterial mutagenicity positive*, no rodent carcinogenicity data)</td>
<td>Control at or below acceptable limits (appropriate TTC)</td>
</tr>
<tr>
<td>3</td>
<td>Alerting structure, unrelated to the structure of the drug substance; no mutagenicity data</td>
<td>Control at or below acceptable limits (appropriate TTC) or conduct bacterial mutagenicity assay; If non-mutagenic = Class 5 If mutagenic = Class 2</td>
</tr>
<tr>
<td>4</td>
<td>Alerting structure, same alert in drug substance or compounds related to the drug substance (e.g., process intermediates) which have been tested and are non-mutagenic</td>
<td>Treat as non-mutagenic impurity</td>
</tr>
<tr>
<td>5</td>
<td>No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity</td>
<td>Treat as non-mutagenic impurity</td>
</tr>
</tbody>
</table>
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