Developing an Analytical Impurity Control Strategy Using QbD

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Quality by Design in Development

Relies upon developing knowledge around processes and products...

... for effective process and product design and control.

Ref: M. Nasr, 2006
An understanding of “What goes in” and “What goes on” in development…

\[ A + B \rightarrow_{solvent\ 1}^{time,\ temp.,\ pH\ \ldots} C \rightarrow_{solvent\ 2,\ reagent}^{\ldots} API \]

\((B')\) \(\rightarrow\) \((C')\) \(\rightarrow\) \((API')\) \(\rightarrow\) \((BP1,\ BP2\ \ldots)\) \(\rightarrow\) \((D1,\ D2\ \ldots)\)

A, B = starting materials  
C = intermediate  
API = active pharmaceutical ingredient  
B' = starting material impurity with potential to form C' and API'  
BP = reaction by-product  
D = degradation product

…leads to knowledge and development of suitable, robust manufacturing and analytical controls for your process
Building a Process Knowledge Base

Consider multiple synthetic variations, suppliers for starting materials, etc.

Utilize chemistry-guided and knowledge-guided approaches to potential impurities

- Knowledge-guided: What has been observed in selected samples
- Chemistry-guided: What is possible/likely from and understanding of the synthetic processes used or considered
  - Any potential genotoxic impurities likely/possible? Use “fit-for purpose” development methods to explore for potential impurities.

Leverage appropriate tools to develop process and impurity formation/fate understanding - e.g., MS, NMR, IR/NIR/Raman

Control strategy development is a dynamic partnership between process and analytical and an iterative strategy

- To search for and identify impurities
- To understand impurity formation and fate
- To design appropriate process and analytical controls to minimize or eliminate impurities.
Example: An HPLC-IR-NMR system to generate development knowledge

- Optical Spectrometer (mid-IR, NIR, Raman, UV-vis)
- HPLC (configured for on-line)
- Reactor
- NMR

Obtain valuable information on kinetics, reactive intermediates, relative response factors, etc.
Impurity Controls Based upon Process Understanding

Step 1

- Imp A’ NMT 0.10%
- Imp B’ NMT 0.15%
- Imp C’ NMT 0.50%
- Imp D’ NMT 1.0%

Step 2

- Imp B” NMT 0.40%
- 30% 70%
- 10% 90%

Step 3

- Imp C NMT 0.25%
- Imp D NMT 0.10%
- Imp B NMT 0.15%
- Imp A NMT 0.10%
- >98% 90% 10%
- 20% 80% 10% 90%

AU

0.000 0.005 0.010 0.015 0.020 0.025 0.030 0.035 0.040 0.045 0.050

Minutes

0.00 5.00 10.00 15.00 20.00 25.00 30.00 35.00
Process knowledge informs analytical controls

Knowledge space studies

ании of measurement requirements for the quality attributes of a product that must be controlled
• What analyte(s)
• What level(s)
• What precision

An Analytical Target Profile (ATP)

Analytical method design space studies
Building an Analytical Knowledge Base - Control Strategy Development

Development Methods

HPLC broad polarity screens, multiple detectors
orthogonal techniques, on-line analysis
targeted methods

Process knowledge - what needs to be monitored/controlled
(Analytical Target Profile definition)

Quality Control Methods
Integral to specifications and/or process controls
Optimized for ruggedness
QbD Tools in Impurities Method Development Strategy

- Identify key impurities from:
  - Typical drug substance/product samples
  - Authentic impurity samples
  - Process development samples with likely impurities (e.g., reaction samples, mother liquors)
  - Samples from designed, forced degradation studies
  - Potential drug product impurities --- review degradation and excipient interaction design study data

- Use **systematic tools** and **designed studies** to aid in appropriate method development (e.g., column screening program for design space impurities)
An example: Analytical Design Space for Impurity Method Development

Use column classification system* to identify column similarities and differences

And

Exploit column differences in HPLC method development

*e.g., Gilroy, Jonathan J.; Dolan, John W.; Snyder, Lloyd R. Column selectivity in reversed-phase liquid chromatography IV. Type-B alkyl-silica columns. Journal of Chromatography, A (2003),1000(1-2), 757-778.
Perform screen with distinctly different conditions/phases

Optimize separation with modeling

Predictions for directing additional studies
Assessing method “robustness” w/o doing experiments – power of modeling tools

evaluate parameters such as temperature, organic strength, and gradient sensitivity for impact on expected minimum resolution
Gradient Assay Identified in Development for Impurity Control

Method selectivity of gradient:
A = unspiked matrix
B = matrix with 0.05% spike for impurities 1, 2, 6, 7, 8 and impurity 5 spiked at 0.15%

