The use of *in-silico* tools to assist in the practical management of impurities under ICH M7.

Dr. Dave J. Yeo
Senior Account Manager
accountmanagement@lhasalimited.org

www.linkedin.com/in/dave-j-yeo-168bb180/
Running Order

- Introduction to Lhasa
- ICH M7 and the key impurity questions
  - Identification
  - Hazard Characterisation
    - Using data and knowledge
  - Risk Assessment
- Control
  - Using knowledge of scientific processes
Introduction to Lhasa Limited

- Established in 1983
- HQ located in Leeds, United Kingdom
- Not-for-profit & Educational Charity
- Facilitate collaborative data sharing projects in the chemistry-related industries
- Controlled by our members
- Creators of knowledge base, statistical and database systems.
We are a Not-For-Profit Company and Educational Charity

- Charitable Objective
  - To promote the development and use of computer-aided reasoning and information systems for the advancement of chemistry.

- Members
  - We work with our software users to really understand and meet their needs.
  - Members have the potential to control the future development of Lhasa Limited software.
To manage impurities...

- What impurities form when we are creating the API...?
  - What hasn’t reacted and is carried over?
  - What has degraded during the reaction?
  - What are the byproducts of synthesis?

- How concerned are we about the impurities...?
  - Is there a potential for toxicity?
  - And what do we do if there is...?
  - What is the quantity of impurities in the API?
  - ICH regulations set the experiments and limits that are required to answer this question...

Introducing ICH M7...
ICH M7 – 2 Key Questions

Is an impurity likely to be genotoxic?

Does an impurity pose a significant risk of carryover?
ICH M7

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

ICH M7 covers...

• The risk and hazard assessment of potentially DNA reactive impurities for post-approval submissions and new marketing applications where there are...

• Changes to synthetic route
• Changes to formulation or manufacturing processes
• Changes in dosing regime

• Refers specifically to data in **bacterial mutagenicity assays** (Ames Tests).
ICH M7

ICH M7 is not intended for...

• Drug substances derived from:
  • Peptides, oligonucleotides, herbal products...

• Drug substances intended for advanced cancer indications
  • Oncology therapeutics possess an increased cancer risk
  • Impurities do not significantly add to this risk
  • Referred in ICH S9.
ICH M7 – Key Sections

Section 6 – Hazard Assessment
- Introduces classifications of impurities
- Specifically refers to the use of (Q)SAR

Section 7 – Risk Characterisation
- Derives acceptable intakes of known and predicted mutagenic impurities

Section 8 – Control
- Provides four options to control the levels of known and predicted mutagenic impurities
- Consistent with ICH Q9.
6. HAZARD ASSESSMENT ELEMENTS

Hazard assessment involves an initial analysis of actual and potential impurities by conducting database and literature searches for carcinogenicity and bacterial mutagenicity data in order to classify them as Class 1, 2, or 5 according to Table 1. If data for such a classification are not available, an assessment of Structure-Activity Relationships (SAR) that focuses on bacterial mutagenicity predictions should be performed. This could lead to a classification into Class 3, 4, or 5.

Table 1: Impurities Classification with Respect to Mutagenic and Carcinogenic Potential and Resulting Control Actions

<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
<th>Proposed action for control (details in Section 7 and 8)</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 (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>

8.1 Control of Process Related Impurities

There are 4 potential approaches to development of a control strategy for drug substance:

**Option 1**

Include a test for the impurity in the drug substance specification with an acceptance criterion at or below the acceptable limit using an appropriate analytical procedure.

For an Option 1 control approach, it is possible to apply periodic verification testing per ICH Q6A (Ref. 10). Periodic verification testing is justified when it can be shown that levels of the mutagenic impurity in the drug substance are less than 30% of the acceptable limit for at least 6 consecutive pilot scale or 3 consecutive production scale batches. If this condition is not fulfilled, a routine test in the drug substance specification is recommended. See Section 8.3 for additional considerations.

**Option 2**

Include a test for the impurity in the specification for a raw material, starting material or intermediate, or as an in-process control, with an acceptance criterion at or below the acceptable limit using an appropriate analytical procedure.

