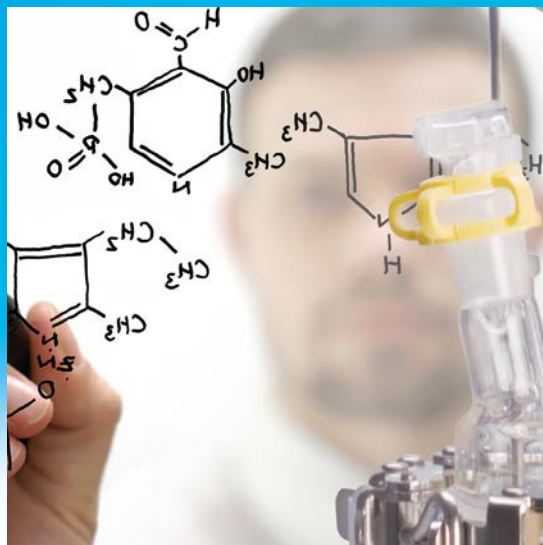


# Recent Advances to Improve Chemical Development



**METTLER TOLEDO**

# Agenda

## Challenges in Today's Pharma Industry

- Industry Drivers for Change
- Four Ways to Improve Organic Synthesis
- Enabling Technology
- Impact of New Tools on API Cost Reduction

# Challenges in Today's Pharma Industry

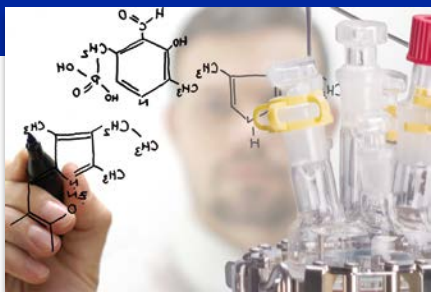
- Development costs continue to increase
- Synthetic targets increasing in complexity
- Increased regulatory demands
- High attrition rate
- Cost pressures
  - Higher manufacturing costs
  - Lower payer costs
- Major patent expiries
- Cost competitive R&D



As pressures on the industry increase, new methods of working are required.

# Addressing Today's Challenges

## Early Phase Development



- Develop compounds
- Establish route
- Provide material early phase clinical trial

## Design and Process Development



- Develop the process
  - Optimized
  - Safe
  - Robust

## Scale-up and Manufacturing



- Establish scalable parameters
- Reduce batch failures
- Reduce cycle time

METTLER TOLEDO works with industry to address these challenges, providing solutions that deliver:

Faster

Lower Cost

Higher Quality

Increased Knowledge

# Agenda

- Challenges in Today's Pharma Industry

## Industry Drivers for Change

- Four Ways to Improve Organic Synthesis
- Enabling Technology
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# Industry Drivers for Change

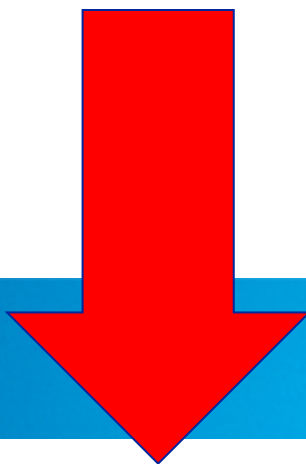
Pharmaceutical Companies are under pressure to develop synthetic routes faster, with increased yield and quality, and lower cost. In a new way of working, new tools are changing how the industry develops and optimizes synthetic routes.

QUALITY



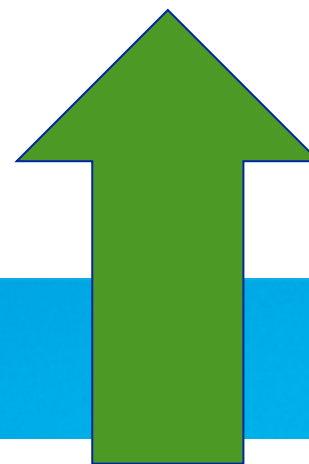
**Better Science**  
results in more robust  
processes

