Interpreting ICHQ11: A Risk Assessment Tool for Assessing Starting Material Acceptability

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Genentech – SMACQC
Webinar - Lhasa Mirabilis Users Group
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Overview

- A Changing Regulatory Climate For Starting Materials
- Selection of Regulatory Starting Material
  - A new Risk Assessment Tool
    - based on EMA Reflection Paper and ICHQ11 Q&A
- Erivedge Example - Disclosure of more Synthetic Steps
  - More Highly Reactive, Potentially Genotoxic Intermediates
    - Leveraging M7 Control Options
    - Applying Purging Rationale
- Opportunity to add RSM Risk Assessment Tool to Mirabilis
Industry and Health Authorities were interpreting ICH-Q11 Differently

- Increased HA Scrutiny of Starting Materials
- Challenges for Phase 3 and Registration
- Significant Queries even for Phase 1
- Route, specifications, COA’s
Changing Regulatory Climate for Starting Materials

• EMA Reflection Paper on ICHQ11

• ICH Question and Answer Paper
  - Focused on:
    • Proximity and Purging Power
    • Stages and Steps
      - “Telescoped” Process

• Complexity and Criticality

• Change Control and GMP
Risk Assessment – A New Tool for Genentech/Roche

- Distilled down to the most essential criteria
  - Proximity
  - sufficient number of Stages

- Purging Power
  - Impurity purging steps/Isolations

- Complexity
  - % Wt of the API
  - Number of Chiral Centers
  - Number of Substitutions
  - Number of rings

- Impurity Carryover

- Stability
## Calculation of the RSM Risk Score

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Instruction</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bond forming stages to API</td>
<td>Count all bond forming (chemical) steps</td>
<td>1 to n</td>
</tr>
<tr>
<td>No of isolated steps to API</td>
<td>Count all isolations (cryst. and product dist.)</td>
<td>1 to n</td>
</tr>
<tr>
<td>% w/w of API</td>
<td>Count only the part which ends-up in the API</td>
<td>1-100</td>
</tr>
<tr>
<td>No of stereogenic centers</td>
<td>Count all stereogenic (chiral) centers</td>
<td>0 to n</td>
</tr>
<tr>
<td>No of substituted aryls or double bonds</td>
<td>Count 1 per substituted aryl and substituted double bond</td>
<td>0 to n</td>
</tr>
<tr>
<td>No of rings</td>
<td>Count all rings</td>
<td>0 to n</td>
</tr>
<tr>
<td>Impurity carry over to API</td>
<td>1 if at least one impurity is carried over to API</td>
<td>0 or 1</td>
</tr>
<tr>
<td>Instability</td>
<td>1 if instability is observed or may arise</td>
<td>0 or 1</td>
</tr>
</tbody>
</table>

\[
\text{Risk Score} = \frac{4}{A} + \frac{8}{B} + (C \times 0.06) + D + E + F + G + H
\]

- < 8 low
- 8 - < 10 medium
- > 10 high
### Demonstration - Vemurafenib

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Bond Forming Stages</th>
<th>Isolation Steps</th>
<th>%W/W of API</th>
<th>Stereogenic Centers</th>
<th>Substituted Aryls or Double Bonds</th>
<th>Rings</th>
<th>Impurity Carry over</th>
<th>Instability</th>
<th>Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>SM 1</td>
<td>4</td>
<td>4</td>
<td>53</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>SM 2</td>
<td>4</td>
<td>4</td>
<td>24</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>SM 3</td>
<td>2</td>
<td>2</td>
<td>23</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>

\(^{a}\) Protection of indole and deprotection of 2,6-dichlorobenzoyl group are counted for bond forming stages by offering quality control opportunities.

