American Chemical Society

ACS Green Chemistry Institute®

ACS GCI Pharmaceutical Roundtable

Collaboration to Deliver a Solvent Selection Guide for the Pharmaceutical Industry

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Presentation Overview

- ACS GCIPR mission, priorities and objectives
- Project background
- Development of a common guide
- Future work
- Questions

ACS GCI Pharmaceutical Roundtable

members as of September 15, 2008

ACS GCI Pharmaceutical Roundtable

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

- Strategic Priorities:
  - Informing and Influencing the Research Agenda
  - Tools for Innovation
  - Education Resource
  - Global Collaboration

2008 Objectives - Summary

- Informing & Influencing the Research Agenda
  - Publish and co-author Green Chemistry Articles of Interest
  - Issue ACS GCIPR Research Grants
  - Identify matching funds for research
- Educating Leaders
  - Fund research lecture tours in the EU and North America
  - Develop GC Student Workshops
- Defining and Developing Tools for Innovation
  - Support CAS project to implement green search capability
  - Perform metrics benchmarking exercise
  - Develop reagent selection guide and solvent selection guide
- Collaborating Globally
  - Initiate/host biocatalysis & EU subgroups
  - Influence solvent manufacturers to develop greener alternatives
  - Determine the role for GCIPR in biopharmaceuticals

Background

- 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

Process Mass Intensity Metric

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

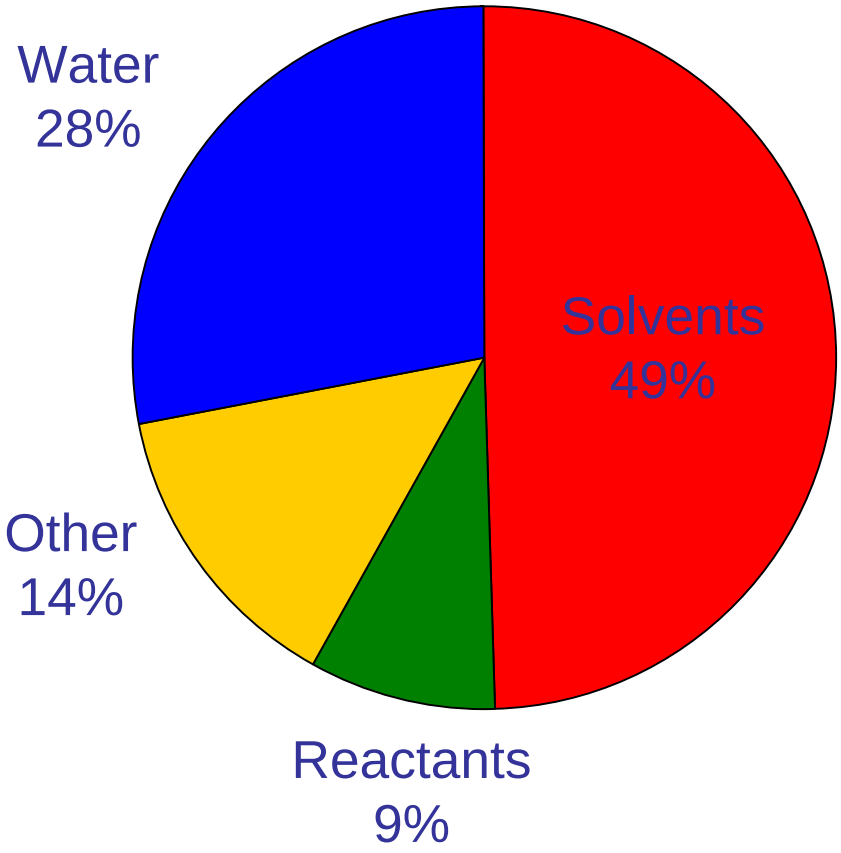
Where:

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

Composition of PMI



- Solvent and water contribute ~80% of the process mass intensity
- Emphasizes need to reduce the use and hazard of the solvent

