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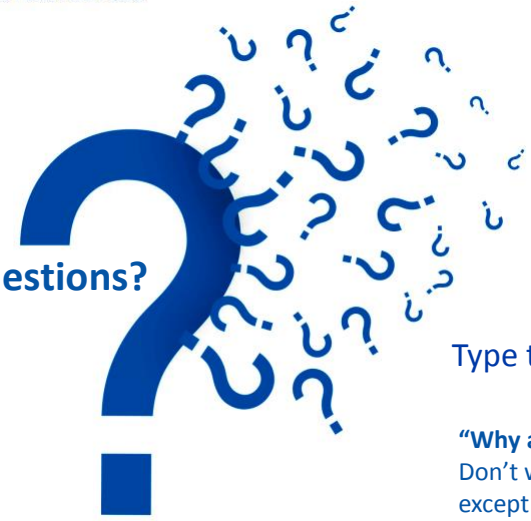

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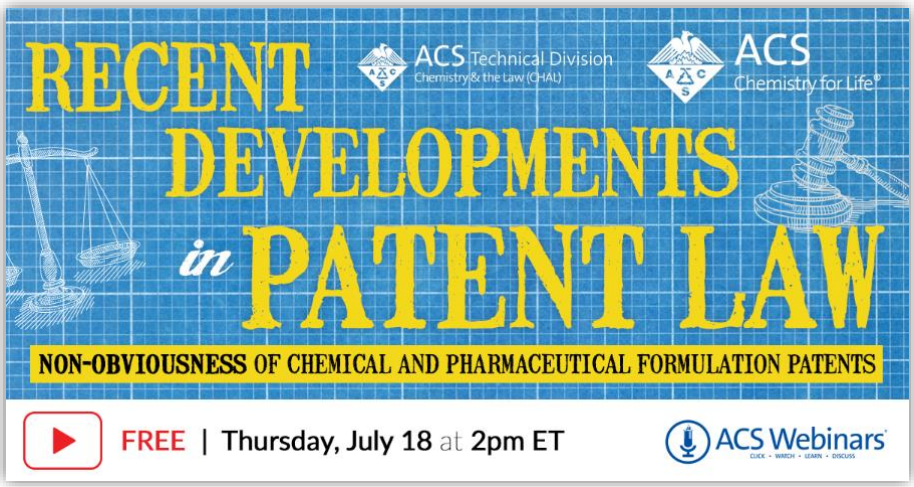

https://www.acs.org/content/acs/en/acs-webinars/business-entrepreneurship/non-obviousness.html

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The ACS Green Chemistry Institute Pharmaceutical Roundtable (ACS GCIPR) Advancing Research!

ACS Green Chemistry Institute Pharmaceutical Roundtable

- The ACS GCIPR has identified key synthetic chemistry and process research challenges whose solutions would result in more efficient pharmaceutical process development and production.

https://www.acsgcipr.org

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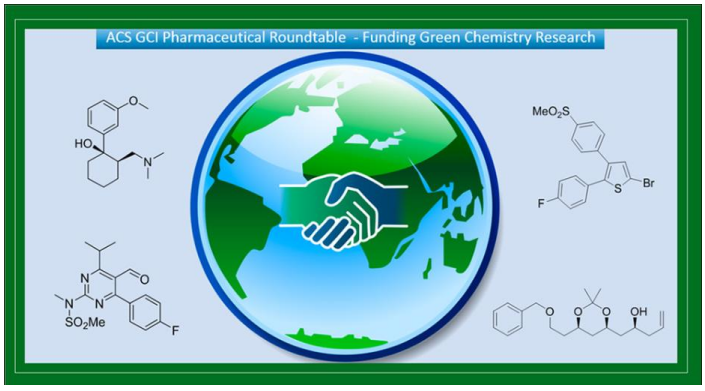
ACS GCIPR: A Decade of Funding!

ACS Green Chemistry Institute Pharmaceutical Roundtable



ORGANIC PROCESS RESEARCH & DEVELOPMENT OPR&D

Evaluating the Impact of a Decade of Funding from the Green Chemistry Institute Pharmaceutical Roundtable

Stefan G. Koenig David K. Leahy and Andrew S. Wells

https://pubs.acs.org/doi/10.1021/acs.oprd.8b00237

- To date, 28 research programs have been funded globally on topics such as C–H activation, flow chemistry, biocatalysis, novel catalytic transformations, base metal catalysis, and solvent substitution. From these research projects, 73 peer-reviewed publications have resulted with over 1700 unique daughter citations.

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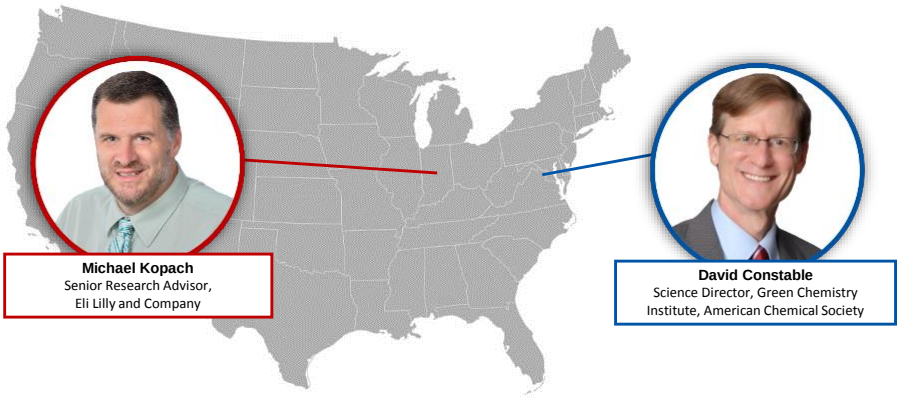
Slimming the Waste-line in Large Molecule Syntheses



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Slimming the Waste–line in Large Molecule Syntheses

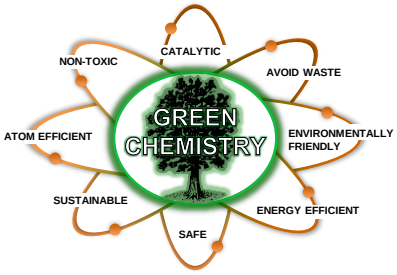
Dr. Michael E. Kopach, Dr. Ben Andrews, Dr. Albert Isidro Llobet and Dr. Isamir Martinez

ACS Webinar
July 11, 2019

Green Chemistry

Green Chemistry *and sustainable science is the strategic design, development, and implementation of chemical products and processes that reduce or eliminate the use and generation of hazardous substances and waste, are inherently safe, and increase efficiency while minimizing environmental footprint and impact.*

Good science *is the key to sustainability, green chemistry, and low cost manufacturing across the globe.*



Noyori - "…green chemistry is not just a catchphrase. It is an indispensable principle of chemical research that will sustain our civilized society in the twenty-first century and further into the future."*[1]

Tucker – "…a privileged opportunity for innovation" representing "an emerging new frontier of exploration."*[2]

If industry focuses on developing the best chemistry, then almost always this leads to the lowest costs and greenest processes.

