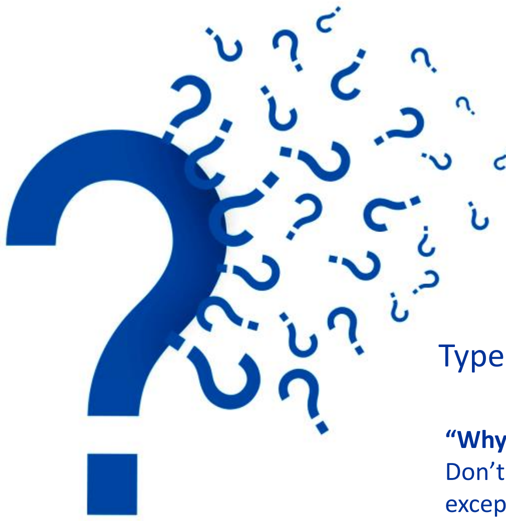
Have Questions?



Type them into questions box!

"Why am I muted?"
Don't worry. Everyone is muted except the presenter and host. Thank you and enjoy the show.

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Emilio Villalobos, Student

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An individual development planning tool for you!

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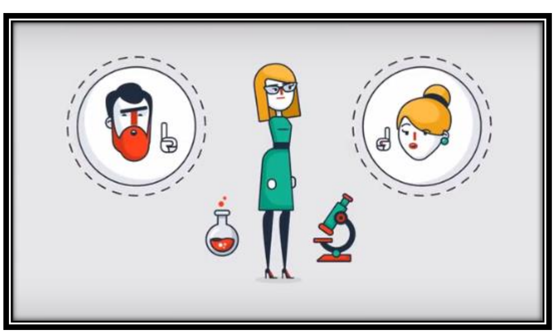

- Know your career options
- Develop strategies to strengthen your skills
- Map a plan to achieve your career goals

ChemIDP.org

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www.gcande.org

Student Research & Travel Awards

Joseph Breen Memorial Fellowship

($2,000) – *Due February 16, 2018*

Sponsors international and domestic students (undergraduate and above) based on estimated travel expenses, up to $2,000, for a green chemistry technical meeting, conference or training program (students are encouraged to consider the GC&E Conference).

Kenneth G. Hancock Memorial Award

($1,000 cash and $1,000 travel stipend) – *Due February 16, 2018*

Sponsors international and domestic students (undergraduate and graduate), up to $2,000, for the GC&E Conference.

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Thursday, January 11, 2018

Painting a Brighter Future with Chemistry: *Innovating with Higher Performing and More Sustainable Pre-composite Polymers*

Jim Bohling, Dow Chemical Company
Stan Brownwell, Dow Chemical Company

Thursday, January 18, 2018

Science-Based Carbon Reduction Targets: *An Entry Ticket to Carbon-Based Business Benefits*

Valerie Patrick, President, Fulcrum Connection
Bryan Tweedy, Manager, Office of Career and Professional Resources, ACS

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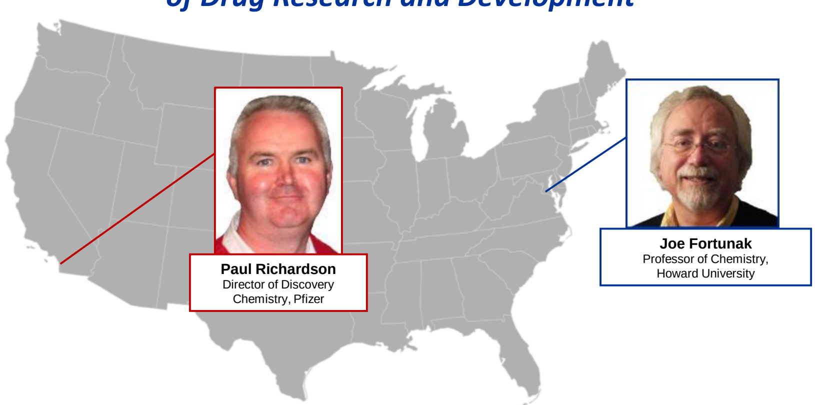
How to Sustainably Innovate Throughout the Life Cycle of Drug Research and Development



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ACS Green Chemistry Institute® Pharmaceutical Roundtable

Where We Stand Today !!!

Researchers prepare to filter crystals at an Amgen small-molecule-manufacturing facility.

Drug companies must adopt green chemistry

"Green chemistry can deliver for people, planet and profit. Those who embrace it will reap the benefits in future. Those who fail to evolve may cease to be relevant".

Nature, **2016**, *534*, 27

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What is a Sustainable Future?

Social

Economic

Environmental

The pharmaceutical industry will be expected to meet the needs of patients around the world at a cost they can afford while minimizing our environmental footprint.

Balance Social, Environmental & Economic Needs Globally and Across Generations

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What is Green Chemistry?

- The highest efficiency potential that exists for each chemical process.
- Green Chemistry is a privileged opportunity for innovation and represents an emerging new frontier of exploration.
- The achievement of superior synthetic efficiency will ultimately deliver a competitive advantage.

OPRD., **2006**, *10*, 315.

Green Chemistry provides a platform to align Corporate environmental, social, and economic goals.

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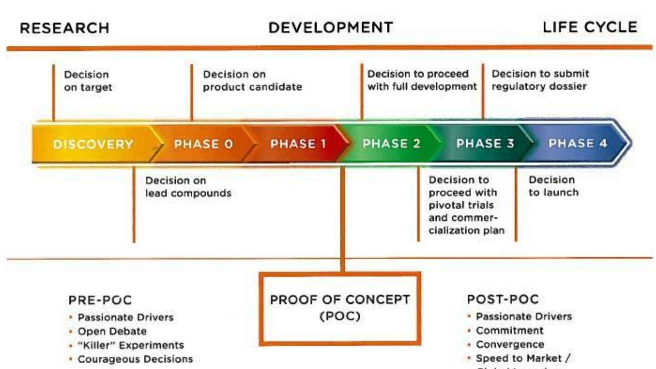
When to Apply Green Chemistry (Pharma)

Integrate green chemistry **throughout the life cycle** of drug research, development and manufacture



Early awareness can deliver large paybacks later!