**Option 3**

Include a test for the impurity in the specification for a raw material, starting material or intermediate, or as an in-process control, with an acceptance criterion above the acceptable limit of the impurity in the drug substance, using an appropriate analytical procedure coupled with demonstrated understanding of fate and purge and associated process controls that assure the level in the drug substance is below the acceptable limit without the need for any additional testing later in the process.

This option can be justified when the level of the impurity in the drug substance will be less than 30% of the acceptable limit by review of data from laboratory scale experiments (spiking experiments are encouraged) and where necessary supported by data from pilot scale or commercial scale batches. See Case Examples 1 and 2. Alternative approaches can be used to justify Option 3.

**Option 4**

Understand process parameters and impact on residual impurity levels (including fate and purge knowledge) with sufficient confidence that the level of the impurity in the drug substance will be below the acceptable limit such that no analytical testing is recommended for this impurity. (i.e., the impurity does not need to be listed on any specification).
ICH M7

6. HAZARD ASSESSMENT ELEMENTS

Hazard assessment involves an initial analysis of actual and potential impurities by conducting database and literature searches for carcinogenicity and bacterial mutagenicity data in order to classify them as Class 1, 2, or 5 according to Table 1. If data for such a classification are not available, an assessment of SAR that focuses on basic chemical structure is used to lead to a classification.

Table 1: Hazard assessment of impurities

<table>
<thead>
<tr>
<th>Impurity Category</th>
<th>Assessment Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1</td>
<td>Toxic, carcinogenic</td>
</tr>
<tr>
<td>Class 2</td>
<td>Mutagenic, clastogenic</td>
</tr>
<tr>
<td>Class 3</td>
<td>Low risk, no evidence</td>
</tr>
<tr>
<td>Class 4</td>
<td>Alerting, no evidence</td>
</tr>
<tr>
<td>Class 5</td>
<td>Non-genotoxic, no evidence</td>
</tr>
</tbody>
</table>

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Include a test for the impurity in the specification for a raw material, starting material or intermediate, or as an in-process control, with an acceptance criterion above the acceptable limit of the impurity in the drug substance, using an appropriate analytical procedure coupled with demonstrated understanding of fate and purge and associated process controls that assure the level in the drug substance is below the acceptable limit without the need for any additional testing later in the process.

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Understand process parameters and impact on residual impurity levels (including fate and purge knowledge) with sufficient confidence that the level of the impurity in the drug substance will be below the acceptable limit such that no analytical testing is recommended for this impurity. (i.e., the impurity does not need to be listed on any specification.)

Is an impurity likely to be genotoxic?
ICH M7

Is an impurity likely to be genotoxic?

Does an impurity pose a significant risk of carryover?
How the impurity questions are answered...

*In cerebro* (using knowledge from education and occupation...)

Data points:
Degradation…
Metabolism…
Toxicity…

Grouping of data:
Chemical Structure
Experimental Study
Chemical properties

I know that I can expect this outcome…
and this is how much it matters.
Or, *in silico* may be able to assist...

- Knowledge based (also known as Expert) systems...
  - Connect data and information to establish knowledge and rules...

- Expert scientists can create knowledge bases
  - ...which can then predict the outcome of unknown chemicals...
Or, *in silico* may be able to assist...

- Statistical systems...
  - Identify a relationship between properties to generate an algorithm or formula...

- Machine learning can also be applied to create a model
  - …which can then predict the outcome of unknown chemicals…
What about degradants?

• Covered in greater detail in ICH Q3a/b

• ICH M7 states…
  • Knowledge of relevant degradation pathways can help guide the selection of potential degradants for mutagenicity evaluation

• Knowledge-based software could assist with…
  • The proposition of potential degradation pathways
  • The structural elucidation of unknown degradants…
Zeneth – predicting forced degradation

• Zeneth predicts potential degradation

• Knowledge base of chemistry transformations
  • Detailing patterns of how one substructure can transform into something else
  • Considers the conditions that are required
    • Presence of air, water, light…
    • Applies reasoning to provide a likelihood of each degradant

• Presents the chemical structure and parent-child relationships to the processor.
Workflow

Identification of potential impurities

Conduct QSAR analysis and expert review. Is the impurity likely to be genotoxic?