*1 Noyori, R. "Synthesizing our future." *Nature Chemistry* **2009**, *1*, 5-6.
*2 Tucker, J.L. "Green Chemistry, a Pharmaceutical Perspective." *Org. Process Res. Dev.* **2006**, *10(2)*, 315-319.

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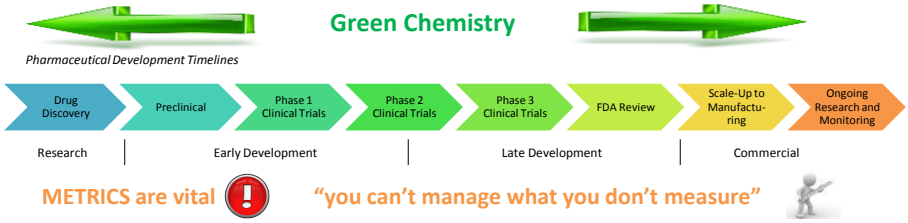
Business Case for Green Chemistry

- pharmaceutical & generics industries may produce ≥ 100 million kg APIs per year *[1]
- cEF ≥ 150 kg waste per kg API (> 99.3%) → ≥ **15 billion kg** of co-produced **waste**
- annual waste disposal cost of ~ **$30 billion** €$£¥

opportunity for industry to utilize **green chemistry** to trim both process inputs and waste, and **create $ billions in economic, environmental, and social value**



METRICS are vital **"you can't manage what you don't measure"**

*1 B. W. Cue, (2012) Green Chemistry Strategies for Medicinal Chemists, in Green Techniques for Organic Synthesis and Medicinal Chemistry (eds. Zhang, W., and Cue, B. W.). John Wiley & Sons,

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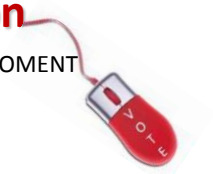
Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT



A majority of the top 10 selling pharmaceuticals in 2018 were:

(More than one correct answer may exist)

- Large Biomolecules (> 10,000 AMU)
- Small Molecules (<500 AMU)
- Cancer Drugs
- Diabetes Drugs

** If your answer differs greatly from the choices above tell us in the chat!*

2018 Top Selling Pharmaceuticals

Medication	Pharmaceutical Company	Total Sales	U.S. Sales	Modality	Indication
1. Humira (Adalimumab)	AbbVie	$19.9 billion	$13.7 billion	Large	Rheumatic Diseases and Inflammatory Bowel Disease
2. Eliquis (Apixaban)	Bristol-Myers Squibb/Pfizer[2]	$9.87 billion	$5.61 billion	Small	Anticoagulant (Blood Thinner) for Heart Arrhythmias
3. Revlimid (Lenalidomide)	Celgene	$9.69 billion	$6.47 billion	Small	Multiple Myeloma
4. Keytruda (Pembrolizumab)	Merck	$7.17 billion	$4.15 billion	Large	Cancer Chemotherapy
5. Enbrel (Etanercept)	Amgen/Pfizer[2]	$7.13 billion	$4.81 billion	Large	Rheumatic Diseases
6. Herceptin (Trastuzumab)	Roche	$6.84 billion	$2.85 billion	Large	Breast Cancer Chemotherapy
7. Eylea (Aflibercept)	Regeneron	$6.75 billion	$4.08 billion	Large	Wet Macular Degeneration
8. Opdivo (Nivolumab)	Bristol-Myers Squibb	$6.74 billion	$4.24 billion	Large	Cancer Chemotherapy
9. Avastin (Bevacizumab)	Roche	$6.71 billion	$2.85 billion	Large	Cancer Chemotherapy
10. Rituxin (Rituximab)	Roche	$6.62 billion	$4.20 billion	Large	Rheumatic Diseases and Cancer Chemotherapy

8 out of 10 are large molecules and 6 out of 10 have cancer related indications

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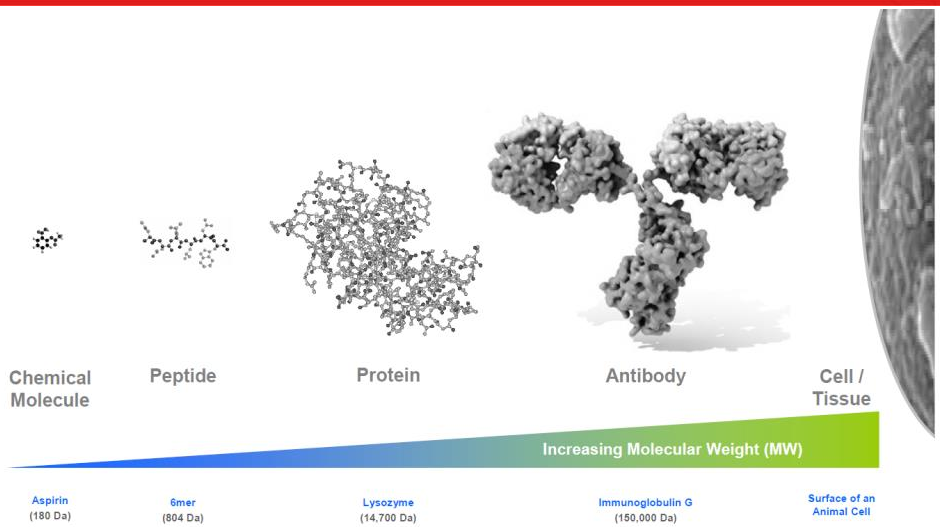
Complexity



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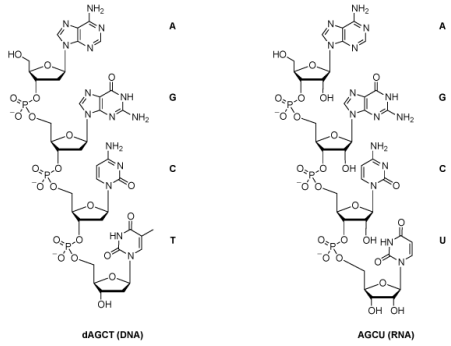
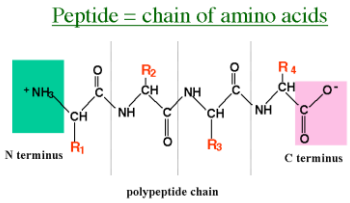
Oligonucleotide and Peptide Products

Oligonucleotide



Nucleic Acid Building Blocks

Peptide



Amino Acid Building Blocks

- Solid Phase Synthesis and Chromatographic Purification are Common to both Platforms

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Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

In 1901 which transformative scientific discovery(s) were made?