Examples of existing guides

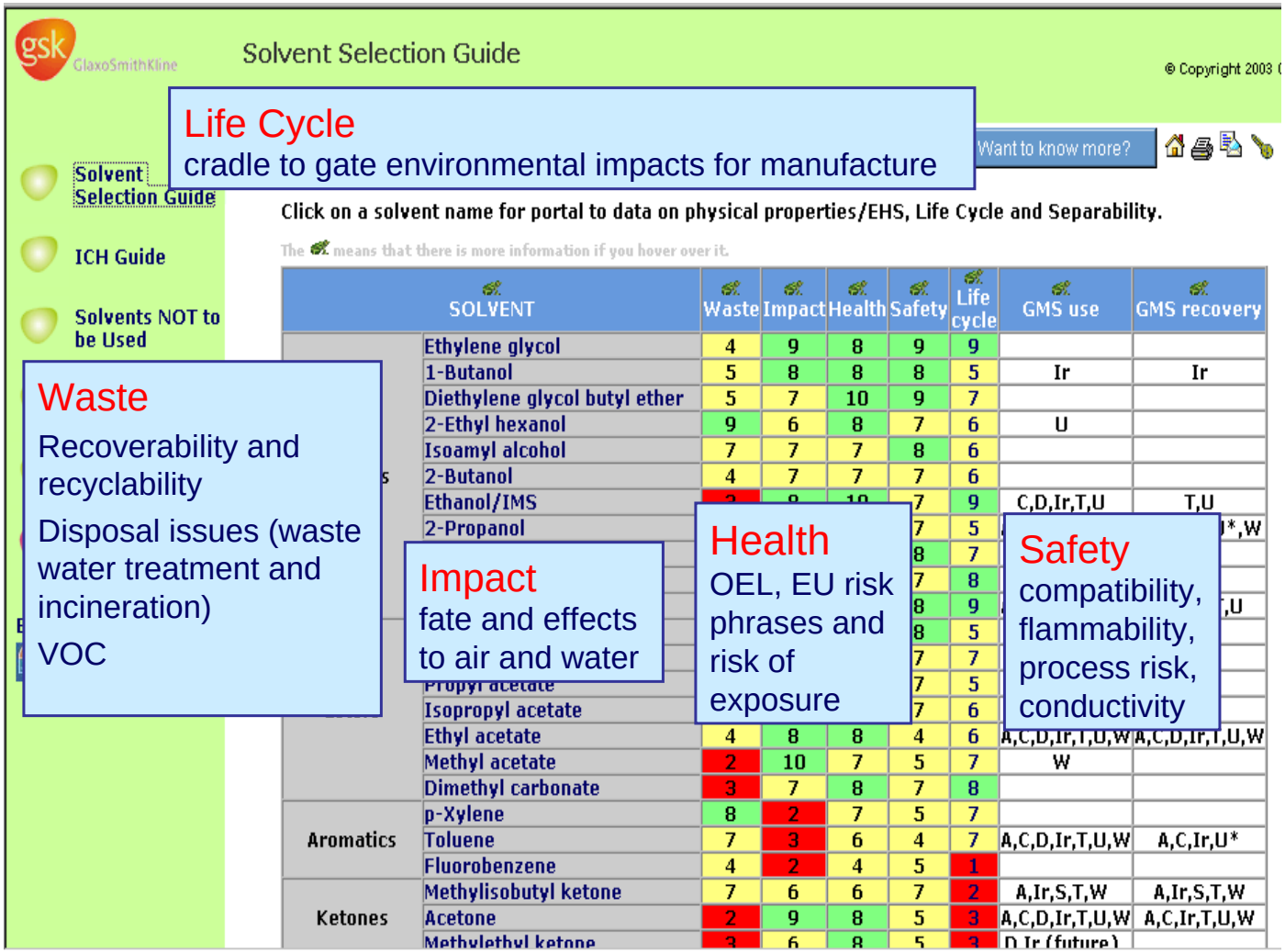
Pfizer Medicinal Chemistry Solvent Selection Guide

Preferred	Usable	Undesirable
Water	Cyclohexane	Pentane
Acetone	Heptane	Hexane(s)
Ethanol	Toluene	Di-isopropyl ether
2-Propanol	Methylcyclohexane	Diethyl ether
1-Propanol	TBME	Dichloromethane
Ethyl Acetate	Isooctane	Dichloroethane
Isopropyl acetate	Acetonitrile	Chloroform
Methanol	2-MeTHF	NMP
MEK	THF	DMF
1-Butanol	Xylenes	Pyridine
t-Butanol	DMSO	DMAc
	Acetic Acid	Dioxane
	Ethylene Glycol	Dimethoxyethane
		Benzene
		Carbon tetrachloride

Pfizer Solvent Replacement Table

Red Solvents	Alternative
Pentane	Heptane
Hexane(s)	Heptane
Di-isopropyl ether or ether	2-MeTHF or t-Butyl methyl ether
Dioxane or dimethoxyethane	2-MeTHF or t-Butyl methyl ether
Chloroform, dichloroethane or carbon tetrachloride	DCM
DMF NMP or DMAc	Acetonitrile
Pyridine	Et_3N (if pyridine used as base)
DCM (extractions)	EtOAc, MTBE, toluene, 2-MeTHF
DCM (chromatography)	EtOAc / Heptanes
Benzene	Toluene