COST



**Reduced cost**  
leads to lower \$/kg

SPEED



Increased speed contributes to  
**cost competitive R&D**

New methods result in increased quality and improved cost performance

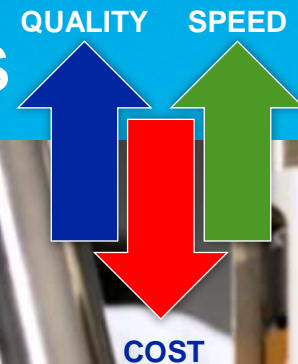
# Agenda

- Challenges in Today's Pharma Industry
- Industry Drivers for Change

## Four Ways to Improve Organic Synthesis

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# Four Ways to Improve Organic Synthesis

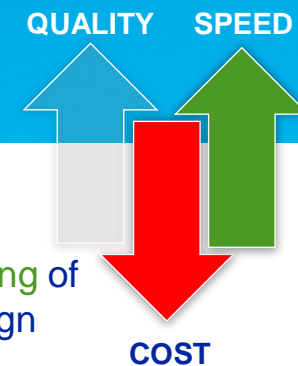


Improve organic synthesis with the new productivity tools for the future:

1. Reducing the Cost of Materials
2. Reducing Development Time
3. Ensuring Successful Process Scalability
4. Delivery of a Robust Process

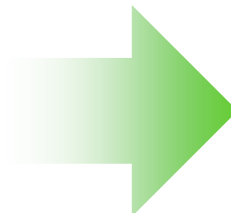


# Reducing the Cost of Materials



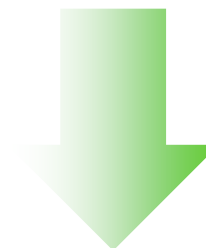
## Situation

- Chemistry inherited not suitable for >2kg campaigns
- 7 steps, 8 reworks, Active Pharmaceutical Ingredient (API) cost of goods >\$85,000/kg
- Long processing times



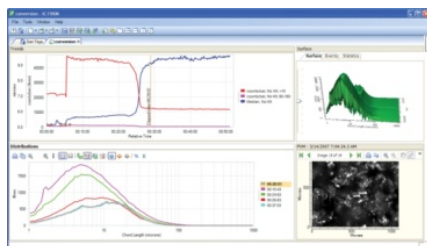
## Science

- Gain in-depth understanding of chemistry issues and design improved synthetic route
- Use Process Analytical Technology (FBRM) to design and optimize a crystallization in two experiments



## Outcome

- New route: 6 steps, 1 rework, 76% reduction in API cost of goods
- 25kg API synthesized per year
- Saving of \$1.6M per year



# Reducing Development Time



## Situation

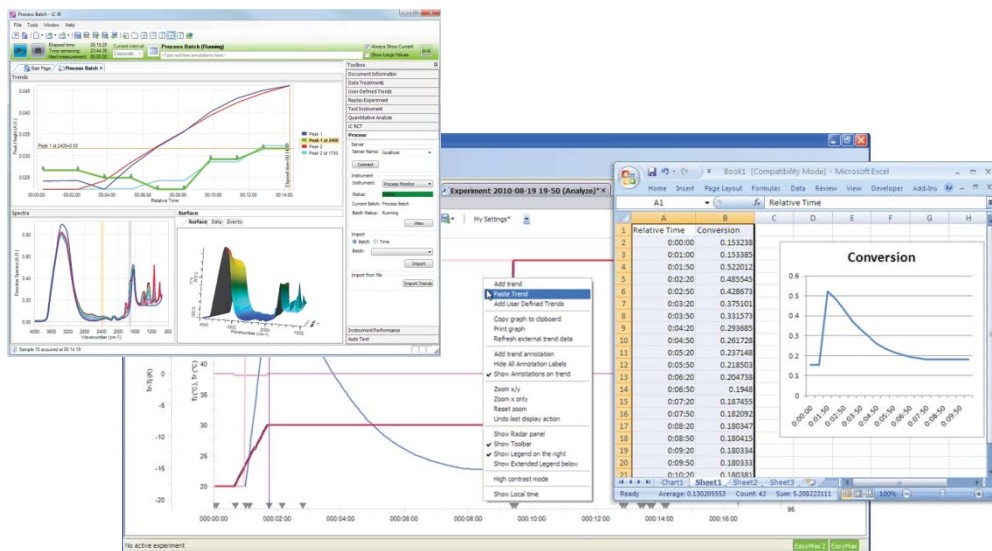
- Inherited Chemistry – Medicinal Chemistry Route
- Estimated development time of 6 months – 1 year
- Non-reproducible synthesis – variable yields of 25-45%
- Moisture and heat sensitive intermediates
- Safety hazard in quench ( $>250^{\circ}\text{C}$  adiabatic temperature rise)