Yes

Assessment of Carryover. Does the impurity pose significant risk of carryover?

No

Non-genotoxic – treat as a general impurity

No

No further action

Yes

Quantification
Analyze level of impurity

OR

Safety Testing
Perform appropriate assay

Finalise Risk Assessment
Is the impurity genotoxic? Is the level >TTC?

Genotoxic

< TTC

Genotoxic

> TTC

Non-genotoxic – treat as a general impurity

Strategy to achieve acceptable limits

Suitable for clinical use
**Workflow**

1. **Identification of potential impurities**
   - Conduct QSAR analysis and expert review. Is the impurity likely to be genotoxic?
     - Yes: **Assessment of Carryover. Does the impurity pose significant risk of carryover?**
       - Yes: **Quantification Analyse level of impurity**
       - No: **No further action**
     - No: **Classify as non-genotoxic – treat as a general impurity**

2. **Finalise Risk Assessment**
   - Is the impurity genotoxic?
     - Yes: **Strategy to achieve acceptable limits**
     - Non-genotoxic: **Suitable for clinical use**
   - Is the level >TTC?
     - Yes: **Non-genotoxic – treat as a general impurity**
     - No-genotoxic: **Suitable for clinical use**

• Class 1 and Class 2 are “known” mutagenic compounds

• Class 5 can be “known” non-mutagenic compounds
  • Class 5 is also for known non-carcinogens…

• Check available data from the public domain and from in-house libraries (if available)

• Review the available data…
Vitic – a structure searchable database

- Vitic houses curated toxicity data from the public domain
- Vitic is also used for the data sharing collaborations where Lhasa acts as the honest broker
- Members can also use Vitic for the storage of their private data
Data Sharing Collaborations

- Vitic Intermediates – 1587 structures
  - Chemical intermediates used and formed in synthesis
- Vitic Aromatic Amines – 863 structures
  - Specifically mutagenicity data of Aromatic Amines
- Vitic Excipients – 1243 vehicles
  - Sharing of vehicle data for drug formulations
- Vitic Elemental Impurities – 295 excipients
  - Sharing of analytical reports of trace metal elements in manufacturing
- Vitic AI/PDE – 142 monographs
  - Harmonisation of Acceptable Intakes and Permitted Daily Exposure limits of impurities
Vitic Intermediates

• Pre-competitive data sharing group for Production Intermediates
  • New members ‘buy-in’ with a donation of data
  • Membership maintained with an annual donation
  • No (additional) monetary cost to join this collaboration

• Benefits
  • All members donate - reducing the cost of duplicate testing
  • Focus on proprietary chemical space for pharmaceuticals
  • No disclosure of targets or projects, only Ames test data.
Carcinogenicity Database

- Free to access database for the retrieval of carcinogenicity data
  - https://carcodb.lhasalimited.org

- Structure and structural parameter searchable database
  - Building on the work of Gold’s Carcinogenic Potency Database
  - Provides $TD_{50}$ values from Lhasa and Gold.
2-Naphthylamine

Summary

<table>
<thead>
<tr>
<th>Species</th>
<th>Lhasa TD50 (mg/kg/day)</th>
<th>Gold TD50 (mg/kg/day)</th>
<th>Result</th>
<th>Sex</th>
<th>Tumour sites</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>-</td>
<td>39.4</td>
<td>POSITIVE</td>
<td>Female</td>
<td>Liver</td>
<td>-</td>
</tr>
<tr>
<td>Rat</td>
<td>-</td>
<td>61.6</td>
<td>POSITIVE</td>
<td>Male</td>
<td>Liver</td>
<td>-</td>
</tr>
<tr>
<td>Rhesus Monkey</td>
<td>-</td>
<td>5.74</td>
<td>POSITIVE</td>
<td>Female</td>
<td>Urinary bladder</td>
<td>-</td>
</tr>
</tbody>
</table>