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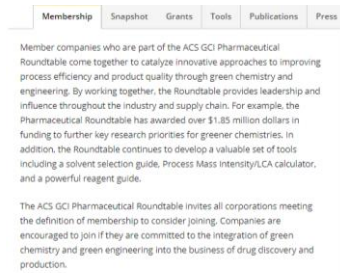
ACS GCI Pharmaceutical Roundtable

In 2005, the ACS Green Chemistry Institute and global pharmaceutical corporations developed the ACS GCI Pharmaceutical Roundtable to encourage innovation while catalyzing the integration of green chemistry and green engineering in the pharmaceutical industry.


Membership | Snapshot | Grants | Tools | Publications | Press

Member companies who are part of the ACS GCI Pharmaceutical Roundtable come together to catalyze innovative approaches to improving process efficiency and product quality through green chemistry and engineering. By working together, the Roundtable provides leadership and influence throughout the industry and supply chain. For example, the Pharmaceutical Roundtable has awarded over $1.85 million dollars in funding to further key research priorities for greener chemistries. In addition, the Roundtable continues to develop a valuable set of tools including a solvent selection guide, Process Mass Intensity/LCA calculator, and a powerful reagent guide.

The ACS GCI Pharmaceutical Roundtable invites all corporations meeting the definition of membership to consider joining. Companies are encouraged to join if they are committed to the integration of green chemistry and green engineering into the business of drug discovery and production.

acs.org/gcipharmaroundtable

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2017 Members

ROUNDTABLE MEMBER COMPANIES

abbvie | AMGEN | AstraZeneca

ASYMCHEM | Bristol-Myers Squibb | Biogen

Boehringer Ingelheim | CODEXIS WE ARE BIOCATALYSIS™ | gsk

Johnson & Johnson | Lilly | MERCK INVENTING FOR LIFE

NOVARTIS | Pfizer | 康龙化成 PHARMARON

Roche | SANOFI | 药明康德 WuXi AppTec

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Mission

To catalyze the implementation of green chemistry and engineering in the pharmaceutical industry globally

Strategic Priorities

Inform and Influence the Research Agenda	Define and Deliver Tools for Innovation
Promote Education and Training	Enable Global Collaboration

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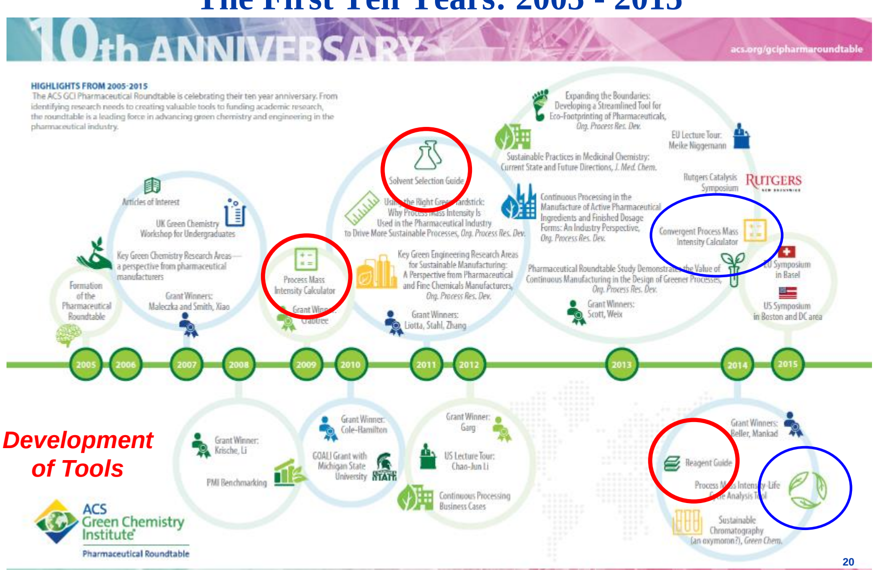
The First Ten Years: 2005 - 2015



Development of Tools

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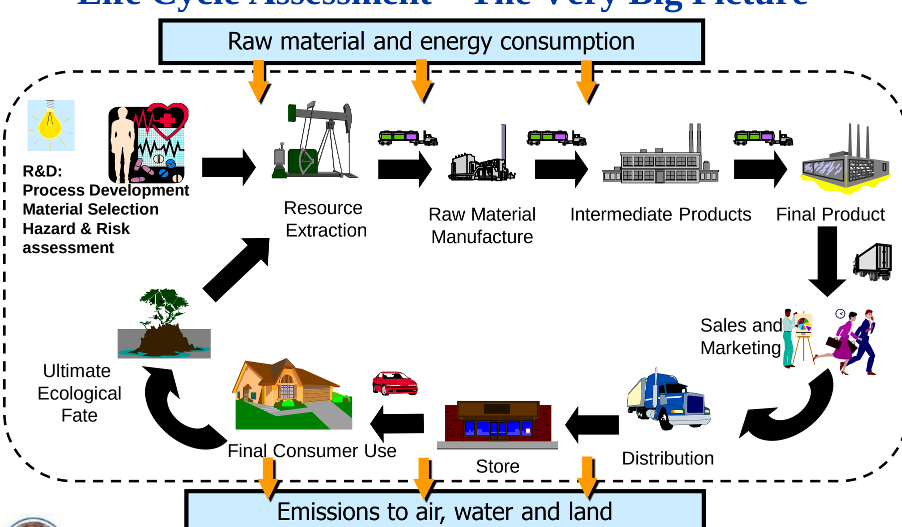
The Challenge…..

- Decreasing the amount of material used to make a drug is one of the major green chemistry challenges for the pharmaceutical industry.
- ACS GCI Pharmaceutical Roundtable members have developed a common process mass intensity metric that allows data from each company to be compared on a transparent and equitable basis.

Life Cycle Assessment – The Very Big Picture



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Why Metrics ???

"You can't manage what you don't measure."

- We measure what we care about ↔ we care about what we measure
- Standardize measurement of chemical process greenness when possible
- Proper choice of metrics is critical for 'behavior of system
- Green metrics correlate to process economics

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Why Not Simply Increase the YIELD ??

