PROCESS SAFETY AND THE PHARMACEUTICAL INDUSTRY

SAFE BATCH SCALE-UP OF AN EXOTHERMIC GRIGNARD

AYMAN ALLIAN
PIVOTAL COMMERCIAL SYNTHETIC

AMGEN®
Pioneering science delivers vital medicines™

OUTLINES

- Role of engineers and process chemist
- Amgen synthetic portfolio: Opportunities and challenges in the pharma industry
- Safety culture at Amgen
- Safe Scale-up of an Exothermic Grignard
  - Continous manufacturing
  - Leveraging pre-competitive space
  - Process safety for CM design

CHEMICAL ENGINEERING IN PHARMA: ADVANCING COMPLEX MOLECULES FROM DISCOVERY TO COMMERCIALIZATION

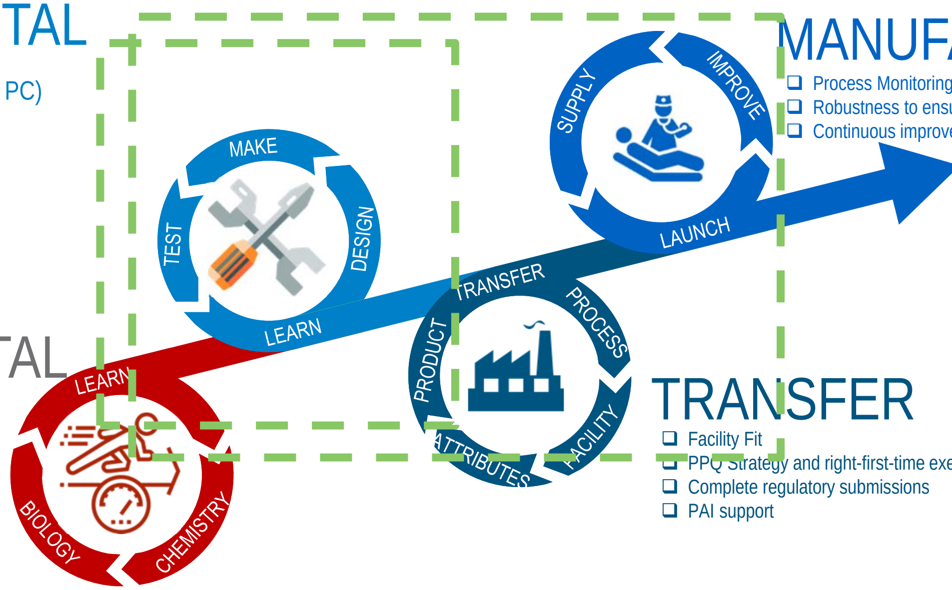
CHEMICAL ENGINEERING IN PHARMA: ADVANCING COMPLEX MOLECULES FROM DISCOVERY TO COMMERCIALIZATION

PIVOTAL

- ❑ Process Design (CPD & PC)

PRE-PIVOTAL

- ❑ Receive programs from R&D
- ❑ Fit-for-purpose processes for FIH deliverables
- ❑ Platforms for catalysis and salt selection



TRANSFER

- ❑ Facility Fit
- ❑ PPQ Strategy and right-first-time execution
- ❑ Complete regulatory submissions
- ❑ PAI support

MANUFACTURE

- ❑ Process Monitoring
- ❑ Robustness to ensure supply
- ❑ Continuous improvement

AMGEN

ENGINEERING ROLE

4 mL reactors

100 L reactors

1K to 10K L reactors

- **Chemical Engineering in Pharma: Advancing complex molecules from discovery to commercialization**
  - **Safety: Process safety testing is our first line of defense against thermal hazard events such as explosions and runaway reactions**
  - **Understand design space: Generate quality product**
  - **Consistent performance: Mass Transfer, Modeling, Continuous Manufacturing**

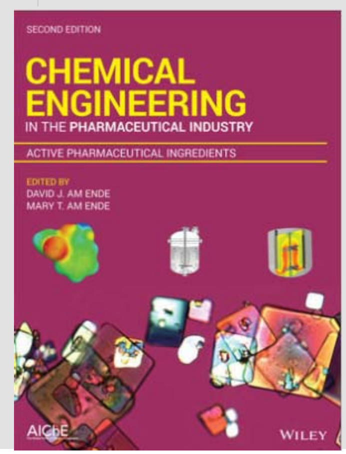
ENGINEERING ROLE

4 mL reactors

100 L reactors

1K to 10K L reactors

David J. am Ende



- Engineering: Advancing complex molecules from discovery to commercialization
  - Safety: Process safety testing is pharma's first line of defense against thermal hazard events such as explosions and runaway reactions
  - Understand design space (PC driven by FMEA, criticality assessment)
  - Consistent performance (Mass Transfer, Modeling, Continuous Manufacturing) -**Scale-Up of Mass Transfer-Limited Reactions: Fundamentals and a Case Study**

OUTLINES

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- **Safety culture at Amgen**
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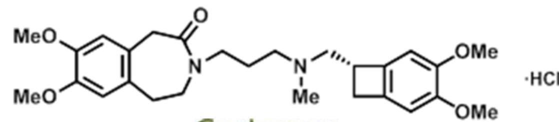
  - **Process safety for CM design**

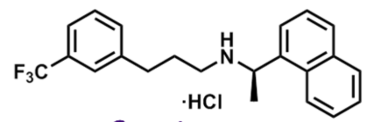
Amgen Synthetic Pipeline

PHASE ONE			PHASE TWO			PHASE THREE		
AMG 119	AMG 160	AMG 176	AMG 714 / PRV-015	BLINCYTO® (blinatumomab)	Tezepelumab	AMG 520 / CNP520	ENBREL® (etanercept)	**EVENITY™ (romosozumab)
AMG 212	AMG 330	AMG 397				IMLYGIC® (talimogene laherparepvec)	KYPROLIS® (carfilzomib)	Omecamtiv mecarbil
AMG 420	AMG 424	AMG 427				Tezepelumab		
AMG 510	AMG 562	AMG 570						
AMG 592	AMG 596	AMG 598						
AMG 673	AMG 701	AMG 757						
AMG 890	AMG 966	AMG 986						
IMLYGIC® (talimogene laherparepvec)								

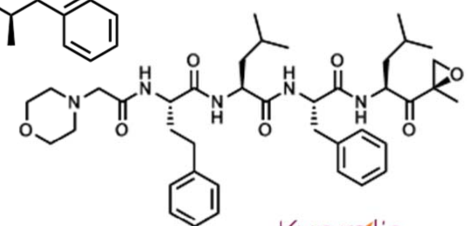
Approved Products



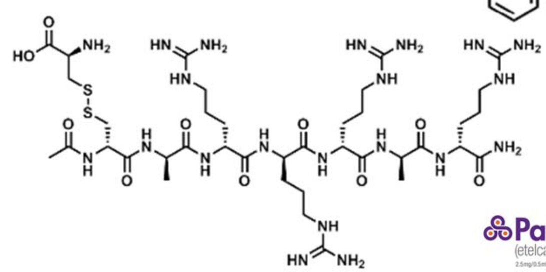
Corlanor (ivabradine) 5 mg 7.5 mg tablets



Sensipar® (cinacalcet HCl) Tablets 30mg · 60mg · 90mg



Kyprolis (carfilzomib) for injection



Parsabiv (etelcalcetide)

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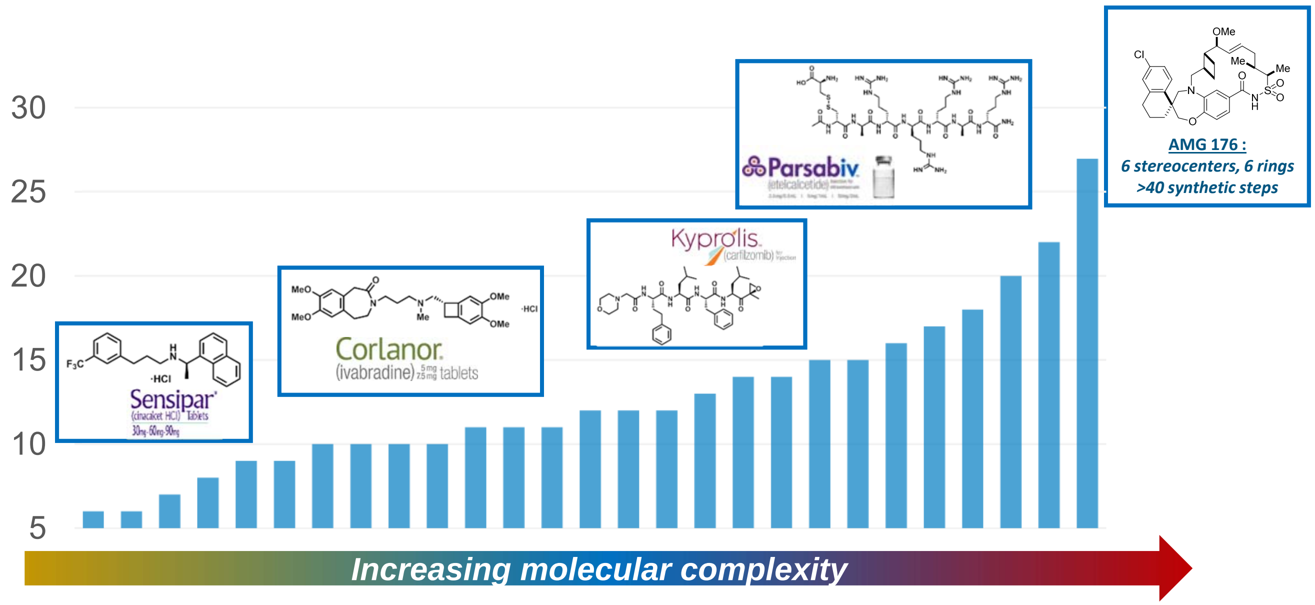
Increasing molecular complexity and shortened development timelines drive the case for innovation