Examples of existing guides



SOLVENT		Waste	Impact	Health	Safety	Life cycle	GMS use	GMS recovery
	Ethylene glycol	4	9	8	9	9		
	1-Butanol	5	8	8	8	5	Ir	Ir
	Diethylene glycol butyl ether	5	7	10	9	7		
	2-Ethyl hexanol	9	6	8	7	6	U	
	Isoamyl alcohol	7	7	7	8	6		
	2-Butanol	4	7	7	7	6		
	Ethanol/IMS				7	9	C,D,Ir,T,U	T,U
	2-Propanol				7	5		*,W
					8	7		
					7	8		
					8	9		,U
					8	5		
					7	7		
	Propyl acetate				7	5		
	Isopropyl acetate				7	6		
	Ethyl acetate	4	8	8	4	6	A,C,D,Ir,T,U,W	A,C,D,Ir,T,U,W
	Methyl acetate	2	10	7	5	7	W	
	Dimethyl carbonate	3	7	8	7	8		
	p-Xylene	8	2	7	5	7		
Aromatics	Toluene	7	3	6	4	7	A,C,D,Ir,T,U,W	A,C,Ir,U*
	Fluorobenzene	4	2	4	5	1		
	Methylisobutyl ketone	7	6	6	7	2	A,Ir,S,T,W	A,Ir,S,T,W
Ketones	Acetone	2	9	8	5	3	A,C,D,Ir,T,U,W	A,C,Ir,T,U,W
	Methylethyl ketone	3	6	8	5	3	D,Ir (future)	

Examples of existing guides

AstraZeneca

Solvent Selection Guide

Solvent selection is a key part of process development. Because of the volumes used, solvents can often result in the biggest SHE impact of a process. This summary table assigns a score from 1 to 10 for each solvent under the respective categories with 10 being of concern and 1 suggesting few issues. This is further simplified by using colour coding with scores between 1 and 3 being green, 4 to 7 yellow and 8 to 10 red.

Substance			Safety		Health	Environment						
	Name	CAS No.	Flammability	Static	Health	Impact in Air	VOC Potential	Impact in Water	Potential Biotreatment Plant Load	Recycle	Incineration	Life Cycle Analysis
Acids:	Methane sulphonic acid[1]	75-75-2	1	1	1	1	1	7	4	6	8	3
	Propionic acid	79-09-4	3	1	4	4	1	1	5	6	6	1
	Acetic acid (glacial)	64-19-7	3	1	8	6	3	1	5	6	6	3
	Formic acid	64-18-6	3	1	10	4	5	1	5	6	7	1
Alcohols:	Isoamyl alcohol	123-51-3	3	1	2	1	1	2	4	5	3	Data not available
	1-Pentanol	71-41-0	7	1	1	2	1	1	4	5	3	4
	Isobutanol	78-83-1	7	1	3	2	2	1	5	7	3	6
	n-Butanol	71-36-3	7	1	4	3	2	1	5	6	3	6
	Isopropanol	67-63-0	7	1	3	1	5	1	6	5	5	6
	IMS/Ethanol	64-17-5	7	1	2	2	5	1	7	5	5	1
	Methanol	67-56-1	7	1	5	3	8	1	7	4	5	1
	t-Butanol	75-65-0	7	1	6	2	4	3	7	5	5	1
	2-Methoxy ethanol	109-86-4	3	1	10	8	2	2	5	6	6	5
Alkanes:	Isopar G	90622-57-4	3	10	1	1	1	10	3	10	1	Data not available
	n-hepane	142-82-5	7	10	3	1	5	8	5	2	1	1
	Isooctane	540-84-1	7	10	3	1	5	10	5	2	1	2
	Cyclohexane	110-82-7	7	10	6	1	6	9	5	2	1	6
	Isohexane	107-83-5	7	10	6	1	8	10	6	1	1	1
Aromatics:	Xylene	1330-20-7	7	10	2	4	2	7	3	4	1	3
	Toluene	108-88-3	7	10	5	2	4	7	4	4	1	2
Basics:	Triethylamine	121-44-8	7	1	10	8	6	5	6	5	4	6
	Pyridine	110-86-1	7	1	9	10	3	4	7	6	6	8
Chlorinated:	Chlorobenzene	108-90-7	7	1	8	4	2	9	2	4	6	7
	Methylene chloride[2]	75-09-2	1	1	9	9	10	6	5	2	8	7
Esters:	n-Butyl acetate	123-86-4	7	1	2	3	2	3	3	4	3	4
	Isopropyl acetate	108-21-4	7	1	4	2	5	2	5	4	3	7
	Ethyl acetate	141-78-6	7	1	5	2	6	2	5	5	4	3
Ethers:	Diphenyl ether	101-84-8	1	1	1	4	1	8	3	4	2	6
	Anisole	100-66-3	3	10	2	1	1	4	3	6	2	5
	Tetrahydrofuran	109-99-9	7	1	8	1	7	3	7	6	5	9
	Diglyme	111-96-6	3	1	8	7	1	5	5	10	5	6
	2-Methyltetrahydrofuran	96-47-9	7	1	8	1	7	5	7	9	4	6
	MTBE	1634-04-4	7	1	9	2	8	7	7	5	3	1
	1,2 Dimethoxyethane	110-71-4	3	1	10	7	6	5	7	8	5	6
	1,4-Dioxane	123-91-1	7	10	9	3	4	4	6	9	5	5
	Diethyl ether	60-29-7	10	10	7	3	10	4	7	6	3	2
Fluorinated:	Trifluorotoluene	98-08-8	7	10	8	6	5	8	3	4	6	9
Ketones:	MIBK	108-10-1	7	1	6	1	3	2	4	7	3	9
	Methylethyl ketone	78-93-3	7	1	7	4	6	1	6	7	4	3
	Acetone	67-64-1	7	1	6	3	9	1	9	4	5	4
Polar aprotic:	DMSO[3]	67-68-5	1	1	1	1	1	3	5	6	6	4
	N-Methyl pyrrolidone[4]	872-50-4	1	1	1	1	1	1	6	6	6	8
	Sulfolane	126-33-0	1	1	1	3	1	4	5	6	7	4
	Dimethyl acetamide	127-19-5	3	1	9	7	1	2	6	6	6	8
	DMF	68-12-2	3	1	9	7	1	1	5	6	6	8
	Acetonitrile	75-05-8	7	1	8	2	6	4	8	5	6	9