- No starting materials identified as high risk
- Materials were globally accepted health authorities
Case Study – Erivedge

- Approved in 2012
  - 150mg Capsule QD
  - Basel Cell Carcinoma

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Case Study – Erivedge

- Approved in 2012
  - 150mg Capsule QD
    - Basel Cell Carcinoma
      - 10 ppm = TTC
        - >10 year dosing, No S9 Consideration

- Synthetic Scheme Analysis
  - For RSM Risk
  - RSM Synthesis: New PGI’s Disclosed

- Selective AMES Testing

- Justifying Options 3
  - no Finished API Specifications for PGI’s
    - Purge Power and Reactivity Rationale
    - Confirmation of Purge Power
GMP Synthesis Scheme – Erivedge (vismodegib)

1) Reduction

2) Activation

3) Coupling
4) Crystallization

Milling

vismodegib (1)
Increased Concern about Impurities from non-GMP Steps

- Route assessment
- Change Control
- Control Strategy
Synthesis Scheme – Risk Assessment of RSM’s

RSM 1

1) Reduction

3)

3) Coupling
4) Crystallization

Milling

vismodegib (1)

RSM 2

2) Activation

2)

SO₂Me

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## Risk Assessment of RSM’s for Erivedge

**Table 1: Risk Assessment of SM 1 and SM 2**

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Bond Forming Stages</th>
<th>Isolation Steps</th>
<th>%W/W of API</th>
<th>Stereogenic Centers</th>
<th>Substituted Aryls or Double Bonds</th>
<th>Rings</th>
<th>Impurity Carry over</th>
<th>Instability</th>
<th>Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>SM 1</td>
<td>1</td>
<td>3</td>
<td>56</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>14.0</td>
</tr>
<tr>
<td>SM 2</td>
<td>2</td>
<td>2</td>
<td>44</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>10.6</td>
</tr>
</tbody>
</table>

**SM1 Nitro aromatic: Characterized as high complexity by health authorities**

- **Structure:** ![SM1 Nitro aromatic](image)

**SM 2 Sulfonic Acid: Commercially available, high purity, well characterized**

- **Structure:** ![SM 2 Sulfonic Acid](image)

Contribution to MW is due to heteroatoms
Mitigate Risks for RSM 1

- Demonstrate Characterization and Purity
- Qualify Vendors and Produce under change control
- Disclose RSM chemistry
- Assess RSM routes for PGI’s
- Develop control strategy for RSM PGI’s
Two Vendors and two Routes to RSM1

Vendor 1
Negish Route

Vendor 2
Pyrimidinium Route

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PGI’s from In-Silico Assessment

Vendor 1
Negishi Route

Vendor 2
Pyrimidinium Route
AMES Testing on In-Silico Alerts

Vendor 1
Negishi Route

Vendor 2
Pyrimidinium Route
Challenging Methods for PPM Level

Vendor 1
Negishi Route

Vendor 2
Pyrimidinium Route

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<table>
<thead>
<tr>
<th>Option</th>
<th>Routine QC</th>
<th>Control</th>
<th>Analytical method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Most Challenging</td>
<td>Impurity specified in drug substance</td>
<td>PPM level methods required for routine analysis -</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acceptance criteria $\leq$ TTC/LTL</td>
<td>Difficult for QC Labs</td>
</tr>
<tr>
<td>2</td>
<td>Challenging</td>
<td>Impurity specified upstream (Starting material, intermediate or as in-process control)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acceptance criteria $\leq$ TTC/LTL</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Typical Testing</td>
<td>Impurity specified upstream (Starting material, intermediate or as in-process control)</td>
<td>PPM Level methods only required to support purge studies and process validation -</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acceptance criteria $&gt; TTC /LTL (TTC or LTL x Purge factor)</td>
<td>Not required for QC Labs</td>
</tr>
<tr>
<td>4</td>
<td>No Testing</td>
<td>Impurity NOT specified and Control is Unnecessary due to high purge factor</td>
<td></td>
</tr>
</tbody>
</table>
Analytical Method Challenges

- PPM Level Sensitivity
- Complex Sample Matrix
- Highly Reactive Analyte
- Wide Range of Properties
  - Polarity
  - Molecular Weight
  - Vapor Pressure
- Low UV Absorbance
Method Development Strategy

