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Engaging you to reimagine chemistry and engineering for a sustainable future!

We believe sustainable and green chemistry innovation holds the key to solving most environmental and human health issues facing our world today.

• Advancing Science
• Advocating for Education
• Accelerating Industry

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16 YEARS of Advancing GC&E in Pharma and Beyond

12 Collaboratively developed, high-quality tools & metrics
$2.4 Million given in research grant funding
Funding of 28+ research programs around the globe
Leveraged $1.3 Million from Federal Agencies

41 Symposia organized since 2016
Supporting travel of 75 professors & 31 students to present research since 2014
17 Educational workshops & webinars since 2017

80+ Publications resulting from funded research, 1700+ unique daughter citations
49 Roundtable authored papers since 2007
The Peter J. Dunn Award for Green Chemistry & Engineering Impact in the Pharma  Established in 2016

Bridging the gap between academics & industry
Enabling better decisions about chemical selection process design
A leading voice for GC&E
Inspiring and educating the next generation
Recognizing excellence in GC&E

https://www.acsgcipr.org
Enabling Greener Pharma Manufacturing
Scaling a Photo-Flow Bromination for Belzutifan

FREE Webinar | TODAY at 2pm ET

THIS ACS WEBINAR WILL BEGIN SHORTLY...

Enabling Greener Pharma Manufacturing: Scaling a Photo-Flow Bromination for Belzutifan

John Tucker
Executive Director, Chemical Development, CMC, Neurocrine Biosciences

Cecilia Bottecchia
Senior Scientist, Merck

François Lévesque
Principal Scientist, Merck

Presentation slides are available now! The edited recording will be made available as soon as possible.

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This ACS Webinar is co-produced with ACS Green Chemistry Institute and the ACS Green Chemistry Institute Pharmaceutical Roundtable.
Academic awards are many and focus on novelty and publication

- Holistic (process) strategies are often shunned in favor of specific methodology
- Green chemistry has yet to fully penetrate academia
- Process development is not a discipline taught in academia, but is learned on-the-job through mentorship and experience

Companies may be less likely to share advances in chemistry as the business model does not support publication as a final deliverable

- There is a risk to any disclosure i.e., IP or trade secrets

Academics drive most public acknowledgement of science

- Subsequently, there are few opportunities for recognition of green process chemistry
A phalerist is someone who studies awards

– Dr. Jana Gallus holds a Ph.D. in Economics from the University of Zurich, is a UCLA professor at the Anderson School of Management, and a phalerist of some renown
  • Consider reading her paper entitled "Awards, Honors and Ribbons: Between Fame and Shame."

There are various reasons why people give awards

– To establish a legacy, e.g., Alfred Nobel and the Nobel Awards
– To shape a field and influence the direction that it takes, e.g., The Academy Awards—in a subjective medium, establishes what is considered high quality, influencing the future production of movies

With the Peter J. Dunn Award, the ACS GCIPR seeks to transform the way green process chemistry is viewed, exemplified, measured and acknowledged...for the inspiration of future science.

J. Tucker

Recognizing Exemplary Industrial Green Chemistry Innovation

Peter J. Dunn Award for Green Chemistry and Engineering Impact in the Pharmaceutical Industry

- Established in 2016 to recognize outstanding industrial development or implementation of novel green chemistry and/or engineering in the pharmaceutical industry that demonstrates compelling environmental, safety, cost, and/or efficiency improvements over current technologies at significant scale
- Award consists of a plaque and an invited lecture at the ACS Green Chemistry Institute’s Annual Green Chemistry & Engineering Conference (travel reimbursed up to $2,500)
- Submissions open through Dec 31 each year at acsgcipr.org/awards

J. Tucker
Inspiring Global Green Chemistry

2022 GCIPR CMO Award for Excellence in Green Chemistry

- Eligibility specific to Asia — seeking to inspire the global pharma supply chain
- Recognize outstanding efforts toward pharmaceutical green chemistry as performed by Asian CMO companies in support of research, development and manufacturing demonstrating compelling environmental, safety and/or efficiency improvements.
- Award consists of a plaque and an invited lecture at the ACS Green Chemistry Institute’s Annual Green Chemistry & Engineering Conference (travel expenses up to $2,500)
- Submissions open through Dec 31 at acsgcipr.org/awards

The 2021 Peter J. Dunn Award
Greener Manufacturing of Belzutifan (MK-6482) Featuing a Photo-Flow Bromination

Presented to:
Stephen Dalby, Ph.D.
Cecilia Bottecchia, Ph.D.
Francois Levesque, Ph.D.
Jonathan McMullen, Ph.D.