Chemical structure

- CAS Number: 91-59-8
- Chemistry unique identifier: 91-59-8
- Chemical name: 2-Naphthylamine
- Synonym(s): 2-Aminonaphthalene; 2-Naphthalenamine; beta-Naphthylamine
- Molecular weight: 143.19
- Molecular formula: C10H9N
- SMILES: C=12C(N)=C(C=C1)=C=C2
- InChI: InChI14C10H9N/c11-19-6-5-3-1-2-4-83-17-12/h1-7H2
Imatinib synthesis…

- Imatinib is an anti-cancer drug with a maximum daily dose of 800mg for up to 3 years
- Hopkin *et al.* published a 3-stage synthesis to Imatinib
  - Additional steps include basic work up/extraction (stages 1 and 3), precipitation and wash (stage 2), and column chromatography (stage 3)
- Six structures in the synthesis need to be analysed for potential ICM M7 control*
- ICH M7 control limit of 10 μg for any PMIs based on dose and duration of treatment
Imatinib synthesis...

- Six potential impurities have been identified
- No data exists on these impurities
- Start *in silico* assessment
  - Derek Nexus – Expert System
  - Sarah Nexus – Statistical System
Expert System

- An expert system aims to capture the knowledge of human experts in a knowledge base so that it can be applied later to make new predictions.
- Knowledge is captured in the form of rules and structural alerts.
- Can provide high levels of transparency:
  - Examples
  - Mechanistic rationale
  - References
Expert Systems contain…

Prediction: Alert and Likelihood

Alert Base
These features have been observed to exhibit this Endpoint...

Rule Base
This is how likely the Endpoint will happen in this situation…
What is an Alert?

An Alert is a set of structural features in a molecule, that make a user suspect that the substance may show a particular effect.

How data becomes knowledge…

• Expert Systems are designed by considering data points…
  • Structurally related compounds…
    • Do these compounds contain the same feature or functional groups?
    • Do these compounds exhibit the same toxicological activity?
    • Are there any patterns in structural features and assay activity?
    • What is the potential mechanism for toxicity?

• Physicochemical properties…
  • Does lipophilicity have an affect on toxicity?
  • Does molecular weight have an influence?

This is the foundation of building a *predictive* system based on Expert Knowledge.
What data can tell you...

Data
“Chloroacetone irritates the eyes”

Tell me about chloroacetone
• It irritates the eyes

Tell me about methyl bromoacetate
• Sorry, not in the database
Knowledge

α-Halocarbonyl compounds may irritate the eyes

Tell me about methyl bromoacetate
• It may irritate the eyes

Tell me about chloroacetone
• It may irritate the eyes

... with general knowledge you can predict, but you cannot be precise
...to build a Knowledge Base...

How we build Alerts and Reasoning rules...

Data → Information → Knowledge

Mutagenicity data

Group epoxides together

Write a structural alert and reasoning rules

Derek Nexus Knowledge Base
The Rule Base...

• Humans *can* use knowledge to *construct arguments* for or against a proposition (in this case, a prediction)

• Expert Systems *may apply reasoning* to structural alerts to give a *likelihood*

• Reasoning considers evidence outlined in a set of rules to *provide a logical outcome*
  • Reasoning can bring in physicochemical descriptors to modulate alerts

• Reasoning rules are present because an *Alert might not be appropriate* in every situation.
Derek Nexus – predicting toxicity

- Derek Nexus predicts for potential toxicity as an expert system

- Knowledge base of structural alerts
  - Details patterns of what chemical features may be responsible for an adverse outcome
  - Alerts written considering data and mechanistic knowledge
  - Rules assign a likelihood for toxicity after considering arguments for and against

- Presents the structural alert, expert comments and evidence to the processor.
Derek Nexus in practice

Query structure to Derek

Alerting feature
Toxicity Endpoint
Likelihood
Comments
References

Alert - 019: Epoxide

Chromosome damage (clastogenicity): in vitro chromosome aberration test, in vivo micronucleus test
Mutagenicity: Ames test, in vivo transgenic rodent mutation assay

Epoxides are electrophilic compounds that readily bind to DNA. As a consequence, they may exhibit mutagenicity in the Ames test; generally, in strains TA100 and TA1535 without S9 mix (Cantar et al., von der Hude et al., Sugita and Goto, Tomura et al., Wade et al.). The effect of S9 mix on the mutagenic response varies depending, for example, on the susceptibility of the test chemical to detoxification by epoxide hydrolases and glutathione S-transferase present in the S9 mix (Castelain et al.).