- **For API manufacture,** (not finished product):
  - "Typical" Pharma manufacturing yield from a single stage ranges between 35 and 95% with an average of **86%**
  - A "typical" Pharma primary manufacturing process is on the order of 6 stages with an overall yield of **30 - 40%**
  - Overall yield does not capture use of reagent, solvent, catalyst. If these are included the average total materials use is **16** kg/kg of stage product (intermediate).
  - Even with a 100% yield at each stage, a 16 kg/kg materials use would result in an overall Mass Productivity of about **2%.**

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Numerous Options Available…..

Atom Economy *(Trost)*

$$\text{Percent Atom Economy} = \frac{\text{Mass of Desired Product}}{\text{Total Mass of all Reagents}} \times 100$$

Science, **199**1, *254*, 1471

E-Factor *(Sheldon)*

$$\text{E Factor} = \frac{\text{Total waste (kg)}}{\text{kg product}}$$

Industry segment	Tonnes per annum	*E* factor (kg waste per kg product)
Oil refining	10^6–10^8	<0.1
Bulk chemicals	10^4–10^6	<1–5
Fine chemicals	10^2–10^4	5–50
Pharmaceuticals	10–10^3	25 – >100

Green Chem., **2017**, *19*, 18

Green Chem., **2002**, *4*, 521

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Process Mass Intensity (PMI) Metric

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

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 final form.

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

Audience Challenge Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

What is the E-Factor and the PMI Value for an "IDEAL" Sustainable/Green Process?

- E-factor = PMI = 0
- E-factor = 0, PMI = 1
- E-factor = PMI = 1
- E-factor = 1, PMI = 0
- All of the above

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Why measure PMI ?

- **Drive change towards more sustainable manufacturing processes**
  - Track environmental manufacturing footprint.
  - Measurement of process efficiency.
- **Quantify improvements throughout process development life-cycle**
- **To be more transparent; basis for objective comparison**
  - Increasing expectations from internal and external audiences to describe progress, demonstrate improvement.
- **Benchmark**
  - Allows a simple comparison to the on-going green efforts throughout the industry in the pursuit of mass efficient pharmaceutical processes.
- **Insight in sustainability of overall manufacturing process, from bulk chemicals to API, is required**

Org. Process Res. Dev., **2011**, *15*, 912

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Audience Challenge Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

What component of a chemical process contributes most to the overall Process Mass Intensity?

- Reagents
- Water
- Catalyst
- Solvents
- Any of the above

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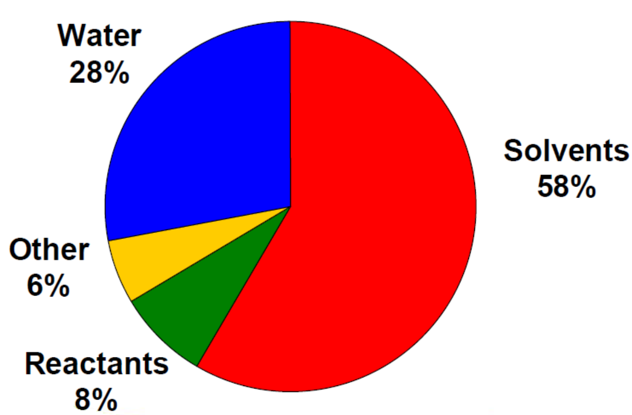
Composition of PMI — Pharma Benchmarking



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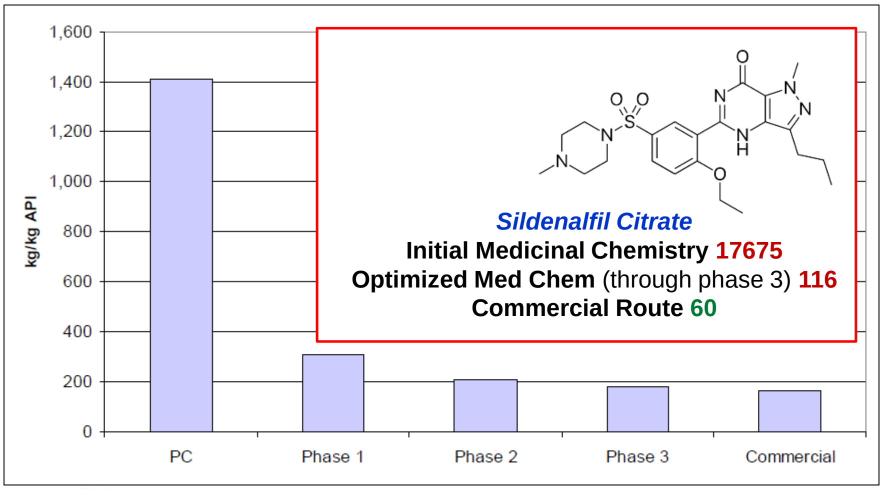
PMI by Development Phase – Median Values



Green Chem., **2015**, *17*, 3390

PMI Calculator Tool

PMI Excel Spreadsheet

– Spreadsheet with embedded Calculations.

– Only need to fill in amounts of reagents, solvents, and aq.

– Spreadsheet calculates step and overall PMI for linear sequences.

– Calculates overall PMI as well as separate PMI for solvents, water, and reagents.

Step Name/Number	1	
	Value	Units
Physical Batch Size		
Assay Purity		
Assay Batch Size		
Yield		
Assay Kg product		
Product Purity		
Raw Materials		Physical Charge (kg)
Substrates		
Reagents		
Solvents		
Aqueous		
PROCESS STEP METRICS		
Mass Substrate (kg)		0
Mass Reagents (kg)		0
Mass Solvents (kg)		0
Mass Aqueous (kg)		
Step PMI		#DIV/0!
Step PMI Excluding H2O		#DIV/0!
Cumulative PMI		#DIV/0!
Cumulative PMI Excluding H2O		#DIV/0!