2022 Nominations open: www.acsgcipr.org/awards
Enabling Greener Pharma Manufacturing

Scaling a Photo-Flow Bromination for Belzutifan

Cecilia Bottecchia, François Lévesque
Stephen Dalby & Jon McMullen

Merck Process R&D

We follow the science

We believe it is our responsibility to deliver healthier tomorrows through our vaccines, medications and animal health products that can help patients and communities around the world.

Core growth drivers:
- Oncology
- Vaccines
- Hospital, specialty and chronic care
- COVID-19

Animal Health:
- Companion animal
- Livestock
Commitment to Green & Sustainable Manufacturing

“Our passion to save and improve lives extends to our commitment to protecting and sustaining the environment.”

“We will minimize our environmental footprint through scientific innovation.”

Commercial Process Development Mission

Our aspirational goal
Develop idealized manufacturing processes

How to get there
Innovations in process chemistry

- Green & Sustainable processes by design
- Scientific creativity – inventing solutions to solve problems
- Innovative technologies for future manufacturing
Belzutifan

- Oral HIF-2α inhibitor for treatment of renal cell carcinoma & non-RCC tumors
- Asset from acquisition of Peloton Therapeutics in mid 2019
- Awarded breakthrough status designation by FDA

Bringing Belzutifan to patients on a highly accelerated timeline

- Commercial process development & validation in <18 months
- Strategic focus for process re-design
- Commitment to Green & Sustainable goals

Inherited Clinical Supply Process

Indanone Core Synthesis (RSM)

Mid-Game

End-Game
Delivering a Greener Commercial Process

Indanone Core Synthesis (RSM) - Develop concise new route

- Dihydrocoumarin as commodity RM
- 4 step process, 3 crystallizations
- Rapidly developed for 1MT campaign in ~4 months

Bromination / Oxidation – The Major Issue

The Problem

- Batch instability risk
- Hazardous Reagent
- Chlorinated solvent

Objectives

- Safe, Robust & drastically Greener conditions for both steps
- Single solvent through process & avoid bromide handling
Challenges with radical Bromination

- Serious robustness liability
  - Unstable end of reaction mixture – short time window before "cliff"
  - Elevated temp shrinks stability window

*Are there better ways to make this radical?*

Photobromination route: Proof of concept

- Photochemistry identified as an enabling technology for this reaction
  - Replaced chlorinated solvent with MeCN
  - Ambient temp - Improved reaction selectivity and stability
  - Initiation successful at different wavelength (312 – 520 nm)
Understanding the benefits of photochemistry

- Key reaction insight achieved by monitoring via photo-NMR.
  - Photochemistry is not a panacea for robustness but pushes failure cliff far from operating conditions.
  - Reaction can be turned on and off with the flick of a switch.

Photochemical bromination – Mechanistic considerations

- Radical mechanism inherently generates acid
  - By-product formation is likely acid-catalyzed mechanism (potentially auto-catalytic)
  - pH drop deriving from HBr accumulation responsible for instability cliff

With this understanding, process development focused on understanding key reaction sensitivities and scale-up challenges.
Process development highlights: sensitivity to starting material quality

Understanding the impact of upstream processing on starting material quality is critical for process robustness.

1. Colored impurities affect initial reaction Abs → carbon treatment implemented to normalize Abs
2. Identified residual copper as strong inhibitor
   • Numerous copper chelator screens were performed, leading to citric acid as a hit.

In your opinion, what is the biggest challenge in scaling up photochemistry?

• Resistance to change – implementing new technology takes time
• Energy and cost requirements compared to thermal processes
• Availability of powerful light sources
• Limited light penetration through a solution
• Other (Tell us more in the chat!)
The grand challenge: scaling up photochemistry

Ideal reactor requirements:

• Powerful LEDs and a reactor design that limits “dark zones.”
• Tight control of reaction time.
• High heat transfer rates to minimize reaction stability risk.

These are all drivers to use flow chemistry in production, but how can we transfer from batch to flow?

Photon stoichiometry: a key parameter across scales

Why are batch vs flow reaction profiles so different?
Reactors vary in terms of:

* Volume
* Geometry
* Surface area
* Light source
Photon stoichiometry: a key parameter across scales

---

**Conversion vs time**

Why are batch vs flow reaction profiles so different?

Reactors vary in terms of:

- Volume
- Surface area
- Geometry
- Light source

---

**Conversion vs photon equiv.**

Photon stoichiometry can be used to

- Predict reaction time across reactors
- Inform on reactor design/efficiency

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Corcoran, E. B.; McMullen, J. P.; Lévesque et al., ACIE, (2020), DOI: 10.1002/anie.201915412.

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• Demonstrated photon equivalents as the scaling factor

Photon equiv. = \( \frac{\text{moles of photons}}{\text{moles of S.M.}} \)

---

LED power & efficiency

Scale-up
Reactor characterization

Not all photons from the light source enter the reactor or interact with the photocatalyst!

