PSCI

PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

ACS Green Chemistry Institute®

Pharmaceutical Roundtable

DEKRA Insight

Conference: Day Two

PSCI
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Introduction to Green Chemistry

Presented by

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MSD

绿色化学工具与技术

Jingjun Yin, PhD

MSD

On behalf of ACS Green Chemistry Institute Pharmaceutical Roundtable

PSCI, Shanghai

21 September 2016

课程纲要:

I. 绿色化学介绍	**9:00 – 9:45 AM**
II. 绿色化学工具与方法	**9:45-10:30 AM**
Break	**10:30 – 11:00 AM**
III. 绿色化学实例与展望	**11:00 – 12:30 PM**

ACS Green Chemistry Institute®
Pharmaceutical Roundtable

INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

I – 绿色化学介绍

PSCI, Shanghai

21 September 2016

IQ API 领导团队-绿色化学

1. **API sustainability challenges**
2. **Education materials**
3. **Share best practices**
4. **Engage regulatory agencies**

美国化学会绿色化学研究中心制药工业圆桌

ACS Green Chemistry Institute®
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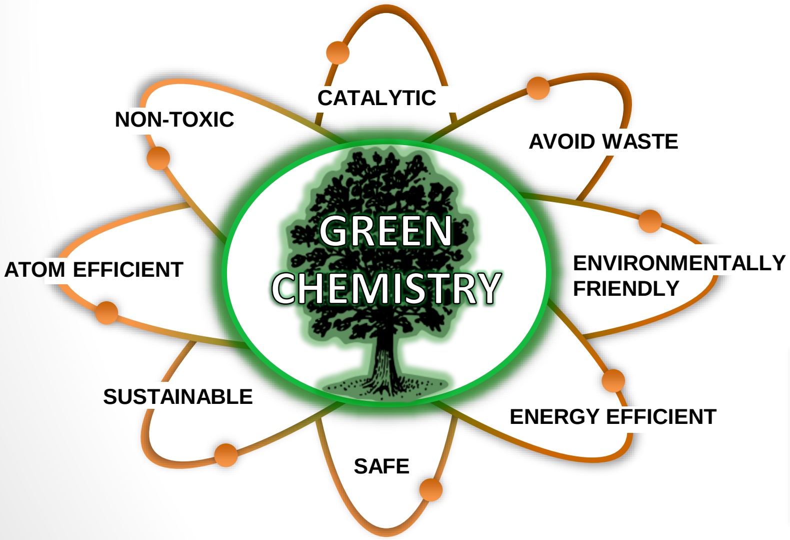
1. **Inform and Influence Research Agenda to Focus on Green / Sustainable Chemistry and Engineering**
2. **Define and Deliver Tools to Enable GC Innovation**
3. **Promote Education and Training in Pharma**
4. **Expand Global Collaboration among Sector Companies**

什么是绿色化学?

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

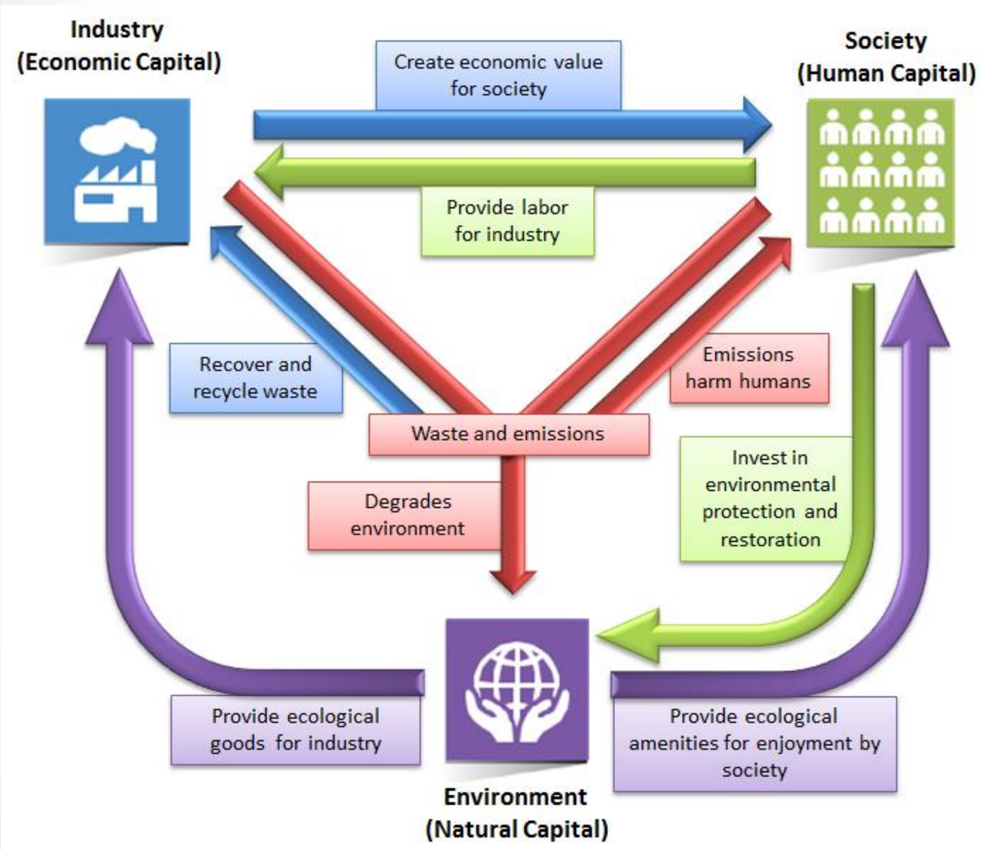
Tucker – "…a privileged opportunity for innovation" representing "an emerging new frontier of exploration."*2

If industry focusses 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.

绿色化学与可持久性



- added

industry

waste ↓ cost ↓

society and environment

affordable drugs

lower environmental impact

The pharmaceutical industry will achieve sustainability if it balances social, environmental, and economic needs of global societies across generations. It is privileged to help patients, do great science, and minimize impact on our planet.

历史背景

1962 Carson – “Silent Spring” (pesticides ↔ pollution). Environmental accidents.

1977 Kletz – “What you don’t have, can’t leak.” → **inherently safe processes**

1991 Trost measured synthetic efficiency with Atom Economy (AE)

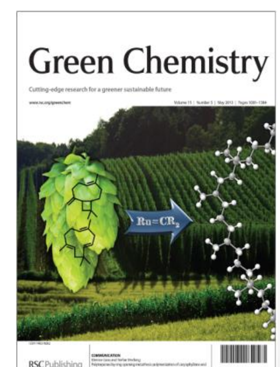
1992 Sheldon introduced environmental impact factor (**E factor**)

1995 President Clinton introduced EPA’s **Presidential Green Chemical Challenge Awards**

1997 Green Chemistry Institute (GCI) was launched by industry, academia, and government

1998 Anastas and Warner - “Green Chemistry: Theory and Practice”. **Twelve Principles of Green Chemistry**

1999 Clark established **first journal** dedicated to sustainable chemistry titled “Green Chemistry” (2014 impact factor 8.02)

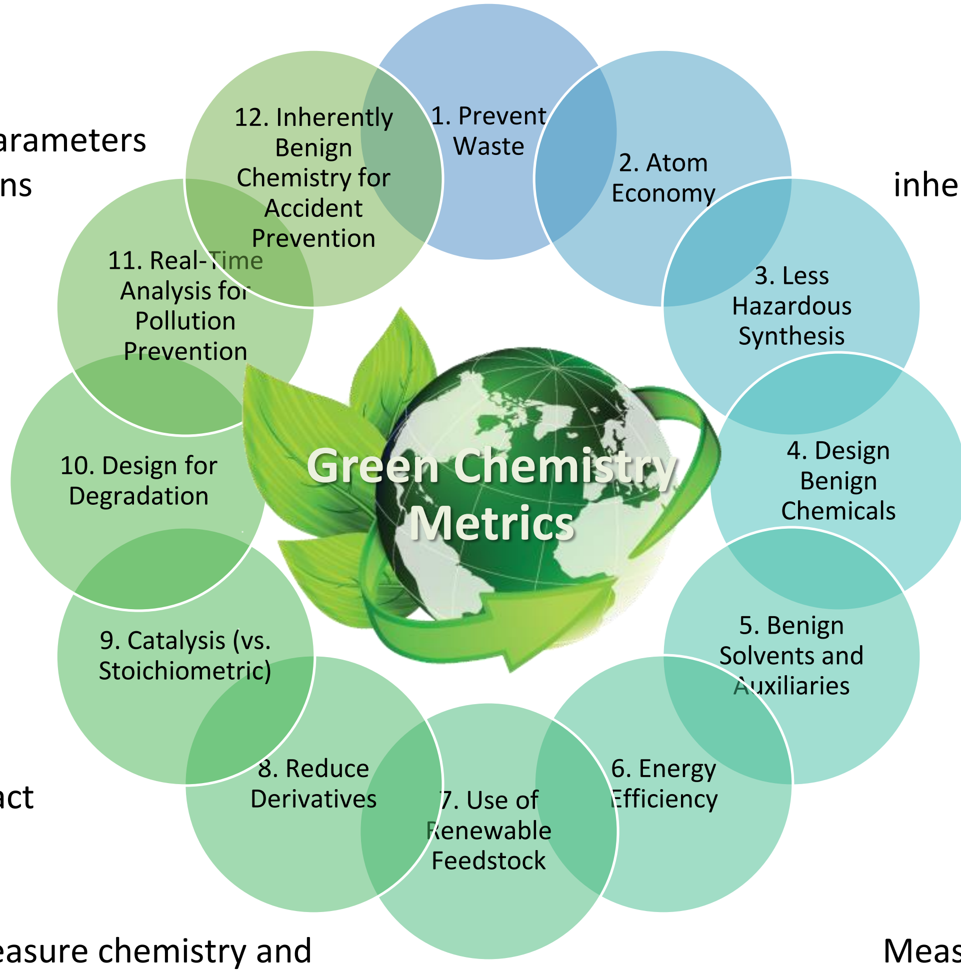


2001 ACS incorporated GCI

2003 Anastas and Zimmerman – “**Twelve Principles of Green Engineering** ”

2010 IQ consortium on green chemistry was chartered

绿色化学的12大原则



Measure process parameters and emissions

Measure inherent process safety

Measure degradation potential

Measure toxicity of all materials

Measure life cycle impact

Measure Energy

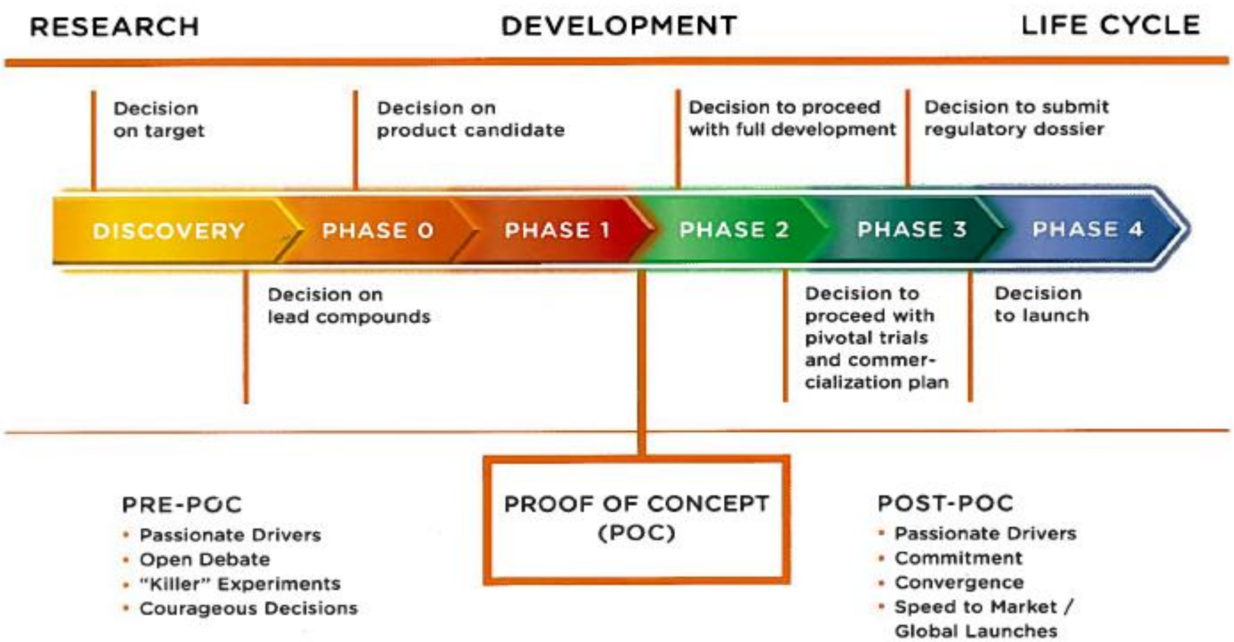
Measure chemistry and process efficiency

Measure resource usage

ACS "Green Chemistry Pocket Guides." Available from: http://www.acs.org/content/acs/en/greenchemistry/what-is-green-chemistry/principles/green-chemistry-pocket-guides.html

何时使用绿色化学原则

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



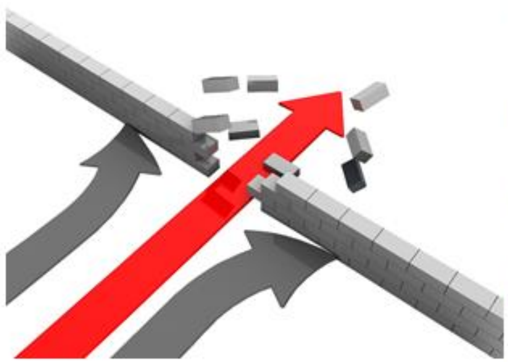
Early awareness can deliver large paybacks later

美国总统绿色化学奖

Year	Awardee	Description of the Technology	Category
2012	Codexis, Professor Yi Tang (UCLA)	Simvastatin, a leading drug for treating high cholesterol, manufactured from a natural product using an engineered enzyme and a practical, low-cost feedstock	Greener Synthetic Pathways
2010	Merck, Codexis	Sitagliptin, the active ingredient in Januvia™, a treatment for type 2 diabetes, manufactured using an evolved, highly stereoselective transaminase	Greener Reaction Conditions
2006	Codexis	The key chiral building block for atorvastatin calcium (the active ingredient in Lipitor® used to lower cholesterol) synthesized by three biocatalysts greatly improved by directed evolution	Greener Reaction Conditions
2006	Merck	Sitagliptin, the active ingredient in Januvia™, used to treat type 2 diabetes, made by a novel green synthesis for ß-amino acids	Greener Synthetic Pathways
2005	Merck	Aprepitant, the active ingredient in Emend®, used to treat chemotherapy-induced nausea and vomiting, made by a convergent, highly atom-economical safer synthesis that also saves water	Greener Synthetic Pathways
2004	Bristol-Myers Squibb	Paclitaxel, the active ingredient in Taxol®, used to treat ovarian and breast cancer, synthesized by plant cell fermentation	Greener Synthetic Pathways
2002	Pfizer	Sertraline, the active ingredient in Zoloft®, used to treat depression, synthesized by a process that eliminates waste, reduces solvents, and doubles overall product yield	Greener Synthetic Pathways
2000	Roche Colorado (now CordenPharma Colorado)	Ganciclovir, the active ingredient in Cytovene®, a potent antiviral agent, synthesized by the Guanine Triester Process, eliminates two hazardous solid waste streams and 11 chemicals	Greener Synthetic Pathways
1999	Lilly Research Laboratories	A drug candidate for the treatment of epilepsy, synthesized by a process including a yeast-mediated asymmetric reaction that eliminates chromium waste and large volumes of solvent	Greener Synthetic Pathways
1997	BHC Company (now BASF)	Ibuprofen, the active ingredient in Advil™, Motrin™, and other over-the-counter pain relievers, synthesized in three catalytic steps with virtually no wasted atoms	Greener Synthetic Pathways

使用绿色化学时的可能障碍

Green Chemistry Barriers in the Pharmaceutical Industry:



- Short Development Cycle
- Limited Patent Life
- Product Quality
- Regulatory Requirements
- Lack of Unified Metrics
- High Cost of Development
- High Project Attrition

IQ published article in *Chemistry & Engineering News* (March 24, 2014) about meeting with FDA in 2012 on "Regulatory Strategies to Enable Green Chemistry" (2nd generation greener processes, pre-NDA green chemistry)

Roschangar, F.; Sheldon, R.A.; Senanayake, C.H. "Overcoming barriers to green chemistry in the pharmaceutical industry – the Green Aspiration Level™ concept", *Green Chem*. **2015**, *17*, 752−768.