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Convergent PMI Tool

Step Name/Number	2	
	Value	Units
Physical Batch Size	155	kg
Substrate Assay Purity	99%	wt%
Assay Batch Size	153.5	kg
Molar Yield	91%	
Assay Kg product	217	kg
Product/Intermediate Purity	100%	wt%
Raw Materials	Physical Charge	Units
Substrates		
Product from step 1	155	kg
Reagents		
Diisopropylethylamine	105	kg
4-chlorobenzoyl chloride	147	kg
		kg
Solvents		
2-MeTHF	700	kg
heptane	450	kg
		kg
Aqueous		
2N HCl	420	kg
25% NaCl	220	kg
		kg
PROCESS STEP METRICS		
Mass Substrate (kg)		155
Mass Reagents (kg)		252
Mass Solvents (kg)		1150
Mass Aqueous (kg)		640
Step PMI		10.1
Step PMI Substrate, Reagents, Solvents		7.2
Step PMI Substrates and Reagents		1.9
Step PMI Solvents		5.3
Step PMI Water		2.9
Cumulative PMI		19.0
Cumulative PMI Substrate, Reagents, Solvents		14.0
Cumulative PMI Substrates and Reagents		3.2
Cumulative PMI Solvents		10.8
Cumulative PMI Water		5.0

Step 1 Input Table		
	Value	Units
Assay Batch Size (input pure)		kg
Assay Kg product (output pure)		kg
Raw Materials	Physical Charge	Units
Main Substrate (Enter only 1 substrate, prepopulated from assay batch size)		
	0.00	kg
Fragment Substrates (fill top down)		
None		kg
None		kg
None		kg
Reagents		
		kg
		kg

Instructions | Summary Table | Final Product PMI | Fragment 1 PMI | Fragment 2

- Up to **11** step linear sequence
- Up to **3** branches for convergent synthesis (11 steps per branch)
- Multiple branch points possible in a single step
- Up to **44** step linear sequence if treating additional steps as branches

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Development of a Solvent Guide

- During pharmaceutical process development solvent selection is key in determining the sustainability of future commercial production methods.
- Benchmarking has demonstrated that solvents contribute to >50% of materials used in manufacture of bulk active pharmaceutical ingredients.
- Several individual member companies have developed solvent selection guides internally.

Org. Process Res. Dev., **2015**, *19*, 740

Audience Challenge Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

The toxicity of benzene is now well-known. However, which of the following is NOT a previous use of this solvent?

- An additive to gasoline (petrol)
- As after-shave lotion
- To decaffeinate coffee
- A deep-cleaning detergent
- All of the above

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Common Themes Evolve….

- **Worker Safety** – including carcinogenicity, mutagenicity, reprotoxicity, skin absorption/sensitization and toxicity
- **Process Safety** – including flammability, potential for high emissions through high vapour pressure, static charge, potential for peroxide formation and odour issues
- **Environmental and Regulatory Considerations** – including ecotoxicity and ground water contamination, potential EHS regulatory restrictions, ozone depletion potential, photoreactive potential. Compliance with regulations and company guidelines

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Benefits of a Common Tool

- Delivery of a resource to all member companies enabling scientists to integrate green chemistry and engineering principles
- Validation of existing member company tools
- Potential resource saving if company specific tools do not need to be created or maintained
- Existence of a common tool will provide basis for influencing solvent manufacturers to develop greener alternatives and ensure holistic approach
- An educational tool, for example, at Green Chemistry student workshops

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Initial Version of the Guide – Solvents Chosen

- **First version of guide to be developed with limited number of solvents** (63)
- **Simple voting to establish the base group**
  - *Include some solvents with obviously poor green profile e.g. benzene, carbon tetrachloride*
  - *Include some new "green alternative" solvents e.g. cyclopentyl methyl ether, 2-methyltetrahydrofuran*
- **5 sub-categories defined for assessing and scoring solvents**
  - Safety
  - Health
  - Environment (Air impact)
  - Environment (Water impact)
  - Environment (Waste impact)

Solvent Guide

ACS GCI Pharmaceutical Roundtable Solvent Selection Guide

www.acs.org/gcipharmaroundtable

Substance Information			Scoring Information				
Solvent Class	Solvent Name	CAS Number	Safety	Health	Env (Air)	Env (Water)	Env (Waste)
Acid	ACETIC ACID	64-19-7	3	6	6	3	6
Acid	ACETIC ANHYDRIDE	108-24-7	3	6	6	2	7
Acid	FORMIC ACID	64-18-6	2	6	5	4	7
Acid	METHANE SULPHONIC ACID	75-75-2			6	6	10
Acid	PROPIONIC ACID	79-09-4	2	5	6	4	6
Alcohol	1-BUTANOL	71-36-3	3	5	5	5	3
Alcohol	1-PROPANOL	71-23-8	4	4	6	2	6
Alcohol	2-BUTANOL	78-92-2	4	5	6	3	5
Alcohol	2-METHOXYETHANOL	109-86-4	4	9	5	3	7
Alcohol	BENZYL ALCOHOL	100-51-6	4	3	4	2	4
Alcohol	ETHANOL	64-17-5	4	3	5	1	6
Alcohol	ETHYLENE GLYCOL	107-21-1	3	3	5	1	7
Alcohol	ISOAMYL ALCOHOL	123-51-3	3	4	5	3	4
Alcohol	ISOBUTANOL	78-83-1	3	5	4	3	3
Alcohol	ISOPROPYL ALCOHOL (IPA)	67-63-0	5	5	6	2	6
Alcohol	METHANOL	67-56-1	3	5	6	3	6
Alcohol	T-BUTANOL	75-65-0	3	5	7	2	6
Aromatic	BENZENE	71-43-2	5	10	6	6	2
Aromatic	TOLUENE	108-88-3	5	7	6	6	2
Base	PYRIDINE	110-86-1	3	6	7	7	6
Base	TRIETHYLAMINE (TEA)	121-44-8	4	7	5	7	4
Dipolar aprotic	ACETONITRILE	75-05-8	3	5	6	4	6
Dipolar aprotic	DIMETHYL ACETAMIDE (DMAC)	127-19-5	2	7	3	7	7

The Numbers behind the Guide….