Complexity Index factors:

- **molecular weight**
- **# of synthetic steps**
- **# stereogenic centers**
- **# rings**

The future of the small molecule? Increased complexity and biologic pairings, says industry

01-May-2018 By Flora Southey

The many roles of molecular complexity in drug discovery

Oscar Méndez-Lucio and José L. Medina-Franco

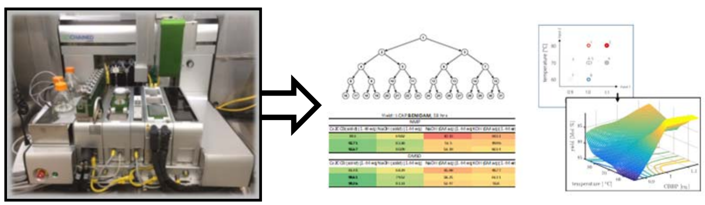
AMGEN

Asset complexity coupled with shrinking timelines.

Representative Platforms to Accelerate Synthetic Process Development

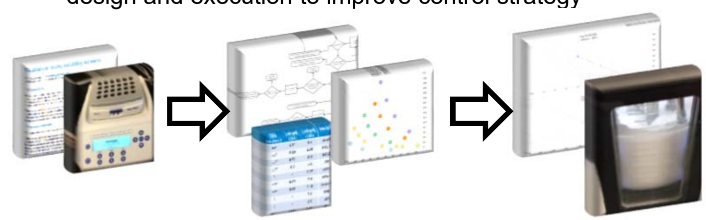
Automated Reaction Development:

- High-throughput and multi-variable reaction screening
- Rich data sets enable development of predictive models



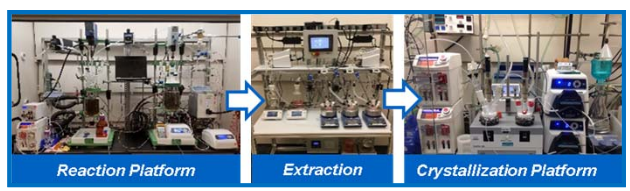
Crystallization - Solubility Modeling:

- Solubility measurements and prediction streamline process design and execution to improve control strategy



Continuous Manufacturing (CM):

- Reduced manufacturing footprint enables integration of analytics & improved processing safety & control



AMGEN

Outlines

- Role of engineers and process chemist
- Amgen synthetic portfolio: Opportunities and challenges in the pharma industry
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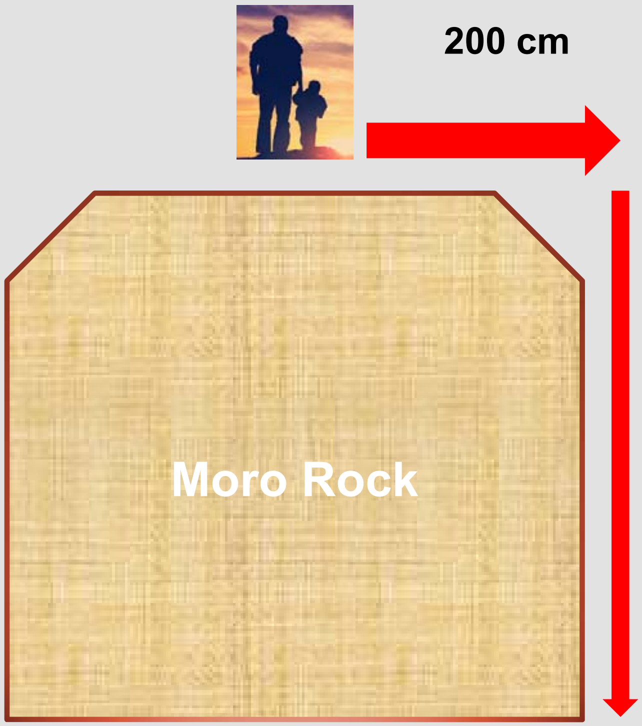
HOW ABOUT PROCESS SAFETY?

Moro Rock

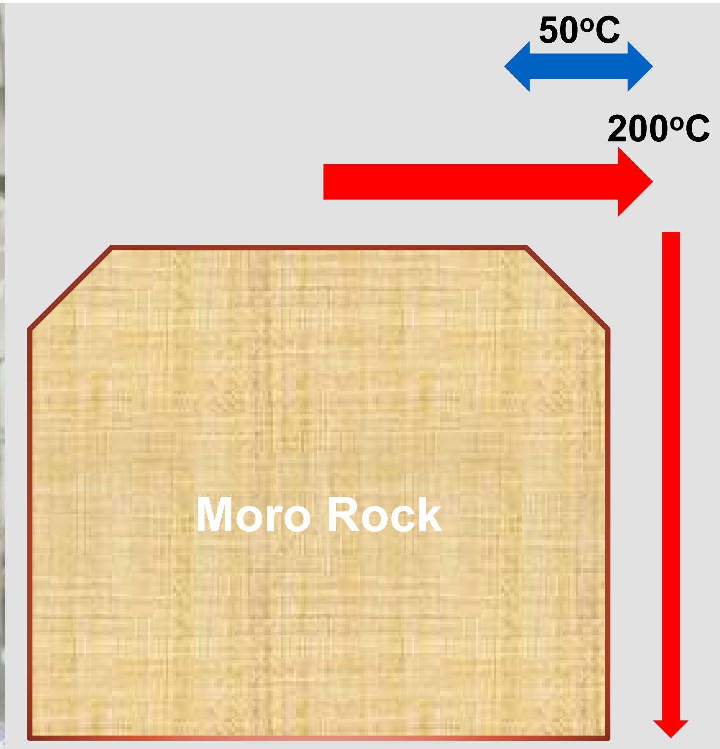
Sequoia National park

SAFETY IS ABOUT PROTECTING YOUR LOVED ONES

- Science tells you
  - You are 2 m from the edge
  - It is 75 m fall
- Your 9 year old son tells you, can he take just one step to get a better view.
- How close is too close?



OUR SCIENTIST HANDLE CHEMICALS DAILY BASIS
ARE THEY SAFE TO HANDLE?



A chemical reagent violently decomposes at 200°C

- What is the appropriate safety window?

BEIRUT EXPLOSION

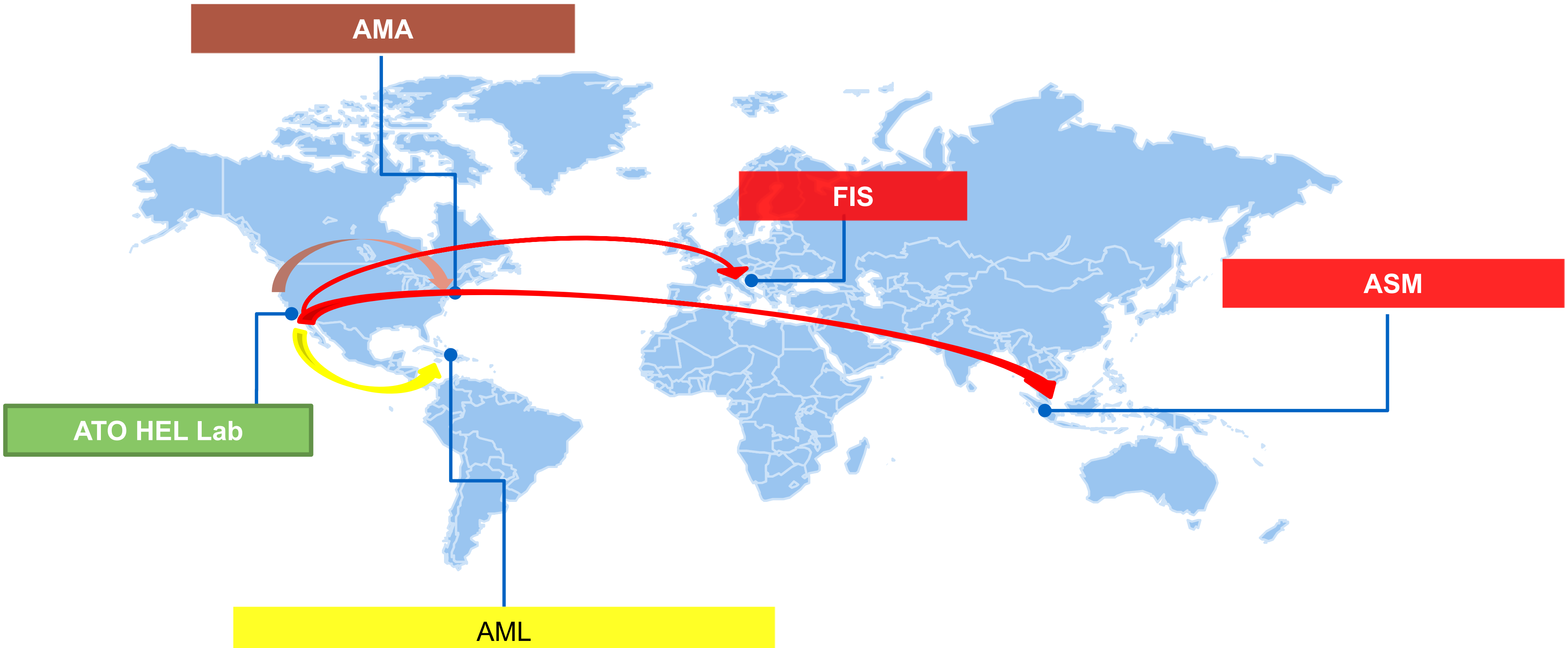
- 2700 tonnes Ammonium nitrate
- Onset temperature is ~200°C
- Magnitude: Heat of decomposition is 700 J/g
- Heat was used to self-heat, temperature will rise to 350 ˚C!!
- Portion of that energy will be converted to destructive pressure wave.