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绿色化学数据

为什么要数据?

"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
- **Proper choice** of metrics is critical for 'behavior of system'
- Green metrics correlate to process **economics***1

<u>Considerations</u>

- Proliferation of green chemistry metrics*2 
- Chemical Terminology 

- **Direct** vs. indirect process materials (Life Cycle Assessment / LCA)

绿色化学数据起源

- How to create the **best possible synthesis**?
  - **1956** Woodward introduced concept of **synthetic design**[*1]
  - **1990** Corey won Nobel Prize for introducing **retrosynthesis** tool[*2]
- Considering **waste** -
  - **1991** Trost measured synthetic efficiency with **Atom Economy** (AE).[*3] Received Presidential Green Chemistry Award for contribution in 1998.
  - **1992** Sheldon introduced environmental impact factor (**E-factor**)[*4]
- **1991** Tellus Institute (EPA) and NJ Dept. of Environmental Protection began development of Total Cost Assessment Tool (TCA) for industry[*5]
- **1995** Heaton outlined economic (COGS, OPEX, CAPEX), technical (plant capacity, utilization, throughput, process variability and robustness, product quality), and **social criteria** (benefit of product to society, **environmental impact**) for viable pharmaceutical manufacturing processes[*6]

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*1 Woodward, R.B. “Perspectives in Organic Chemistry.” (Ed.) Todd, A.. Interscience, **1956**, p. 155–184.

*2 Corey, E.J.; Cheng, X.-M. “The Logic of Chemical Synthesis.” Wiley, **1989**.

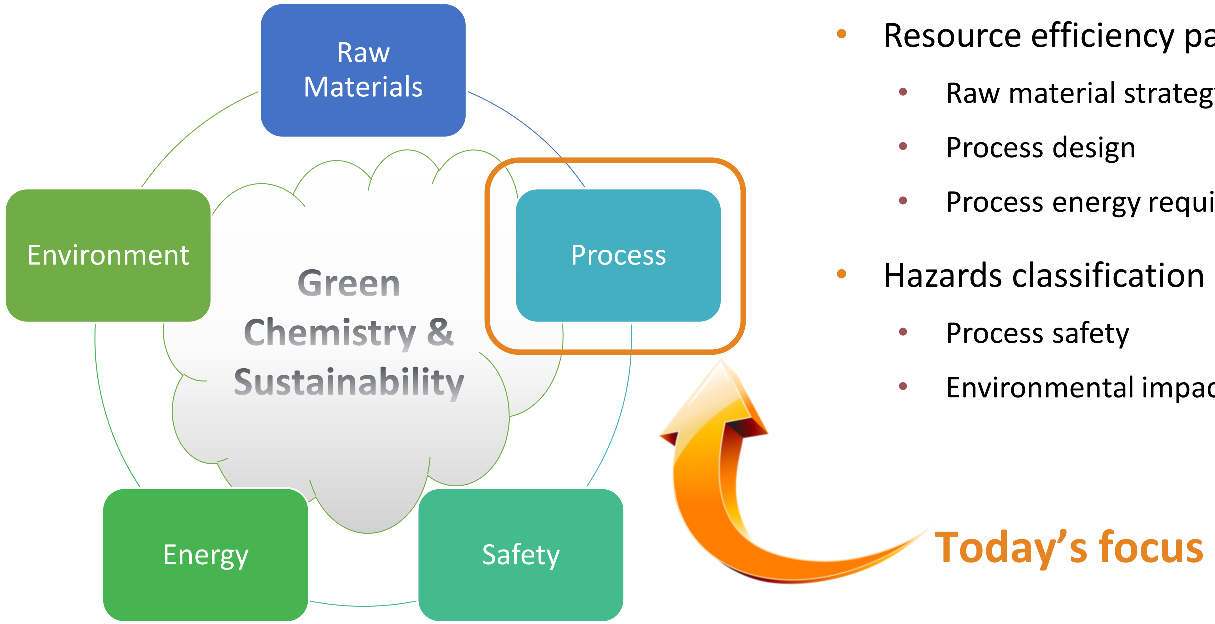
*3 Trost, B.M. “The atom economy--a search for synthetic efficiency.” *Science* **1991**, *254 (5037)*, 1471-1477.

*4 Sheldon, R.A. “Organic synthesis; past, present and future.” *Chem. Ind. (London)* **1992**, 903-906.

*5 Tellus Institute “Alternative Approaches to the Financial Evaluation of Industrial Pollution Prevention Instruments.” Boston, MA, **1991**.

*6 Heaton, C.A. “An Introduction to Industrial Chemistry.” Blackie Academic and Professional (Springer), **1995**. ISBN-10: 0751402729.

绿色化学数据种类



- Resource efficiency parameters
  - Raw material strategy
  - Process design
  - Process energy requirements
- Hazards classification parameters
  - Process safety
  - Environmental impact

- **Raw materials** strategy and supply chain are paramount for the design of a green and sustainable manufacturing process
- In addition to cost, we need to consider raw material manufacture and associated waste generation, toxicity, and hazard. More on this later…

常用的合成工艺数据

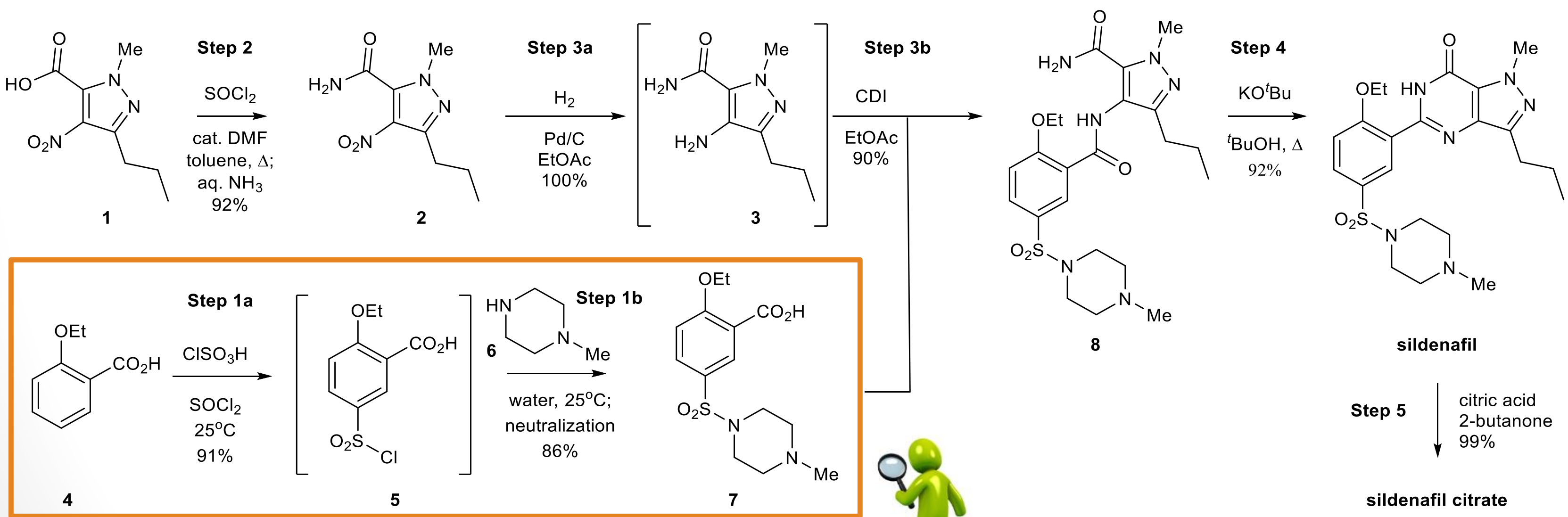
Common Green Chemistry Process Metrics	Common Abbreviation	Unit of Measure	Consideration for Waste?	Yield?	Stoichiometry?	Solvents?	Water?	Optimum Value	Inventor
Chemical Yield	CY	%	✓	✓	✗	✗	✗	100%	
Atom Economy	AE	%	✓	✗	✗	✗	✗	100%	Trost (1991)
Environmental Impact Factor	E-Factor		✓	✓	✓	✓	✗	0	Sheldon (1992)
Mass Intensity	MI		✓	✓	✓	✓	✗	1	Constable, Curzons (2001)
Process Mass Intensity	PMI		✓	✓	✓	✓	✓	1	ACS GCI Pharmaceutical Roundtable (2007)
Process Mass Efficiency	PME	%	✓	✓	✓	✓	✓	100%	EPA & Hanson (2006)
Mass Productivity	MP	%	✓	✓	✓	✓	✗	100%	Constable, Curzons (2001)
Reaction Mass Efficiency	RME	%	✓	✓	✓	✗	✗	100%	Constable, Curzons (2001)
Effective Mass Yield	EMY	%	✓	✓	✓	✗	✗	100%	Hudlicky (1999)
Reaction Mass Intensity	RMI		✓	✓	✓	✗	✗	1	Senanayake (2012)
Carbon Efficiency	CE	%	✓	✓	✓	✗	✗	100%	Constable, Curzons (2001)
Solvent Intensity	SI		✓	✗	✗	✓	✗	0	Constable, Curzons (2001)
Wastewater Intensity	WWI		✓	✗	✗	✗	✓	0	Constable, Curzons (2001)

Roschangar, F.; Sheldon, R.A.; Senanayake, C.H. "Overcoming barriers to green chemistry in the pharmaceutical industry – the Green Aspiration Level™ concept", *Green Chem*. **2015**, *17*, 752–768. *Note:* input materials = all used materials except water.

合成工艺数据解析

Example: Pfizer's Viagra™ manufacturing process:*[1]

2003 UK Institute of Chemical Engineers (IChemE)
Crystal Faraday Award for Green Chemical Technology



化学产率

CY is productivity of a step relative to isolated step product

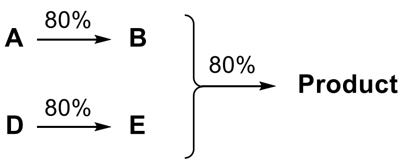
Step 1 Viagra: $CY = \frac{m(Product) \times MW(Raw\ Material) \times 100}{m(Raw\ Material) \times MW(Product)} = \frac{1 \times 166.18 \times 100}{0.649 \times 328.38} = 78\%$ *limiting reactant is 2-ethoxybenzoic acid (4)*

- CY ↑ ↔ raw material-derived waste ↓
- Step and process yields → importance of synthetic convergence

Linear Synthesis

Overall Yield = 80% x 80% x 80% = 51%

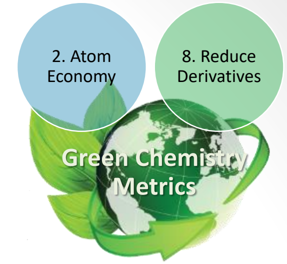
Convergent Synthesis



Overall Yield = 80% x 80% = 64%

- Due to CY considerations, costly materials are introduced late in processes

原子效率



AE aimed at addressing waste more effectively than CY

- Measures how many atoms of the raw materials are transferred to the product

Step 1 Viagra: $$AE = \frac{MW(Product) \times 100}{\sum MW(Raw\ Materials) + \sum MW(Reagents)} = \frac{328.38 \times 100}{(166.18 + 116.52 + 100.16) + (118.97)} = 65\%$$

- We can have a process with 100% CY that produces <u>more waste than product</u>, e.g. first commercial phenol process

$$\underset{\text{MW } 180.15}{PhSO_3Na} + \underset{\text{MW } 40.00}{2\ NaOH} \xrightarrow{300^{o}C} \underset{\text{MW } 116.09}{PhONa} + \underset{\text{MW } 126.04}{Na_2SO_3} + \underset{\text{MW } 18.02}{H_2O}$$

- Emphasizes disadvantages of high MW protecting groups, auxiliaries, and reagents

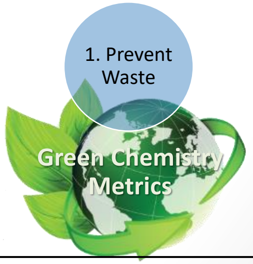
环境影响指数

E factor expands AE concept by measuring total waste relative to product

- High E factor indicates more waste generation and negative environmental impact. Ideal E factor is 0.
- Waste defined as "anything that is not the desired product", but water was excluded*[1]
- If solvent losses unknown, assume 90% recycling*[2]

Step 1 Viagra: $$E - Factor = \frac{\sum m(Input\ Materials) - m(Product)}{m(Product)} = \frac{(3.357 + 0.466) - 1.000}{1.000} = 2.82 \frac{kg}{kg}$$

- Current trend in pharmaceutical industry is towards including water in analysis



环境污染指数

- Typical E factors for various segments of the chemical and allied industries*[1]

Industry Segment (Examples)	Annual Product Tonnage (each)	E-Factor (kg waste / kg product)	Total Annual Waste Tonnage	No. of Steps	Years of Development
Petrochemicals (solvents, detergents)	1,000,000 – 100,000,000	~ 0.1	10,000,000 *2	'Separations'	100+
Bulk Chemicals (plastics, polymers)	10,000 – 1,000,000	<1 – 5	5,000,000	1-2	10-50
Fine Chemicals (coatings, electronic parts, pharmaceutical raw materials)	100 – 10,000	5 – >50	500,000	3-4	4-7
Pharmaceuticals (antibiotics, drugs, vaccines)	10-1,000	25 – >100	100,000	6+	3-5

- **High waste burden** for pharmaceutical industry

1. Prevent Waste

Green Chemistry Metrics

工艺用料指数(PMI)

PMI*[1] and Process Mass Efficiency (PME = 100/PMI) were introduced by EPA and ACS GCI PR in 2006 and 2007 as extension to MI and MP

- Most comprehensive process metric
- Considers all materials including water and workup chemicals

Step 1 Viagra: $$PMI = \frac{\sum m(Input\ Materials\ incl.\ Process\ Water)}{m(Product)} = \frac{3.357 + 0.466 + 18.299}{1.000} = 22.1\,\frac{kg}{kg}$$