Substance Information			Safety Scoring Information											
			Flammability			Auto Ignition		Static Conductivity		Peroxide Former		
Solvent Class	Solvent Name	CAS Number	Boiling Point (°C)	Flash Point (°C)	Score	Auto Ignition Temperature (°C)	Score	Conductivity (pS/m)	Score	Peroxide formation	Score	TOTAL SCORE
Acid	ACETIC ACID	64-19-7	117.9	39	1	426	1	1.12E+06	1	N	0	3
Acid	ACETIC ANHYDRIDE	108-24-7	139.5	53.9	1	390	1	4.76E+07	1	N	0	3
Acid	FORMIC ACID	64-18-6	101	69	1	520	0	6.40E+09	1	N	0	2
Acid	METHANE SULPHONIC ACID	75-75-2	167	189	1	500	0			N	0	
Acid	PROPIONIC ACID	79-09-4	141.15	51	1	465	0	1.00E+05	1	N	0	2
Alcohol	1-BUTANOL	71-36-3	117.73	37	1	343	1	9.00E+05	1	N	0	3
Alcohol	1-PROPANOL	71-23-8	97.2	23	2	412	1	2.00E+06	1	N	0	4
Alcohol	2-BUTANOL	78-92-2	99.51	24	1	390	1	3.00E+06	1	2	1	4
Alcohol	2-METHOXYETHANOL	109-86-4	124.1	39	1	285	1	9.30E+08	1	1	1	4
Alcohol	BENZYL ALCOHOL	100-51-6	205.31	93	1	436	1	1.80E+08	1	2	1	4
Alcohol	ETHANOL	64-17-5	78.29	12	2	363	1	1.43E+08	1	N	0	4
Alcohol	ETHYLENE GLYCOL	107-21-1	197.3	111	1	398	1	1.16E+08	1	N	0	3
Alcohol	ISOAMYL ALCOHOL	123-51-3	131.1	43	1	350	1	1.40E+05	1	N	0	3
Alcohol	ISOBUTANOL	78-83-1	108	27	1	415	1	2.00E+06	1	N	0	3
Alcohol	ISOPROPYL ALCOHOL (IPA)	67-63-0	82.3	12	2	360	1	6.00E+07	1	2	1	5
Alcohol	METHANOL	67-56-1	64.6	11	2	464	0	4.40E+07	1	N	0	3
Alcohol	T-BUTANOL	75-65-0	82.4	11	2	478	0	1.00E+08	1	N	0	3
Aromatic	BENZENE	71-43-2	80.09	-11	2	498	0	1.00E-01	3	N	0	5
Aromatic	TOLUENE	108-88-3	110.63	4	2	480	0	1.00E+00	3	N	0	5

Similar worksheets exist for "Health" (reprotoxic, carcinogenic and mutagenic effects, toxicity, skin effects etc)**, "Environment** (Air impact)**"** (Volatility, Odour, ozone depletion Potential)**, "Environment** (Water impact)**"** (persistence, ecotoxicity, solubility, etc.)**, and "Environment** (Waste)**"** (potential for incineration, potential for recycling).

Example for Safety Scoring…..

Flammability

Score (color/number)	Flammability category	Flash Point (FP) and/or Boiling Point (BP)
Red (3)	Extreme flammability	FP ≤ 23°C and BP ≤ 35°C
Yellow (2)	Flammability of concern	FP ≤ 23°C and BP > 35°C
Green (1)	No concern	FP > 23°C
Green (0)	No concern	No FP

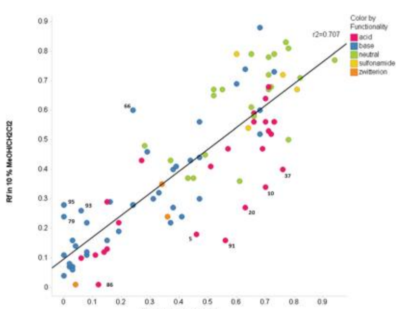
Peroxide Formation

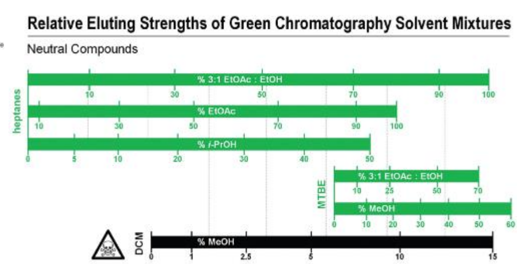
Score (color/number)	Peroxide former	Risk
Red (1)	1 – High risk 2 – Medium risk	Known risk
Green (0)	N – No risk	No known risk

Alternatives for Chromatography…..

Replacement of dichloromethane within chromatographic purification: a guide to alternative solvents†‡

Donna S. MacMillan,[a] Jane Murray,[b] Helen F. Sneddon,[c] Craig Jamieson[a] and Allan J. B. Watson*[a]





A convenient guide to help select replacement solvents for dichloromethane in chromatography†

Joshua P. Taygerly,*[a] Larry M. Miller,[b] Alicia Yee[c] and Emily A. Peterson*[d]

Green Chem., **2012**, *14*, 3016 and 3020

MedChem Tips and Tricks

https://www.acs.org/content/acs/en/greenchemistry/research-innovation/tools-for-green-chemistry/medchem-tips-and-tricks.html

Purification Green Chromatography decision tree (*Green Chem*. 2014, **16**, 4060)

Solvent GSK, Pfizer, Sanofi solvent guides

Alternatives to DMF and DCM in amide couplings (*Green Chem.* 2012, **14**, 596)

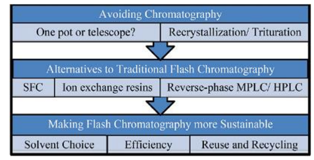


Table 2 Illustrative representation of the amidation dataset.[a]

Amide Coupling Type: Aryl Acid – Aryl Amine

Solvent	HATU	COMU	DIC HOBt	PyBOP	T3P
TBME	* (green)	(green)	* (green)	* (green)	(red)
CPME	(green)	(orange)	(red)	(green)	* (green)
CH_2Cl_2	** (green)	(green)	* (green)	* (green)	* (green)
DMC	* (green)	* (green)	* (green)	* (green)	** (green)
DMF	** (green)	** (green)	** (green)	(green)	(red)
EtOAc	* (green)	* (green)	* (green)	* (green)	** (green)
IPA	* (green)	* (green)	* (green)	* (green)	(green)
2-MeTHF	* (green)	* (green)	* (green)	* (green)	(green)