## Science

- Use heat flow to understand reaction attributes – dosing control, heat evolution, safety issues, initiation
- Use *in situ* IR to follow intermediate formation and consumption

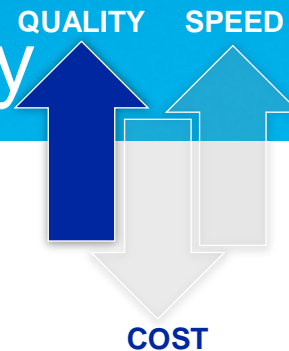
## Outcome

- Development time reduced by 66%
- Reproducible yields  $>50\%$
- Safe process with reduced cycle time delivered



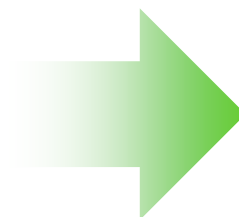
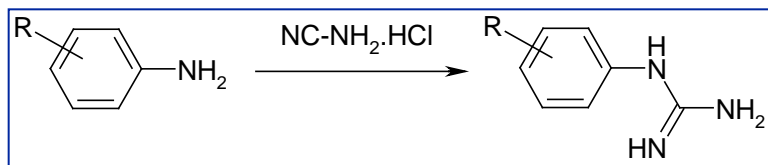
Source: Geraldine Taber PhD. "Demise of the Round Bottomed Flask – Battle Tools for the R&D Laboratory of the Future", Presented at ISPE, New England Chapter BioPharma 2010

# Ensuring Successful Process Scalability



## Situation:

### Synthesis of a Guanidine





## Science

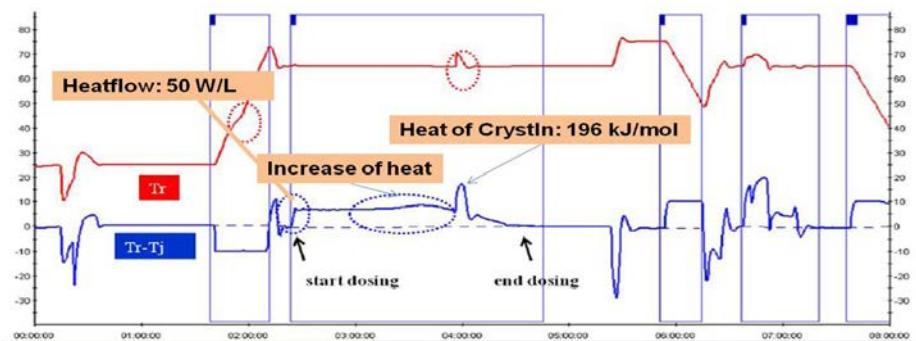
- Use heat flow to understand reaction attributes – dosing control, heat evolution, safety issues, initiation, etc



## Outcome

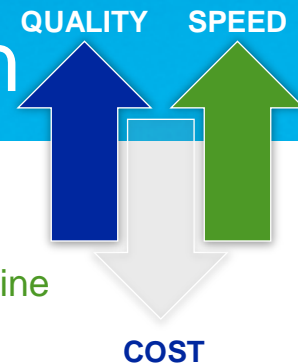
- **Process Scalability** - Process was redesigned with the dosing of HCl at higher temperatures to avoid crystallization during the reaction.
- **Process Scalability** - Decreased Cyanamid to avoid decomposition, use dosing controlled reaction based on HCl dosage.
- **Calorimetric calculations** - Longer HCl dosing time to avoid large heat release in production. Seeding of crystals at different temperature to eliminate major heat release (100W/Liter)
- **Production of >300 batches or >200 tons of API and Intermediates with no Out Of Spec product with no post approval support activities!**