**Volatile**
- Thermally stable
- GC
  - Direct Injection
  - Headspace
  - Derivatization
    - To improve volatility
    - To improve ionization for MS
  - LLE
  - LLME
  - SPE
  - SPME
  - High column loading LC-UV
  - LC-MS (SIM) LC-MS/MS (SRM)

**Limited volatility**
- Thermally Labile
- HPLC
  - Backflushing
  - Analyte Extraction
  - Matrix Deactivation
  - 2D-GC
  - Derivatization
Challenging Methods for PPM Level

Vendor 1
Negishi Route

Vendor 2
Pyrimidinium Route
QC Friendly method (HPLC-UV)

Column: Zorbax XDB C18, 15cm 3.0mm 3.5 micron
Mobile Phase: 1ml/min 0.05% TFA water/ACN gradient
Detection: 225 nm

LOQ 500 ppm, LOD 200 ppm
LC-MS analysis Positive Ion Mode, SIM

Aromatic nitro compound are difficult to ionize: LOD ~ percentage levels – lacks sensitivity
LC-MS negative ion mode, SIM
For Compound 8 (non-volatile acid)

<table>
<thead>
<tr>
<th>Component</th>
<th>Condition</th>
</tr>
</thead>
</table>
| Column        | CSH C18 or equivalent  
15.0 cm x 3.0 mm, 1.7 micron                                             |
| Detector      | Mass Spectrometer  
Operation mode: negative, selective ion monitoring  
Ion monitored: 156                                                              |
| Suggested operation conditions | Fragmentor: ~ 70 eV  
Capillary voltage: ~ 1300 V  
Nozzle voltage: ~ 2000 V  
Drying gas: ~ 12 l/min  
Drying gas temperature: ~ 250°C  
Nebulizer pressure: ~ 35 psig  
Sheath gas temperature: ~ 160°C  
Sheath gas flow: ~ 3.0 l/min |
| Mobile Phase  | Mobile Phase A: 0.05% Formic acid in water  
Mobile Phase B: Acetonitrile                                                 |
| Time (min)    | MP-A | MP-B |
| 0             | 95%  | 5%   |
| 5             | 5%   | 95%  |
| 6             | 5%   | 95%  |
| 6.1           | 95%  | 5%   |
| Column Flow Rate | 0.5 ml/min                                                                 |
| Column Temperature | 45°C                                                                 |
| Injection Volume | 5 µL                                                                 |
| UV Detection  | Optional at 265 nm                                                        |

4 ppm standard

Sample: HO₂C-\(\text{Cl}\)NO₂

Blank
GC-MS (SIM) analysis of Compounds 6, 7 and 9

<table>
<thead>
<tr>
<th>Component</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Column</td>
<td>Capillary, fused silica with (5%-Phenyl)-methylpolysiloxane phase, 30 m x 0.32 mm inner diameter, 0.1 μm film thickness or equivalent</td>
</tr>
<tr>
<td>Detector</td>
<td>Mass spectrometer</td>
</tr>
<tr>
<td></td>
<td>Operation mode: selective ion monitoring ions monitored: 172, 184, 283</td>
</tr>
<tr>
<td></td>
<td>Suggested operation conditions: Ion source temperature: ~150°C  MSD transfer temperature: ~150°C</td>
</tr>
<tr>
<td>Carrier Gas</td>
<td>Helium</td>
</tr>
<tr>
<td>Column Flow Rate</td>
<td>Helium (carrier gas), approximately 5.8 mL/min</td>
</tr>
<tr>
<td>Inlet Temperature</td>
<td>200°C</td>
</tr>
<tr>
<td>Inlet</td>
<td>Split, ratio 1:2</td>
</tr>
<tr>
<td>Split Flow</td>
<td>~ 20mL/min</td>
</tr>
<tr>
<td>Injection Volume</td>
<td>1 μL</td>
</tr>
<tr>
<td>Temperature Program</td>
<td>Initial temperature: 135°C for 3.5 minutes  Program rate: 40°C/min to 315°C  Hold 7 minutes</td>
</tr>
</tbody>
</table>

