API BATCH PROCESS SIMULATION

SCALE UP METHODOLOGY

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OVERVIEW

GOAL
Share with you actually methodology used in ChemAgis for simulation – scale up of our API batch process from laboratory to production scale.

CONTENTS
1. Background
2. Methodology
3. Application
4. Conclusion
5. References
6. Discussion
1. BACKGROUND

- UPGRADE CAPE UTILIZATION and STAFF PREPARATION
- QbD – MECHANISTIC MODELING

- Combined + QbD 2008 - …
- Combined 2005 - 2008
- Advanced 2001 - 2005
- Poor Before 2001

API BATCH PROCESS SIMULATION - SCALE UP RESULTS

EXPERIMENTAL DATA

DYNOCHEM

VISIMIX

CAPE

API BATCH PROCESS SIMULATION - SCALE UP RESULTS

EXPERIMENTAL DATA
1. BACKGROUND – SCALE UP PROCEEDING

- R & D LABORATORY
- PILOT 1-2 L REACTORS
- MINI-PILOT 3 – 50 L REACTORS
- PILOT REACTORS 100 – 1000 L

- RECIPE and DATA
- PRODUCTION REACTORS

API Batch Process Simulation – Scale Up Methodology.
Roberto Novoa and Moshe Bentolila
Scale Up Methodology

Circular
LABORATORY (R&D)

BENCH SCALE (RC1, HEL)

PILOT (Mini Pilot)

PLANT (Pilot, Production)

Design

Build

Final Design

Scale Down

Analyze

J.M. Berty. CEP, 1979

Roberto Novoa and Moshe Bentolila

API Batch Process Simulation – Scale Up Methodology.
Quality by Design – Statistical Challenges
Yi Tsong,
CDER, FDA 2007 FDA/Industry Statistics Workshop
2. METHODOLOGY
CHEMAGIS PILOT ORGANIZATIONAL SCHEME FOR PROJECT DEVELOPMENT

MECHANISTIC THINKING
Process Scheme

STATISTICAL DESIGN OF EXPERIMENTS (DOE)

CPPs

DESIGN SPACE

SCALE - UP

MECHANISTIC MODEL

PROCESS UNDERSTANDING

Who?

Project Engineer
Project Chemist
QC Laboratory
Simulation Engineer

Meeting – Team Work

How?

When?

At Project beginning, before starting with experimental batches.

Experimental Data.
Processing Data for Simulation.

End of Fitting & Modeling Process
End of Simulation Process

Who?

When?

Who?

How?
MECHANISTIC MODEL

• A model that has a structure that explicitly represents an understanding of physical, chemical, and/or biological processes. Mechanistic models quantitatively describe the relationship between some phenomenon and underlying first principles of cause. Hence, in theory, they are useful for inferring solutions outside of the domain that the initial data was collected and used to parameterize the mechanisms.

• Mechanistic modeling techniques offer most value in developing a science based understanding of many of the common bulk unit operations in API processes.

The DOE approach tells us the “what”, whereas the mechanistic approach tells us more about the “why and how”, therefore giving us enhanced process understanding.
WHY WE USE DYNOCHEM AND VISIMIX?

DynoChem – Chemical dynamic simulation software.
✓ Fitting in chemical reaction models.
✓ Prediction of scale-up conditions for ideal reactors.
✓ Optimization of laboratory and production results in ideal conditions.
✓ Provides the necessary tools for Mechanistic Modelling and QbD.

VisiMix – Mixing simulation and calculation software.
✓ Mathematical modeling of mixing phenomena.
✓ Calculation of average and local characteristics of mixing flow and distribution of concentration.
✓ Simulation and calculation of real “non perfect” mixing.

PROCESS UNDERSTANDING - SCALE UP
HIGH ACCURACY – LOW COST

For a given reactor scale, if PROCESS UNDERSTANDING then, Scale-Up (or Down) will be successfully if Hydrodynamics - Turbulent - Mixing characteristics are similar between reactors.
3. Applications

3.1 GENERAL SCIENTIFIC METHOD IMPLIES MECHANISTIC MODELING

- Fit unknown parameters
- Quantify uncertainty
- Determine optimum processing conditions
- Explore the design space and the risk associated with operating away from target conditions.
- Explore the potential criticality of any factor
- Report the results

LABORATORY DATA
TECHNICAL REPORT

PROCESS SCHEME
(SUPPORTS A MECHANISTIC APPROACH)