HIGH-ENERGY MATERIALS IN USE AT AMGEN

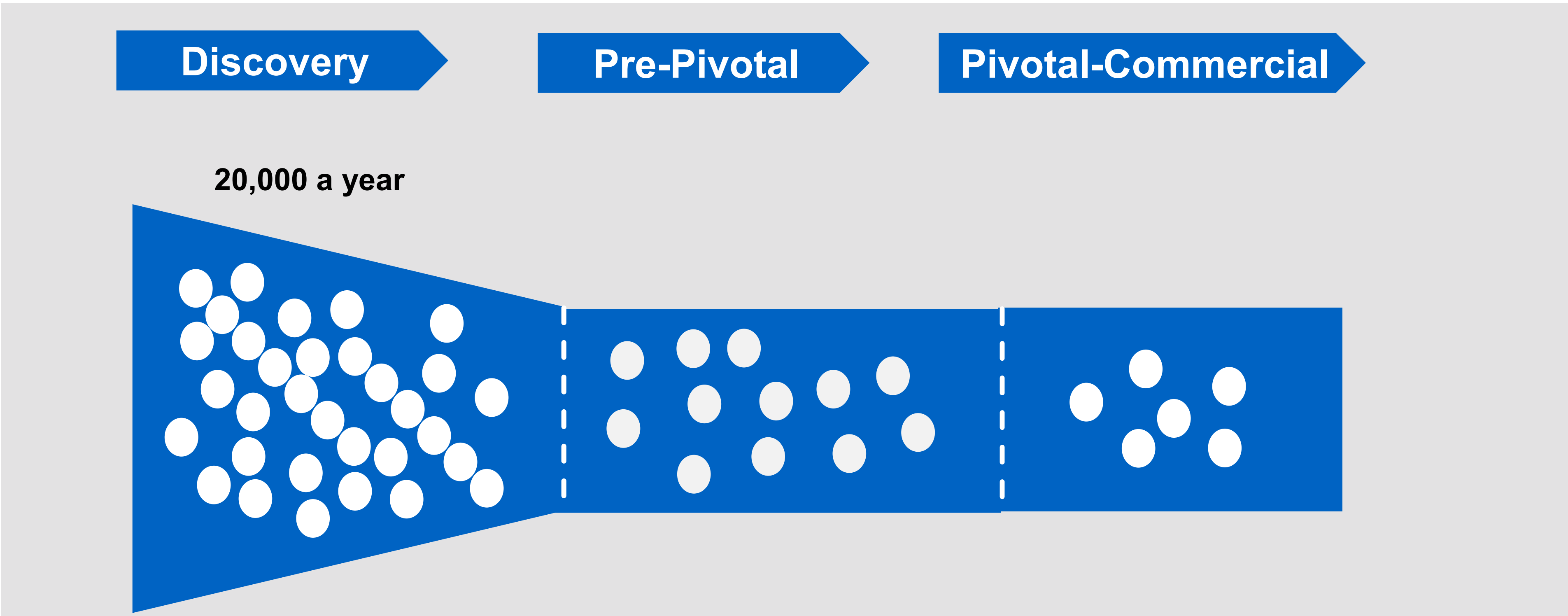
Reagent	Onset Temperature	Energy Released
TNT	309 °C	2,510 J/g
Propargyl Alcohol	103 °C	3,675 J/g
HBTU	162 °C	1,004 J/g
TBTU	178 °C	1,208 J/g
HOBt.xH_2O	158 °C	1,984 J/g
Amgen T790M intermediate	158 °C	2,370 J/g
Amgen BACE intermediate	123 °C	2,718 J/g

1. Reagents and intermediates that are worse than Ammonium nitrate
2. Close in energy to TNT
3. Have lower onset temperature than TNT

HAZARD EVALUATION LAB LOCATED AT ATO SUPPORT AMGEN SYNTHETIC PORTFOLIO

RISK BASED APPROACH

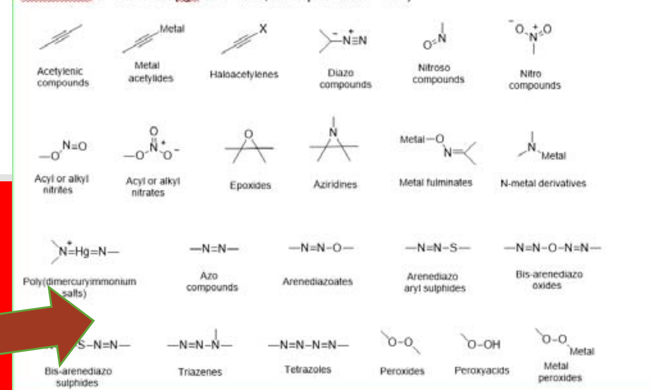


RISK BASED SAFETY TESTING APPROACH

Scale

Full Safety Evaluation

Examples of Chemical Structures Associated with Explosibility (High-Energy Decomposition - See Brethericks 6th Ed. Vol 2 pgs 128 – 131; no depiction in 7th Ed.)[8.3]



Quick Screening Test
-Onset Temperature
-Amount of Energy Released

No Testing
Administrative Control
Follow Best Practices
Chemistry Lab Procedure

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DOCUMENT APPROVAL INFORMATION

Document Number: SOP-027763
Document Version: 1.0

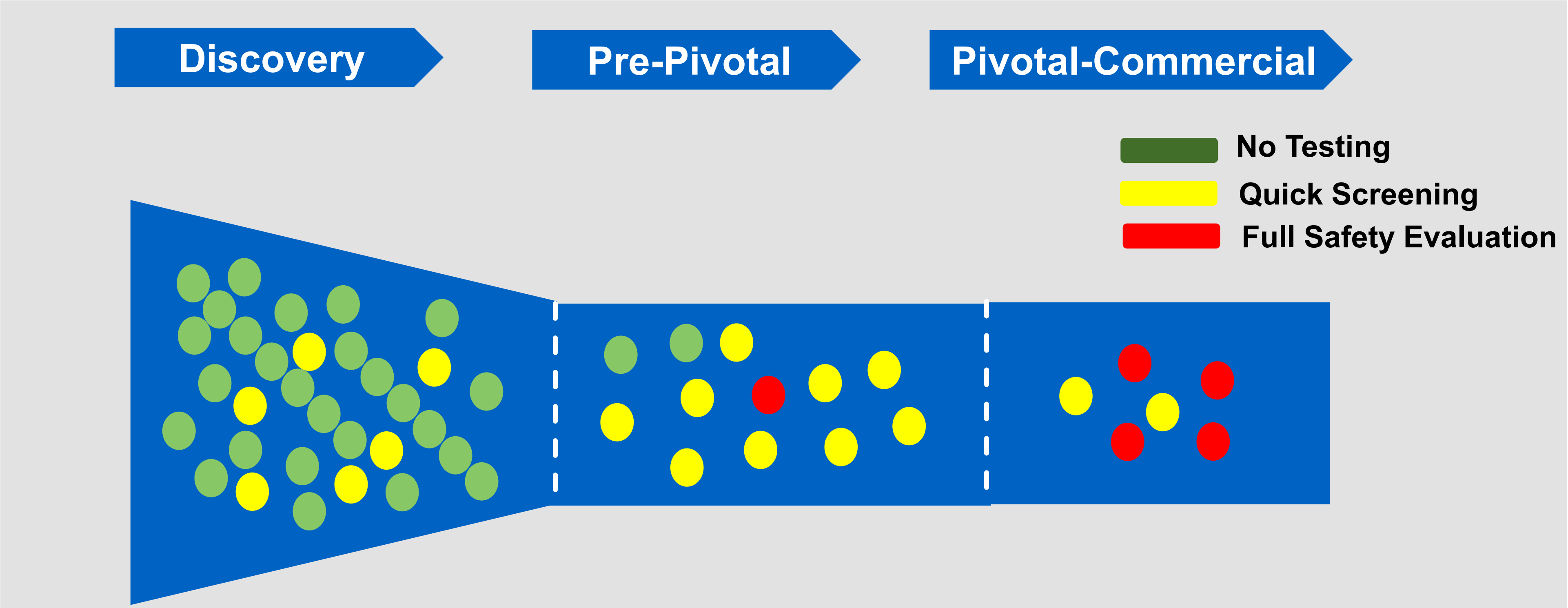
Document Title: AMGEN CHEMISTRY LABORATORY PRACTICES