Amide Coupling Type: Aryl Acid – Alkyl Amine

Solvent	HATU	COMU	DIC HOBt	PyBOP	T3P
TBME	(red)	(red)	* (green)	(red)	(red)
CPME	(red)	(red)	(orange)	(red)	** (green)
CH_2Cl_2	* (green)	** (green)	* (green)	* (green)	* (green)
DMC	** (green)	** (green)	** (green)	** (green)	** (green)
DMF	* (green)	* (green)	** (green)	** (green)	* (green)
EtOAc	** (green)	** (green)	** (green)	** (green)	** (green)
IPA	* (green)	** (green)	* (green)	** (green)	* (green)
2-MeTHF	(green)	* (green)	* (green)	* (green)	* (green)

Amide Coupling Type: Alkyl Acid – Aryl Amine

Solvent	HATU	COMU	DIC HOBt	PyBOP	T3P
TBME	(green)	(red)	(red)	(red)	(red)
CPME	(red)	(red)	(red)	(orange)	(red)
CH_2Cl_2	** (green)	** (green)	* (green)	* (green)	(orange)
DMC	* (green)	* (green)	(green)	(green)	(orange)
DMF	** (green)	** (green)	* (green)	* (green)	(red)
EtOAc	* (green)	** (green)	* (green)	(green)	(orange)
IPA	* (green)	* (green)	(red)	(red)	(red)
2-MeTHF	* (green)	** (green)	* (green)	* (green)	(red)

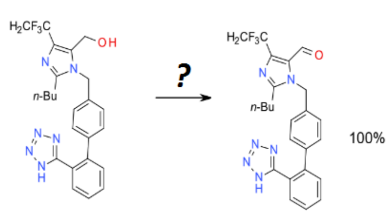
Amide Coupling Type: Alkyl Acid – Alkyl Amine

Solvent	HATU	COMU	DIC HOBt	PyBOP	T3P
TBME	** (green)	** (green)	** (green)	* (green)	* (green)
CPME	** (green)	* (green)	** (green)	** (green)	** (green)
CH_2Cl_2	* (green)	** (green)	** (green)	** (green)	** (green)
DMC	** (green)	** (green)	* (green)	** (green)	* (green)
DMF	** (green)	** (green)	** (green)	* (green)	** (green)
EtOAc	** (green)	** (green)	** (green)	** (green)	** (green)
IPA	** (green)	** (green)	** (green)	** (green)	(orange)
2-MeTHF	* (green)	** (green)	* (green)	* (green)	** (green)

[a] Key: Red = <50% conv., orange = 50-70% conv., green = >70% conv.; * Indicates 100% conv. within 4 h. ** Indicates 100% conv. within 1 h.

Reagents, Energy, Resources

Why Do We Need A Reagent Guide ?



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Development of a Reagent Guide

Three Ideal Characteristics……

1) **To provide a balanced assessment of chemical methods.**
   - Ability to work in good yield in a wide variety of "drug-like" molecules
   - Ability to be utilized for "scale-up" purposes
   - To be as "green as possible". (worker safety, atom economy etc.)

2) **To provide easy access to the chemical literature**

3) **To raise awareness of newer emerging "greener" methodologies**

Dunn *et al*., *Green Chem*., **2008**, *10*, 31

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Online at "reagentguides.com"

The reagent guides purpose is to encourage chemists to choose a 'greener' choice of reaction conditions. The guides aim to achieve this by providing transparency through the use of Venn diagrams in addition to improving understanding by discussion and up to date references.

The Reagent Guides	How to Interpret the Venn Diagrams	Ethos of the Reagent Guides
Select the chemical transformation of interest		Understand the purpose behind the construction of the guides.
VIEW »	VIEW »	VIEW »

Name: reagent
Password: guide

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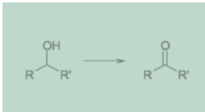
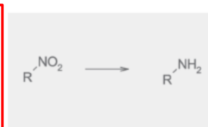
Sixteen Guides and Counting…..

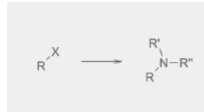
Reagent Guides



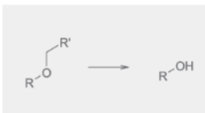
Oxidation to aldehyde and ketones



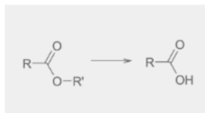
Nitro reduction



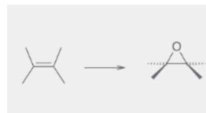
N-Alkylation



O-dealkylation



Ester Deprotection



Epoxidation

Also….

Boc deprotection
Amide reduction
Bromination
Reductive amination
Metals removal
Buchwald-Hartwig
Iodination
Chlorination
Chiral Hydrogenation
Suzuki-Miyaura

Coming soon….

Fluorination
Amide bond formation

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Initially…..

Home / Reagent Guides / Oxidation to aldehyde and ketones

Oxidation of Alcohols Reagent Guide

The inclusion of an article in this document does not give any indication of safety or operability. Anyone wishing to use any reaction or reagent must consult and follow their internal chemical safety and hazard procedures and local laws regarding handling chemicals

View circa Jan 2014

Cr reagents used for oxidation seem to have been replaced largely by greener reagents, although publications persist on 'green' variants of Cr (VI) oxidants.

MnO_2 and hypervalent iodine oxidations are still fairly common in early phase development/med chem publications and occur frequently in early routes – these reagents tend to be designed out or replaced with greener ones. Hypervalent iodine reagents do still find use with some complex substrates. Variants of catalytic hypervalent iodine reagents are now appearing. The most common oxidation pathways use TEMPO-type catalysts with a terminal oxidant, the Corey- Kim method, and activated DMSO variants (Swern oxidation). A very popular DMSO activating agent for larger scale work is the pyridine SO_3 complex.

Chlorine –pyridine, $Ba(MnO_4)_2$ and, to a lesser extent, nickel peroxide [probably $NiO(OH)_2$] find little use as oxidants for the synthesis of aldehydes or ketones. Over the past five years, there has been an exponential increase in the number of publications related to the use of metals and air (O_2) or H_2O_2, presumably due to the good atom economy and ease of processing. Process intensification and flow chemistry are used to minimize issues with exothermic chemistry and hazards associated with flammable solvents and oxidants. Many more biocatalytic approaches to alcohol oxidation are also being developed.