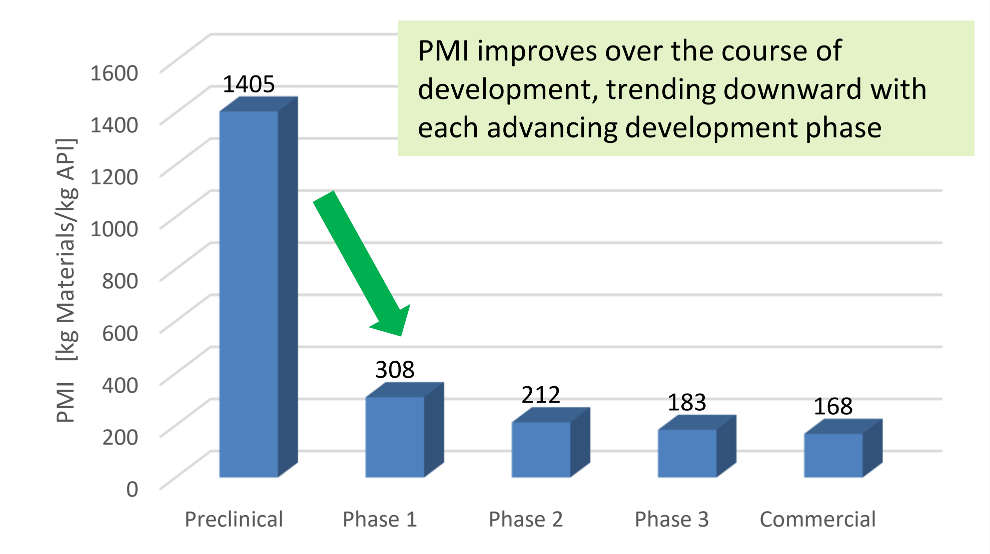
$$PME = \frac{m(Product) \times 100}{\sum m(Input\ Materials\ incl.\ Process\ Water)} = \frac{1.000 \times 100}{3.357 + 0.466 + 18.299} = 4.5\%$$

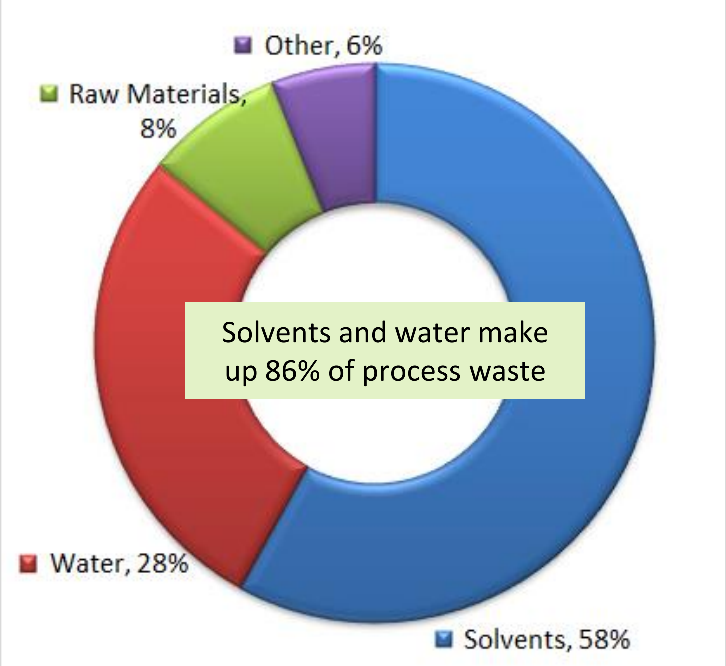
工艺用料指数(PMI)

1. Prevent Waste

Green Chemistry Metrics

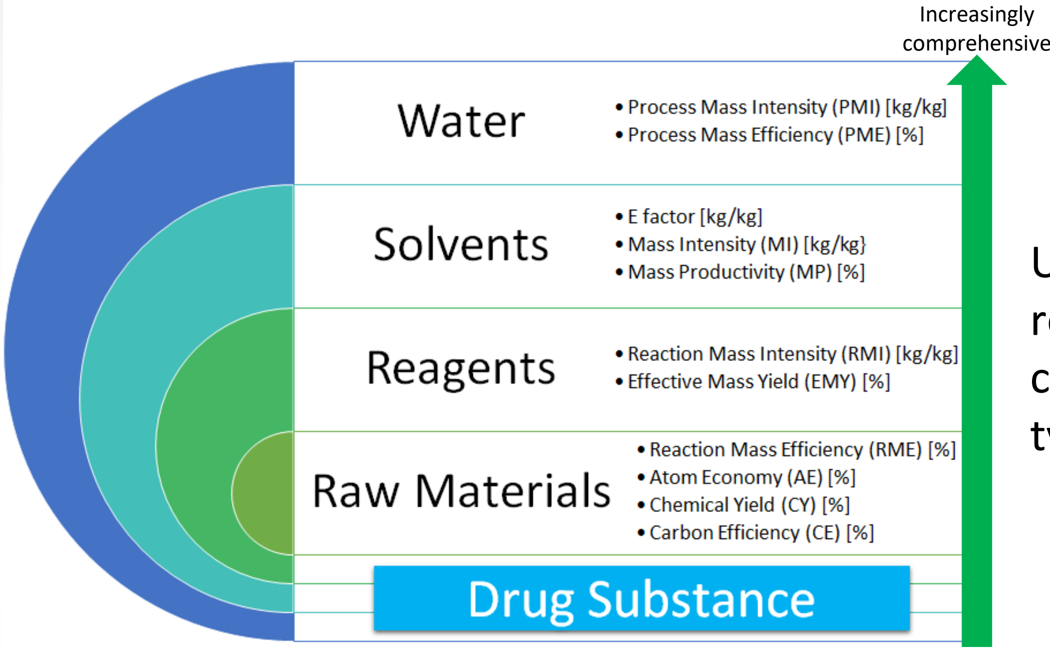
ACS GCI compiled industry waste data for pharmaceutical manufacturing across development and commercial in 2007 and 2008*[1-3]





ACS GCI PR availed free Excel PMI calculator*[2]

工艺用料指数(PMI)总结



Upside-down waterfall diagram relates green process metrics to considered process material types*[1]

Summary of Metrics Results for Step 1 of the Commercial Viagra™ Process.*[1]

→ Metric becoming increasingly comprehensive →													
Metric	CY	SI	WWI	AE	E factor	CE	RME	EMY	RMI	MP	MI	PME	PMI
Result	78%	0 kg/kg	18.3 kg/kg	65%	2.82 kg/kg	56%	30%	26%	3.82 kg/kg	26%	3.82 kg/kg	4.5%	22.1 kg/kg

修正的E指数

Complete E factor (cEF).*1

- consistent application for total waste
- cEFI contributions are additive to calculate process cEF
- reactor cleaning and solvent recycling are excluded

cEF analyzes total waste stream during process development of a selected route

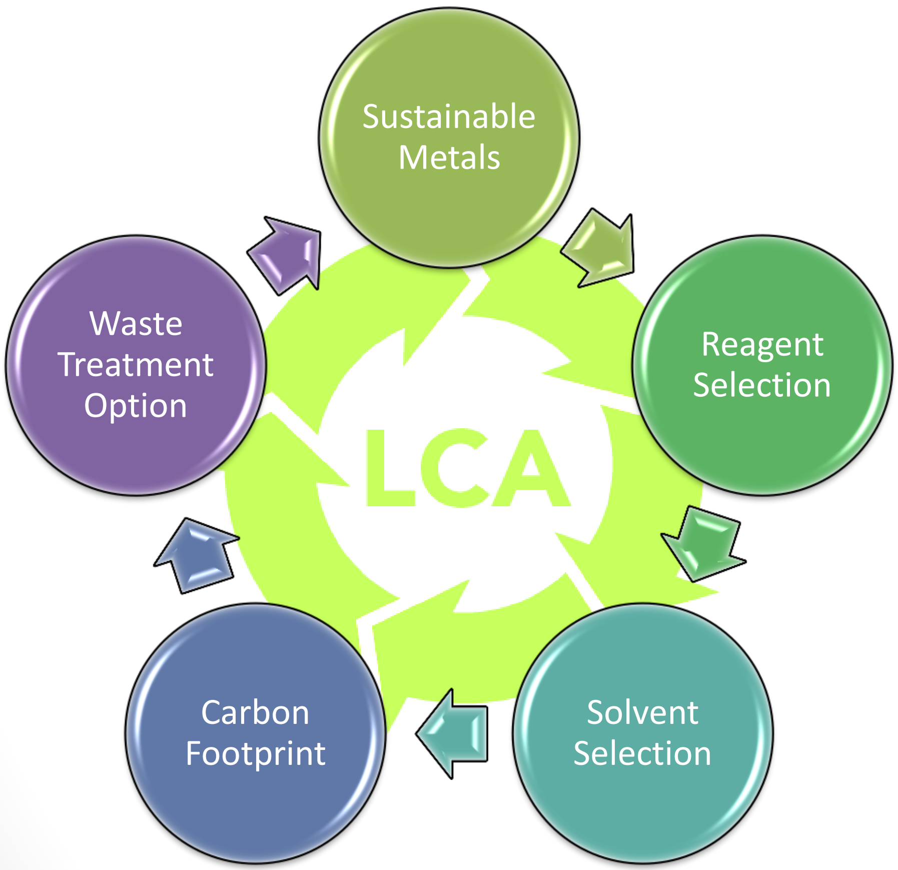
Simple E factor (sEF) discounts water and solvents

$$simple\ E\ factor = sEF = \frac{\sum m(Raw\ Materials) + \sum m(Reagents) - m(Product)}{m(Product)}$$

$$complete\ E\ factor = cEF = \frac{\sum m(Raw\ Materials) + \sum m(Reagents) + \sum m(Solvents) + \sum m(Water) - m(Product)}{m(Product)}$$

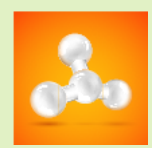
*1 Roschangar, F.; Sheldon, R.A.; Senanayake, C.H. "Overcoming barriers to green chemistry in the pharmaceutical industry – the Green Aspiration Level™ concept", *Green Chem*. **2015**, *17*, 752−768.

其它注意点



Process “Ideality”

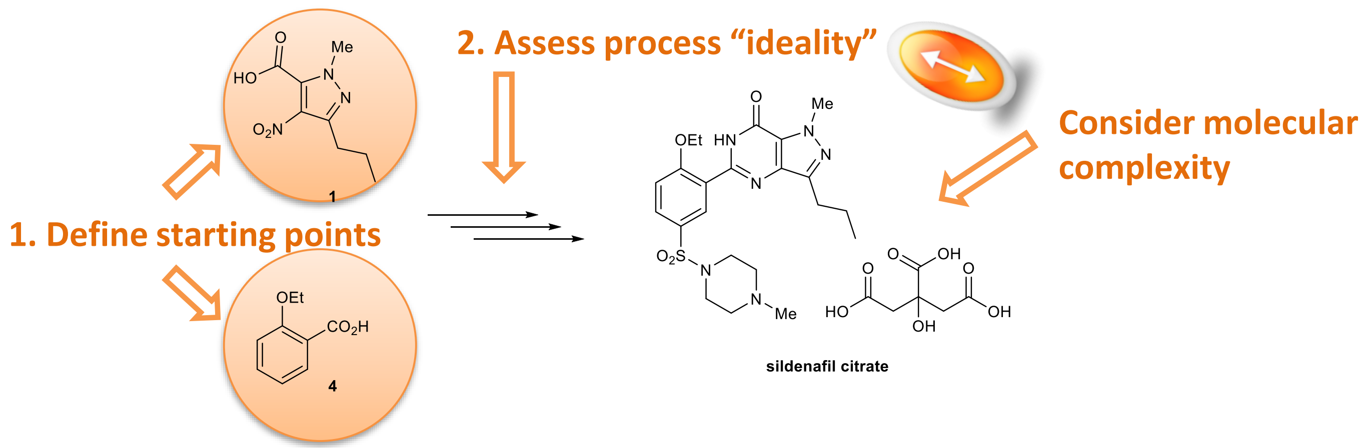
Sustainable Supply Chain


Materials


Suppliers

机会

1) plethora of process waste metrics
2) inconsistent <u>**M**</u>easure/consideration of intrinsic raw material waste (process starting points)
3) no consideration for **API complexity and process ideality**
4) → absence of "<u>**S**</u>M<u>**AR**</u>T" green process goals



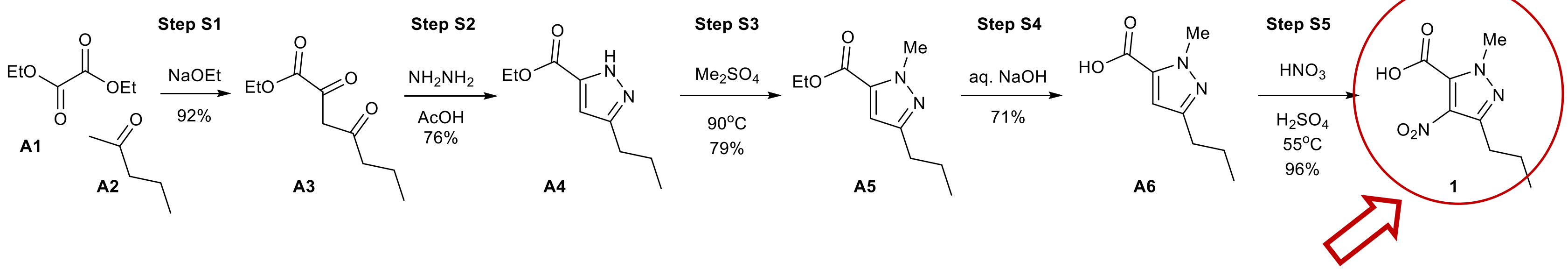
*1 Roschangar, F.; Sheldon, R.A.; Senanayake, C.H. "Overcoming barriers to green chemistry in the pharmaceutical industry – the Green Aspiration Level™ concept", *Green Chem*. **2015**, *17*, 752–768.

工艺出发点

Proposed **standardized** raw material **starting point concept**:

- raw material is commercially available from reputable catalog company, AND
- cost at its largest offered quantity does not exceed \$100/mol

Sub-process for Viagra's 1-methyl-4-nitro-3-propyl-1H-pyrazole-5-carboxylic acid (**1**)



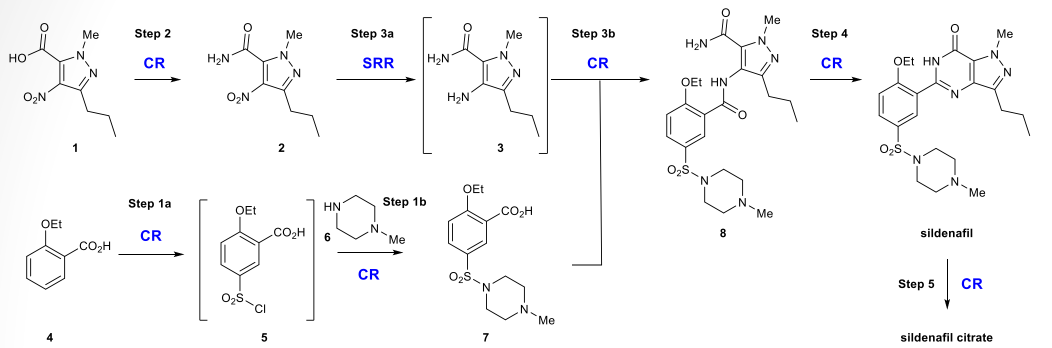
Not available from Sigma-Aldrich → complex raw material → need to consider intrinsic waste (cEF or PMI)

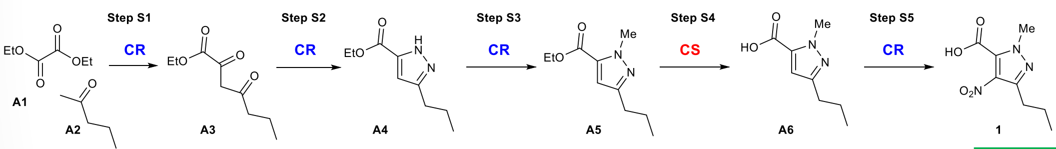
How much waste did we miss?