Mono-alkyl substituted epoxides generally give a positive response in the Ames test except where the alkyl substituent is long (Cantar et al., 1,1- and 1,2-dialkyl epoxides have been shown to give a weaker or negative response, with trans epoxides being less active than their cis isomers (Wade et al., von der Hude et al., Castelain et al.). The following structural classes are excluded from the alert.
Statistical models – general principles

Dataset
- Curated data – resolve conflicts, duplicates, invalid structures...

Descriptors
- Grouping: Fragments, physicochemical properties...

Validation
- Performance against ‘new’ data

Applicability Domain
- What can be predicted

Model

Training Set – the library of compounds used to build the model
Validation Set – a compound set which tests the model. This should be different to the Training Set.
In the simplest case, you can consider one parameter…

- $Y = mx + c$

...and use this algorithm to obtain a prediction.
Introducing Machine Learning…

• Classic statistical methods investigate the relationships between parameters
  • …to establish a line of fit…
  • …and use this for the prediction of new cases

• Machine Learning is an applicable technique to build a predictive model
  • Automated learning from a data set…
  • Validation against a test set…
  • …and then refine the algorithm from lessons learned.
Machine learning is a discipline which aims to learn automatically from a data set and apply this knowledge to the prediction of new cases.

DeepMind’s Go-playing AI doesn’t need human help to beat us anymore.

*The company’s latest AlphaGo AI learned superhuman skills by playing itself over and over*.
Machine Learning

• Machine learning is a discipline which aims to learn automatically from a data set and apply this knowledge to the prediction of new cases.

• It embraces a range of techniques, many of which have been applied to the prediction of toxicity from chemical structure.

• Some of these explore the automatic generation of structural alert-type features.
What is Sarah Nexus?

- **Statistical** model for prediction of mutagenicity
- Model uses a dataset of ~10K compounds
- Uses a Self Organising Hypothesis Network (SOHN) methodology.

1. Generate fragments for chemicals with known experimental data

2. Consider each fragment and determine whether it is associated with toxicity/non-toxicity

3. Store fragments and look for them in new chemicals to determine whether they are toxic or non-toxic
How does Sarah Nexus predict?

- User enters query compound
- Query compound is fragmented
- Sarah uses the dataset to identify relevant hypotheses
- A confidence value is calculated
  - Considering Ames Result and Similarity of supporting examples

**Hypothesis 1:** Positive 65% confidence
- Supporting Examples:
  - 

**Hypothesis 2:** Positive 78% confidence
- Supporting Examples:
  - Decreasing similarity
Sarah Nexus – predicting mutagenicity

- Sarah Nexus predicts for potential bacterial mutagenicity using a statistical model (SOHN)

- Statistical model of structural fragments and data
  - Sarah generates a dictionary of fragments for chemicals with known experimental data
  - Each fragment is assessed and associated with mutagenicity/non-mutagenicity
  - This assessment is a ‘Hypothesis’ which is referred to for new queries

- Presents hypotheses, data and supporting examples to the processor.
For the 'Mutagenicity in vitro' endpoint the prediction is:

**POSITIVE**

with 65% confidence.

The compound is predicted to be positive with 65% confidence for the 'Mutagenicity in vitro' endpoint in the model 'Sarah Model - 2.0'. Supporting hypothesis containing similar examples from the training set has been found.

Model: Sarah Model - 2.0
Endpoint: Mutagenicity in vitro
Reasoning type: Weighted
Equivocal: 8%
Sensitivity: 8%
Certified model: Yes
Prediction date: 27 November 2019 09:04
Back to Imatinib…
Review the consensus predictions...