(More than one correct answer may exist)

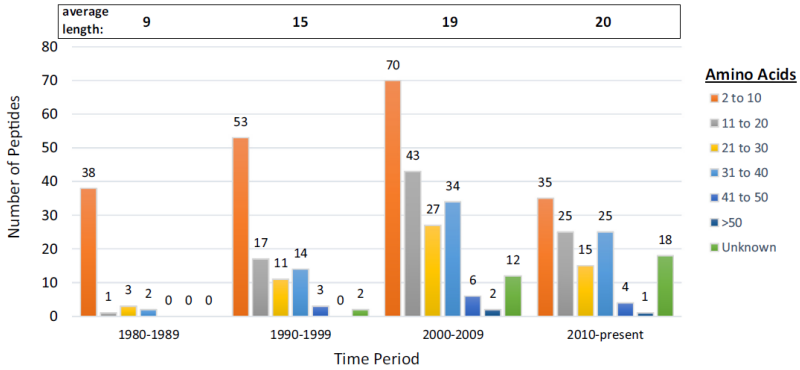
- Robert Merrifield invents solid phase peptide synthesis
- Emil Fischer discovers first synthetic peptide
- Victor Grignard discovers the Grignard Reaction
- None of the above

** If your answer differs greatly from the choices above tell us in the chat!*

Peptide Overview

Peptides have been around since insulin in the 1920s.

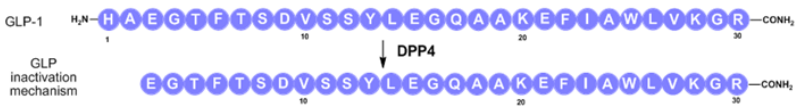
Once solid phase peptide synthesis was introduced by Merrifield in 1963 they dramatically increased in popularity and complexity as production was feasible.

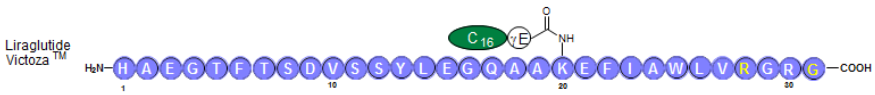


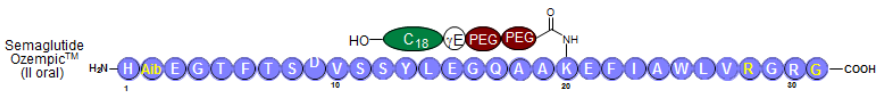
Lau et al. Bioorganic & Medicinal Chemistry. 26 (2018) 2700-2707

Examples of Increasing Peptide Complexity

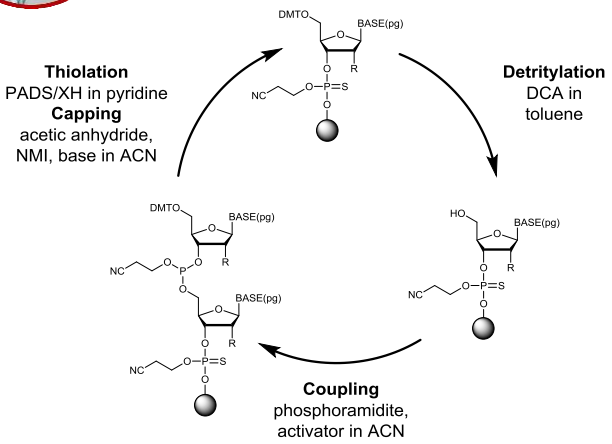
Natural incretins:

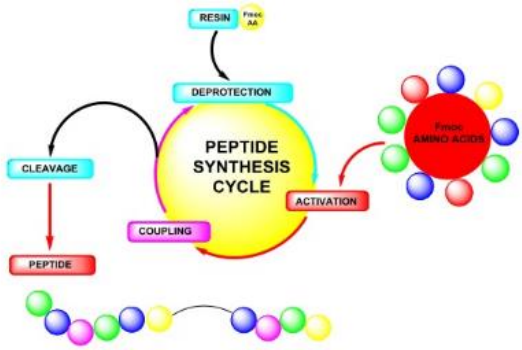






Oligonucleotide and Peptide SPS





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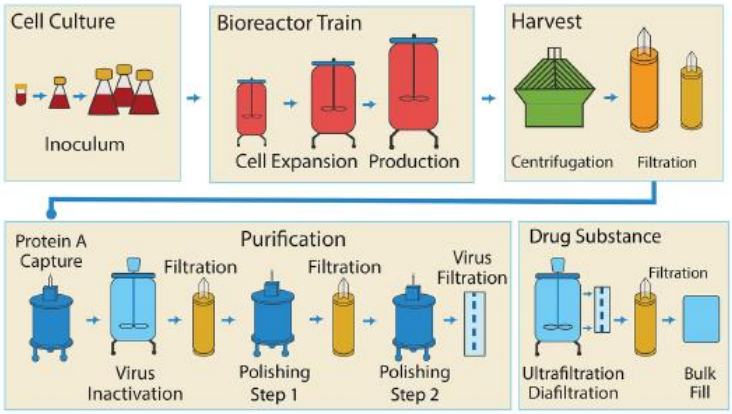
Common Large Molecule Processes



- Excludes Synthetic Peptides and Oligonucleotides

https://www.sciencedirect.com/science/article/pii/S1871678418302255

Budzinski et. al. *New Biotechnology* Volume 49, 25 March 2019, Pages 37-42.

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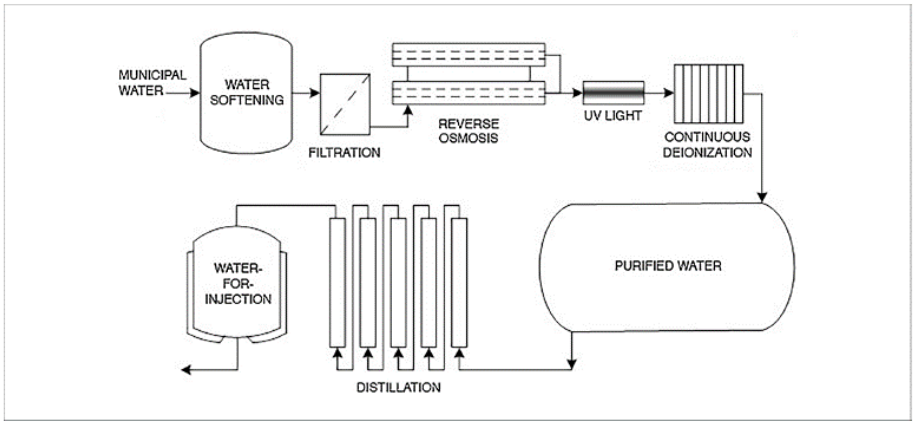
Water For Injection Processes



Budzinski et. al. *New Biotechnology* Volume 49, 25 March 2019, Pages 37-42.