- compound **1** has an intrinsic cEF of 83 kg/kg
- 0.4 kg of **1** needed to make 1 kg Viagra
- cEF contribution of **1** is 35.1 kg/kg → we neglected (35.1-0.4=) **34.7 kg/kg intrinsic waste**
- → cEF for Viagra process jumps from 50.3 to 85.5 kg/kg.

cEF = complete E factor.   sEF = simple E factor.   PMI = Process Mass Intensity = cEF + 1.

工艺的理想性和复杂性





Complete' Commercial Viagra™ Process

CR = Construction Reaction

SRR = Strategic Redox Reaction

CS = Concession Step

complexity **(Viagra)** = 10+1 = **11**

%ideality **(Viagra)** = (10+1)/12 = **92%**

$$Complexity = \%ideality \times total\ no.of\ reactions$$
$$= no.of\ construction\ reactions$$
$$+ no.of\ strategic\ redox\ reactions \quad *2$$

$$\%ideality \ ^{*1} = \frac{no.of\ construction\ reactions + no.of\ strategic\ redox\ reactions}{total\ no.of\ reactions}$$

*1 Gaich, T.; Baran, P.S. "Aiming for the Ideal Synthesis." *J. Org. Chem*. **2010**, *75*, 4657–4673.

*2 Roschangar, F.; Sheldon, R.A.; Senanayake, C.H. "Overcoming barriers to green chemistry in the pharmaceutical industry – the Green Aspiration Level™ concept", *Green Chem.* **2015**, *17*, 752–768.

答案:绿色追求指数(GAL) *1

we have plenty of measures, but had no common green efficiency **goal** for an API manufacturing processes

can we measure our process against a *common* GC goal? YES!

how? utilize 2007-08 ACS GCI PR process analysis

Process waste (kg/kg API)	PMI	cEF
Phase I	308	307
Commercial	168	167

$$cEF = PMI - 1$$

we assume an average **process complexity** of **9**

Process waste goal per step (kg/kg API)	tGAL
Phase I	34
Commercial	19

$$tGAL = \frac{PMI\ or\ cEF}{Average\ Complexity}$$

*1 Roschangar, F.; Sheldon, R.A.; Senanayake, C.H. "Overcoming barriers to green chemistry in the pharmaceutical industry – the Green Aspiration Level™ concept", *Green Chem.* **2015**, *17*, 752–768.

GAL = Green Aspiration Level

简单计算

very easy – just two calculations:

1) determine complexity and calculate GAL

Complexity (Viagra) = 11

$$GAL = tGAL \; x \; Complexity$$

with tGAL(commercial) = 19 kg/kg

GAL (Pradaxa) = 209 kg/kg

process E factor or PMI goal

2) determine process cEF and calculate RPG

Relative Process Greeness (**RPG**): green status of synthetic process relative to its aspiration level

$$RPG = \frac{GAL}{cEF}$$

cEF (Pradaxa) = 86 kg/kg

RPG (Pradaxa) = 243%

GAL = Green Aspiration Level. cEF = complete E factor. RPG = Relative Process Greenness.

工业界合作发展绿色化学

- closely collaborate within ACS GCI PR and IQ Green Chemistry working group

- integrate **Green Aspiration Level** as first green process goal
  - ✓ remove ambiguity around process starting points
  - ✓ consider process complexity
  - ✓ allows simple measure of **Relative Process Greenness** (RPG) vs. industry

- currently 8 pharmaceutical firms collect process waste data with plan to publish follow-on paper and propose GAL as industry metric of choice (e.g. use for project goals, green chemistry awards)

- use GAL and RPG as communication tool to upper management to showcase value-added of manufacturing departments to the business

- use GAL and RPG as communication means to show value-added to society

ACS Green Chemistry Institute®
Pharmaceutical Roundtable

INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

II – 绿色化学工具

- 溶剂指南
- 试剂指南

ACS Green Chemistry Institute® Pharmaceutical Roundtable

INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

溶剂:

更聪明与可持久性的选择

纲要

- Introduction to solvents and related generated waste
- Guidance on Solvent Selection and potential impact
  - Examples
  - Methodology of solvent selection
- Examples of replacing methylene chloride in chromatography
- Replacing DCM and DMF in amidation/red. amination
- Take home message

溶剂

- **Solvents** – a substance usually a liquid, capable of dissolving or dispersing another substance

Some common classes of solvents

Solvent Class	**Example**
Alkanes	Hexane
Aromatics	Toluene
Alcohols	Ethanol
Ethers	Diethyl ether
Polar aprotic	Acetonitrile
Chlorinated	Dichloromethane
Ketones	Acetone
Acids	Acetic acid
Bases	Pyridine

溶剂使用

Why do we use organic solvents

- Mixing (mass transport/phases)
- Selectivity
- Reaction rate
- Scalability
- Safety – (exotherm control)
- Isolation
- Cleaning

What are greener alternatives

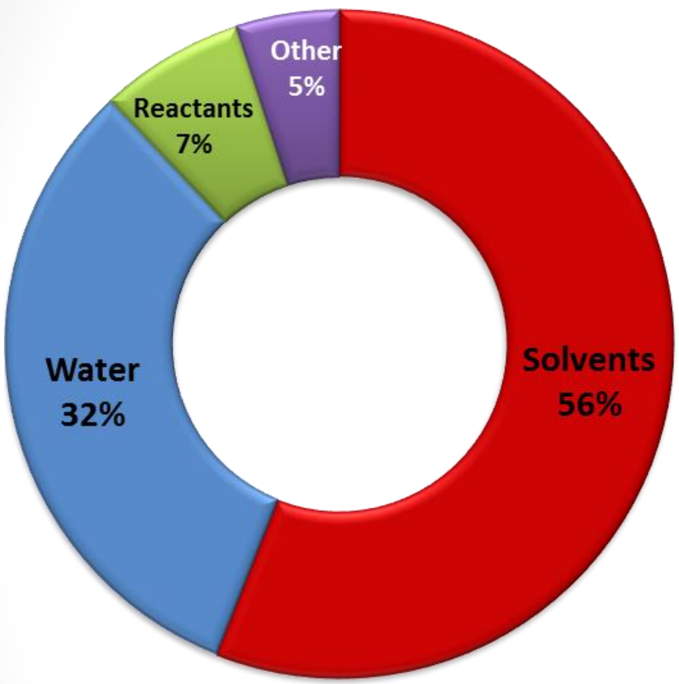
- Neat – no solvent!
- Solid phase reactions
- Water - depends
- Compressed gases
- Supercritical fluids

各个工业的溶剂使用
(在瑞典,吨/年)

- Graphic industry - **85,988**
- Paint manufacturers - **62,367**
- Manufacture of organic base chemicals - **13,421**
- **Chemicals (incl. pharmaceuticals) - 12 616**
- Plastic and plastic goods industry - **12,972**
- Manufacture of metal goods - **11,978**
- Manufacture of wood goods (not furniture) - **9,874**
- Construction - **8,749**
- Food industry - **4,997**
- Pulp and paper industry - **4,825**

Source: KemI's Products Register 2010

制药工业里溶剂对绿色工艺的影响

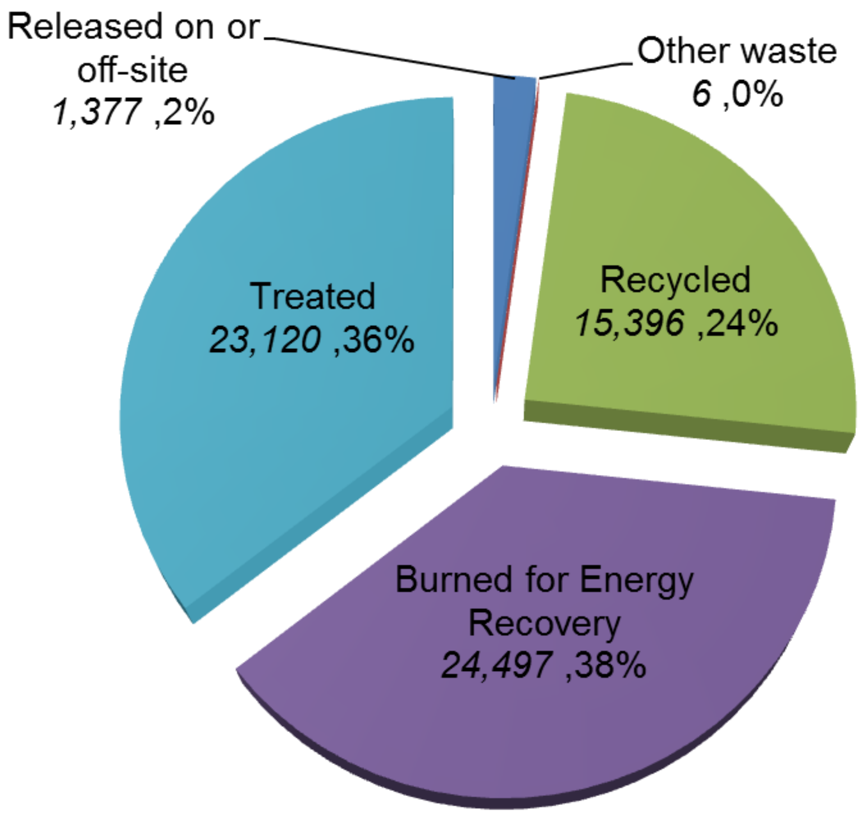


- Solvent and water contribute >80% to the process mass intensity PMI
  - PMI = 100
  - 1 kg of API needs 100 kg of materials
  - Solvents and water represent > 80% of these
- Emphasizes need for research to reduce the use and hazard of the solvent

C. Jimenez-Gonzalez *et al*, *OPRD*, 2011, *15*, 912.

Source: 2008 ACS Green Chemistry Institute Pharmaceutical Roundtable benchmarking exercise of 10 member companies

美国制药工业废料处理数据, 2012 (吨, 百分比)



溶剂– VOCs
(易挥发有机溶剂)

- Active Pharmaceutical Ingredient Manufacture
  - Waste stream: 60-70% consist of solvents
  - Energy usage: ~75% attributed to solvent
  - Photochemical ozone creation potential: 70% attributed to solvents
  - Greenhouse gases: 50% attributed to solvents
  - Cost: 10-40% is attributed to solvents
- Cleaning
  - 30-40% total VOC solvent use in pharmaceutical plant is used in cleaning! A 4,000L reactor uses how much solvent in a traditional cleaning process?

~5,000L

Clean Tech. Environ. Policy 2005, 7, 41
EPSCR START 2005
Green Chem. 2002, 4,521

Constable, D.J.C. "Solvent Considerations in Green Chemistry." ACS GCI IGCW-180o seminar, December 2013.

VOCs对环境的影响

- Harmful effects on
  - Human health e.g. 1,2-Dichloroethane and DMF
  - Natural ecosystems e.g. Hexanes
- Damage to materials e.g. acids
- Stratospheric ozone depletion e.g. carbon tetrachloride, methyl bromide, Freon 22
- Global Climate change
- Odour e.g. amines – pyridine, triethylamine, DMS

Many Controls are in place

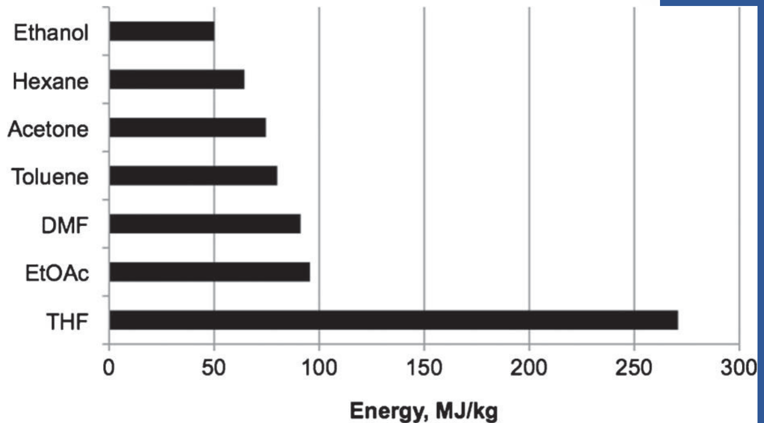
- Releases to air and Solvent Emission Directive (SED)
- Releases to water and the Water Framework Directive (WFD)
- REACH – Registration, Evaluation, Authorization and Restriction of Chemicals
- Montreal Protocol

选择溶剂的考虑因素

- Inert under reaction conditions
- Chemistry must work
- Isolation/work-up/crystallisation
- Safety and operability
- Human health issues
- Can the solvent be recovered/recycled?
- Can wastes be incinerated/treated?
- Environment and legislation compliance
- Overall cost burden to final product

什么是绿色溶剂?

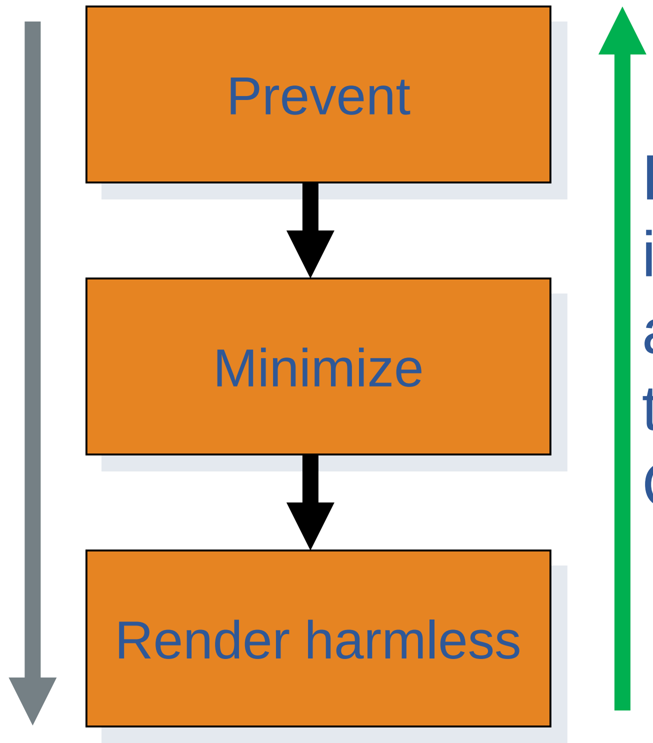
- Criteria for a green solvent
  - From renewable feedstock
  - Low energy demand
  - Biodegradable
  - Not soluble in water
  - No VOCs (BP not too low)
  - Easy to recycle: BP not too high
- Criteria for a safe solvent
  - Stability
  - Low flammability (high FP)
  - Moderate toxicity



P. G. Jessop, *Green Chem*, 2011, *13*, 1391.

绿色设计!