Retention time (minutes)
Purging Power Demonstrated

1% of 6, 7, 8 and 9 Spiked

1) Reduction

2) Activation

3) Coupling

4) Crystallization

<4 PPM of 6, 7, 8 and 9

>2500 Purge Power

Confirmed 1000X prediction

Justified Option 3
• Regulatory approval of proposed RSM’s
  • Based on Route, Control Strategy and Manufacturers/Change Control

• Control Strategy for RSM 1
  • Developed & validated PPM Level methods
    • for 6, 7, 8 and 9 in Starting Material 1 and API
  • Generated lot history data for multiple lots
    • SM 1 and resulting API lots
      • All results < 4 ppm
  • Generated purging data for 6, 7, 8 and 9 for 1% Spiked Starting Material
    • API levels <4PPM
    • Purge factor of >25000

• Justified Option 3
  • Specification of ≤ 0.10% for 6, 7, 8 and 9 in Starting Material 1 established
  • QC HPLC Method Developed
Acknowledgements

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Stefan Hildbrand
Fabian Schwarb
Jean-Philippe Crochard

References


Mutagenicity (Genotoxicity)

Induce genetic damage and fixation
- Gene mutation
- Larger scale chromosomal damage
- Recombination and numerical chromosome changes

Cause cancer or heritable changes
- Carcinogenicity more easily detected

<table>
<thead>
<tr>
<th>Impurity Classification</th>
<th>Definition Weight of Evidence</th>
<th>Approach to Control Human Exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1</td>
<td>Mutagenic and carcinogenic</td>
<td></td>
</tr>
<tr>
<td>Category 2</td>
<td>Mutagens with unknown carcinogenic potential or a “close-in” analog</td>
<td></td>
</tr>
<tr>
<td>Category 3</td>
<td>Alerting structure – Unique but uncertain Relevance</td>
<td></td>
</tr>
<tr>
<td>Category 4</td>
<td>Alerting structure – Non-unique compared to API</td>
<td></td>
</tr>
<tr>
<td>Category 5</td>
<td>No Structural Alerts</td>
<td></td>
</tr>
</tbody>
</table>

M7 Guidance

M7 provides a risk based exemption (up to 14 days) for Phase 1 (treat as non-genotoxics)

ICH Q3 controls apply
Compound Evaluation

- Synthesis scheme
  - Raw materials
  - Intermediates
  - Reagents

- Impurities detected in the API
  - Byproducts
  - Degradation products

- Readily predicted Impurities
  - Predominantly in final steps
  - Stress Studies

M7 specifies Full AMES/GLP Like Testing – expect more positive results than from AMES II Tests
M7 LTL limits: Individual and Multiple Mutagenic Impurities

Acceptable Intakes in relation to ‘less-than-lifetime’ (LTL) exposure

<table>
<thead>
<tr>
<th>Duration of Treatment</th>
<th>&lt; 1 month</th>
<th>&gt;1-12 months</th>
<th>&gt;1-10 years</th>
<th>&gt;10 years to lifetime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily intake [µg/day]</td>
<td>120</td>
<td>20</td>
<td>10</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Acceptable Intakes for **multiple mutagenic impurities (NMT 3x individual limit)**

**When 3 or more mutagenic impurities are controlled**

<table>
<thead>
<tr>
<th>Duration of Treatment</th>
<th>&lt; 1 month</th>
<th>&gt;1-12 months</th>
<th>&gt;1-10 years</th>
<th>&gt;10 years to lifetime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily intake [µg/day]</td>
<td>120</td>
<td>60</td>
<td>30</td>
<td>5</td>
</tr>
</tbody>
</table>

Only impurities that are specified in the final drug substance specification contribute to the calculation for Total.