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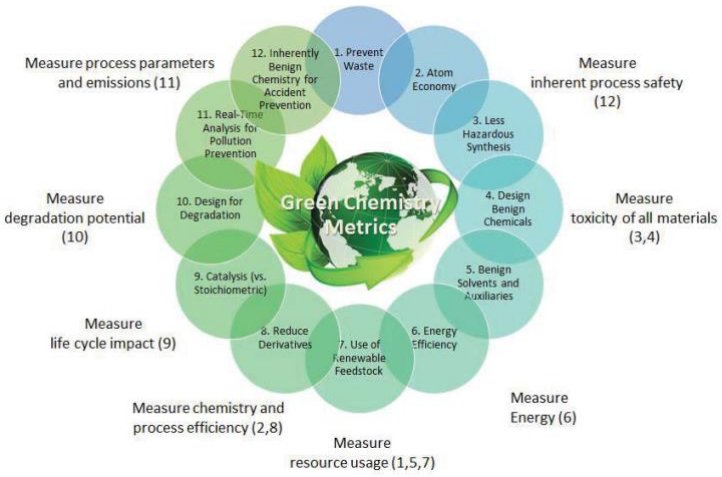
12 Principles of Green Chemistry



P. T. *Anastas* & J. C. *Warner*, *Green Chemistry*: *Theory* and *Practice*, Oxford University Press: New York, *1998*.

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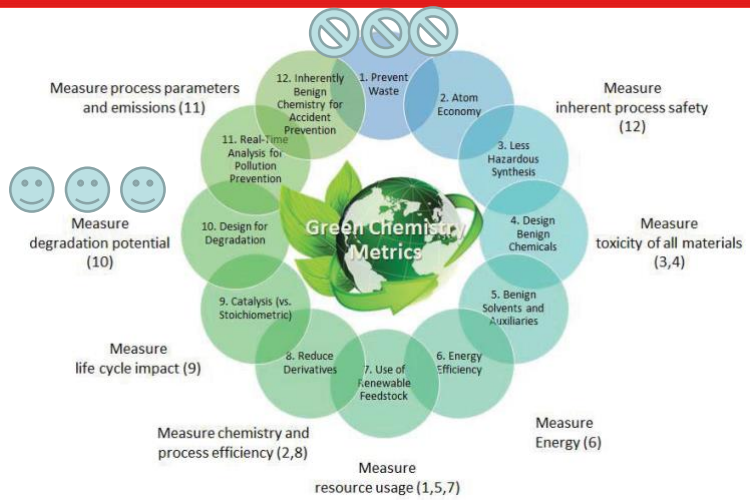
12 Principles of Green Peptides



P. T. *Anastas* & J. C. *Warner*, *Green Chemistry*: *Theory* and *Practice*, Oxford University Press: New York, *1998*.

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Tools for Innovation in Chemistry

Solvent Selection
Reagent Guides
PMI-LCA & PMI Prediction
MedChem Tips & Tricks

Advancing Research

Key Research Areas
Research Grants
Journal Publications
Impact

Educating Leaders

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Pharma Roundtable Key Research Areas

753 Citations

- ***2007 KRA Manuscript:** Green Chem., 2007,9, 411-420

Key green chemistry research areas—a perspective from pharmaceutical manufacturers

David J. C. Constable,[a] Peter J. Dunn,*[b] John D. Hayler,[c] Guy R. Humphrey,[d] Johnnie L. Leazer, Jr.,[d] Russell J. Linderman,[e] Kurt Lorenz,[f] Julie Manley,[g] Bruce A. Pearlman,[h] Andrew Wells,[i] Aleksey Zaks[g] and Tony Y. Zhang[f]

Received 7th March 2007, Accepted 26th March 2007
First published as an Advance Article on the web 17th April 2007
DOI: 10.1039/b703488c

In 2005, the ACS Green Chemistry Institute (GCI) and the global pharmaceutical corporations developed the ACS GCI Pharmaceutical Roundtable to encourage the integration of green chemistry and green engineering into the pharmaceutical industry. The Roundtable has developed a list of key research areas. The purpose of this perspective is to summarise how that list was agreed, provide an assessment of the current state of the art in those areas and to highlight areas for future improvement.

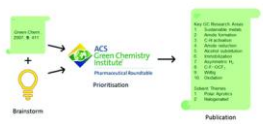
- **2018 KRA Manuscript:** Green Chem., 2018,20, 5082-5103.

Key Green Chemistry research areas from a pharmaceutical manufacturers' perspective revisited

Check for updates

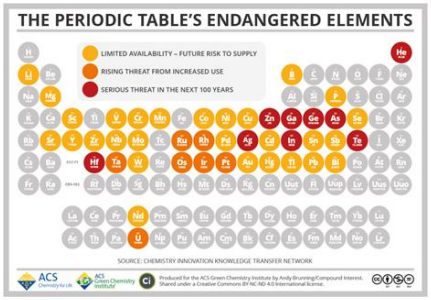
Marian C. Bryan,[a] Peter J. Dunn,[b] David Entwistle,[c] Fabrice Gallou,[d] Stefan G. Koenig,[e] John D. Hayler,[e,f] Matthew R. Hickey,*[g] Shaun Hughes,[h] Michael E. Kopach,[i] Gerard Moine,[j] Paul Richardson,[k] Frank Roschangar,[l] Alan Steven[h] and Franz J. Weiberth[m]

Author affiliations



Overview: Pharma Key Research Areas

- Inexpensive /**sustainable metals** methodologies
- Sustainable catalysis for (direct) **amide or peptide formation**
- **Green oxidants** aliphatic and aromatic **C–H activation**
- **Amide reductions** avoiding $LiAlH_4$ and diborane
- Direct **substitution of alcohols**
- **Catalyst immobilization (**no loss of kinetics)
- **Asymmetric hydrogenation** of unfunctionalized olefins/ enamines/imines
- Improved **fluorination/trifluoromethoxylation**
- **Wittig** chemistry without Ph_3PO
- **Alternatives for oxidations**, C–O *or* C–N redox processes
- **Polar aprotic solvents** replacements
- **Halogenated solvents replacements**



acsgcipr.org

Green Chem., **2018**, *20*, 5082. DOI: 10.1039/C8GC01276H

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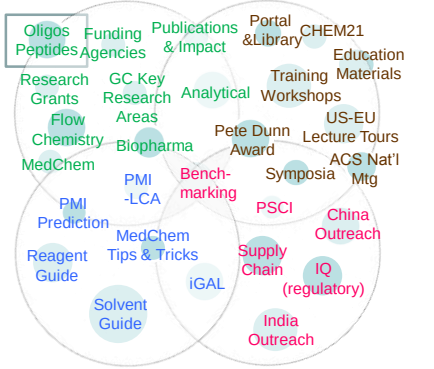
Pharma RT 2025 Strategic Priorities

Inform & Influence Research Agenda | Educate Leaders



Deliver Tools for Innovation | Collaborate Globally

MISSION

catalyze GC&E in the global pharmaceutical industry

- Peptides and Oligos Relatively New Team founded in 2016
- **Charter:** To educate and influence today's and tomorrow's scientists and industries in the business value and scientific merit to utilize green chemistry and engineering principles to guide development and manufacture of peptide, oligonucleotide products.