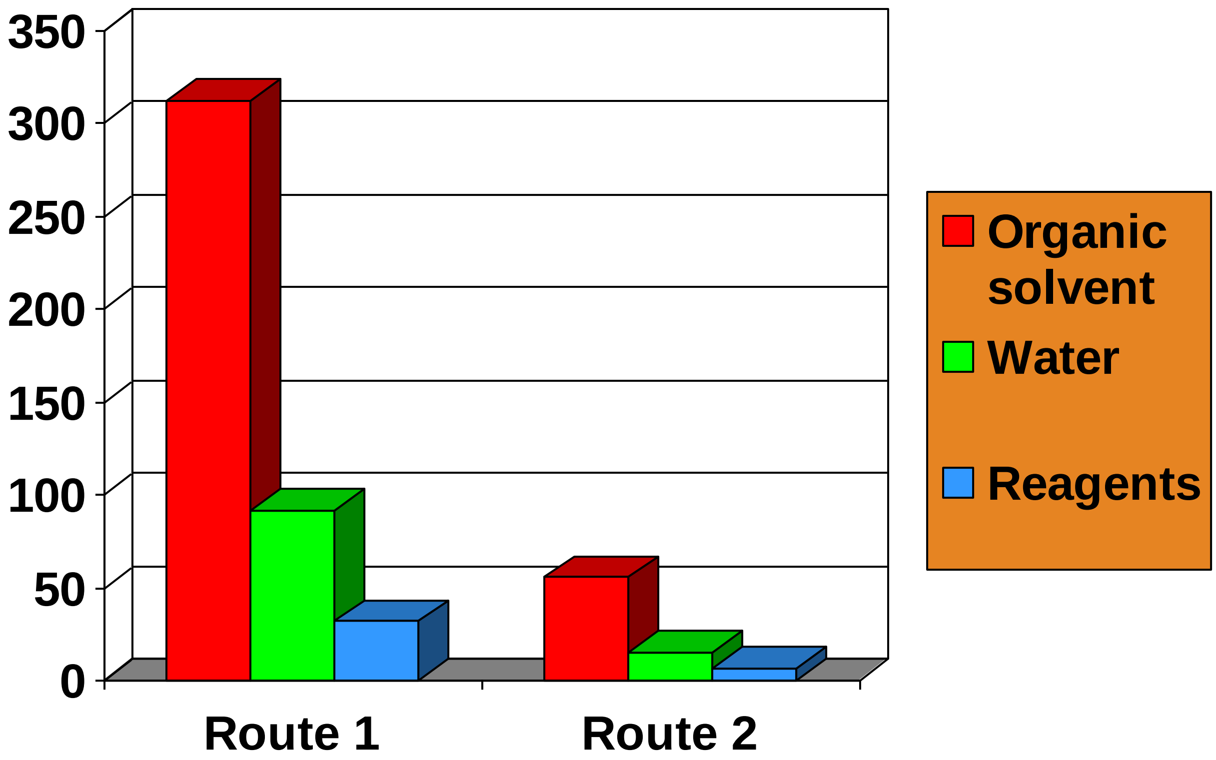
Costs increase, no longer acceptable just to incinerate all waste



Likelihood of success increases if issues addressed earlier in the Development Chain

一期临床到二期临床的路线改变实例

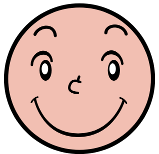
PMI



API = Active Pharmaceutical Ingredient

Route 1 :7 steps, Route 2 : 3 steps

Reduce steps, reduce solvent, reduce # of isolations (also cost of molecule drops by 80%!)



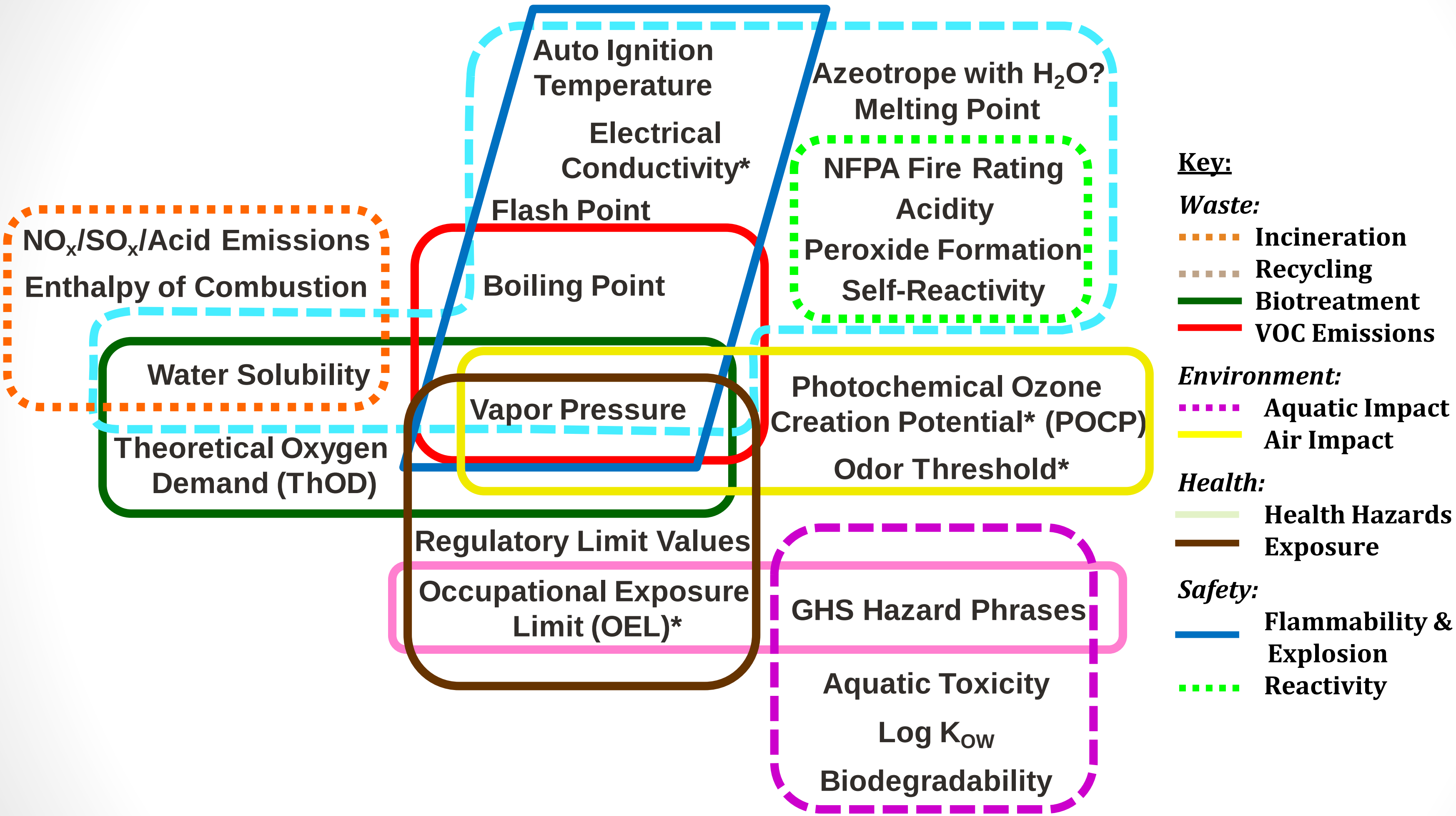
绿色清洗

6.3m^3 reactor – detergent/water cleaning

Reduces solvent use 60-90%!

(previously 5,000-10,000 litres acetone used)

溶剂选择考虑因素

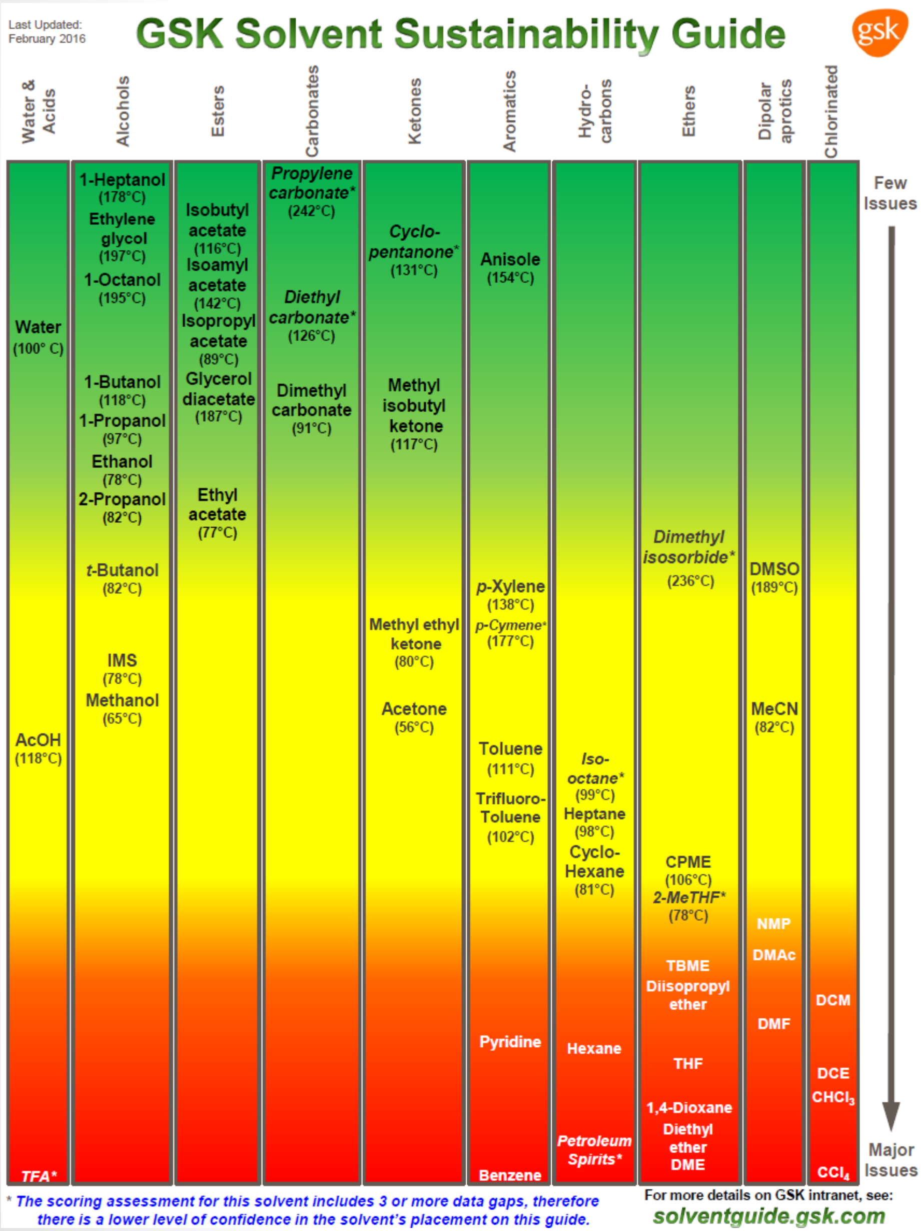


***This data point includes a particularly large number of data gaps.**

溶剂选择指南

- The definition of a green solvent is not straightforward
- Some criteria are contradictory
- There is no universal metrics set to compare the greenness criteria
- Some companies/ institutions have edited solvent selection guides in order to help chemists in their choice
  - Occupational health
  - Safety (Flash point, resistivity, peroxides,…)
  - Environment
  - Industrial & regulation issues
- These guides reflect their policy and culture
  - Local constraints
  - Accidents
  - Habits

溶剂选择指南



- New format emphasizes **spectrum** of green chemistry assessments
- Ease of comparison both within **a solvent class** and **across multiple classes**
- Highlight those solvents with significant **data gaps**
- Reverse side of guide provides more detailed scoring information

GSK Solvent Sustainability Guide

Classification	Solvent Name	CAS Number	Composite Colour‡	Boiling Point (°C)	Incineration	Recycling	Biotreatment	VOC Emissions	Aquatic Impact	Air Impact	Health Hazard	Exposure potential	Flammability & Explosion	Reactivity & Stability	Life Cycle Analysis†
Water & Acids	Water	7732-18-5		100	3	2	4	6	10	8	10	9	7	10	10
	Acetic Acid	64-19-7		118	3	5	4	7	8	4	7	5	8	6	8
	*Trifluoroacetic acid**	76-05-1		72	1	5	2	4	4	4	4	3	7	6	
Alcohols	1-Heptanol	111-70-6		178	9	8	10	9	8	4	10	7	9	10	
	Ethylene glycol	107-21-1		197	4	5	5	10	10	8	7	10	10	10	9
	1-Octanol	111-87-5		195	9	7	8	10	5	4	7	10	9	10	
	1-Butanol	71-36-3		118	6	7	5	8	9	3	7	7	8	9	5
	1-Propanol	71-23-8		97	5	3	3	6	10	4	10	7	8	10	7
	Ethanol	64-17-5		78	5	5	3	4	9	5	10	8	6	10	
	2-Propanol	67-63-0		82	5	5	3	5	8	7	10	6	6	8	4
	t-Butanol	75-65-0		82	5	5	3	5	9	7	7	5	6	10	8
	IMS (ethanol, denatured)	64-17-5		78	5	5	3	5	9	5	4	7	6	10	
	Methanol	67-56-1		65	4	7	3	3	10	7	4	6	5	10	9
Esters	Isobutyl acetate	110-19-0		116	7	9	8	6	9	6	10	6	8	10	
	Isoamyl acetate	123-92-2		142	9	9	8	8	4	6	7	8	8	10	
	Isopropyl acetate	108-21-4		89	6	7	5	5	9	5	10	6	6	10	7
	Glycerol diacetate	111-55-7		187	5	6	6	10	6	8	4	8	10	10	
	Ethyl acetate	141-78-6		77	5	6	5	4	9	5	10	7	5	10	6
Carbonates	*Propylene carbonate**	108-32-7		242	4	5	6	10	10	10	10	10	10	10	
	*Diethyl carbonate**	105-58-8		126	7	9	9	7	9	8	4	5	8	10	
	Dimethyl carbonate	616-38-6		91	4	3	5	5	9	7	10	6	6	10	8
Ketones	*Cyclopentanone**	120-92-3		131	8	9	6	7	10	5	7	6	8	10	6
	Methylisobutyl ketone	108-10-1		117	7	8	5	7	9	3	7	6	7	9	2
	Methylethyl ketone	78-93-3		80	5	5	3	4	8	4	10	6	5	9	3
	Acetone	67-64-1		56	5	6	2	2	10	6	10	6	4	9	7
Aromatics	Anisole	100-66-3		154	8	8	8	8	7	6	7	8	7	9	5
	p-Xylene	106-42-3		138	10	9	6	7	5	2	7	7	5	10	7
	p-*Cymene**	99-87-6		177	10	8	7	9	3	2	10	6	6	9	
	Toluene	108-88-3		111	10	7	6	7	7	2	7	6	5	10	7
	Trifluorotoluene	98-08-8		102	4	4	5	6	3	8	10	4	4	10	
	Pyridine	110-86-1		115	3	6	2	7	7	3	4	4	8	9	2
	Benzene	71-43-2		80	9	6	6	4	7	5	1	1	3	10	7
Hydrocarbons	*Isooctane**	540-84-1		99	10	4	5	6	2	5	10	7	3	10	7
	Heptane	142-82-5		98	10	4	5	6	3	5	10	6	3	10	7
	Cyclohexane	110-82-7		81	10	6	5	4	3	5	10	6	2	10	7
	Hexane	110-54-3		69	10	8	4	3	3	5	7	4	2	10	7
	*Petroleum spirits**	8032-32-4		55	6	9	4	2	5	5	1	6	2	10	7
Ethers	*Dimethyl isosorbide**	5306-85-4		236	3	4	5	10	9	6	4	9	9	8	
	Cyclopentyl methyl ether	5614-37-9		106	8	4	5	6	4	3	4	4	6	9	4
	*2-Methyltetrahydrofuran**	96-47-9		78	6	5	3	4	7	4	4	3	4	6	4
	t-Butylmethyl ether	1634-04-4		55	7	8	4	2	7	5	7	4	3	9	8
	Diisopropyl ether	108-20-3		68	9	7	6	3	5	4	10	6	4	3	9
	Tetrahydrofuran	109-99-9		65	5	5	2	3	9	3	7	5	4	6	4
	1,4-Dioxane	123-91-1		102	4	1	3	6	8	4	4	3	4	6	6
	Diethyl ether	60-29-7		35	7	7	3	1	5	3	10	4	2	6	6
	1,2-Dimethoxyethane	110-71-4		85	4	4	3	5	8	7	1	4	4	6	7
Dipolar Aprotics	Dimethyl sulphoxide	67-68-5		189	3	4	4	9	8	6	7	9	9	5	6
	Acetonitrile	75-05-8		82	3	5	1	4	10	8	7	5	6	10	4
	N-Methyl pyrrolidone	872-50-4		202	3	4	3	10	10	6	1	9	9	9	4
	N,N-Dimethyl acetamide	127-19-5		165	3	6	3	9	10	6	1	7	9	9	2
	N,N-Dimethyl formamide	68-12-2		153	3	6	3	8	10	4	1	6	9	9	7
Chlorinated	Dichloromethane	75-09-2		40	2	10	4	1	8	6	7	4	4	10	7
	1,2-Dichloroethane	107-06-2		84	2	7	5	5	9	7	1	2	5	10	7
	Chloroform	67-66-3		61	3	9	5	3	7	5	4	1	5	10	6
	Carbon tetrachloride	56-23-5		77	3	7	5	4	4	1	4	1	4	10	7

For more details, at GSK internally, see:

solventguide.gsk.com

Column Headings Colour Key

	Waste
	Environment
	Human Health
	Safety

Composite Colour Key

	Few Known Issues
	Some Known Issues
	Major Known Issues

**The scoring assessment for this solvent includes 3 or more data gaps, therefore there is a lower level of confidence in the solvent's placement on this guide.*

†A blank value for Life Cycle Analysis (LCA) indicates that this data is currently not available.