Server Date	Signed by / Reason for Signature
12-Jul-2018 19:20:40 GMT	Ayman Allian Owner

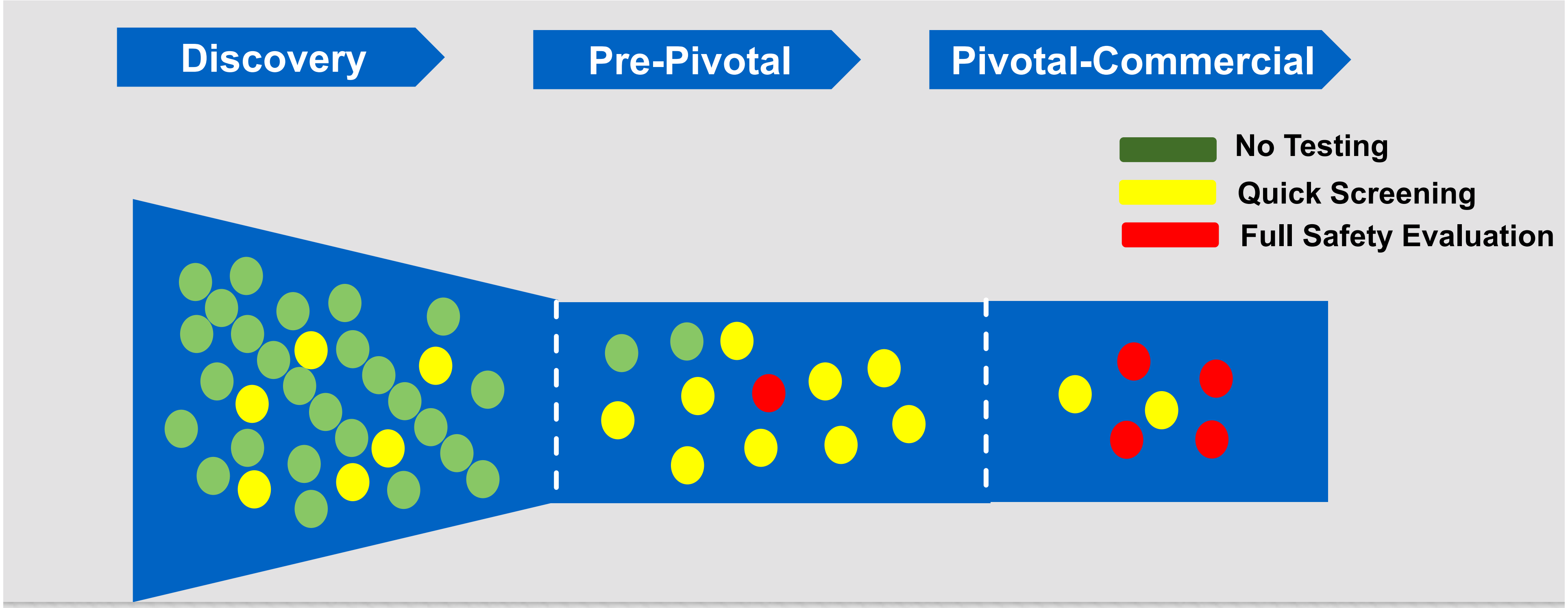
Energetic Materials

Normal Reaction — **High Energy Functional Group**

AFTER RISK ASSESSMENT



AFTER RISK ASSESSMENT- REVISIT OUR WORK FLOW



EXTERNAL ENGAGEMENT

This is just one approach.

How about other pharma companies?

How do they handle this challenge?

CREATED AND LEAD A GLOBAL THERMAL HAZARD

VERTEX
Celgene
Boehringer Ingelheim
Takeda
Shire
Genentech
abbvie
GILEAD
AMGEN
Lilly
gsk
Johnson & Johnson
TEVA
TEVA PHARMACEUTICALS LTD
Pfizer
Bristol-Myers Squibb
MERCK

AMGEN RESOURCES NEEDED TO ESTABLISH THIS TASK

- **Amgen resources, we meet monthly meeting on-line**
  - **Spend 1-4 FTE hour a month for the meeting**
  - **Target a face-to-face meeting once a year. This year was done at Amgen ATO.**

Recognition for being the most active and best attended group

A MANUSCRIPT WAS JUST PUBLISHED

Survey 1 – Manuscript in Preparation!

Process Safety in the Pharmaceutical Companies– Part I:

Thermal Hazards Evaluation Processes and Techniques

Ayman D. Allian,[†] Nisha P. Shah,[‡] Antonio Ferretti,[§] Derek Brown,[†] Stanley P Kolis,[┴] Jeffery Sperry[ǁ]*

- **Won the ACS award allowing free access for non ACS member**
- **One the most read/downloaded paper in OPRD**

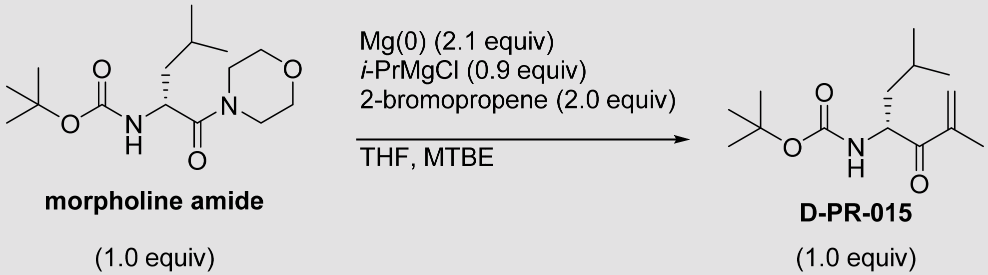
OUTLINES

- Role of engineers and process chemist
- Challenges in the pharma industry
- Safety culture at Amgen
- **Safe Scale-up of an Exothermic Grignard using thermal hazard testing and engineering control**
  - **Continous manufacturing**
  - **Leveraging pre-competitive space**
  - **Process safety for CM design**

CASE STUDY: GRIGNARD REACTION

- **Thermal hazard evaluation of every reaction before any scale up in the kilo lab**

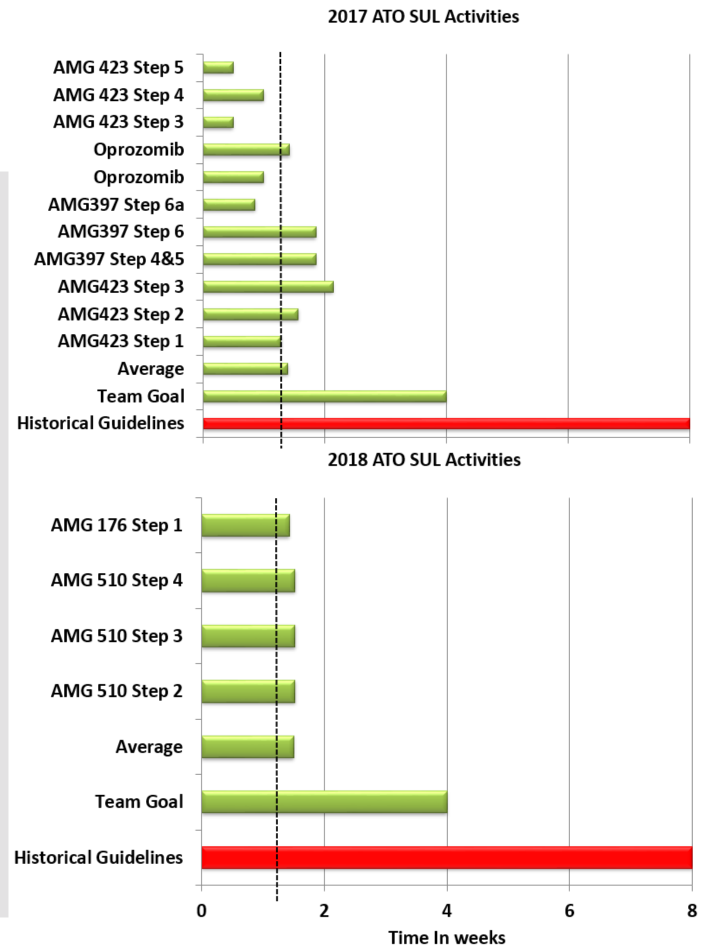
CHEMISTRY



- **Inherited from 3rd party through acquisition**
- **Grignard Reaction**
- **Intended for Scale up at 2 Kg scale**