- HCl, increased amount results in :
  - Higher yield
  - Higher stability of mixture
-  - Cyanamid instability: potential runaway
- NC-NH<sub>2</sub> (solid or sol.), increased amount results in:
  - Faster reaction
  -  - Unstable conditions (cyanamide decomp at higher temp. and pH)
  - Higher decomp. potential upon storage



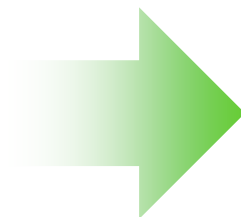
Source: Luc Moens PhD. Janssen Pharmaceutica Belgium, a J&J Company: 'The Use of New Technologies to detect scalability issues early on in development'

# Speed High Quality Process Optimization



## Situation

- Synthetic route commercially viable but not optimized
- Need to quickly establish kinetics to support reaction optimization for scale up



## Science

- Use *in situ* IR to quickly determine reaction rate under various conditions
- *In situ* IR to determine catalyst performance during the course of the reaction
- Use Reaction Progress Kinetic Analysis\* and iC Kinetics™ to develop kinetic model and simulate multiple experiments



## Outcome

- Full kinetic model generated in 9 experiments
- Reaction simulated and optimal conditions selected
- Conditions verified with confirmation experiments



\*Reaction Progress Kinetic Analysis: A Powerful Methodology for Mechanistic Studies of Complex Catalytic Reactions, Donna G. Blackmond, *Angew. Chem. Int. Ed.* **2005**, *44*, 4302 - 4320

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## Enabling Technology

- Impact of New Tools on API Cost Reduction



# Enabling Technology



## Replacing the round bottom flask

**EasyMax™** and **OptiMax™** eliminate the need to use heating mantles, oil and ice baths and cryostats. With no training requirement, these synthesis workstations are fast and easy to set up, making users immediately productive.

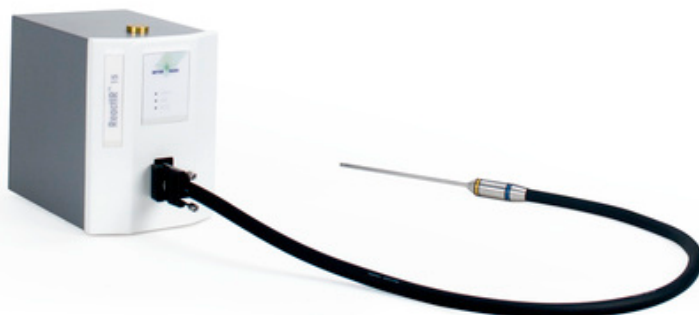
The systems capture experimental data to deliver an enhanced understanding of the reaction under investigation, leading to faster reaction optimization.



# Enabling Technology

ReactIR™ is used by chemists and engineers to gain important insights into reaction initiation, endpoint, mechanism, pathway and kinetics.

Results are delivered in real time, streamlining analysis and eliminating the need for offline sampling.



# Enabling Technology



Scientists and Engineers use **FBRM®** to measure particles as they naturally exist in process, improving the ability to understand, optimize and control particle and droplet systems.