‡The composite colour represents an overall categorization of the holistic sustainability of a solvent, taking all category scores into consideration.

Last Updated: February 3, 2016

ACS溶剂选择指南

- ACS GCI Pharmaceutical Roundtable guide available free of charge
  - Considers safety, health and environmental impact of solvents
  - www.acs.org/gcipharmaroundtable

ACS GCI Pharmaceutical Roundtable Solvent Selection Guide
Version 2.0 Issued April 1, 2011
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
Dipolar aprotic	DIMETHYL SULFOXIDE (DMSO)	67-68-5	3	4	4	4	8
Dipolar aprotic	N,N-DIMETHYLFORMAMIDE (DMF)	68-12-2	3	7	3	2	7
Dipolar aprotic	N-METHYL-2-PYRROLIDONE (NMP)	872-50-4	3	6	6	2	7
Dipolar aprotic	DIMETHYLIMIDAZOLIDINONE	80-73-9	3				
Dipolar aprotic	N-ETHYL-PYRROLIDONE (NEP)	2687-91-4					
Dipolar aprotic	SULFOLANE	126-33-0	2	3		5	8
Dipolar aprotic	TETRAMETHYLUREA	632-22-4	3				
Ester	DIMETHYL CARBONATE	616-38-6		3			5
Ester	ETHYL ACETATE (ETOAC)	141-78-6	5	4	6	4	4
Ester	ISOBUTYL ACETATE (IBUOAC)	110-19-0	5	3	5	2	2
Ester	ISOPROPYL ACETATE (IPAC)	108-21-4	3	4	6	3	3
Ester	METHYL ACETATE	79-20-9	3	5	6	3	5
Ester	METHYL FORMATE	107-31-3	5	7	7		6
Ester	N-BUTYL ACETATE	123-86-4	4	4	6	3	4
Ether	1,2-DIMETHOXYETHANE (DME)	110-71-4		9		3	6
Ether	1,4-DIOXANE	123-91-1	8	7	4	4	6
Ether	2-METHOXYETHYL ETHER (DIGLYME)	111-96-6		8		3	7
Ether	ANISOLE	100-66-3	5	4		3	4
Ether	ETHYL ETHER	60-29-7	9	5	7	4	4
Ether	METHYL TERT-BUTYL ETHER (MTBE)	1634-04-4	8	5	8	5	2
Ether	TETRAHYDROFURAN (THF)	109-99-9	5	6	5	4	5
Ether	2-METHYL TETRAHYDROFURAN	96-47-9	5	6			4
Ether	CYCLOPENTYL METHYL ETHER (CPME)	5614-37-9	6			5	3
Halogenated	1,2-DICHLOROETHANE (DCE)	107-06-2	4	9	6	6	6
Halogenated	CHLOROBENZENE	108-90-7	3	5	5	8	6
Halogenated	CHLOROFORM	67-66-3	2	9	7	7	6
Halogenated	DICHLOROMETHANE	75-09-2	2	7	9	6	7
Halogenated	CARBON TETRACHLORIDE	56-23-5	3	8	8	5	7
Halogenated	TRIFLUOROTOLUENE	98-08-8		6	7	7	6
Hydrocarbon	CYCLOHEXANE	110-82-7	6	5	4	7	2
Hydrocarbon	METHYL CYCLOHEXANE	108-87-2	6	4	4		2
Hydrocarbon	N-HEPTANE	142-82-5	6	4	4	7	2
Hydrocarbon	N-HEXANE	110-54-3	6	7	5	8	1
Hydrocarbon	XYLENE (MIXED ISOMERS)	1330-20-7	4	4	4	7	3
Hydrocarbon	ISOOCTANE	540-84-1	6	4	4		2
Ketone	ACETONE	67-64-1	4	4	7	1	5
Ketone	AMYL ACETATE	628-63-7	3	3	5	5	4
Ketone	CYCLOHEXANONE	108-94-1	4	4	6	3	5
Ketone	METHYL ETHYL KETONE (MEK)	78-93-3	5	4	7	2	5
Ketone	METHYL ISOBUTYL KETONE (MIBK)	108-10-1	5	6	6	4	2

Note: A blank cell indicates that data are missing so a score could not be calculated.

Page 2 of 2

This version of the ACS GCI Pharmaceutical Roundtable Solvent Selection Guide reflects ongoing evaluation of publicly available information by the ACS GCI Pharmaceutical Roundtable. Comments may be sent to gcipr@acs.org. No warranty is made and all warranties are expressly disclaimed. The guide has been developed considering safety, health, environment aspects of solvent selection. Other aspects may need to be considered in process design. The ACS GCI Pharmaceutical Roundtable does not accept responsibility for any errors or omissions.

IMI-CHEM21 课题

- IMI-CHEM21 – 4 year project:
  - Created in 2012
  - Six pharmaceutical companies from the European Foundation of Pharmaceutical Industries and Associations (EFPIA)
    - GSK, Sanofi, Orion, J&J, Bayer, Pfizer
  - Ten Universities
  - Five small to medium companies
  - Funded by EFPIA and the European Union
- Develops sustainable biological and chemical methodologies
  - Supports research projects
    - Catalytic chemistry
    - Enzymatic chemistry
    - Synthetic biology
  - Provides training packages
    - Education of the future chemists
    - Developed Solvent Selection guide

不同溶剂选择指南对比

Ranking	Solvents
Recommended	Water, EtOH, iPrOH, nBuOH, AcOEt, AcOiPr, AcOnBu, PhOMe, sulfolane
Recommended or Problematic ?	MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, cyclohexanone, AcOMe, AcOH, Ac_2O
Problematic	Me-THF, heptane, Me-cyclohexane, toluene, xylene, chlorobenzene, acetonitrile, DMPU, DMSO
Problematic or Hazardous ?	THF, MTBE, cyclohexane, DCM, formic acid, pyridine
Hazardous	iPr_2O, dioxane, DME, pentane, hexane, DMF, DMA, NMP, TEA, methoxyethanol
Highly hazardous	Et_2O, Benzene, CCl_4, chloroform, DCE, nitromethane

- 67% convergence (AZ, ACS GCI, GSK, Pfizer, Sanofi)
- The divergences reflect the different weighing of criteria

D. Prat, J. Hayler, A. Wells, *Green Chem.*, 2014, *16*, 4546

Chem21溶剂指南

- Ranking methodology:
  - Collect physical data and GHS statements from SDS
  - Safety Score is calculated from the FP, AIT, resistivity, ability to form peroxides etc.
  - Health score derives from the most stringent H3xx statement +1 if BP < 86°C
    - H314 (skin irritant)
  - Environment score depends on the BP and on the H4xx statement
    - H420 (ozone layer hazard)
  - Ranking by default is given by the combination of HS&E scores

Combination of SH&E scores	Solvent ranking by default
One score ≥ 8 (red)	Hazardous
Two scores ≥ 7 (red)	Hazardous
One score = 7 (red)	Problematic
4 ≤ Two scores ≤ 6 (yellow)	Problematic
Other	Recommended

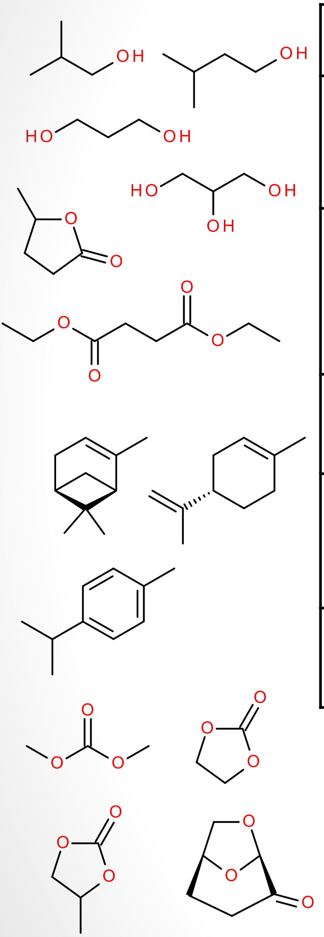
Chem21溶剂指南

- The ranking thus obtained is consistent with the ranking based on the survey of classical solvents (81% agreement)

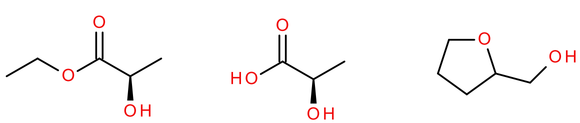
Family	Solvent	BP (°C)	FP (°C)	Worst H3xx	H4xx	Safety score	Health score	Env. score	Ranking by default	Ranking from the survey
Water	Water	100	na	none	none	1	1	1	Recommended	Recommended
Alcohols	EtOH	78	13	H319	none	4	3	3	Recommended	Recommended
	i-PrOH	82	12	H319	none	4	3	3	Recommended	Recommended
	n-BuOH	118	29	H318	none	3	4	3	Recommended	Recommended
Esters	Ethyl acetate	77	-4	H319	none	5	3	3	Recommended	Recommended
	i-PrOAc	89	2	H319	none	4	2	3	Recommended	Recommended
	n-BuOAc	126	22	H336	none	4	2	3	Recommended	Recommended
Ethers	Diethyl ether	34	-45	H302	none	10	3	7	Hazardous	HH
	Diisopropyl ether	69	-28	H336	none	9	3	5	Hazardous	Hazardous
	Me-THF	80	-11	H318	none	6	5	3	Problematic	Problematic
	1,4-Dioxane	101	12	H351	none	7	6	3	Problematic	Hazardous
	Anisole	154	52	none	none	4	1	5	Problematic	Recommended
	DME	85	-6	H360	none	7	9	3	Hazardous	Hazardous
Hydrocarbons	Pentane	36	-40	H304	H411	8	3	7	Hazardous	Hazardous
	Hexane	69	-22	H361	H411	8	7	7	Hazardous	Hazardous
	Heptane	98	-4	H304	H410	6	2	7	Problematic	Problematic
	Me-Cyclohexane	101	-4	H304	H411	6	2	7	Problematic	Problematic
	Benzene	80	-11	H350	none	6	10	3	Hazardous	HH
	Toluene	111	4	H351	none	5	6	3	Problematic	Problematic
	Xylenes	140	27	H312	none	4	2	5	Problematic	Problematic

Chem21溶剂指南

- Ranking of bio-derived solvents



Family	Solvent	BP (°C)	FP (°C)	Worst H3xx	H4xx	Safety score[#]	Health score	Env. score	Ranking by default
Alcohols	*i*-Butanol	107	28	H318	none	3	4	3	Recommended
	i-Amyl alcohol	131	43	H315	none	3	2	3	Recommended
	1, 3-Propane diol	214	>100	none	none	1	1	7	Problematic
	Glycerol	290	177	none	none	1	1	7	Problematic
Esters	*i*-Butyl acetate	115	22	H336	none	4	2	3	Recommended
	i-Amyl acetate	142	25	none	none	3	1	5	Recommended
	Glycol diacetate	186	82	none	none	1	1	5	Recommended
	γ-Valerolactone	207	100	n.a.	n.a.	1	5	7	Problematic
	Diethyl succinate	218	91	n.a.	n.a.	1	5	7	Problematic
Hydrocarbons	D-Limonene	175	49	H304	H400	4	2	7	Problematic
	Turpentine	166	38	H302	H411	4	2	7	Problematic
	p-Cymene	177	27	n.a.	n.a.	4	5	5	Problematic
Aprotic polar	Dimethyl carbonate	90	16	none	none	4	1	3	Recommended
	Ethylene carbonate	248	143	H302	none	1	2	7	Problematic
	Propylene carbonate	242	132	H319	none	1	2	7	Problematic
	Cyrene	203	61	H319	n.a.	1	2	7	Problematic
Miscellaneous	Ethyl lactate	155	47	H318	none	3	4	5	Problematic
	Lactic acid	230	113	H318	none	1	4	7	Problematic
	TH-Furfuryl alcohol	178	75	H360	none	1	9	5	Hazardous



Innovative Medicines Initiative

efpia

Chem21溶剂指南

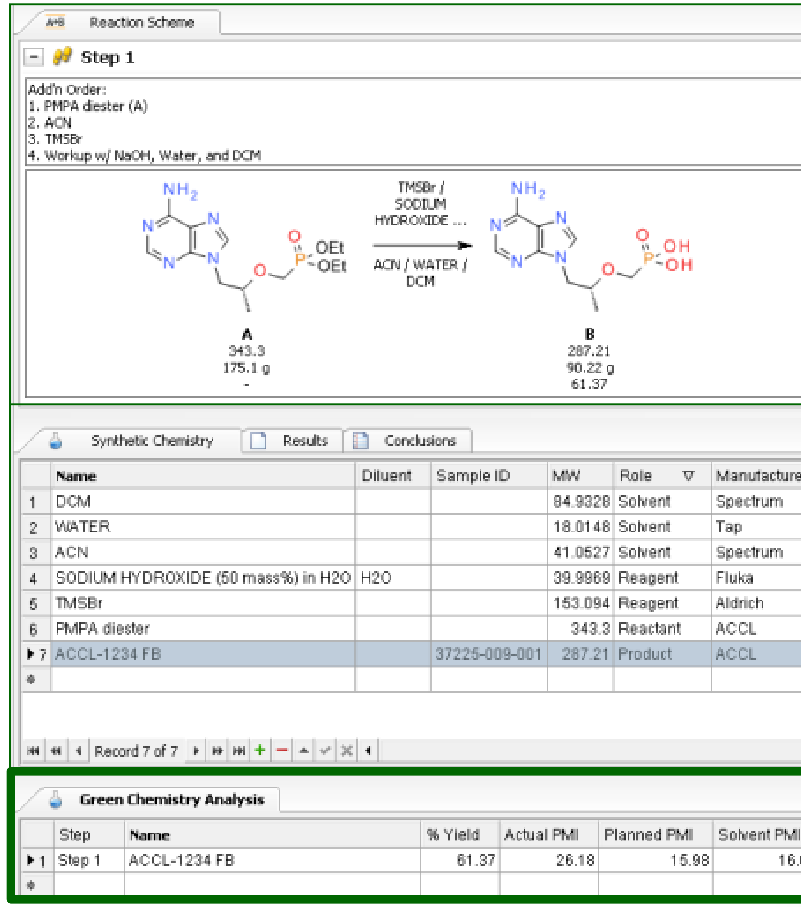
- Gives a preliminary desirability of any solvents for fine chemistry scale-up purposes
  - Classical solvents
  - Bio-derived solvents
  - Newer solvents
- Is the fruit of a successful collaboration between (*inter alia*) Sanofi, GSK, Pfizer, Orion, J&J, and the University of York
- The methodology is not perfect
  - The health criterion should be based on OEL
  - It only gives a preliminary assessment, a discussion is needed in each institution to challenge the ranking
  - The environment criterion should include the CO_2 synthesis impact