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ACS GCI Peptide and Oligo Subteams

AstraZeneca	Louis Diorazio, Anna Watson, and Martin Kenworthy
Biogen	Firoz Antia
Boehringer Ingelheim	Heewon Lee
Bristol-Myers Squibb	Shawn Brueggemeier and Subha Mukherjee
gsk	Ben Andrews* and Albert Isidro Llobet**
Lilly	Michael Kopach
Roche	Martin Olbrich
IPSEN	Katrzyna Wegner
NOVARTIS	Fabrice Gallou
AMGEN	Austin Smith
ACS Green Chemistry Institute	Isamir Martinez

*Oligonucleotide Team Lead

** Peptide Team Lead

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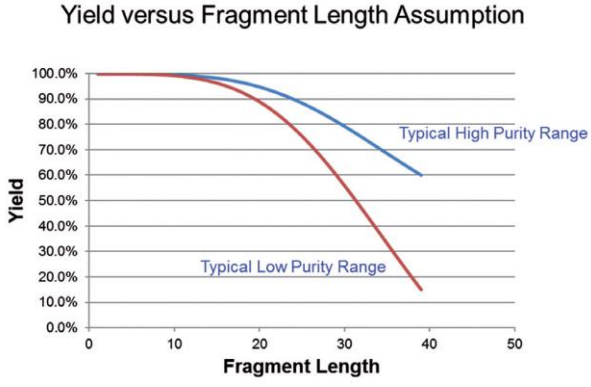
Solid Phase Peptide Synthesis

Advantages:

- ✓ Proven technology
- ✓ Efficient method of production for short sequences
- ✓ Accepted current practice

Challenges:

- ✓ Solvent intensive process
- ✓ Yield and purity significantly decrease as peptide length increases
- ✓ Addition and deletion (and analog) impurities are possible and propagate
- ✓ Up to 20% risk of total loss increases as a function of peptide length*



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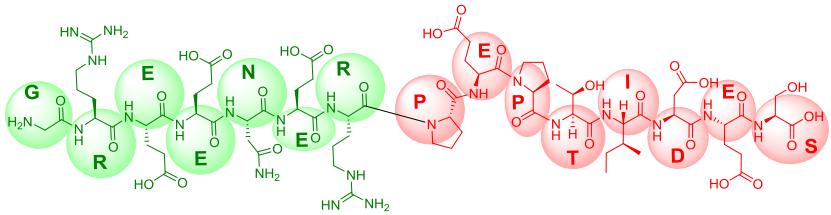
Pharma RT Peptide Key Research Areas

Sustainability challenges in peptide synthesis and purification: from R&D to production

Albert Isidro-Llobet,*[a] Martin N. Kenworthy,[b] Subha Mukherjee,[c] Michael E. Kopach,[d] Katarzyna Wegner, [e] Fabrice Gallou,[f] Austin G. Smith, [g] Frank Roschangar[h]



(1) **Convergent** hybrid synthesis
(2) **Greener solvent** choices
(3) Improved **resins/recycling**
(4) Unprotected peptide **ligation**
(5) Peptide synthesis in **flow**
(6) **Greener separation** technologies
(7) Innovation to **reduce PMI**

Sustainability Aspirations

Call to Innovation

(1) **Linear** synthesis
(2) Heavy **toxic solvent** usage
(3) Poor **resin loading**
(4) **Protecting group** usage
(5) **Batch** synthesis
(6) Intensive **chromatography**
(7) **High PMI**

https://pubs.acs.org/doi/10.1021/acs.joc.8b03001 *J. Org. Chem.*, **2019**, *84* (8), pp 4615–4628

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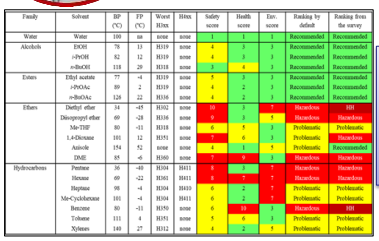
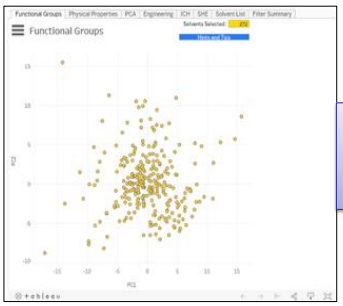
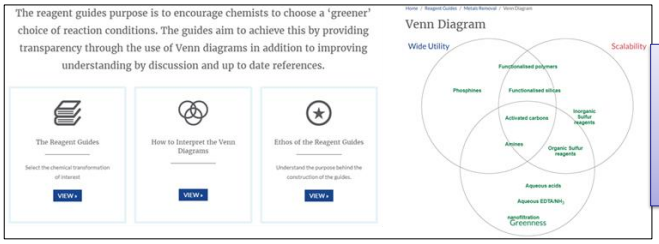
Tools to Make Processes Greener



Solvent Guides: 77 solvents; 3 criteria: safety, health, environment



Solvent Interactive Tool: 272 solvents / selection based on physical properties, functional groups and environmental data.



Reagent Guides: reagentguides.com

18 guides, > 150 reagents, citation links

Coming soon!
Amide bond reagent guide specific to polypeptides

acsgcipr.org

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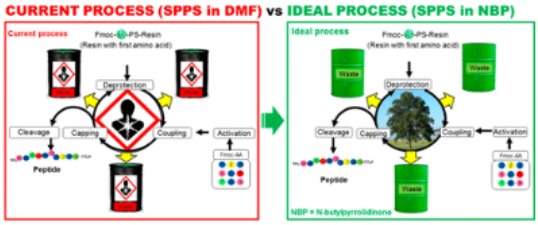
Key 2018 Novartis Contribution

_N_-Butylpyrrolidinone as Alternative Solvent for Solid-Phase Peptide Synthesis

John Lopez, Stefan Pletscher, Andreas Aemissegger, Christoph Bucher, and Fabrice Gallou

Org. Process Res. Dev., **2018**, *22* (4), pp 494-503
Publication Date (Web): March 14, 2018 (Article)
DOI: 10.1021/acs.oprd.7b00389

By means of a systematic approach, several green solvent candidates were tested for their feasibility to replace the reprotoxic dimethylformamide (DMF) as a solvent used in solid-phase peptide synthesis (SPPS). According to the results presented in this ...