General Review

Caron, S.; Dugger, R. W.; Gut Ruggeri, S.; Ragan, J. A.; Brown Ripin, D. H. Large-Scale Oxidations in the Pharmaceutical Industry. *Chem. Rev.* **2006**, 106 (7), 2943–2989.

Oxidation to aldehyde and ketones

Overview

List of Reagents

- Nickel Peroxide, $NiO(OH)_2$
- Manganese Dioxide, MnO_2
- Hypervalent Iodine reagents – general overview
- IBX 2-Iodoxybenzenesulfonic Acid
- Dess Martin Periodate
- $NaICl_2$ A simple system for the oxidation of alcohols
- PDC Pyridium dichromate oxidations
- PCC Review on Cr(VI) oxidation
- Oppenauer oxidation: An Integrated Approach
- DMSO –Oxalyl Chloride, Swern oxidation
- DMSO/DCC Pfitzner-Moffat (also TFAA activation)
- DMSO – Pyridine-SO_3 (Parikh-Doering)
- DMSO activation in Pseudo-Swern reaction
- Me2S./NCS Corey - Kim oxidation
- NaOCl bleach oxidation
- TCA Trichloroisocyanuric Acid: A Safe and Efficient Oxidant
- TPAP/NMO (tetrapropylammonium perruthenate)

** Brief Intro to the Transformation Highlighting Common Approaches with General Reviews*

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List of Reagents….

Full Review

- NiO_2 oxidation of alcohols
- MnO_2 oxidations in organic chemistry
- Hypervalent Iodine reagents – general overview
- IBX 2-Iodoxybenzenesulfonic Acid
- Dess Martin Periodate
- $NaICl_2$ A simple system for the oxidation of alcohols
- PDC Pyridium dichromate oxidations
- PCC Review on Cr(VI) oxidation
- Oppenauer oxidation: An Integrated Approach
- DMSO –Oxalyl Chloride, Swern oxidation
- DMSO/DCC Pfitzner-Moffat (also TFAA activation)
- DMSO – Pyridine-SO_3 (Parikh-Doering)
- DMSO activation in Pseudo-Swern reaction
- Me_2S/NCS Corey - Kim oxidation
- NaOCl bleach oxidation
- TCA Trichloroisocyanuric Acid: A Safe and Efficient Oxidant

Light touch overview

- $BaMnO_4$ oxidation of primary and secondary alcohols
- Potassium Ferrate A Novel Oxidizing Reagent Based on Potassium Ferrate(VI)
- Oxidation with Chlorine /Pyridine complexes
- $RuCl_3$
- PIPO- Polymer immobilised TEMPO
- Ce Cerium(IV) ammonium nitrate
- Aqueous oxone
- AZIDO (TEMPO variants)

Two Categories in Terms of Depth of Coverage

$RuCl_3$
PIPO- Polymer immobilised TEMPO
Ce Cerium(IV) ammonium nitrate
Aqueous oxone
AZIDO (TEMPO variants)

Alternatively…. → Venn Diagram

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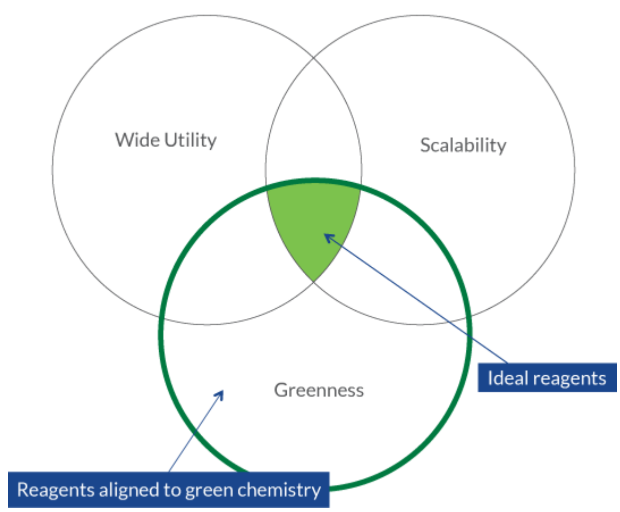
Interpretation of Venn Diagrams



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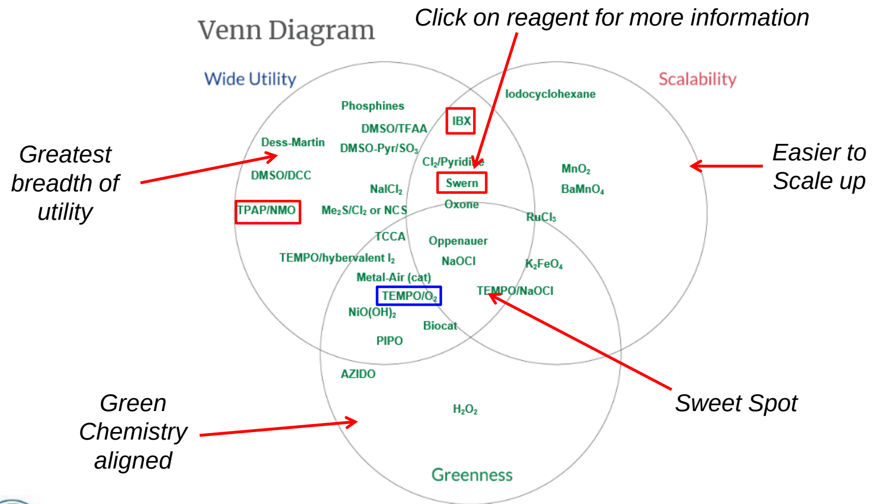
Visual Depiction of Reagent Ranking

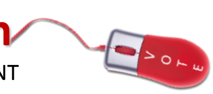
Venn Diagram

Click on reagent for more information



Audience Challenge Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT



Due to the cheap reagents involved, and it's tolerance to a wide variety of functional groups, the Swern oxidation was once widely used. Why do chemists tend to look for alternatives today?

- The reaction requires cryogenic temperatures
- To avoid the use of chlorinated solvents
- The odor of Me_2S as a by-product
- The reaction liberates CO
- All of the above

Tetrahedron, **1978**, *34*, 1651.

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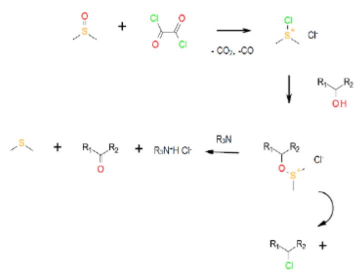
For Each Reagent…..