Due to similarities of reactor design and light source, emitted photons was used to estimate reaction time

Photochemical bromination – Photon stoichiometry

Absorbing species is formed during reaction (induction period):
Abs changes over time!
Photo-flow bromination

Visible-light trigger reaction

Starting material → Brominating agent
Acetonitrile, 2 to 4 min res.time
25 °C, 90-95% yield

Product
No isolation of mutagenic intermediate

Photochemical initiation
Merck process

- 20°C
- Higher end of reaction stability
- Improved control in continuous-flow

Photo-flow selected as manufacturing route

First kilo scale demonstration

Light source
Reactor build

Small but mighty!
Photochemical bromination – Plug Flow Reactor

PFR reactor (890ml)

Light Panels (2 total)
- 500 W input power (each)
- 150 W output (each)
- Water cooled
- Under N₂ to prevent intrusion of solvents and condensation

Peristaltic pump recirculating water through heat exchanger

Thermocouples monitoring
- Inlet
- Outlet
- LED panels
- Water

What you can’t see:
- Fish tank is filled with water
- Collection vessel
- Sampling tube
- HBr sensor
- Scrubber

Peristaltic pump for reaction mixture

Reactor Characterization – Stop Flow Approach

No background reaction is observed in the absence of light.

Reactor was emptied and the reaction mixture was mixed prior to each illumination period.
Reactors Characterization – Stop Flow Approach

By using a stop flow approach, we were able to generate reaction profile with 1 L (50g SM) of stock solution.

Collecting the same data at steady state for each condition would have required 21 L (>1kg SM)!

Scale-Up in Flow

Good agreement between the stop flow and continuous flow.
Scaling up to the pilot plant

Working closely with pilot plant staff and external capabilities colleagues, a modular photoreactor skid with tunable LED power was developed which interfaced well with existing batch equipment.

Production scale system – generating kilos and knowledge

- Pilot unit was designed with data-rich experimentation in mind
- Engineering batch explored ~80 different operating conditions.

### Engineering Design Space

<table>
<thead>
<tr>
<th>Factor</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (min)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Power (W)</td>
<td>1000</td>
<td>1600</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>15</td>
<td>35</td>
</tr>
</tbody>
</table>

Sensors to monitor temperature, flow, pressure

Inline NIR PAT

Starting material in

Photoreactor jacket service

EOR Stream To quench
Pilot plant results

- Demonstrated quality of material maintained over wide range of conditions
- Verified photon equivalence as scale up factor
- Identified conditions for pilot plant batches (2 x 50 kg each)

Engineering Design Space

Pilot plant campaign in Rahway

First photochemical reaction in our pilot plant

3x multi-kg batches, average 93% product yield

Productivity of 38 kg/day

Wide range of robustness conditions identified
API and Process qualification campaigns

- Manufacturing train: 8 units in series
- GMP-qualified
- Productivity of 149 kg/day
- > 1 MT produced, > 94% average yield

Bromination / Oxidation – The Solution

- Robust & Reproducible
- HTHM -> Light!
- Non-chlorinated solvent

Stable stream
No Isolation

- Intrinsically Safe
- Benign oxidant - No Stench
- Direct crystallization

- Single solvent through process with direct isolation
- Robust and safe to operate with no stench
- Removed 2 x aqueous workups
Delivering a Greener Commercial Process – GMP Pocket

- Single solvent through-processes with direct isolations for all steps — no aqueous workups!
- 5/6 steps using MeCN – solvent recycling at commercial vendor
- Significant efficiency gains & waste reduction

Conclusions

- Significant PMI reduction and sustainability gains for belzutifan process
- First photo-flow process for commercial manufacturing at Merck
- Capability established for future more efficient, robust and greener processes

- Keys to delivering on Green & Sustainable goals
  - Problem solving through best science
  - Risk-taking to innovate on critical path
  - Pre-investment in future technologies

INVENTING FOR LIFE
Collaboration – On Behalf of the Merck Team

Enabling Greener Pharma Manufacturing
Scaling a Photo-Flow Bromination for Belzutifan

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Enabling Greener Pharma Manufacturing: Scaling a Photo-Flow Bromination for Belzutifan

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Principal Scientist, Merck

Cecilia Bottecchia
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Fecha: Miércoles, 18 de Agosto, 2021 @ 2-3pm ET
Panel: Dra. Leticia Myriam Torres Guerra, Centro de Investigación en Materiales Avanzados S.C. (CEMAV)
Moderaadora: Dra. Maria del Jesus Rosales Hoz, Cinvestav y Sociedad Química de México

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• El uso de un co-activador para mejorar el transporte de carga y lograr una mayor actividad fotocatalítica
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