Peptide Research Grant: Professor Jennifer Stockdill

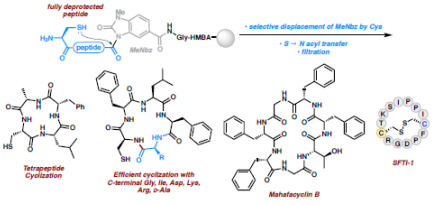
Bringing Macrolactamization Full Circle: Self-Cleaving Head-to-Tail Macrocyclization of Unprotected Peptides via Mild _N_-Acyl Urea Activation

Christine A. Arbour,[a] Kayla J. Belavek,[a] Rooha Tariq,[a] Subha Mukherjee,[b] Janine K. Tom,[c] Albert Isidro-Llobet,[d] Michael E. Kopach,[e] and Jennifer L. Stockdill*[a]

[a]Department of Chemistry, Wayne State University, Detroit, MI, USA 48202
[b]Bristol-Myers Squibb, Chemical and Synthetic Development, New Brunswick, NJ, 08903, USA
[c]Amgen, Inc.
[d]GlaxoSmithKline, Medicines Research Centre, Stevenage SG1 2NY, UK
[e]Eli Lilly and Company, Indianapolis, IN, 46285, USA

Supporting Information Placeholder

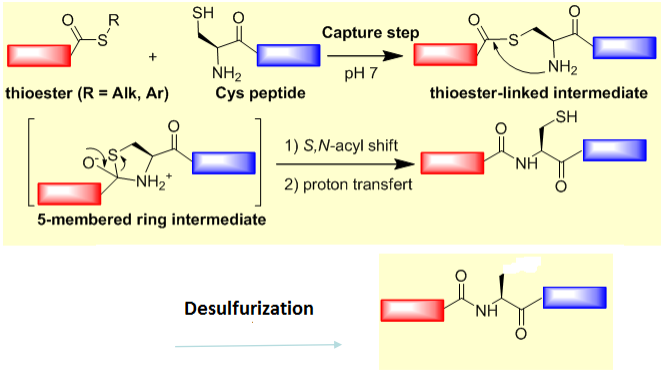
ABSTRACT: We establish herein conditions for the efficient self-cleaving cyclization of unprotected _N_-acyl urea-linked peptides to form head-to-tail macrocyclic peptides mediated by N-terminal cysteine. We report a detailed investigation of the parameters of the reaction, including variation of the reaction conditions, the N-terminal residue, the C-terminal residue, the rinsing protocol, and the macrocycle size. Two sets of optimized conditions are employed in the synthesis of macrocyclic targets ranging from a tetrapeptide to the disulfide-linked 14-mer, sunflower trypsin inhibitor 1, and a Gly analog thereof. Under these conditions, no C-terminal epimerization, hydrolysis, or disulfide dimer formation is observed.



https://pubs.acs.org/doi/abs/10.1021/acs.joc.8b02418

J. Org. Chem., **2019**, *84* (2), pp 1035–1041

Native Chemical Ligation (NCL)



- Coupling of unprotected Peptides, potentially attractive option to produce peptides with cysteine and alanine
- Lack of Green Desulfurization Methodology has limited utility
- Prof. Stockdill Awarded Roundtable Research grant extension to develop greener desulfurization methodology

Pharmaceutical Roundtable Metrics

Process Mass Intensity Metric

Process mass intensity = $\frac{\text{quantity of raw materials input (kg)}}{\text{quantity of bulk API out (kg)}}$

Where:

Process is all steps of a synthetic path from commonly available materials to the final bulk active pharmaceutical ingredient ("API")

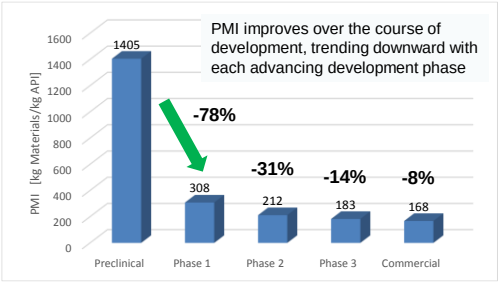
Raw Materials are all materials including water that are used directly in the process of synthesizing, isolating, and purifying the API salt

Bulk API out is the final salt form of the active ingredient that was produced in the synthesis, dried to the expected specification

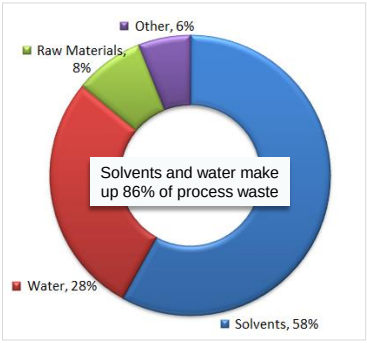
Jimenez-Gonzalez,C. *et al*. *Org. Process Res. Dev*. **2011**, 15, 912–917.

Process Mass Intensity (PMI)

ACS GCI compiled industry waste data for pharmaceutical manufacturing across development and commercial in 2007 and 2008*[1-3]



Excel PMI calculator available: acsgcipr.org*[2]



*1 R. K. Henderson, J. Kindervater and J. B. Manley, *Lessons Learned Through Measuring Green Chemistry Performance – The Pharmaceutical Experience* (2007).

*2 ACS GCI Pharmaceutical Roundtable presentation "Convergent PMI Calculator" (2014).

*3 The PMI data, which exclude solvent and water-intensive biopharmaceutical fermentation processes, were significantly higher in 2008 compared to 2007, possibly due to reassessment of synthesis starting points. We show the 2008 data.

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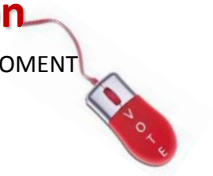
Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT



Which Therapeutic Class generally has the highest Process Mass Intensity (PMI) and generates the most waste?