- No Alerts fired
- Exact match with experimental data and this data checked

Class 5
- Treat as non-mutagenic
Review the consensus predictions…

- No Alerts fired
- No related compounds of concern

**Class 5**
- Treat as non-mutagenic
Review the undetermined predictions...

- No structural alerts fired
- Reviewing training set compounds raises no concerns

**Class 5**
- Treat as non-mutagenic
Review the conflicted predictions...

Alerts fire:
- Alkylating agent and acid chloride
- Statistical prediction is negative
  - But the supporting data is not strong enough to overturn Expert System

Class 3
- Alerting
Review the conflicted predictions...

- No Alerts fire
- Statistical prediction is positive
  - Supporting compounds are similar and Ames positive

Class 3
- Alerting
Review the conflicted predictions…

- Alerts fire:
  - Alkylating agent
  - Statistical prediction is negative
    - But the supporting data is not strong enough to overturn Expert System

Class 3
- Alerting
Decision making on the impurities…

Class 3 – Alerting
- Control to thresholds?
- Purge Argument?
- Ames test?

Class 5 – Treat as non mutagenic

Imatinib
Is the impurity likely to be genotoxic?

- Expert Assessment
- Statistical-based QSAR
- Expert Rule-based QSAR
- In-house knowledge
- Public Experimental Data
- Proprietary Experimental Data
Is the impurity likely to be genotoxic?

- In-house knowledge
- Public Experimental Data
- Expert Assessment
- Proprietary Experimental Data
- Expert Rule-based QSAR
- Statistical-based QSAR
Introducing Setaria

- Expert Assessment
- Statistical-based QSAR
- Expert Rule-based QSAR
- In-house knowledge
- Public Experimental Data
- Proprietary Experimental Data
What is Setaria?

Stores all (Q)SAR information

Summarised mutagenicity and carcinogenicity data

Direct link to experimental data

Conclusions from expert review

Assigned ICH M7 class

Import results from Nexus M7 workflow

Export information for regulatory submission
Setaria – manages ICH knowledge

• Setaria is a database tool for ICH M7

• Setaria links data and predictive toxicology
  • Recalling Vitic data
  • Storage of Derek and Sarah Predictions
  • Allowing users to store their Expert Review comments
  • Organises data and knowledge in projects to reduce duplication of work across a business
  • Enables risk management across discovery programs

• User is presented with all of the above through structure searches.
Moving onto Section 8…

• *In-silico* methods described above meet the hazard characterisation of impurities (Section 6)

• Risk characterisation (Section 7) sets the acceptable thresholds of potentially mutagenic impurities

• Controlling impurities is outlined in Section 8…
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Option 3
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Impurities are understood and the risk or an impurity residing in the final drug substance above the acceptable limit is determined to be negligible. In many cases justification of this control approach based on scientific principles alone is sufficient. Elements of a scientific risk assessment can be used to justify an Option 4 approach. The risk assessment can be based

Option 4
Understand process parameters and impact on residual impurity levels (including fate and purge knowledge) with sufficient confidence that the level of the impurity in the drug substance will be below the acceptable limit such that no analytical testing is recommended for this impurity. (i.e., the impurity does not need to be listed on any specification).
Purging – Principles

- The following key factors have been defined in order to assess the potential carryover of an impurity:
  - Reactivity, solubility, volatility and any additional physical processes designed to eliminate impurities e.g. chromatography

- A score is assigned on the basis of physiochemical properties of the impurity relative to the process conditions
  - These are then simply multiplied together to determine a “purge factor” (for each stage)

- The overall purge factor is the product of the factors for individual stages

- Predicted purge is then compared to required purge (this being based on the safety limit and initial level introduced into the process)
The purging challenge...

Reactive chemicals used in pharmaceutical synthesis pose a mutagenicity risk as an impurity.

- Can be purged by chemical processes...
- ...but each chemist has a different view on the extent of purging

Mutagenic concern
- Control to thresholds?
- **Purge argument**?
- *In vitro* testing?

