In Silico Drug Degradation Assessment in Early Phase Development

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Introduction

There is increasing interest in stability or forced degradation studies that lead to the identification of degradation products (and pathways) of an active pharmaceutical ingredient (API). Stability assessment is crucial as API impurities can appear due to its chemical breakdown. The FDA and ICH guidelines require performance of stability testing which include long-term (12 months) and accelerated (6 months) investigations with further studies on degradation products. This latter aspect overlaps with the ICH M7 guideline (risk posed by mutagenic degradants). Stability assessment impacts on the already heavy time constraints of API development and therefore an in silico approach to support and streamline this part of the development process is desirable.

Our group is concerned with encapsulating drug degradation knowledge (from pharmaceutical reports, chemistry literature, consultation with experts) within a knowledge base as a series of transformations that can be accessed through the in silico tool Zeneth™ 1-2. The transformation dictionary (what reaction could occur) in combination with a reasoning engine (how likely is this) can generate a full degradation profile under various environmental conditions (pH, oxidation, light, temperature, humidity) that can assist in the identification of potential degradants. We detail the diverse range of chemistries in the knowledge base and illustrate how pre-existing knowledge and reactivity rules can make valuable drug degradation predictions during the development cycle.

Predictions method

A

Query

Reactions with singlet oxygen are classified as oxidations as opposed to photochemical reactions.

B

Query

Knowledge base transformation dictionary

Transformation engine

Reasoning

Relative

Absolute

Degradants

Relative reasoning:
Compares the likelihood of competing transformations
Absolute reasoning:
Evaluates the level of likelihood that a degradation will occur

Scheme 1: Part A shows the full overview of the method that is used to make predictions. Part B is an actual example, showing the results for Bromazepam.

Degradation chemistry knowledge base

<table>
<thead>
<tr>
<th>Transformation category</th>
<th>Number of transformations in the knowledge base</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidations</td>
<td>132</td>
</tr>
<tr>
<td>Hydrolyses</td>
<td>81</td>
</tr>
<tr>
<td>Condensations &amp; additions</td>
<td>77</td>
</tr>
<tr>
<td>Isomerisations &amp; rearrangements</td>
<td>32</td>
</tr>
<tr>
<td>Eliminations &amp; fragmentations</td>
<td>49</td>
</tr>
<tr>
<td>Photochemical reactions</td>
<td>38</td>
</tr>
<tr>
<td>Total</td>
<td>409</td>
</tr>
</tbody>
</table>

Table 1: Constitution of the knowledge base (Zeneth™ Master 271115_10) according to reaction type. Reactions with singlet oxygen are classified as oxidations as opposed to photochemical reactions.

Summary and conclusions

This in silico approach to predicting potential degradants and their formation pathways1-2 is an invaluable tool for the drug development process. It can be used in conjunction with experimental forced degradation studies3, to augment the knowledge gained from in vitro studies as well as to bridge the knowledge to new or novel compounds. In addition the approach can help to rationalise mass spectrometry data by helping to match up empirically observed m/z values with predicted structures. The knowledge base transformation dictionary is continually being enhanced by the addition of new chemistry as well the refinement of the existing rules.

References