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

Solvents chosen

- First version of guide to be developed with limited number of solvents (~50)
- 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-methyl tetrahydrofuran

Criteria and data points for scoring

- Safety
  - NFPA rating
  - Flammability
  - Auto Ignition temperature
  - Boiling point
  - Flash point
  - Conductivity (static risk)
  - Peroxide formation
- Health
  - Reprotoxic, carcinogenic and mutagenic effects
  - Toxicity
  - Skin effects
  - Sensitisation
  - Occupational Exposure Limit values
  - Vapour pressure
- Environment (Air impact)
  - Volatility
  - Odour
  - Photochemical Ozone Creation (POCP) potential
  - Photolysis
  - Ozone Depletion Potential (ODP)
  - Global Warming Potential (GWP)
- Environment (Water impact)
  - Persistence (Biodegradation)
  - Bioaccumulation (LogPow)
  - Ecotoxicity
  - Water solubility
- Environment (Waste)
  - Potential for incineration (degree of halogenation, heat of combustion)
  - Potential for recycle (boiling point, miscibility with water, number of close boiling solvents, ease of drying, azeotrope formation)

12 Principles of Green Chemistry

Green Chemistry, Theory & Practice, Anastas & Warner, (1998)

1. Prevent waste rather than treat
2. Maximise incorporation of all materials – atom economy
3. Design synthesis to use or generate least hazardous chemical substances
4. Design safer chemicals to do the desired function
5. Minimise or use innocuous auxiliary agents (solvents,etc)
6. Minimise energy requirements
7. Use renewable raw materials
8. Minimise unnecessary derivatisation
9. Use catalytic versus stoichiometric reagents
10. Process related products should be designed to be biodegradable
11. Use on-line analytical process monitoring to minimise formation of hazardous by-products
12. Choose safer reagents that minimise the potential for accidents

Outputs

- Both outputs will be based on the same data set
- Output 1: Simple Solvent Selection Guide
  - Target audience Discovery/Medicinal scientists
  - Single Red/Amber/Green rating
- Output 2: Full Solvent Selection Guide
  - Target audience Process/Chemical Development scientists
  - Red/Amber/Green rating for each criterion
  - More underlying detail provided on criteria/data

Future work

2009 and beyond:

- Launch and test the guide with member company scientists
- Use the output to support CAS project to implement green search capabilities for existing scientific research tools
- Wider publication, for example, as an education tool for students
- Expand the guide to include more solvents and relevant criteria to measure “green” profile

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Thank-you for listening!

Any questions?

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