Mirabilis
2.0
Lhasa Limited vICGM

11 January 2017
Martin Ott
Overview

• Introduction
  • What is Mirabilis?
  • Impurities
  • Purge parameters and factors
• Scientific prioritisation
• Mirabilis reactivity knowledge matrix
• Conclusion
A tool to estimate the purge (removal) of potentially mutagenic impurities in drugs

• To support the application of ICH M7* guidance

Section 8, 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”

• Develop a knowledge-based approach to provide support, evidence and guidance for expert assessment

Mirabilis – objective

• Precompetitive consortium of 19 member companies
  • Started end of 2013 with 7 companies
  • Sharing expertise, knowledge and data

• Desire for
  • A standardised process with clear definitions of steps
  • Application of an accepted scientific approach
  • Conservative, robust, trustworthy and regulatory accepted predictions

• A transparent tool that
  • Can be challenged by experts
  • Provides evidence that can support good decisions
  • Creates reports with direct access to more support if needed
Mirabilis – led by a consortium

• Continued scientific guidance and oversight by consortium
  • Including review of functionality and usability of the software
• Sharing examples of purge estimates
  • Confirm that these are conservative and robust
  • Part of the validation of the science
• Establishing agreement on
  • When an estimated purge is considered sufficient (itself currently outside the remit of Mirabilis)
  • Level of information needed to support decision
Primary goal for Mirabilis

• Trusted by regulators

• Purge predictions are:
  • Conservative
  • Consistent/standardised
  • Transparent
Impurities and (P)MIs

• The threat posed by potentially mutagenic impurities (MI) arises from reagents used in synthesis:
  • electrophilic reagents (alkylating agents)
  • DNA intercalators
  • pro-mutagenic e.g. metabolically activated

• Therefore virtually any synthetic drug has a latent MI-related risk

Scheme from Teasdale et al, Org. Process Res. Dev. 2013, 17, 221-230
Impurities and (P)MIs

- The synthetic route of drug substances (APIs) involves the introduction of impurities by:
  - Starting materials and reagents (possibly with impurities)
  - Intermediates
  - By-products
- There is a possibility for some of these (potentially mutagenic) impurities to be present in the final product
- Quantity of these impurities are to be strictly monitored and/or controlled
- By generating a semi-quantitative, repeatable and standardised methodology it is possible to predict the purge factor for each reaction stage and final product
Purge factor assignment

- Impurities can be purged due to their reactivity, solubility or volatility (= purge factor parameters)
- A synthesis can consist of various stages, each with one or more steps (operations)
- Steps (operations) can be:
  - Reaction
  - Work-up:
    - Quench
    - Precipitation
    - Wash
  - Purification:
    - Extraction
    - Crystallisation
    - Distillation

- Each operation type allows purge factors to be assigned for specific parameters (reactivity/solubility/volatility) only
Purge factor assignment

• Examples of allowed purge parameters:

  • Reaction
  • Work-up:
    • Quench
    • Precipitation
    • Wash
  • Purification:
    • Extraction
    • Crystallisation
    • Distillation

  • Reactivity: 1 / 10 / 100
  • Solubility: 1 / 3 / 10
  • Volatility: 1 / 3 / 10

Scientific prioritisation

1. Reactivity purge predictions
   - Development of “knowledge matrix”
   - Reaction mining to supplement/support predictions

2. Solubility purge predictions
   - Data-driven approach for common compounds
   - Solubility prediction (research)

3. Other, e.g. volatility purge predictions
Scientific prioritisation – Reactivity

• Knowledge gathering to fill matrix
  • Prioritised – fill most crucial gaps first
  • Coverage (2016 and beyond) agreed with members

• Reaction mining to supplement/support predictions
  • In research phase – demonstrate concept first
  • Pilot study in preparation to mine member lab data
Knowledge matrix (reactivity)

Impurity classes (15):

- Acyl chloride
- Aliphatic aldehyde
- Aromatic amine
- Aromatic nitro compound
- Arylboronic acid or ester
- Epoxide
- Haloalkene
- Hydrazide
- Hydrazine

- Michael-reactive acceptor
- Mustard compound (N or S)
- Primary alkyl bromide
- Primary alkyl chloride
- Primary alkyl iodide
- Alkyl sulfonate
## Knowledge matrix (reactivity)

### Reaction classes (57 + 1):

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<tr>
<th>Reaction</th>
<th>Reaction</th>
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<td>N-Alkylation of aliphatic amine</td>
<td>Reduction of aromatic ring</td>
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<tr>
<td>N-Alkylation of amide</td>
<td>Reduction of ester to alcohol</td>
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<td>Reduction of ester to aldehyde</td>
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<td>Claisen condensation</td>
<td>Oxidation of alcohol</td>
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<td>Friedel-Crafts acylation</td>
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<td>Reduction of amide to amine</td>
<td>N-Oxidation of primary amine</td>
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**Knowledge matrix (reactivity)**

Reaction classes (57 + 1) (ctd.):