SAFETY AND COMPLIANCE CULTURE

- **Successfully executed more than 45 campaigns in the last 5 years**
- **No safety incident**
- **Two detailed GMP corporate audits in 2016 and 2019 without any critical findings**
- **Still reducing turnaround by 50%**

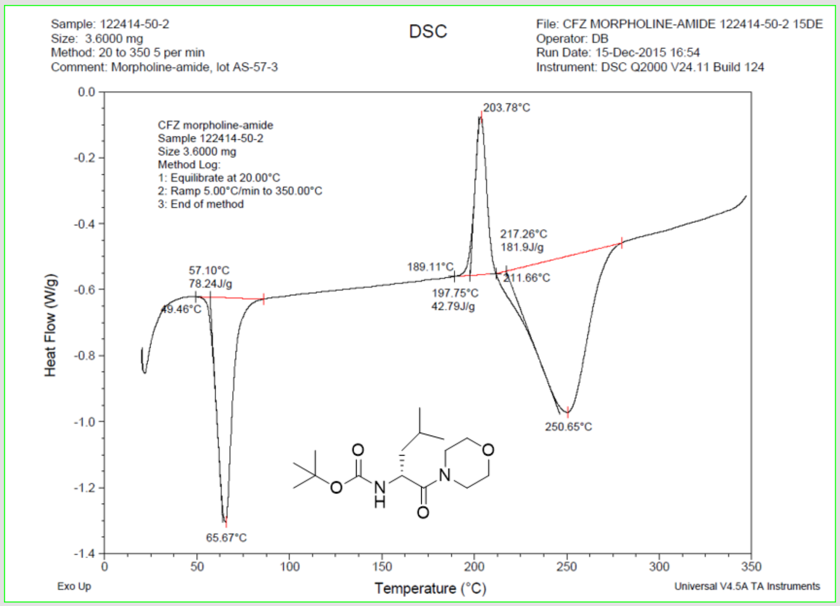


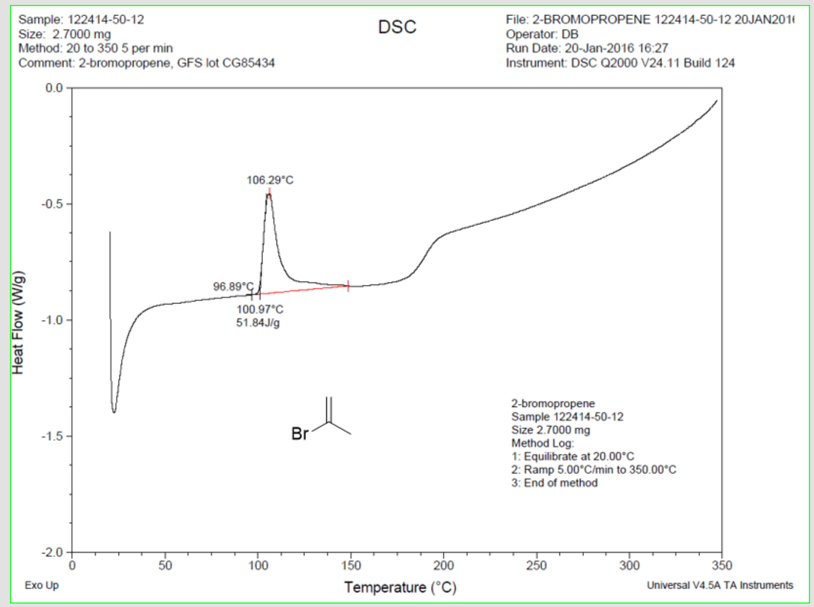
AMGEN

OUR APPROACH TO THERMAL HAZARD

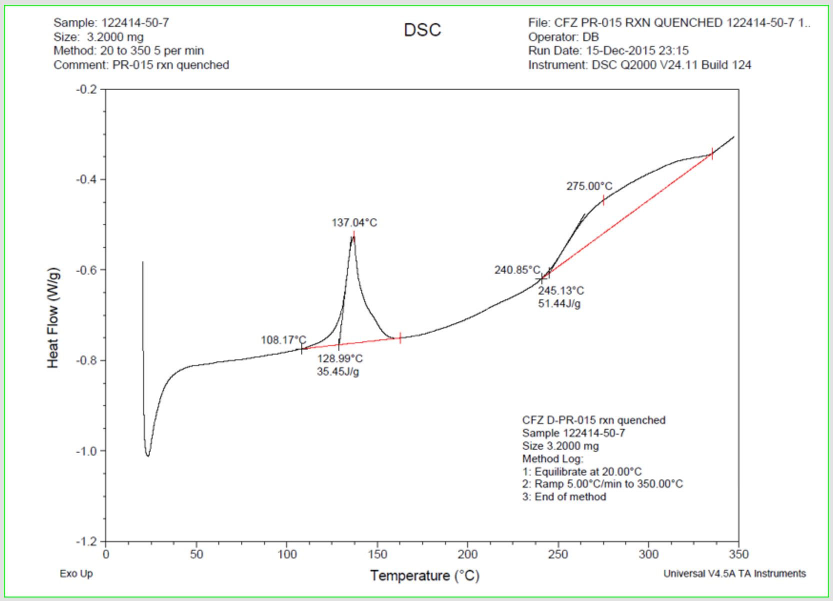
- **Screen all reagents and starting material**
- **Screen isolated product (s)**
- **Screen reaction mixture (quenched solution)**
- **Measure Heat of reaction**

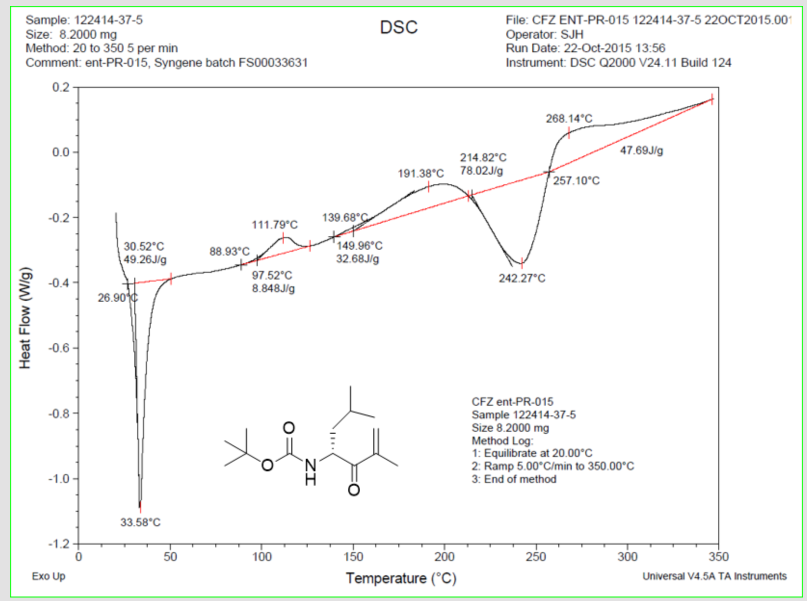
DSC OF ISOLATED STARTING MATERIAL



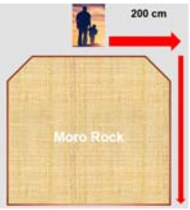


DSC OF ISOLATED PRODUCT AND QUENCHED REACTION MIXTURE

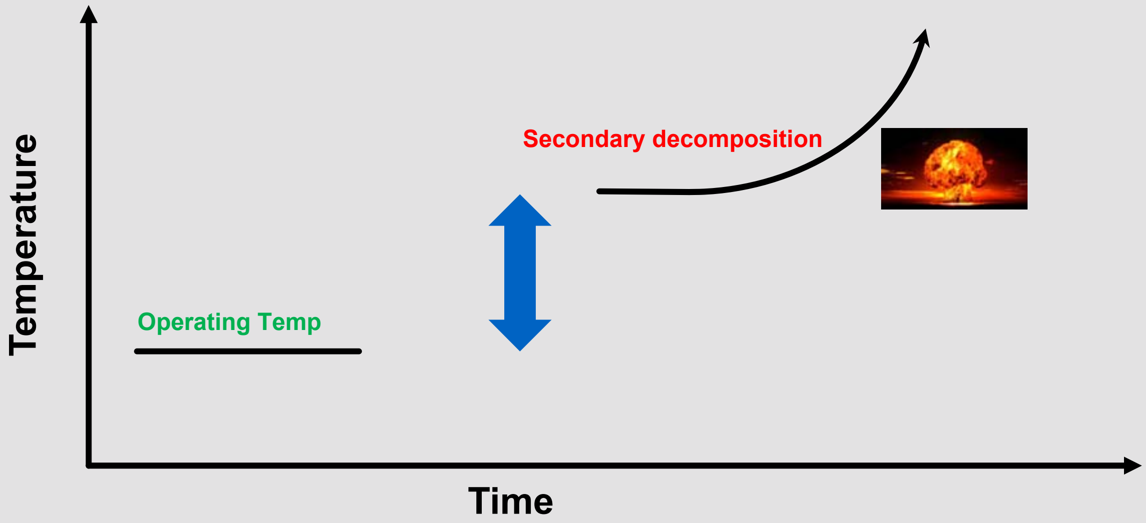




REACTION HAZARD CLASSIFICATION
EXOTHERMIC REACTION BRING ABOUT A VIOLENT DECOMPOSITION?