D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehada, P. J. Dunn, *Green Chem.*, 2016, *18*, 288

Innovative Medicines Initiative

电子实验记录本(ELN)

- Essential component of a successful GC program
  - Incorporates GC into scientist’s daily activities
  - Solvent selection guides can be incorporated to flag for example red solvents and show greener alternatives
  - Green metrics easily calculated
    - PMI (process input/output)
    - E-factor (process waste/output)
    - Atom economy



Green Chemistry Analysis

取代液相分离中用的二氯甲烷溶剂

- The biggest usage of DCM for small scale chemistry is in column chromatography.
- **Some useful starting points for greener alternatives –**
- Neutral compounds
  - 3:1 EtOAc:EtOH in heptane or TBME
  - EtOAc in heptane
  - IPA in heptane
  - MeOH in TBME
- Basic Compounds
  - 3:1 EtOAc:EtOH (with 2% NH4OH) in heptane
  - 10:1 MeOH : NH4OH in EtOAc
  - 10:1 MeOH : NH4OH in TBME
- Acidic Compounds
  - 3:1 EtOAc:EtOH (with 2% AcOH) in heptane
  - 10:1 MeOH : AcOH in EtOAc
  - 10:1 MeOH : AcOH in TBME

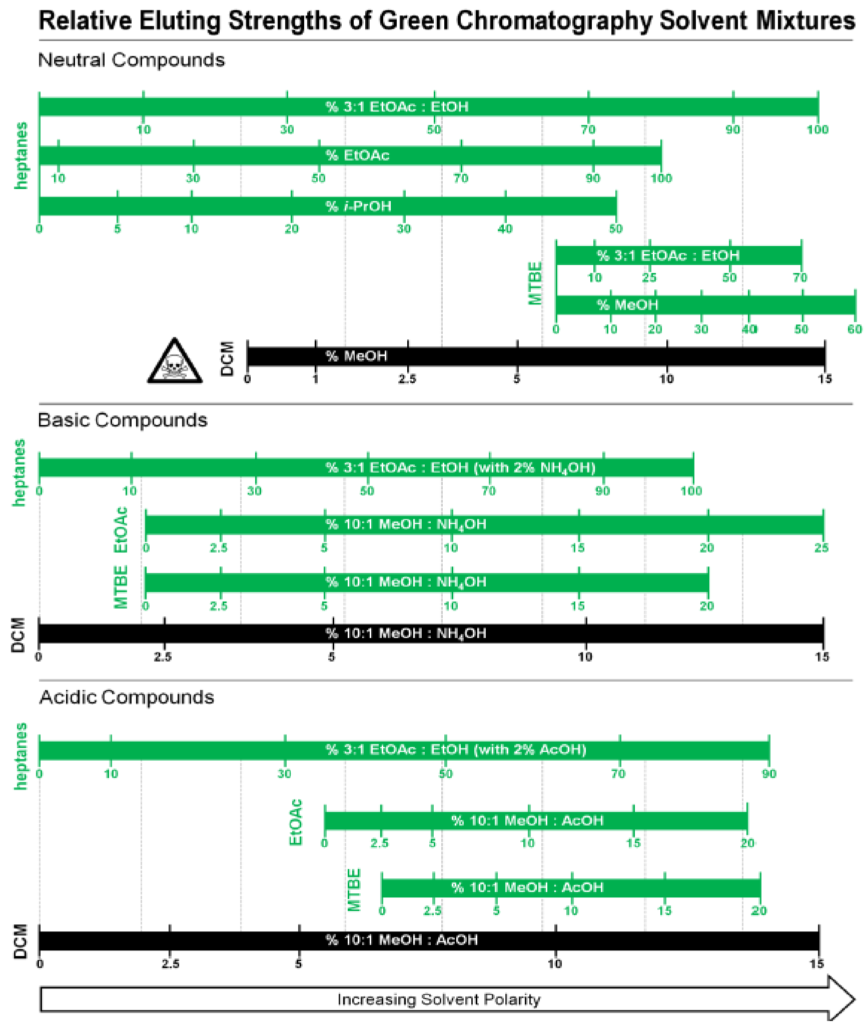
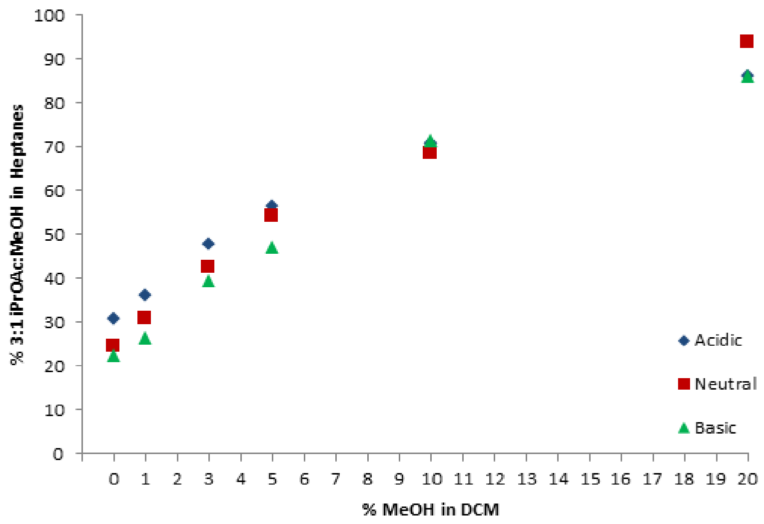


Figure 4. **Green Chromatography Solvent Selection Guide**. Starting from the appropriate DCM/MeOH concentration, compare vertically across the bar chart to identify greener solvent mixtures of similar eluting ability. For example, if a compound suitably elutes in 5% DCM/MeOH in the absence of an additive, the "Neutral Compounds" bar chart predicts that 60% 3:1 EtOAc:EtOH in heptanes or 40% of *i*-PrOH in heptanes would be suitable starting points to evaluate greener solvent alternatives.

A Convenient Guide to Help Select Replacement Solvents for Dichloromethane in Chromatography, Green Chem. Advance Article 2012, http://dx.doi.org/10.1039/C2GC36064K

取代液相分离中用的二氯甲烷溶剂

- Comparison of MeOH in DCM vs. 3:1 *i*-PrOAc : MeOH in heptane (greener solvent blend)
- 3:1 *i*-PrOAc : MeOH in heptane presents greater polarity window than 3:1 EtOAc (MeOH – higher polarity vs. EtOH, *i*-PrOAc – lower polarity vs. EtOAc)



- Graph shows percentage equivalence between 3:1 *i*-PrOAc : MeOH in heptane & MeOH in DCM
  - Higher gradient required with green solvent mix - potential to better separate trickier mixtures of polar compounds
  - Dilution of MeOH with *i*-PrOAc enables better separation between closely spaced peaks
  - Significant cost reductions by using greener alternatives

Chardon, F. M.; Blaquiere, N.; Castanedo, G. M.; Koenig, S. G., Green Chem. ***2014****, 16, 4102*

取代 DCM & DMF: 酰胺化反应

Solvent	Aryl Acid – Aryl Amine					Aryl Acid – Alkyl Amine					Alkyl Acid – Aryl Amine					Alkyl Acid – Alkyl Amine				
	HATU	COMU	DIC HOBt	PyBOP	T3P	HATU	COMU	DIC HOBt	PyBOP	T3P	HATU	COMU	DIC HOBt	PyBOP	T3P	HATU	COMU	DIC HOBt	PyBOP	T3P
TBME	*		*	*				*								**	**	**	*	*
CPME					*					**						**	*	**	**	**
CH_2Cl_2	**		*	*	*	*	**	*	*	*	**	**	*	*		*	**	**	**	**
DMC	*	*	*	*	**	**	**	**	**	**	*	*				**	**	*	**	*
DMF	**	**	**			*	*	**	**	*	**	**	*	*		**	**	**	*	**
EtOAc	*	*	*	*	**	**	**	**	**	**	*	**	*			**	**	**	**	**
IPA	*	*	*	*		*	**	*	**	*	*	*				**	**	**	**	
2-MeTHF	*	*	*	*			*	*	*	*	*	**	*	*		*	**	*	*	**

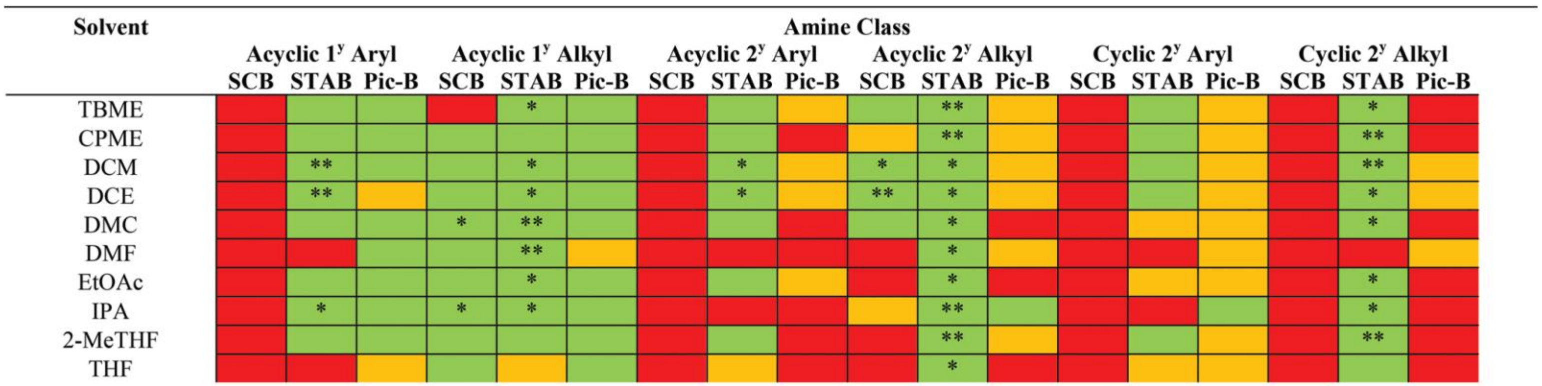
[a] Key: Red = <50% conv., orange = 50–70% conv., green = >70% conv.; * Indicates 100% conv. within 4 h. ** Indicates 100% conv. within 1 h.

Evaluation of Alternative Solvents in Common Amide Coupling Reactions: Replacement of Dichloromethane and *N,N*-Dimethylformamide

D. S. MacMillan, J. Murray, H. F. Sneddon, C. Jamieson, A. J. B. Watson *Green Chem.* **2013**, *15*, 596-600

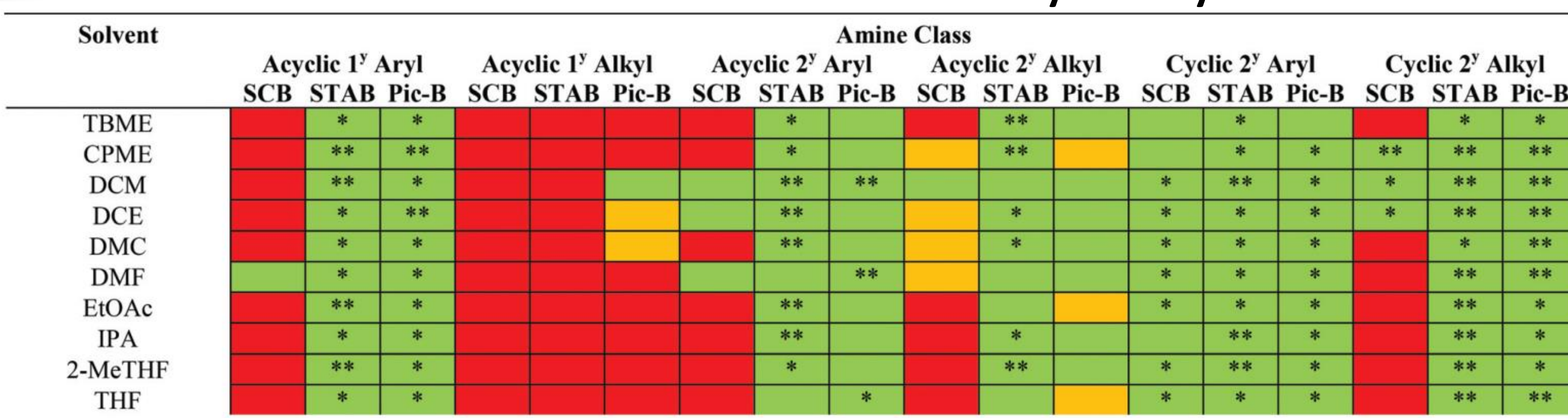
不用DCM & DMF: 还原胺化

Reductive Amination dataset for aryl aldehydes



[a] Key: red = <50% conv., orange = 50–70% conv., green = >70% conv. *Indicates 100% conv. within 4 h. **Indicates 100% conv. within 1 h. SCB = $NaBH_3CN$, STAB = $NaBH(OAc)_3$, Pic-B = picoline–borane complex.

Reductive Amination dataset for alkyl aldehydes



[a] Key: red = <50% conv., orange = 50–70% conv., green = >70% conv. *Indicates 100% conv. within 4 h. **Indicates 100% conv. within 1 h. SCB = $NaBH_3CN$, STAB = $NaBH(OAc)_3$, Pic-B = picoline–borane complex.