- Small Molecule
- Oligonucleotide
- Synthetic Peptide
- Recombinant Protein

** If your answer differs greatly from the choices above tell us in the chat!*

Therapeutic Class PMI Data Comparison

- Small molecule PMI ~ 168 (industry average)
- Peptide PMI > 5000 (≥ 40 mer)
- Biopharmaceutical PMI ~7700 (Mabs)
- Oligonucleotide
  - MOE Gapmer PMI ~3300
  - SiRNA PMI ~7000
- Common Starting point are purchased amidites or amino acids

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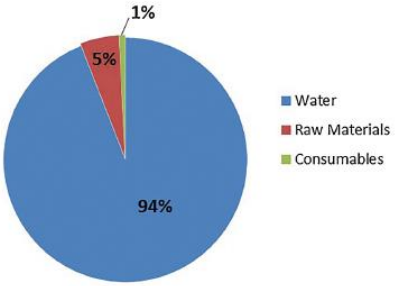
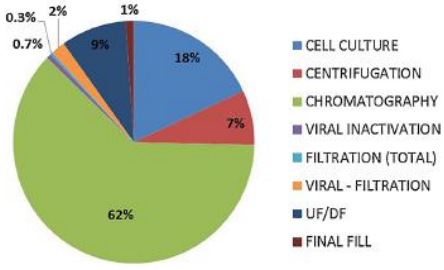
Biologics PMI Data

Overall PMI ~ 7700 kg/kg APi





- 14 process data sets covering ≥ 12,000 L and ≤ 5,000 L operation volumes for MABS processes
- PMI per amino acid is lower than oligonucleotides and peptides

Budzinski et. al. *New Biotechnology* Volume 49, 25 March 2019, Pages 37-42.

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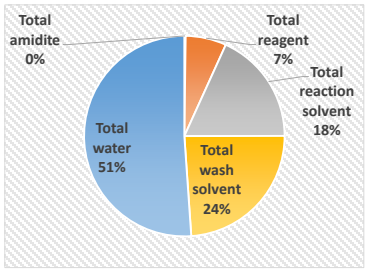
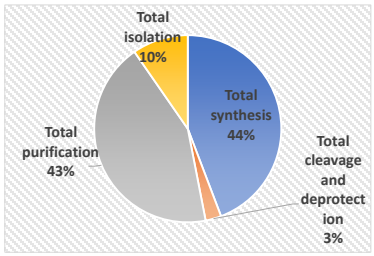
Oligonucleotide PMI Data

Solvents and Water

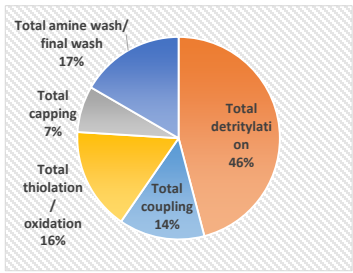


Unit Ops



- Avg. PMI ~ 4300 kg/kg API
- Starting point = amidite raw materials
- Acetontitrile is primary process solvent

Chemistry Steps



- 2019 ACS Pharma RT Benchmarking Study

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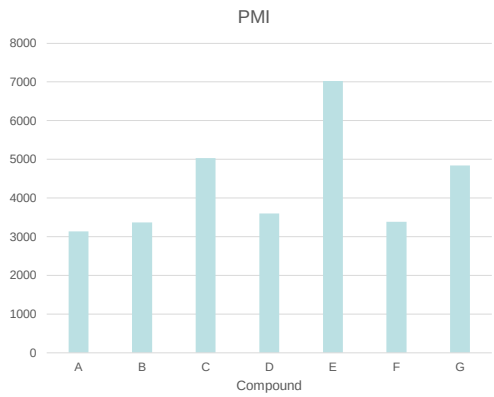
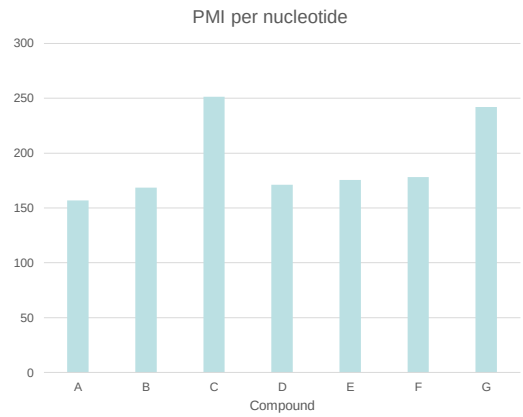
Oligonucleotide by Compound

- No trend with development phase





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Improving Sustainability for Oligonucleotide Manufacture

Purification:

- Optimising the purification step, re-purification of mixed fractions?
- Remove the lyophilisation, ship API solution (refrigerated or frozen) or package straight into vials? Reduce cycle time and energy use
- Other isolation techniques, e.g. precipitation
- Reduction of waste in the supply chain
- Can cold chain be solved? -20 ºC API storage and shipping adds 10-15% to product costs – common to nearly all large molecules

Alternative Synthetic Approaches:

- Scalable solution phase synthesis via precipitation (Ajinomoto)
- Scalable solution phase synthesis via membrane filtration (Imperial)
- Enzyme catalysed templated ligation
- ACN used exclusively for chemistry steps – replace?
- Molecular Design for Stability - cold chain only if necessary

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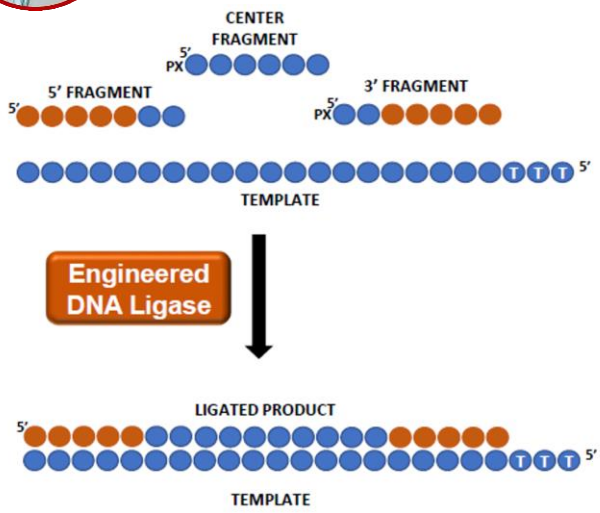
Enzyme Catalyzed Templated Ligation



- Shortmers assemble on a template strand
- Ligase enzyme joins the shortmers together
- Heat to wash off impurities and incomplete intermediates
- Heat further to dissociate the product from the template
- Aqueous based
- Removes the need for a purification step

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Conclusions

- Significant environmental business case for Green Chemistry and Engineering adoption
- Peptide, Oligonucleotide and Biologics Manufacture in largest need of innovations to improve Environmental Profile.
- The ACS Green Chemistry Institute Pharmaceutical Roundtable provides **leadership and influence** throughout industry and supply chain.
  - Developed powerful set of tools (e.g. solvent selection guide, PMI/LCA calculator, reagent guide, etc.) available to all.
  - Funding of key research priorities as non-profit.
- The ACS Green Chemistry Institute Pharmaceutical Roundtable has evolved its mission since 2005, from exclusive small molecule focus initially to include other modalities in 2019 such as **peptides, proteins and oligonucleotides**.
- Open call for Innovation!