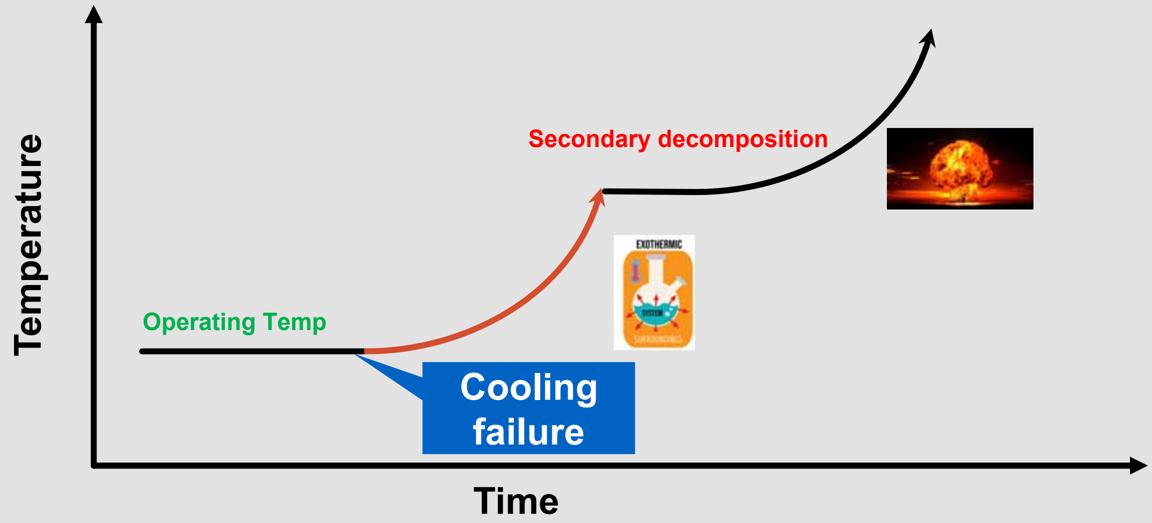


- **Operating with a good safety window**



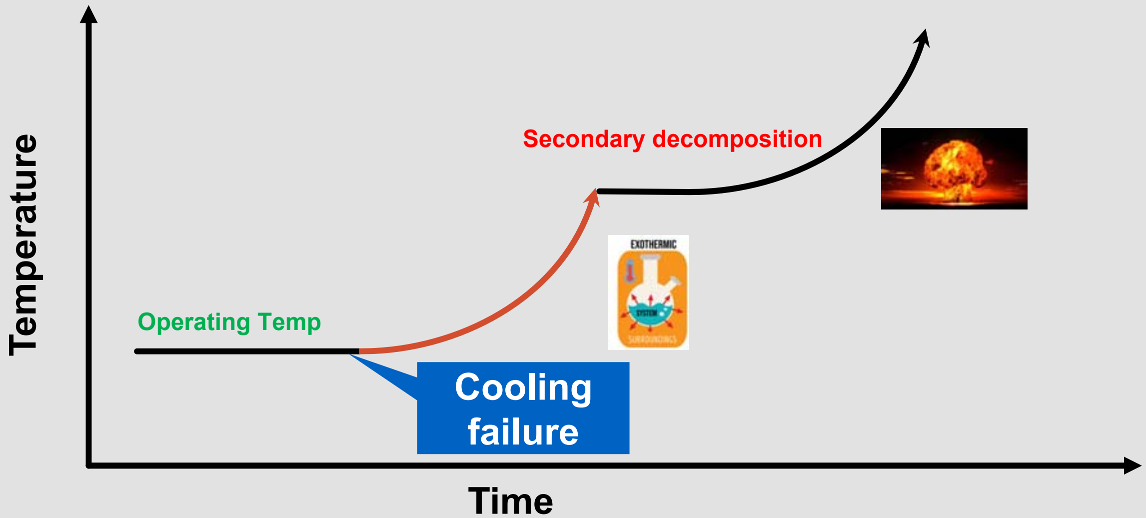
EXOTHERMIC REACTION BRING ABOUT A VIOLENT DECOMPOSITION

- Operating with a good safety window
- **Cooling failure for an exothermic reaction**



EXOTHERMIC REACTION BRING ABOUT A VIOLENT DECOMPOSITION

- Operating with a good safety window
- **Cooling failure for an exothermic reaction**
- **Ozonolysis 216^{0}C**



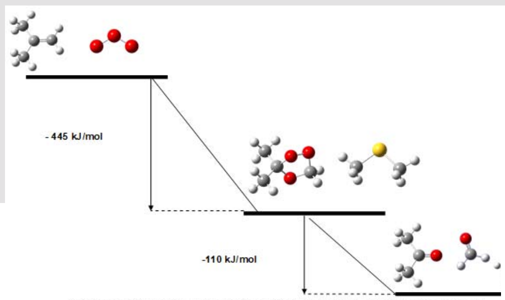
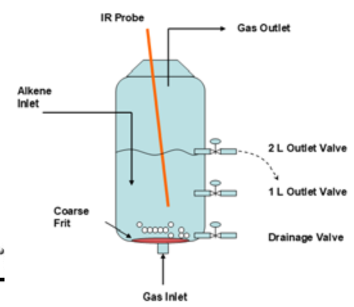
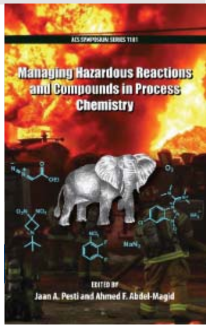
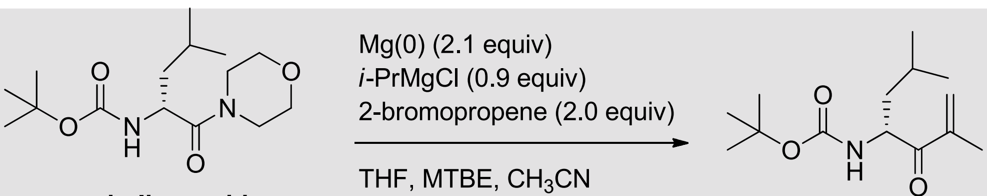


Figure 2. Calculation of Enthalpy of Reaction for Isobutylene Ozonolysis





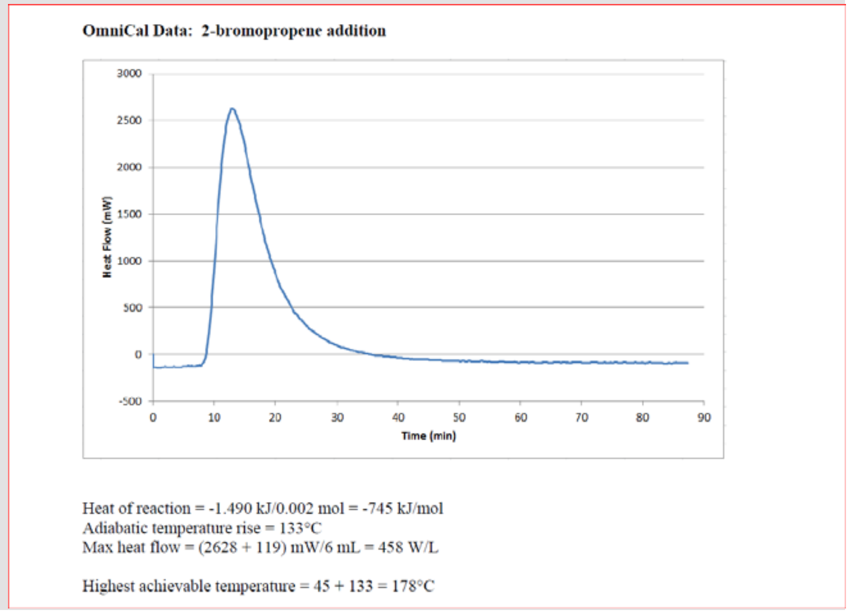
THERMAL HAZARD EVALUATION



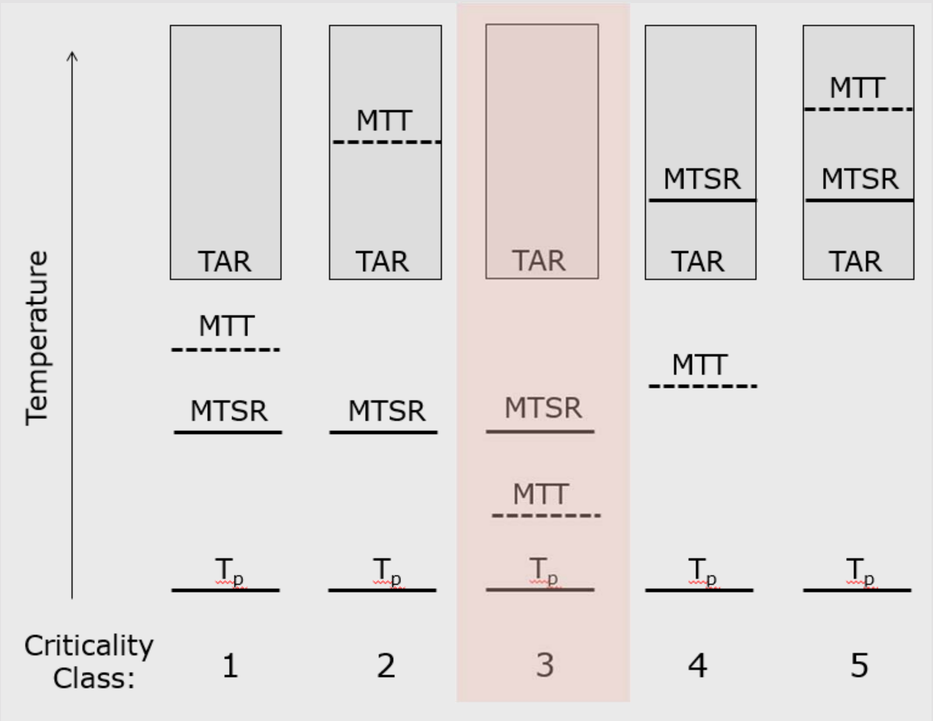
morpholine amide (1.0 equiv)