No mutagenic concern
Mirabilis – A standardised purge calculator

- Mirabilis predicts the purging fate of impurities

- Knowledge matrix of reactions and impurity classes
  - Mirabilis can predict a purge factor for reactivity
  - User can input all the synthetic stages and processes
  - Mirabilis predicts the overall purge factor of impurities

- Presents the synthesis scheme and reports the predicted purge factors for the processor to decide the next steps.
### Analysis of purge predictions

<table>
<thead>
<tr>
<th>Stage</th>
<th>Reactivity</th>
<th>Solubility</th>
<th>Volatility</th>
<th>Other</th>
<th>Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>1000</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1000</td>
</tr>
<tr>
<td>Stage 2</td>
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<td>10</td>
<td>1</td>
<td>1</td>
<td>1000</td>
</tr>
<tr>
<td>Stage 3</td>
<td>1000</td>
<td>1</td>
<td>1</td>
<td>100</td>
<td>100000</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$1 \times 10^{11}$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Reactivity</th>
<th>Solubility</th>
<th>Volatility</th>
<th>Other</th>
<th>Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Stage 2</td>
<td>10</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>Stage 3</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>100</td>
<td>1000</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$1 \times 10^6$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Reactivity</th>
<th>Solubility</th>
<th>Volatility</th>
<th>Other</th>
<th>Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 2</td>
<td>10</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>30</td>
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<tr>
<td>Stage 3</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>100</td>
<td>1000</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30000</td>
</tr>
</tbody>
</table>
Purge Ratios

\[ \text{Required purge} = \frac{\text{Starting level (µg/g)}}{\frac{\text{Acceptable intake (µg)}}{\text{Daily dose (g)}}} \]

**Impurity requiring management as PMI**

**Determine Purge ratio (PR) of PMI in the API synthesis**

\[ PR = \frac{\text{Predicted purge factor}}{\text{Required purge}} \]

**Control options**
- Option 1: Test the API
- Option 2: Test an intermediate
- Option 3: Test an intermediate then use purge argument
- Option 4: Purge argument

- **PR > 1000**
  - Option 4 supported.
  - Provide purge ratio.

- **1000 > PR > 100**
  - Option 4 supported.
  - Full purge calculation and supporting literature evidence for key purges.

- **100 > PR > 1**
  - Option 4 supported only with strong supporting data.
  - Full purge calculation, supporting literature evidence and trace level experiments (e.g. spiking).

- **PR < 1**
  - Control option 4 not supported.
  - Option 3, 2 or 1 required.

**Examples**

- **PR = 1.25 \times 10^6**
- **PR = 12.5**
- **PR = < 1**

*Barber et al, Regul. Toxicol. Pharmacol., 2017, 90, 22-28*
<table>
<thead>
<tr>
<th>Name</th>
<th>ICH M7 Classification</th>
<th>Purge Ratio</th>
<th>Action</th>
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<tbody>
<tr>
<td>Impurity 1</td>
<td>Class 3</td>
<td>1,250,000 (&gt;1,000)</td>
<td>No further action (control option 4)</td>
</tr>
<tr>
<td>Impurity 2</td>
<td>Class 3</td>
<td>12.5 (1-100)</td>
<td>Quantification / Safety Testing</td>
</tr>
<tr>
<td>Impurity 3</td>
<td>Class 3</td>
<td>&lt;1 (&lt;1)</td>
<td>Quantification / Safety Testing</td>
</tr>
<tr>
<td>Impurity 4</td>
<td>Class 5</td>
<td>Not required</td>
<td>Treat as general impurity</td>
</tr>
<tr>
<td>Impurity 5</td>
<td>Class 5</td>
<td>Not required</td>
<td>Treat as general impurity</td>
</tr>
<tr>
<td>Impurity 6</td>
<td>Class 5</td>
<td>Not required</td>
<td>Treat as general impurity</td>
</tr>
</tbody>
</table>
How *in silico* can assist…

- For impurity identification…
  - Prediction of degradants

- For hazard characterisation…
  - Database platforms for Class 1, 2 and 5
  - Predictive toxicity systems for Class 3, 4 and 5…
  - …with (human!) Expert Review

- For control strategies…
  - Calculation of purge factors of impurities of concern.
Acknowledgements, Gratitude & Questions.