Historically, a gradient assay has been used in development to evaluate material quality and confirm the lack of late-eluting impurities.
Initial Gradient Method – no significant later-eluting impurities for drug
Can be simplified to an isocratic assay for routine control
Identify meaningful system suitability controls to ensure reliable method performance
Use of system suitability samples and a “method performance sample” (if it contains measurable impurity levels and is stable) can be useful for method robustness and method transfers.
Using Design Studies to Evaluate Method Robustness

Consider design studies during method development for more method knowledge

Leverage modeling studies (e.g., DryLab) to cover wide operating ranges, when possible, in final method
## Robustness – Statistical Design Results

<table>
<thead>
<tr>
<th>Pattern #</th>
<th>Design</th>
<th>Standard Area</th>
<th>Total Impurities (Direct area-%)</th>
<th>Total Impurities (vs ext std)</th>
<th>Rs (resolution pair 1)</th>
<th>Rs (resolution pair 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pattern 0</td>
<td>000000</td>
<td>10002</td>
<td>0.68</td>
<td>0.71</td>
<td>1.96</td>
<td>3.71</td>
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<tr>
<td>pattern 1</td>
<td>++++++</td>
<td>9908</td>
<td>0.69</td>
<td>0.67</td>
<td>1.88</td>
<td>2.38</td>
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<tr>
<td>pattern 2</td>
<td>++</td>
<td>1061</td>
<td>0.69</td>
<td>0.71</td>
<td>2.00</td>
<td>3.43</td>
</tr>
<tr>
<td>pattern 3</td>
<td>−+++++</td>
<td>10759</td>
<td>0.68</td>
<td>0.70</td>
<td>1.89</td>
<td>5.20</td>
</tr>
<tr>
<td>pattern 4</td>
<td>−+++++</td>
<td>9985</td>
<td>0.69</td>
<td>0.77</td>
<td>1.92</td>
<td>5.34</td>
</tr>
<tr>
<td>pattern 5</td>
<td>+−−−−−−</td>
<td>10354</td>
<td>0.67</td>
<td>0.74</td>
<td>2.03</td>
<td>2.18</td>
</tr>
<tr>
<td>pattern 6</td>
<td>+−−−−−−</td>
<td>9983</td>
<td>0.67</td>
<td>0.74</td>
<td>2.09</td>
<td>3.41</td>
</tr>
<tr>
<td>pattern 7</td>
<td>−−−−++</td>
<td>9145</td>
<td>0.67</td>
<td>0.73</td>
<td>1.95</td>
<td>3.85</td>
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<tr>
<td>pattern 8</td>
<td>−−−−++</td>
<td>9525</td>
<td>0.69</td>
<td>0.70</td>
<td>1.97</td>
<td>3.68</td>
</tr>
</tbody>
</table>

Collect important performance information to justify acceptable method performance – aids in setting meaningful system suitability criteria.
Wavelength Robustness

Evaluate response for each impurity to assess robustness as structural differences may cause spectral response differences.

Ref: *J. Chrom A*, 762 (1997), 227-233

LY297802  chloro impurity  ethoxy impurity  hydroxy impurity
Wavelength Robustness

Indeed, different spectral profiles exist for the various compounds (with need for ~280 nm detection)...

...and a simple wavelength system suitability sample can be developed with commercially-available materials

Ref: J. Chrom A, 762 (1997), 227-233
Method Transfers and Maintenance

Method transfers should include:

• An assessment for capability to perform the analysis AND

• The process and product knowledge and overall control strategy for intended use of the method

➤ Important for proper method use and for reference in any future improvements

Useful tools to assess performance/variability:

• Data from robustness studies to interpret system suitability results

• Data from method performance (control) samples in development aid in confirming appropriate performance during transfer and beyond.

Transfer of knowledge regarding “investigational” methods (e.g., broader-based gradient methods, spectroscopic studies) is also useful for studying potential impact of future process design space changes relative to the analytical design space

  • Example: Evaluation of new sources of starting materials or excipients
Performance data allows trends to be identified (and understood)

Then…

…and more recently

(Tailing limit NMT 1.5)

Change in instrumentation affected performance
Opportunities

With potential manufacturing changes…

If studies to define the knowledge space are well captured, one can leverage historical knowledge and investigational methods to study continuous improvement opportunities and either re-confirm suitability of existing controls or recognize potential concerns

- Example: use of gradient HPLC investigational method versus isocratic method to ensure appropriate evaluation for potential late-eluting impurities, if anticipated or possible

Use appropriate chromatographic and spectroscopic tools to assess post-approval process changes for method impact.
QbD/Analytical Lifecycle Summary

Advantages

• Acknowledges control strategy is integrated with both process and analytical understanding and controls
• Effectively aligned with information/knowledge generation; possibilities to leverage a wide variety of tools for effective process understanding
• Logical progression throughout development with evolution of method focus to meet varying “customer” demands

Disadvantages

• Analytical methods used in development not necessarily same as for routine control
  – Possibly more method development time
  – Possible utilization of more and varied analytical tools
  – More method “bridging” considerations
The QbD/ analytical lifecycle approach supports a methodical, integrated, requirements-based approach to method development and implementation.