D-PR-015 (1.0 equiv)

- **Heat of reaction measured**
  - **i-PrMgCl addition**
  - **2-bromopropane addition**
  - **Citric acid quench**
- **Adiabatic temperature rise of 133°C for 2-bromopropane addition.**
- **MTBE boiling point (55 °C)**



STOESSEL CRITICALITY CLASS OF CHEMICAL REACTIONS



- Class 1 are safest
- Class 3 can very dangerous if significant amount of solvent is boiled
- Class 4 and 5 are potentially very hazardous.

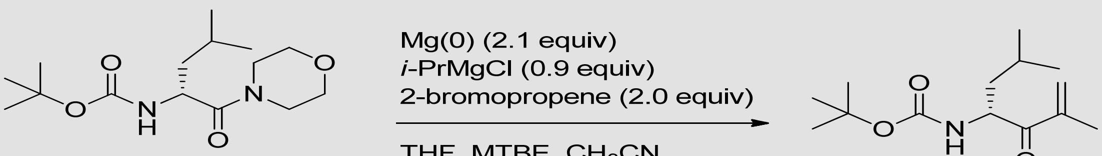
CONSEQUENCES OF THE HIGH EXOTHERMIC REACTION

- Mitigate the risk by physically breaking the charge into 7 charges of 0.2 to 0.3 equivalents each.
- Literature showed that despite slow addition of reagent, accidents happened because of lack of understanding of the reaction initiation time.
  - There is a need to confirm reaction progress during scale up to ensure safety.
- FTIR was used as FIO

DEPLOYMENT OF IN-SITU IR IN THE GMP FACILITY

Using FTIR to ensure no buildup of energetic intermediates

IN SITU FTIR SPECTRA EXAMPLE

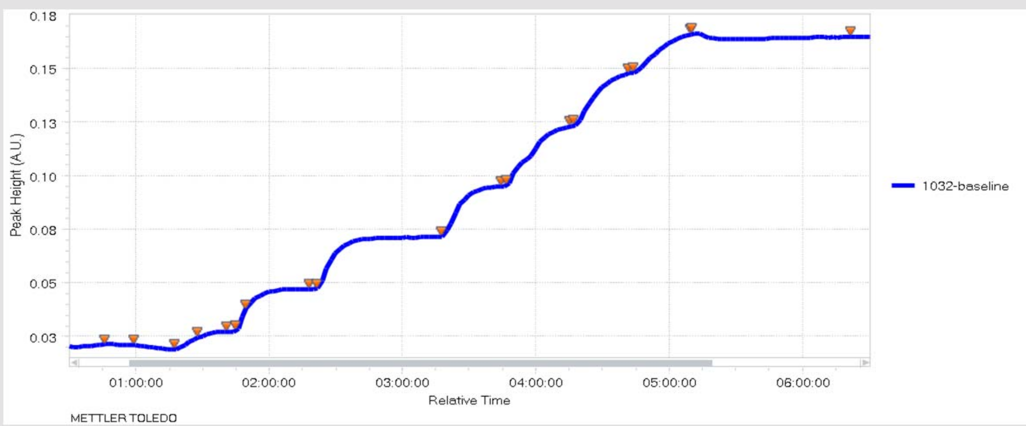


morpholine amide

(1.0 equiv)

D-PR-015

(1.0 equiv)



- **Campaign utilized in-situ IR spectroscopic data to study these intermediates.**
- **IR profile consistent with HPLC measurement**

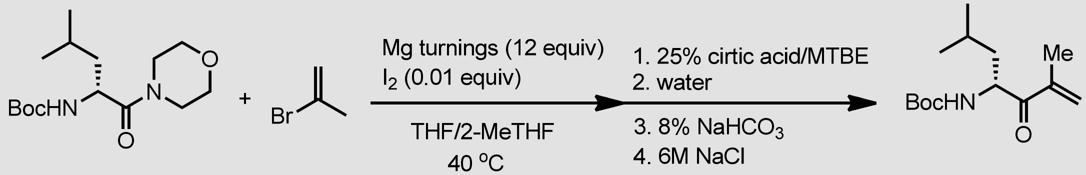
CONCLUSION PART1

- **Successful scale up of energetic reaction using thermal hazard evaluation and engineering control**

- **During the run every 0.2 equivalent caused about 5°C rise**
  - **Batch sheet ask for 40± 5°C, and add over no less than 10 min**
  - **Reality**
    - **Cool the batch to ~37°C, after each addition reactor warmed up to 43°C**
    - **Took 20 min for each addition**

- **From bench to scale up initiation, 3 weeks**
  - **Thermal hazard evaluation**
  - **Equipment readiness and batch sheet writing**
  - **Raw material ordering**

SECOND GENERATION CHEMISTRY



Morpholine amide (~22 wt% in 2-MeTHF)

D-PR-015

+ bromo magnesium citrate
+ morpholinium citrate
+ magnesium citrate
+ hydrogen
+ propene
+ sodium citrate
+ CO_2

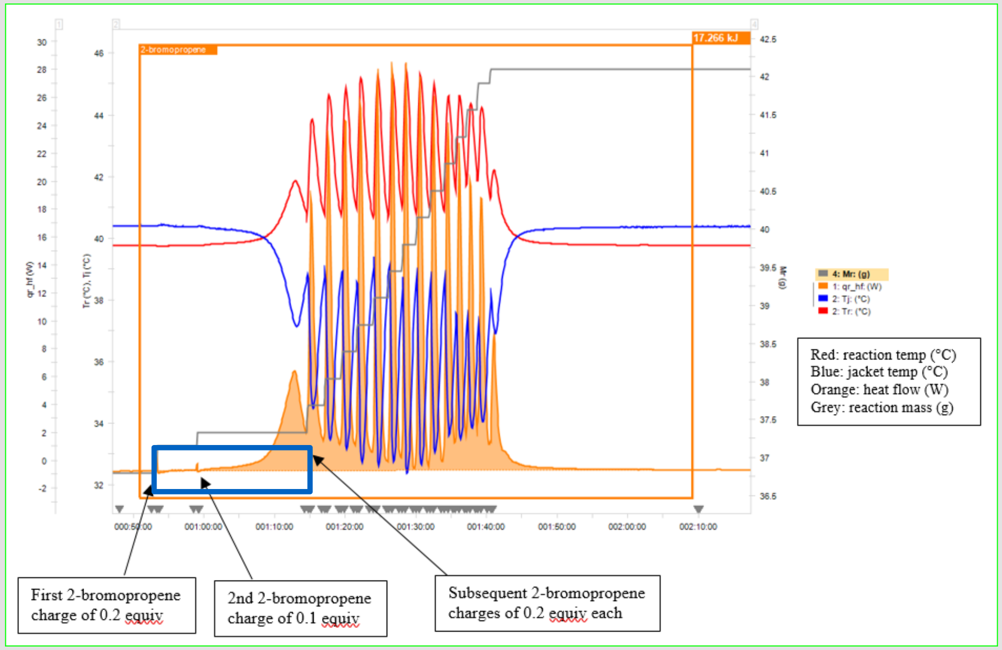
- **No longer using i-PrMgCl as a reagent**
- **Switch to THF/2-MeTHF solvent from MTBE**

OUR APPROACH TO THERMAL HAZARD

- **Changes warranted thermal hazard reevaluation**
- **Screen all reagents and starting material**
- **Screen isolated product (s)**
- **Screen reaction mixture (quenched solution)**
- **Measure Heat of reaction**

THERMAL HAZARD EVALUAITON

- **Adiabatic temperature rise of 203°C.**
- **Heat flow of 705 W/L**
- **RC1 equipped with huge thermal sink and have high surface-to-volume ratio**
  - **Still every 0.2 equivalent resulted in 5°C rise.**
- **Note initiation time**