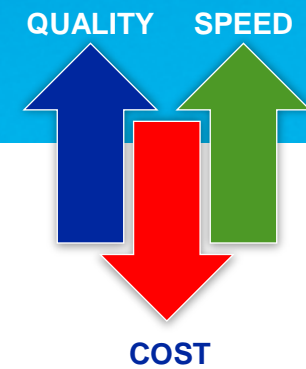


# Agenda

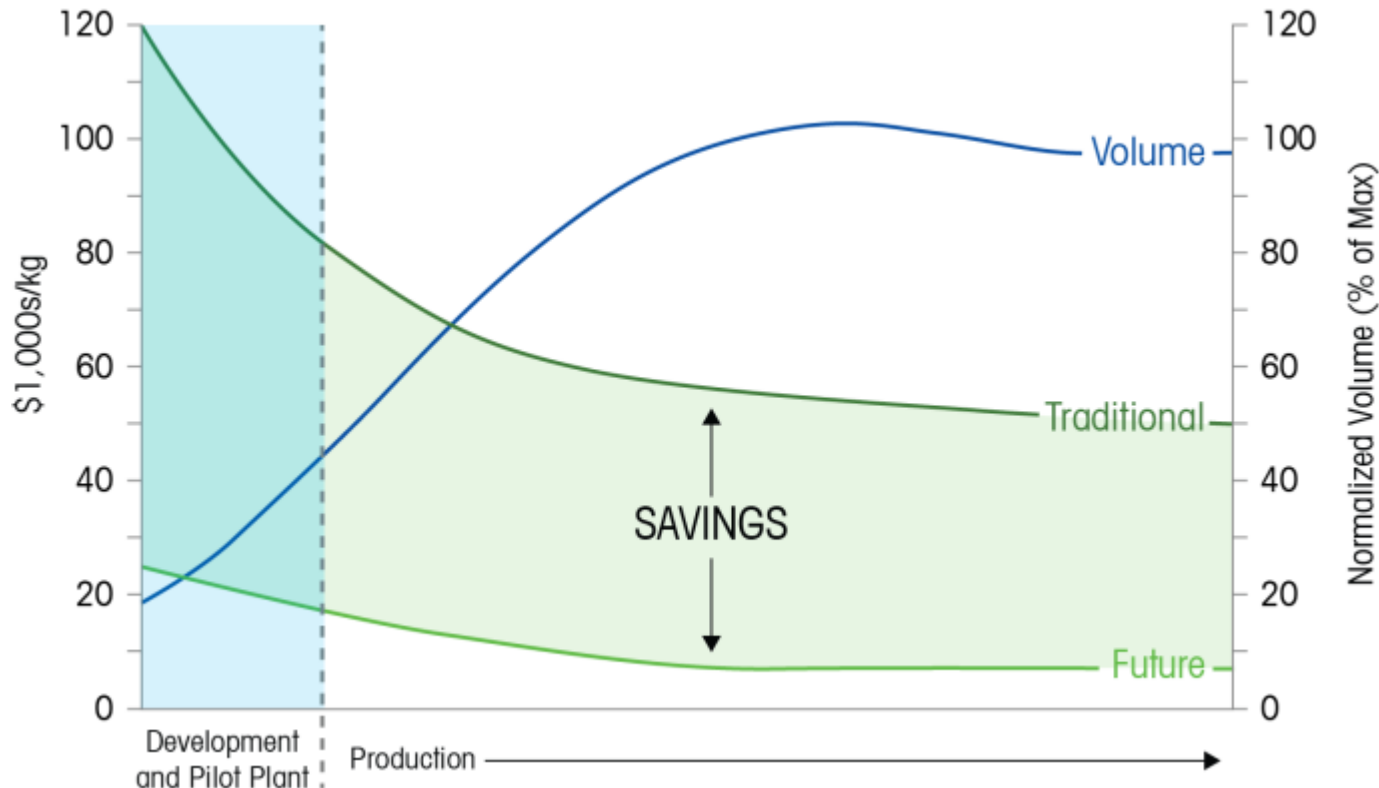
- Challenges in Today's Pharma Industry
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Impact of New Tools on API Cost Reduction

# Impact of New Tools on API Cost Reduction



Comparison of cost per kg over lifetime of API using traditional and future approaches



# More Resources and Links

For more information, such as **white papers**, **brochures** and for a more detailed description on each **case study**, visit:

[www.mt.com/autochem](http://www.mt.com/autochem)

**Live and on-demand webinars** provide application and industry information relevant to you:

[www.mt.com/ac-webinars](http://www.mt.com/ac-webinars)

Talk to our industry experts:

[autochem@mt.com](mailto:autochem@mt.com)



**Mettler-Toledo AutoChem, Inc.**

7075 Samuel Morse Drive  
Columbia, MD 21046 USA  
410.910.8500

**Mettler-Toledo AutoChem**

Sonnenbergstrasse 74, SA781, CH – 8603,  
Schwerzenbach, Switzerland  
41 44 806 77 11