DOE
REACTOR 1-2 L

MODEL
PROCESS SIMULATION

EXPERIMENTAL
DATA

SCALE UP

MODEL VALIDATION

YES

FINAL REPORT
THE END

NO
3.2 PROJECT EXAMPLE FROM CHEMAGIS

API REACTION STAGE: SIMULATION - SCALE UP

TEMOZOLOMIDE PROCESS SCHEME

Solvent
Substrate = S
Reagent = R (Solid)
Product = P
Impurities = I1 and I2

EOR is achieved when:
R ≤ 2 %
Yield ≥ 97 %

Under this conditions, at EOR:
CQA= \[\frac{R}{R+P}\] \times 100 \leq 2 %

DOE: 4 experiments at different stirrer speed and temperatures In RC – 1
Stirrer speed: 250 and 650 rpm
Temperature: 20 and 40 C
Fitting Results

Fitted values from experimental data:

<table>
<thead>
<tr>
<th>Constant Rate of Reaction</th>
<th>Activation Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K$</td>
<td>$E_a$</td>
</tr>
<tr>
<td>$K_1 = 7 \times 10^8 \text{ m}^3/\text{mol.s}$</td>
<td>$E_{a1} = 60 \text{ kJ/mol}$</td>
</tr>
<tr>
<td>$K_2 = 2.72 \times 10^{-12} \text{ m}^3/\text{mol.s}$</td>
<td>$E_{a2} = 14.6 \text{ kJ/mol}$</td>
</tr>
<tr>
<td>$K_3 = 3.13 \times 10^{-7} \text{ 1/s}$</td>
<td>$E_{a3} = 55.8 \text{ kJ/mol}$</td>
</tr>
</tbody>
</table>

Mass Transfer Coefficient, $K_{La}$

<table>
<thead>
<tr>
<th>Experiment</th>
<th>$Tr, C$</th>
<th>Speed $\text{rpm}$</th>
<th>EOR $\text{h}$</th>
<th>$K_{La}$ $\text{1/s}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.M 533</td>
<td>20</td>
<td>250</td>
<td>14</td>
<td>0.58</td>
</tr>
<tr>
<td>S.M 535</td>
<td>20</td>
<td>650</td>
<td>10</td>
<td>0.75</td>
</tr>
<tr>
<td>S.M 532</td>
<td>40</td>
<td>250</td>
<td>2</td>
<td>0.58</td>
</tr>
<tr>
<td>S.M 534</td>
<td>40</td>
<td>650</td>
<td>1.5</td>
<td>0.75</td>
</tr>
<tr>
<td>S.M 536</td>
<td>35</td>
<td>400</td>
<td>3</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Uncertainty

95% Confidence and Prediction bands for DynoChem model (140 dof) of SM 535

95% Confidence and Prediction bands for DynoChem model (140 dof) of SM 535
Optimum Processing Conditions

Target: Yield = 97%; CQA = 1%

Requirement: production plant prefer to work at reactor temperature 20 - 25°C and at higher possible stirrer speed.

Result:

From SM 535: T = 20°C, KLa = 0.77 1/s and EOR = 11.2 h (672 min)

Uncertainty

95% Confidence and Prediction bands for DynoChem model (140 dof) of Scenario 7

Optimization result for Yield and CQA

CQA = 1.07%
If reaction is performed at 25 C and similar mixing characteristics as at 650 rpm in RC – 1 simulation expected results must be as follow:

EOR = 8.45 – 11 h
Yield = 98.2 – 98 %
CQA = 0.34 – 0.1 %
**EXPLORE DESIGN SPACE – PROCESS ROBUSTNESS - CPPs**

**Design Space:** varying reactor temperature and mass transfer coefficient

From optimized simulation model: Examine the risk associated with operating the process near, but not at, the optimized conditions.

Reactor temperature (Tr) variation: 20 - 30°C

Mass transfer coefficient (kLa) variation: 0.2 – 0.8 1/s

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**Exploration result:**

For 20°C ≤ Tr ≤ 30°C if kLa ≥ 0.65 1/s

Yield ≥ 97 % and CQA ≤ 2% have to expected

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**Process Robustness – CPPs**

From optimized simulation model: Explore the risk of sensitivity of the results to any factor that may vary due to common cause variability, including factors no considered during optimization.

Potential factors: Two – level sensitivity

Solvent Volume = ± 10 %

Solid reagent = ± 1 %

Stirrer speed = ± 5.3 % (620 – 685 rpm) <> kLa ≈ 0.7 – 0.8 1/s
### Process Robustness – CPPs ……

From the 8 new ran scenarios, in a fractional factorial screening design of simulations, we achieve the following results:

<table>
<thead>
<tr>
<th>Responses:</th>
<th>Yield</th>
<th>CQA</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>97.09</td>
<td>1.65</td>
<td></td>
</tr>
<tr>
<td>97.82</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>97.76</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>97.14</td>
<td>1.65</td>
<td></td>
</tr>
<tr>
<td>97.74</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>97.14</td>
<td>1.64</td>
<td></td>
</tr>
<tr>
<td>97.09</td>
<td>1.65</td>
<td></td>
</tr>
<tr>
<td>97.82</td>
<td>0.91</td>
<td></td>
</tr>
</tbody>
</table>