- S-Oxidation of thioether
- O-Dealkylation of ether
- O-Debenzylation of ether
- O-Deacylation of ester
- N-Debenzyl[oxycarbonylation]
- N-De-tert-butyloxycarbonylation
- O-Desilylation
- S-Dealkylation of thioether
- Esterification
- N-Benzylolation of amine
- N-Alkoxy carbonylation of amine
- O-Alkylation of aromatic alcohol
- O-Benzylolation of alcohol
- O-Silylation of alcohol
- Halogenation of aromatic ring
- Nitration of aromatic ring
- Sulfonation of aromatic ring
- Formation of acid chloride from acid
- Formation of halide from alcohol
- Formation of imidoyl chloride from amide
- Condensation of carboxyl cpd and amine
- Dehydration of alcohol
- Fischer esterification
- N-Acylation of amine
- N-Sulfonation of amine
- O-Acylation of alcohol
- O-Sulfonation of alcohol
- Nucleophilic aromatic substitution
## Knowledge matrix (reactivity)

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Knowledge matrix (reactivity)

- 57 reaction classes - 28 prioritised (→ 31)
- 15 impurity classes - 4 prioritised

855 “Predicted Reactivity Purge Factor Knowledge Matrix” points (now called “Cells”) have been filled with the results of an “expert elicitation” conducted in 2014 among the original seven members.

124 / 855 (14.5%) Cells have been further researched (by Lhasa) in 2016 and the resulting knowledge has been included into Mirabilis 2.0

Speed of development can be expected to increase in 2017
Expert elicitation (in 2014)

855 “Predicted Reactivity Purge Factor Knowledge Matrix” points (now called “Cells”) have been filled with the results of an “expert elicitation” conducted in 2014 among the original seven members.

Examples:

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<th>Consensus</th>
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Reactivity prediction & knowledge base

The matrix is implemented in Mirabilis 2.0 as an *in silico* knowledge base, which will:

- Automatically recognise the *structural class* of an impurity
- Automatically recognise the *reaction (transformation) class* in a synthetic step
- Generate an assigned *reactivity purge factor* based on the recognised classes (prediction)
- Present *transparent and robust scientific evidence* to support the predicted reactivity purge factor assigned
Arylboranes are a commonly used substrate in the Suzuki reaction and readily react with a number of organohalides (aryl, benzyl and 1-alkenyl, 1-alkynyl and allyl), organotriflates and other pseudo halides such as aryltosylates in the presence of palladium(0) catalyst and base.

- Poor nucleophilicity of the arylboronic acid can reduce reactivity.
- Hindered arylboronic acids require strong negatively charged bases to react.
- Proto-deboronation of electron-poor arylboronic acids can occur.

<table>
<thead>
<tr>
<th>Cell Summary</th>
<th>Range</th>
<th>Effect on purge</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>20-120</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Time (h)</td>
<td>0.25 - 24</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Solvents</td>
<td>Biphasic (e.g. water and ethanol, THF, toluene or dioxane), organic (methanol, toluene, dioxane, THF, DMF) and aqueous</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Reagents</td>
<td>Pd(0) catalyst, base</td>
<td>Not significantly</td>
<td>Purge efficiency may decrease with sterically hindered substrates and weak bases.</td>
</tr>
</tbody>
</table>

Under the conditions described for the Suzuki reaction in the cell summary, a range of arylboronic acids readily react with organohalides (aryl, benzyl and 1-alkenyl, 1-alkynyl and allyl), organotriflates and other pseudo halides such as aryltosylates (Example 1). The general mechanism for this reaction is oxidative addition of the organic halide (aryl, benzyl, 1-alkenyl, 1-alkynyl or allyl) to a palladium(0) complex to give a stable trans-o-palladium(II) complex. This is followed by transmetallation of the organoboron component, isomerisation to the cis-complex, finalised by reductive elimination to give the coupled compound and regenerate the palladium(0) complex [Miyaura and Suzuki].

Reduced nucleophilicity of the organic group on boron may slow down the transmetallation process.
Knowledge base editor – cell contents

Purge factor
Summary
Dependencies
Comments
A reactivity-based purge usually generates a new compound, which may or may not be a impurity of concern.

This does not affect the effectiveness of that purge – the new compound, if it is a (P)MI, should itself be treated as a new impurity.

It is the user’s decision whether this impurity should be tracked.

The new impurity should “inherit” any purge value from its parent.

Mirabilis does not support this yet.

This will be part of a future treatment of concentrations.
Plans for 2017

• Improved reaction type recognition
  • Add recognition of reactants by their name

• Better graphical treatment of by-products
  • By-products = impurities that are not part of the main synthetic route

• Treatment of concentrations
  • Allows user to specify initial concentration
  • Better tracking of impurities formed from impurities
Conclusion

• The purge tool concept provides a cost-effective, quick and effective way of assessing the risk posed by an MI in a regulatory risk assessment.

• The development of an *in silico* tool provides the basis for a consistent and systematic cross-industry approach which is based on expert knowledge.

• Use of these predictions and transparent expert knowledge aligns directly with principles defined in ICH M7.
Conclusion

• Development of the tool is progressing well
• Enthusiastic and committed consortium of 19 members
  • Providing scientific guidance and oversight
• Knowledge will be expanded and refined
• Datamining techniques may assist in finding supporting evidence for reactivity purge factors
• Further research into solubility is planned for the future