DMSO –Oxalyl Chloride, Swern oxidation

Mechanism + Description

The Swern oxidation is one of a related series of oxidations based on activated DMSO. In the Swern varient, oxalyl chloride generates the dimethylchlorosulfonium chloride. Reaction with the alcohol produces an oxy sulphonium ion which undergoes base –catalyzed elimination to give the ketone and Me_2S.



General comments

This non-catalytic oxidation that avoids heavy metals was once widely used. Drawbacks are that it needs cryogenic temperatures (-60 °C) and generates Me_2S as a by-product. Other issues include dealing with exothermic chemistry and the potential for side reactions to occur if the temperature is not well-controlled. Other activators that give more controlled reactions and allow operation at higher temperatures have generally replaced oxalyl chloride.

The highly exothermic nature of Swern-type oxidations and the need for cryogenics to minimize side reactions make these oxidations good candidates for continuous flow reactions.

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For Each Reagent…..

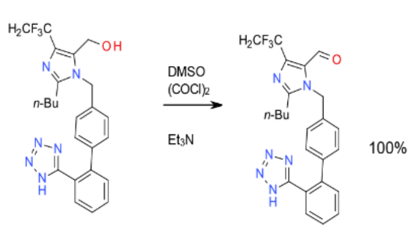
Key references

Omura, K.; Swern, D. Oxidation of alcohols "activated dimethyl sulfoxide. A preparative, steric and mechanistic study. *Tetrahedron.* **1978**, 34 (11), 1651-1660.

Mancuso, A. J.; Brownfain, D. S.; Swern, D. Structure of the dimethyl sulfoxide-oxalyl chloride reaction product. Oxidation of heteroaromatic and diverse alcohols to carboynl compounds. *J. Org. Chem.* **1979**, 44 (23), 4148–4150.

Russell McConnell, J.; Hitt, J. E.; Daugs, E. D.; Rey, T. A. The Swern Oxidation: Development of a High-Temperature Semicontinuous Process. *Org. Process Res. Dev.* **2008**, 12 (5), 940-945.

Relevant scale-up example



Tetrahedron 1997, 53, 10953

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For Each Reagent. Green Review.

1. **Atom efficiency (by-products)**
   Moderately atom efficient for an oxidation with 172 for loss of H_2.
2. **Safety concerns**
   CO_2 and CO evolution from oxalyl chloride – very exothermic reaction and needs careful handling on scale. Me_2S by-product needs to be controlled.
3. **Toxicity and environmental/aquatic impact**
   Has similar effects to phosgene.
4. **Cost, availability & sustainable feedstocks**
   Reagents are cheap and readily available, but the use of oxalyl chloride has now been largely phased out with other DMSO activators.
5. **Sustainable implications**
   No large issues with reagents. Sustainability issues are usually dominated by solvents, normally chlorinated, used for the Swern oxidation.

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Continuous Improvement/Feedback

Guide Comments?

We are continually improving the reagent guides. If you have any references, corrections, or comments, please use this form to let us know.

Your Name (*)

Your Email (*)

Reference URL

Comment (*)

Please enter the string of letters and numbers seen below to validate your entry.

yuo/

Send

Look for the comment sidebar on the reagent pages and contact page

www.reagentguides.com

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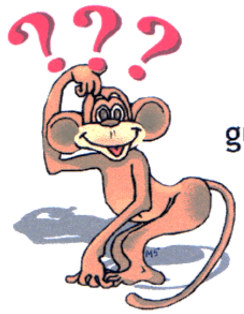
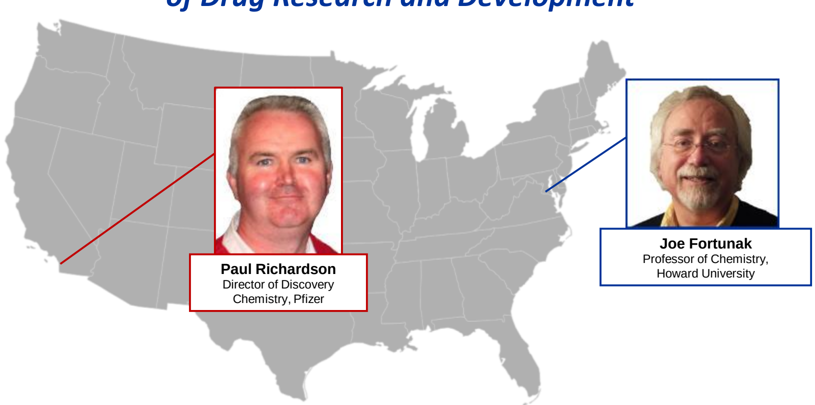
Thank you !!!



Questions are guaranteed in life; Answers aren't.

Paul.F.Richardson@pfizer.com

How to Sustainably Innovate Throughout the Life Cycle of Drug Research and Development



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Valerie Patrick, President, Fulcrum Connection

Bryan Tweedy, Manager, Office of Career and Professional Resources, ACS

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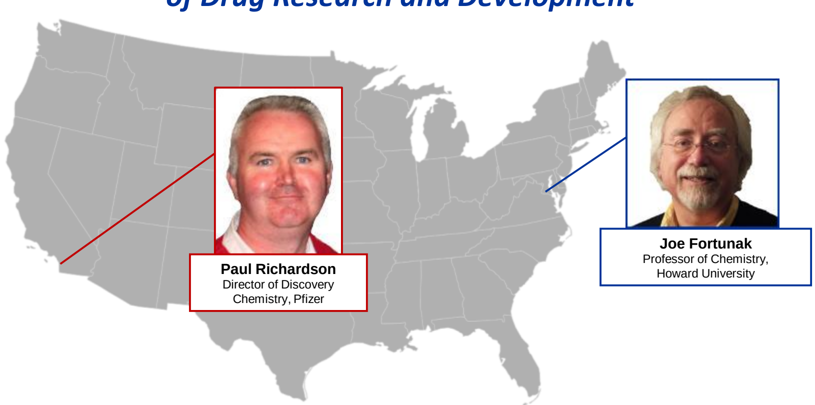

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