**Fractional Factorial Analysis**

<table>
<thead>
<tr>
<th>Effects (factors and Interactions)</th>
<th>CQA High setting</th>
<th>CQA Low setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvent volume (ml)</td>
<td>1.2795</td>
<td>1.2801</td>
</tr>
<tr>
<td>Temperature (C)</td>
<td>1.2799</td>
<td>1.2797</td>
</tr>
<tr>
<td>Solid reagent (mmol)</td>
<td>1.2798</td>
<td>1.2798</td>
</tr>
<tr>
<td>kLa (1/s)</td>
<td>0.914</td>
<td>1.6456</td>
</tr>
<tr>
<td>Solvent volume* Temperature</td>
<td>1.2799</td>
<td>1.2797</td>
</tr>
<tr>
<td>Solvent volume* Solid reagent</td>
<td>1.2797</td>
<td>1.2799</td>
</tr>
<tr>
<td>Solvent volume*kLa</td>
<td>1.2800</td>
<td>1.2796</td>
</tr>
</tbody>
</table>

Based on these simulations Yield and CQA will be always in the range of target values.

The biggest effect on the Yield and CQA response is from kLa.

At EOR = 11 h

1.65 ≥ CQA ≥ 0.91
97.82 ≥ Yield ≥ 97.09
SCALE – UP FROM RC – 1 TO PRODUCTION

According to Design Space exploration we need to achieve $k_{La} \geq 0.65 \text{ 1/s}$ in production reactor to ensure Yield and CQA values as expected.

From fitted $k_{La}$ values – stirrer speed during reaction in RC - 1

- Operating RC-1
  - Stirrer Speed $\geq 475$ rpm
  - $k_{La} \geq 0.65 \text{ 1/s}$

Reactor for production stage will be adequate if it could be possible to achieve similar Hydrodynamics-Turbulent-Mixing characteristics as obtained in RC – 1 at minimum 475 rpm.
SCALE – UP……… VISIMIX

Production decide to operate with Volume = 10 L using reactor R4501 (25 L, Curved Tubes De Dietrich Impeller 250 mm, One dip pipe-thermometer acting as baffle).

Main Hydrodynamics-Turbulent-Mixing Characteristics

<table>
<thead>
<tr>
<th>Characteristic/Reactor</th>
<th>RC-1</th>
<th>R4501</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum useful volume, L</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>Operational volume, L</td>
<td>0.6</td>
<td>10</td>
</tr>
<tr>
<td>Stirrer speed, rpm</td>
<td>500</td>
<td>100</td>
</tr>
<tr>
<td>Reynolds</td>
<td>13700</td>
<td>58350</td>
</tr>
<tr>
<td>Energy distribution average, W/kg</td>
<td>1.18</td>
<td>0.089</td>
</tr>
<tr>
<td>Energy distribution in bulk volume, W/kg</td>
<td>0.623</td>
<td>0.03</td>
</tr>
<tr>
<td>Micro mixing time, s</td>
<td>1.53</td>
<td>11.2</td>
</tr>
<tr>
<td>Complete Suspension Expected</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Maximum degree of non-uniformity Axial, %</td>
<td>1.74</td>
<td>6.16</td>
</tr>
<tr>
<td>Maximum degree of non-uniformity Radial, %</td>
<td>0.77</td>
<td>11.9</td>
</tr>
<tr>
<td>Maximum energy of collisions, J</td>
<td>4.4E-9</td>
<td>2.2E-9</td>
</tr>
<tr>
<td>Characteristic time between two strong collisions, J</td>
<td>5.05</td>
<td>67.9</td>
</tr>
</tbody>
</table>

5 Test results:
T = 20 - 23 C
EOR = 23 – 50 h
Yield = 97 – 98 %
CQA = 0.3 – 2.3 %
Fitted kLa
0.3 – 0.37 1/s
SCALE – UP……. VISIMIX

Two new reactors were evaluated for API reaction operation:
R 4504-1, One dip pipe-thermometer acting as baffle and R4504-3, 3 Flat baffle-2, same capacity (15 L) and same impeller (3 blade paddle, 175 mm). Results as follow.