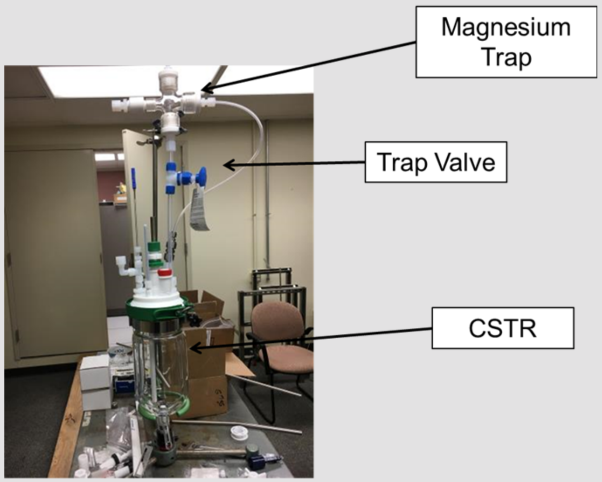
HEAT OF REACTION CONSEQUENCES AT SCALE

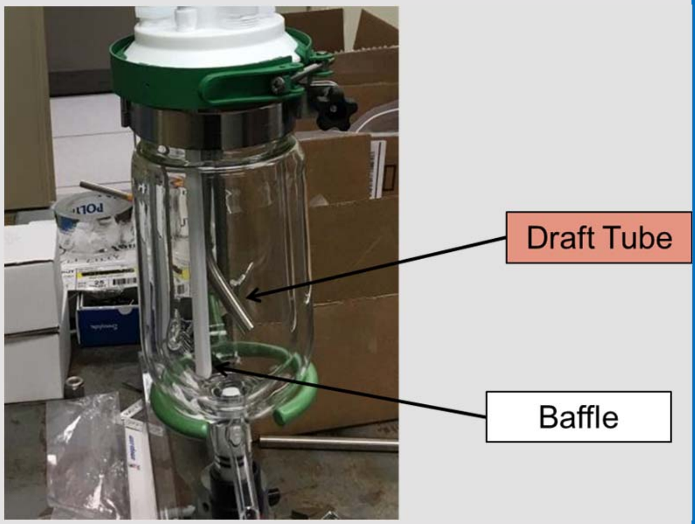
- Even breaking up charges will cause significant temperature rise
- Even if product demand increases, reaction must be done in small reactors to keep high surface to volume ratio
- Emergence of continuous processing.

The Evolving State of Continuous Processing in Pharmaceutical API Manufacturing: A Survey of Pharmaceutical Companies and Contract Manufacturing Organizations

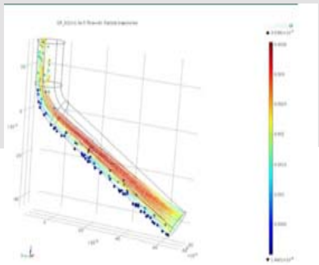
J. Christopher McWilliams*, Ayman D. Allian, Suzanne M. Opalka, Scott A. May, Michel Journet, and Timothy M. Braden

ADOPTING LILLY PLATFORM



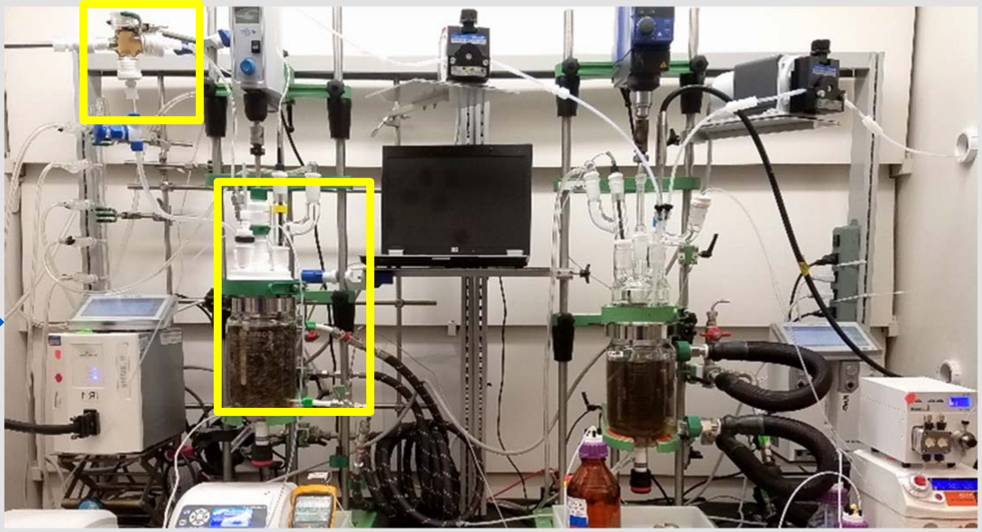


- **Periodic addition of magnesium turnings**
- **Magnesium particles should be trapped**

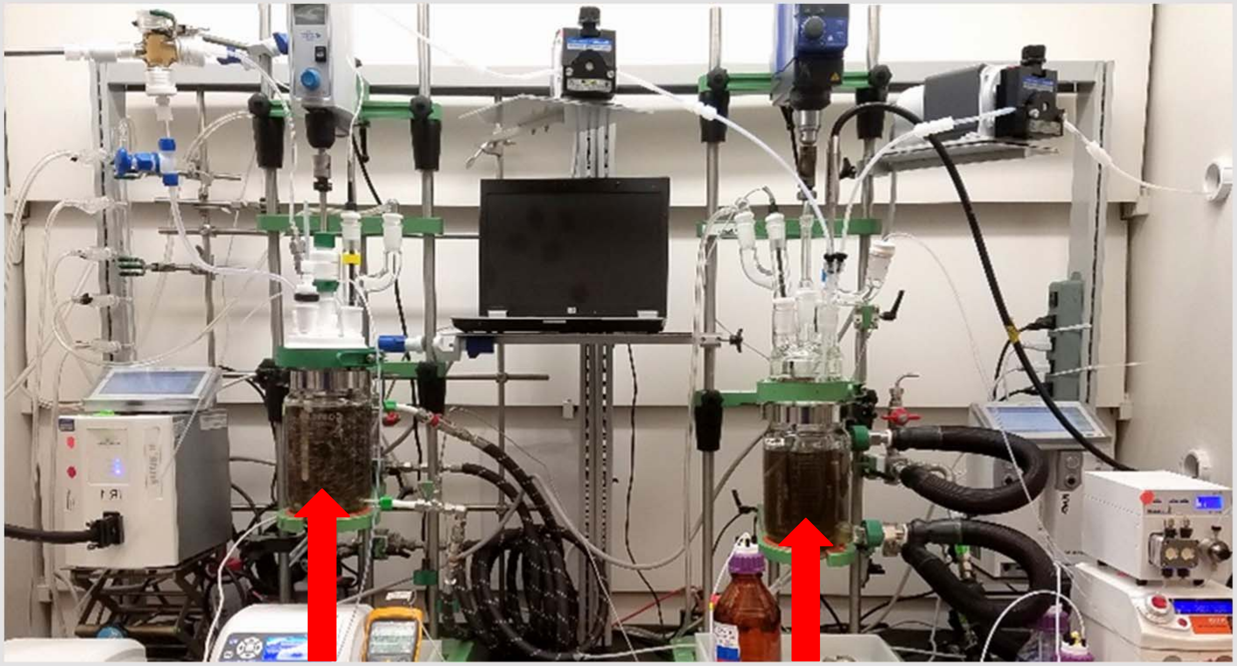


The continuous flow Barbier reaction: an improved environmental alternative to the Grignard reaction?
Michael E. Kopach *a, Dilwyn J. Roberts a, Martin D. Johnson a, Jennifer McClary Groh a, Jonathan J. Adler b, John P. Schafer b, Michael E. Kobierski a and William G. Trankle a

FROM PLANT TO HOOD



PLANT IN THE HOOD



CSTR1 CSTR2

- 1 L reactor
- No solids were observed in the trap
- High throughput
  - 143 g/h (3.6 kg/day)
- Other safety concerns
  - $T_{r1} - T_{j1}$ = 35-40 ˚C

flow direction

CONCLUSION PART2

- **Successful scale up of a very energetic reaction using continuous manufacturing**
- **Leveraging precompetitive collaboration and adopting Lilly's platform**
- **At 1-L scale, temperature across the jacket is about 40°C**
- **GMP proof of concept was successful**

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Thank you

Scale-up Systems

Celebration of Dr Wilfried Hoffmann, online, 17 December at 9AM Eastern

Marking Wilfried's official retirement at end 2020

- Following career of almost 40 years in process safety at Parke Davis, Warner Lambert, Pfizer and Scale-up Systems
- Purchased the first RC-1 in Germany (!); former chairman of the Mettler RXE Forum
- Has made extensive use of RC1 data, MTSR, TMR and the criticality classes outlined by Prof Stoessel when using predictive modeling alongside experimental data in process thermal safety
- Flash talks by Wilfried and collaborators including Flavien Susanne (Sanofi), Yossi Mendel (Teva) and Joe Hannon (Scale-up Systems), with open mic at the end
- Register at https://dcresources.scale-up.com/?id=6427