From an industrial perspective, the knowledge, design, and control spaces are studied relative to the specific process/formulation that is being commercialized.

This approach delivers robust process and analytical understanding and controls which focus on the selected process.

Analytical method development from a lifecycle perspective is performed in two parts:

- Defining and developing the overall product control strategy and method requirements
- Method definition, using well-selected control parameters (system suitability) and method performance samples can be used to ensure quality of future results. Method robustness and modeling tools help to define meaningful conditions and controls.

Analytical control methods are tailored for the selected combination of process and analytical controls for that process.

Therefore, one needs to assess a compendial method for suitability with the intended manufacturing process.
A few references


Thank You!

Acknowledgements:

Bernie Olsen          Steven Baertschi
Tim Wozniak          Eric Jensen
Peter Gavin           John Stafford
Zhenqui Shi          Gordon Lambertus
Robert Forbes
backups
Use of ICP-MS to confirm absence of “concerning” elemental impurities for simplified control

<table>
<thead>
<tr>
<th>Range of results (n=27 batches) across development, scale-up and validation</th>
<th>Pd (µg/g)</th>
<th>As (µg/g)</th>
<th>Cd (µg/g)</th>
<th>Hg (µg/g)</th>
<th>Pb (µg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.005 to 5.20</td>
<td>All &lt;0.005</td>
<td>All &lt;0.005</td>
<td>All &lt;0.005</td>
<td>&lt;0.005 to 0.198</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oral PDE(^a), µg/day</th>
<th>100</th>
<th>1.5</th>
<th>25</th>
<th>5</th>
<th>15</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Limit in API assuming &lt;20 mg/day MDD(^b), µg/g</th>
<th>5560</th>
<th>83</th>
<th>1390</th>
<th>278</th>
<th>833</th>
</tr>
</thead>
</table>

| Limit in API assuming a 10 g/day dose, µg/g | 10 | 0.15 | 2.5 | 0.5 | 1.5 |

\(^a\) Permissible Daily Exposure  
\(^b\) Maximum Daily Dosage

- Most elements are <1/100\(^{th}\) of safety limits (even conservative limits)
- Only Pd, which was intentionally used in the manufacturing process was >30% of the most conservative safety limit (and only in an early development batch)
  - Control Pd routinely to NMT 10 ppm using robust, widely available ICP-OES approach
  - Justify non routine testing/control for other elemental impurities
Another example – Use of robustness studies to define useful system suitability

Method developed to resolve many potential impurities (a); only a few impurities typically seen (b)

Robustness study through design of experiments

- Fractional factorial design for 5 variables with 4 center points $\rightarrow$ 16+4 = 20 runs
- Tracked resolution of key resolution pairs in addition to run time and tailing data with carefully selected crude sample (contained key impurities)
Robustness Study Prediction Profile

Results support robustness to buffer conc. and pH; note runtime and pressure changes with n-propanol and T changes

Rs (1-2) is correlated with Rs changes for other peak pairs and is sensitive to n-propanol and T changes

→ Impurities 1 and 2 are good candidates for meaningful system suitability assessment of method separation performance

- Impurity 2 is commercially-available
- Impurity 1 can be procured or easily formed with in-situ degradation
In-situ generation of meaningful system suitability sample
Method change and comparability – an example

**Situation:** A method change was desired after manufacturing/process change to also detect a potential new impurity (Impurity 7)

(Gradient method could detect impurity 7 but isocratic impurity method 1 could not.)

**Result:** Changed both Assay and Impurities methods to new methods that were more appropriate and capable for the new manufacturing process.
Gradient Impurity Method

Method selectivity of gradient:

A= unspiked matrix

B= matrix with 0.05% spike for impurities 1,2,6,7,8 and impurity 5 spiked at 0.15%
Analytical Profile – Method 1

IFPAC 2014
M. Argentine
Analytical Profile – Method 2

New method can see all of the impurities of the previous method as well as the new method.
Method Comparison - Impurities

Oneway Analysis of Results By Method

A = Method 1
B = Method 2

Evaluation of one “impurity rich” sample by both methods

No statistical difference between methods
Method Comparison - Assay

Lot 1

Lot 2

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M. Argentine
Method Comparison

No practical or statistical difference between the two methods