<table>
<thead>
<tr>
<th>Characteristic/Reactor</th>
<th>RC-1</th>
<th>R4504-1</th>
<th>R4504-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum useful volume, L</td>
<td>2</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Operational volume, L</td>
<td>0.6</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Stirrer speed, rpm</td>
<td>500</td>
<td>285</td>
<td>285</td>
</tr>
<tr>
<td>Reynolds</td>
<td>13700</td>
<td>70300</td>
<td>56400</td>
</tr>
<tr>
<td>Energy distribution average, W/kg</td>
<td>1.18</td>
<td>1.83</td>
<td>2.5</td>
</tr>
<tr>
<td>Energy distribution in bulk volume, W/kg</td>
<td>0.623</td>
<td>0.72</td>
<td>0.90</td>
</tr>
<tr>
<td>Micro mixing time, s</td>
<td>1.53</td>
<td>2.71</td>
<td>2.27</td>
</tr>
<tr>
<td>Complete Suspension Expected</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Maximum degree of non-uniformity Axial, %</td>
<td>1.74</td>
<td>2.77</td>
<td>1.52</td>
</tr>
<tr>
<td>Maximum degree of non-uniformity Radial, %</td>
<td>0.77</td>
<td>12.9</td>
<td>0.63</td>
</tr>
<tr>
<td>Maximum energy of collisions, J</td>
<td>4.4E-9</td>
<td>7.7E-9</td>
<td>1.17E-8</td>
</tr>
<tr>
<td>Characteristic time between two strong collisions, J</td>
<td>5.05</td>
<td>4.5</td>
<td>5</td>
</tr>
</tbody>
</table>
PRODUCTION RESULTS

2 Test results from R4504-1:

- \( T = 23 - 25 \, ^\circ\text{C} \)
- \( \text{EOR} = 11 \, \text{h} \)
- \( \text{Yield} = 97 - 98 \, \% \)
- \( \text{CQA} = 0.35 - 0.61 \, \% \)
- Fitted \( k_{La} \) = 0.611 \, 1/\text{s} \\

Similar results were obtained in R4504-3 but:

- \( \text{EOR} = 9 \, \text{h} \)

Reaction results during production until April 2011:

- Total Batches \( N^0 = 380 \) (150 in R4504-1 + 230 in R4504-3)
- Temperature = 24 - 25 \, ^\circ\text{C} 
- Yield \approx 98 \, \% \) at \( \text{EOR} = 9 - 11 \, \text{h} \)
- \( \text{CQA} = 0.3 \, \% \)

Finally, reaction is performed in R4504-3.
Implementation of simulation scale-up results to production stage for Temozolomide reaction gives the following batch characteristics:

<table>
<thead>
<tr>
<th>Batch Characteristic</th>
<th>R4501</th>
<th>R4504-1</th>
<th>R4504-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>EOR time, h</td>
<td>23 - 50</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Yield, %</td>
<td>97 - 98</td>
<td>97 - 98</td>
<td>98</td>
</tr>
<tr>
<td>CQA, %</td>
<td>0.3 – 2.3</td>
<td>0.35 – 0.61</td>
<td>0.3</td>
</tr>
<tr>
<td>kLa, 1/s</td>
<td>0.3 - 0.37</td>
<td>0.61</td>
<td>&gt;0.61</td>
</tr>
</tbody>
</table>

VisiMix help us to determine the adequate reactor – stirrer system and the best Hydrodynamics – Turbulent – Mixing characteristics during operation process to guarantee desired steady results.
4. CONCLUSIONS

- Integration of experts-team work in presented methodology is a warranty of success during all the experimental – simulation – scale up period focused on QbD expectative.

- VisiMix program used in conjunction with another simulation tool – for example DynoChem - contributed to the improvement of simulation – scale up results, particularly from pilot to production stage.

- VisiMix is an excellent tool, not only to improve scale up, it is also very useful to study and understand different mixing-operations taking place in batch/semi batch reactors.
5. REFERENCES

1. Moshe Ben Tolila, Roberto Novoa, Michal Hasson, Efrat Manoff, **INTRODUCTION OF CAPE INTO AN ACTIVE PHARMACEUTICALS INGREDIENTS COMPANY.** ChemAgis a Subsidiary of PERRIGO, 18 European symposium on computer aided Process Engineering (ESCAPE 18)
2. M. Bentolila, R. S. Kenett, S. Malca, R. Novoa, E. Manoff, B. N. Yoskovich, **Scale up optimization using simulation experiments.** AIChE 2006. USA
3. PDF, **Model verification and design space exploration in DynoChem.** September 2008. www.scale-up.com
7. Joe Hannon & Peter Clark, **Application of mechanistic thinking in pharmaceutical process development and scale—up.** DynoChem. Presentation to FDA CDER/ONDQA 28 Feb 2008
9. VisiMix, **Examples and Case Study.** www.visimix.com
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- Michal Hasson, Yaniv Caspi. ChemAgis-Perrigo, ISRAEL
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IF YOU HAVE QUESTIONS OR ANY THING ELSE TO SAY, PLEASE………..

Thanks for your time and patience!