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ACS GCI Pharma Roundtable: Fall 2019 Meeting in China

Wednesday 18th Sept 2019: Day 1 GCIPR **(Asymchem)**

Thursday 19th Sept 2019: Day 2 GCIPR

Onsite at Asymchem Tianjin

- Roundtable meeting (~100 people)
- Tour of Asymchem green chemistry capabilities

Friday 20th Sept 2019: Day 3 GCIPR (**Pharmaron**)

Onsite at Pharmaron Beijing site (Taihe Road, BDA, Beijing 100176)

- Roundtable meeting (~100 people)
- Tour of Pharmaron site

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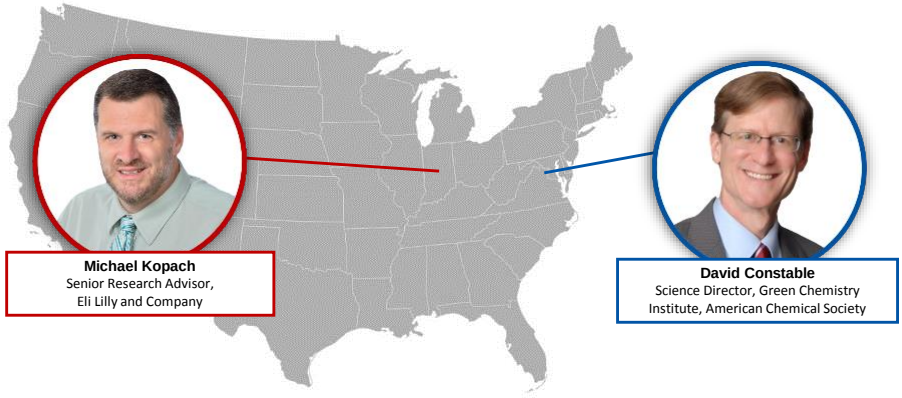

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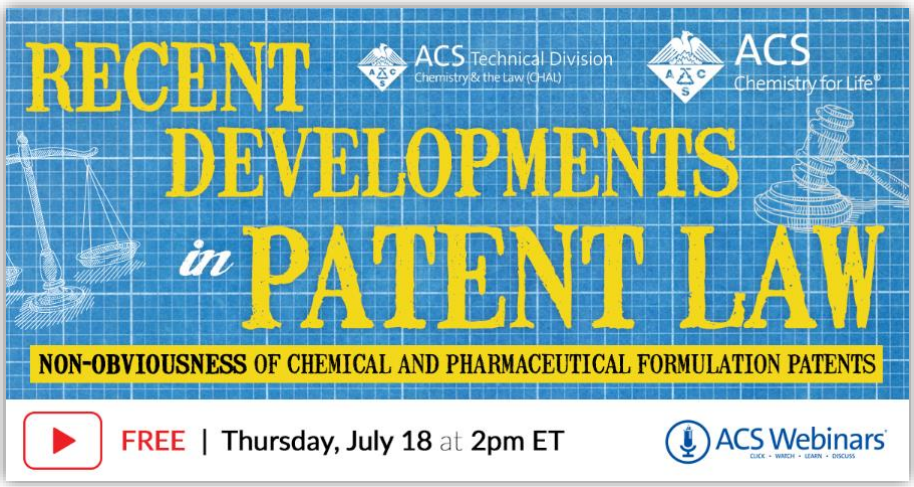

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The ACS Green Chemistry Institute Pharmaceutical Roundtable (ACS GCIPR) Advancing Research!

ACS Green Chemistry Institute Pharmaceutical Roundtable

- **The ACS GCIPR has identified key synthetic chemistry and process research challenges whose solutions would result in more efficient pharmaceutical process development and production.**

https://www.acsgcipr.org

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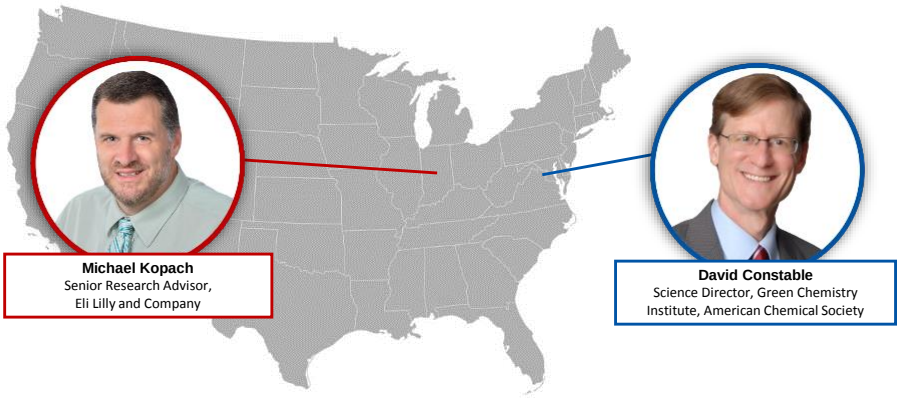

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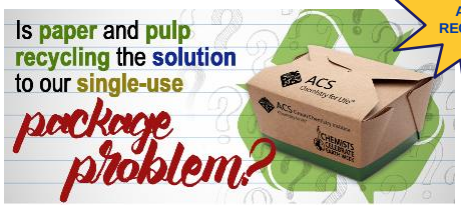
Fan of the Week

Jeanne Shoulder
QC Manager, DSM Nutritional Products
ACS member 7 years strong!



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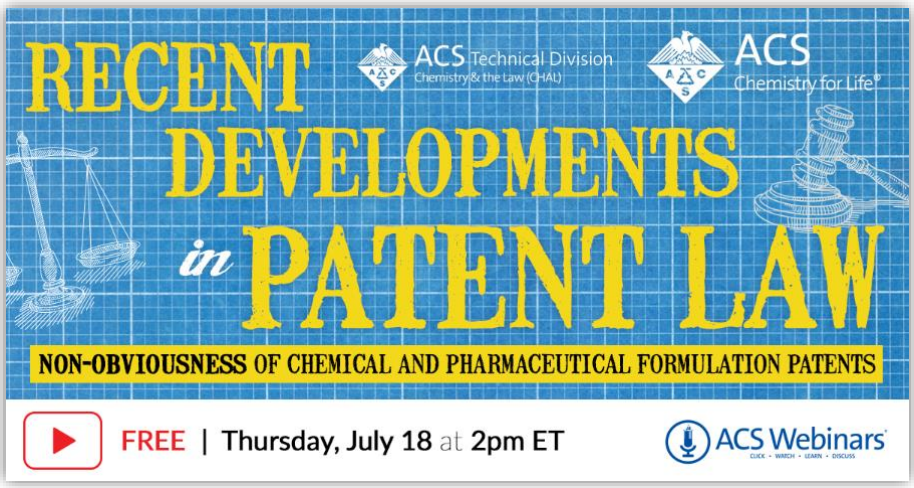

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