Development of a Solvent Selection Guide for Aldehyde-based Direct Reductive Amination Processes

F. I. McGonagle, D. S. MacMillan, J. Murray, H. F. Sneddon, C. Jamieson, A. J. B. Watson, *Green Chem.*, **2013**, *15*, 1159-1165

总结

- What solvents are you using?
- Are they potentially hazardous to the environment?
  - Consult solvent selection guides:
    - Survey of Solvent Selection Guides: D. Prat et al. Green Chem. 2014, 16, 4546-4551
    - ACS GCI Pharmaceutical Roundtable guide available free of charge

      www.acs.org/gcipharmaroundtable
  - The biggest usage of DCM for small scale chemistry is in column chromatography – try discussed alternatives
- Make the right solvent choice – there are alternatives
    - Survey of Solvent Usage in Papers Published in Organic Process Research & Development 1997–2012; C. P. Ashcroft et al. Org. Process Res. Dev. Article ASAP link: http://dx.doi.org/10.1021/op500276u
- Think green – think sustainable

ACS Green Chemistry Institute®
Pharmaceutical Roundtable

INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

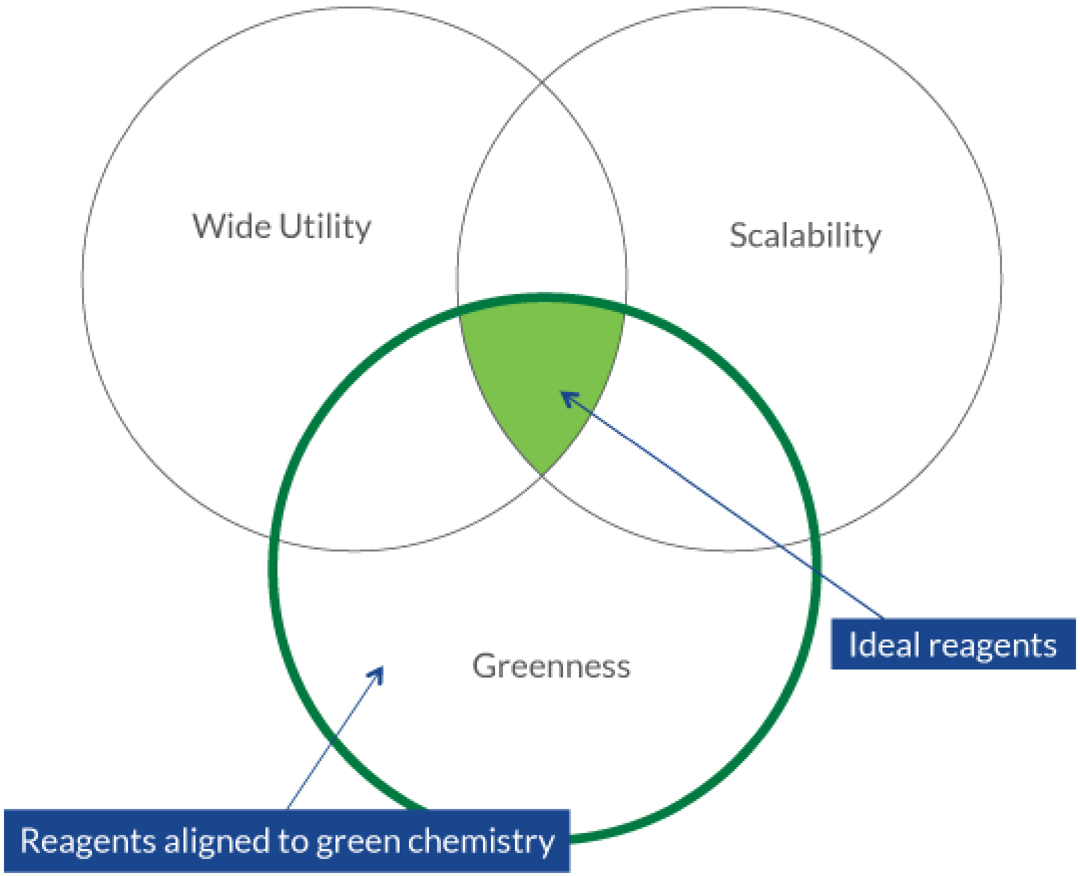
试剂指南

试剂选择指南

ACS Green Chemistry Institute® Pharmaceutical Roundtable

Reagent guides

reagentguides.com



Visual Selection using a Venn diagram

试剂选择指南

reagentguides.com

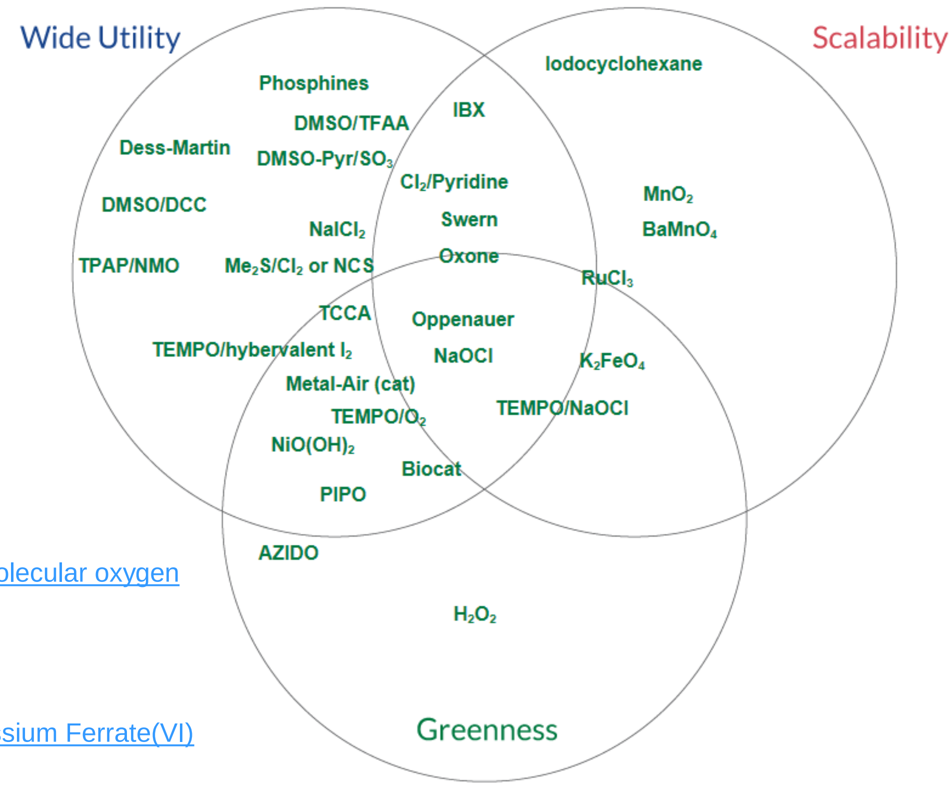
ACS Green Chemistry Institute
Pharmaceutical Roundtable

Reagent guides

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
- TPAP/NMO (tetrapropylammonium perruthenate)
- *TEMPO (General overview)*
- TEMPO-Bleach
- TEMPO –air –catalyst
- TEMPO-hypervalent iodine
- Air-Metal catalyst transition-metal catalyzed reactions using molecular oxygen
- Activated H_2O_2 hydrogen peroxide
- Biocatalysis biocatalytic methods for oxidation

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)

Venn Diagram



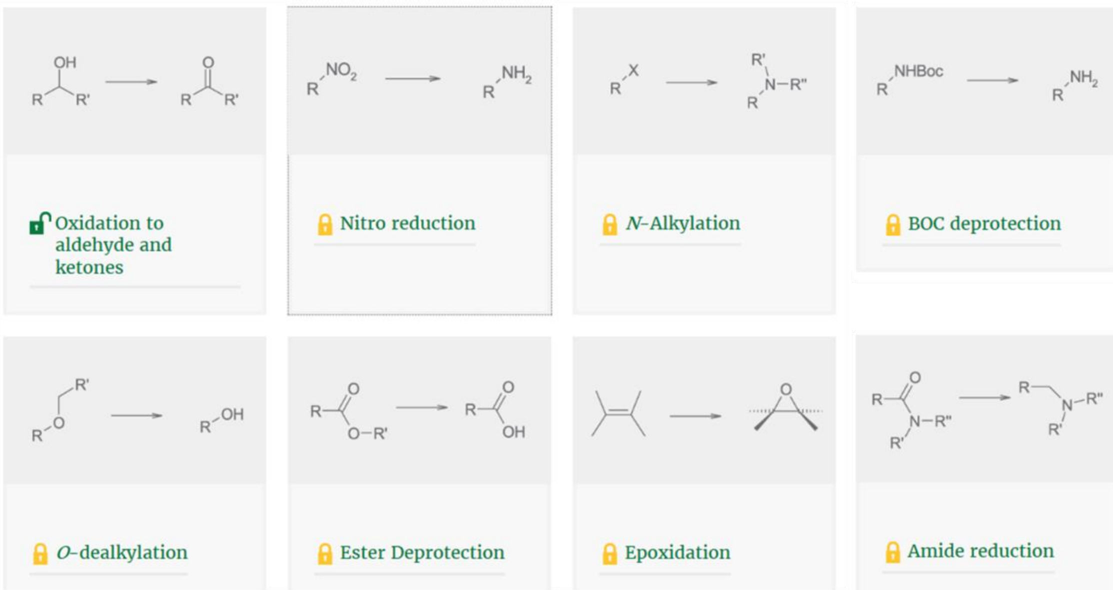
Oxidation to aldehydes and ketones

试剂选择指南

Reagent guides

reagentguides.com

8 Guides Now Publically Available…



More Guides Coming

Bromination
Fluorination
Chlorination
Iodination
Metals Removal
Chiral Hydrogenation
Oxidation to Acids
Suzuki Rxn
Buchwald-Hartwig Rxn

试剂选择指南

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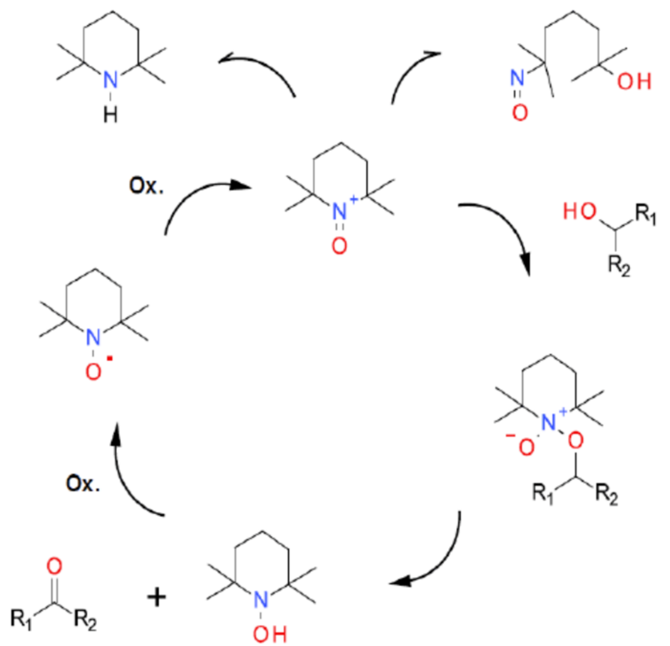
ACS Green Chemistry Institute
Pharmaceutical Roundtable

Reagent guides

TEMPO-Bleach oxidation

Mechanism + Description

As previous for TEMPO NaOCl is often used as a co-oxidant which generates NaCl as a by-product.
NaBr or borates are often added as a promoter.



General Comments

A common terminal oxidant is bleach (NaOCl) which is often employed with a Bromide or borate co-catalyst. Reactions in water of bi-phasic reactions are often helped by the addition of a phase transfer catalyst

Key References

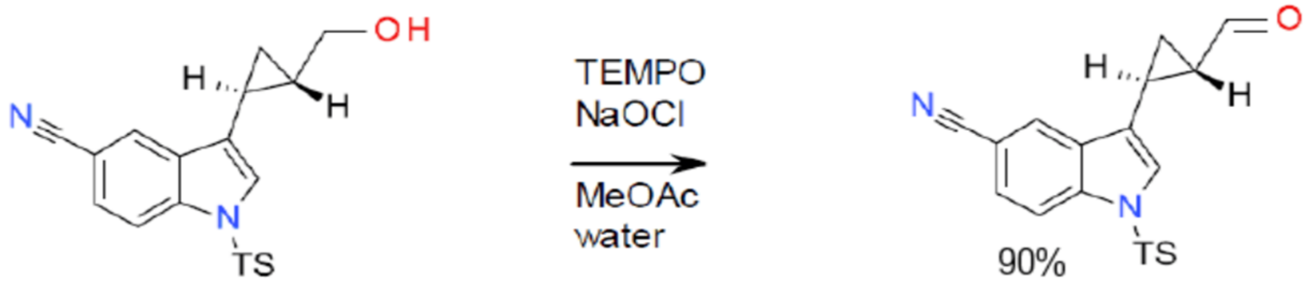
Org. Process Res. Dev., 2005, 9 (5), 577–582 - Production of Aldehydes by Continuous Bleach Oxidation of Alcohols Catalyzed by 4-Hydroxy-TEMPO
Org. Process Res. Dev., 2008, 12 (2), 322–338– Discussion of optimisation to prevent racemisation (50 L scale)
Org. Process Res. Dev., 2010, 14 (2), 441–458 - DOE and robustness studies on TEMPO stage statin oxd'n (2000 L scale)
Org. Process Res. Dev., 2010, 14 (1), 142–151 - Use of NaI to prevent chlorination of heteroaromatic (50 L scale)

试剂选择指南

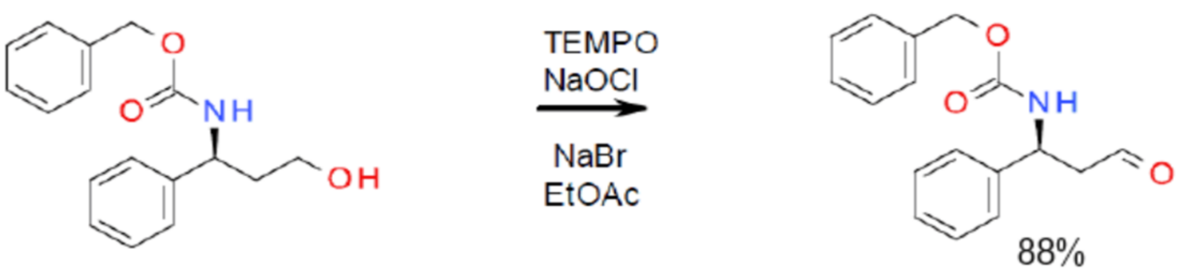
reagentguides.com

Reagent guides

Relevant Scale up examples



Org. Process Res. Dev., 2008, 12 (2), 168–177 – 100 L oxd'n in MeOAc or THF



Org. Process Res. Dev., 2008, 12 (6), 1104–1113– 2000 L prep of Maraviroc intermediate

III- 绿色化学实例

纲要

Case Studies

Indole carboxylic acid (INDAC) approaches

Macrocyclic RCM for hepatitis C protease inhibitor

PG-free route to PI3K/mTOR inhibitor GDC-0980

Sitagliptin evolution: hydrogenation to transaminase

Other themes

Sustainable metals, continuous flow, organic solvent nanofiltration (OSN), reactions in water, medicinal chemistry, lifecycle analysis (LCA)

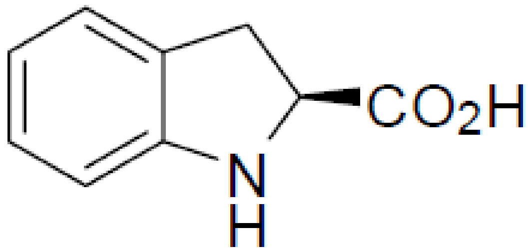
Literature

Articles of interest, Key Research Areas

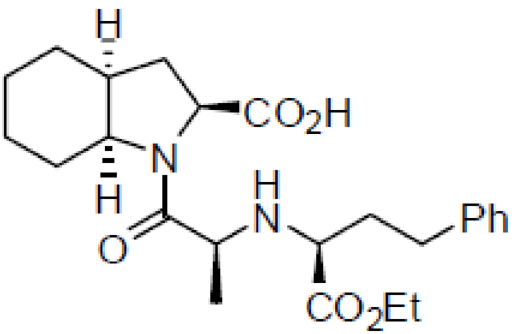
Summary / Conclusions

Indole Carboxylic Acid (INDAC)

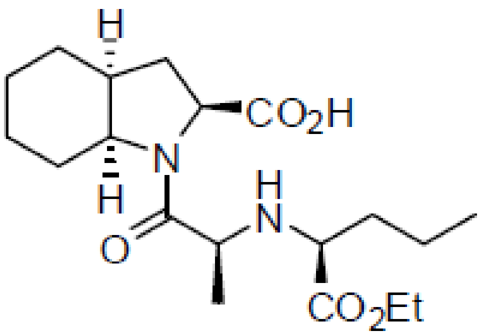
(S)-Indoline-2-carboxylic acid:



Key intermediate for angiotensin 1-converting enzyme inhibitors (so called ACE inhibitors) that are used for the treatment of hypertension:



Indolapril



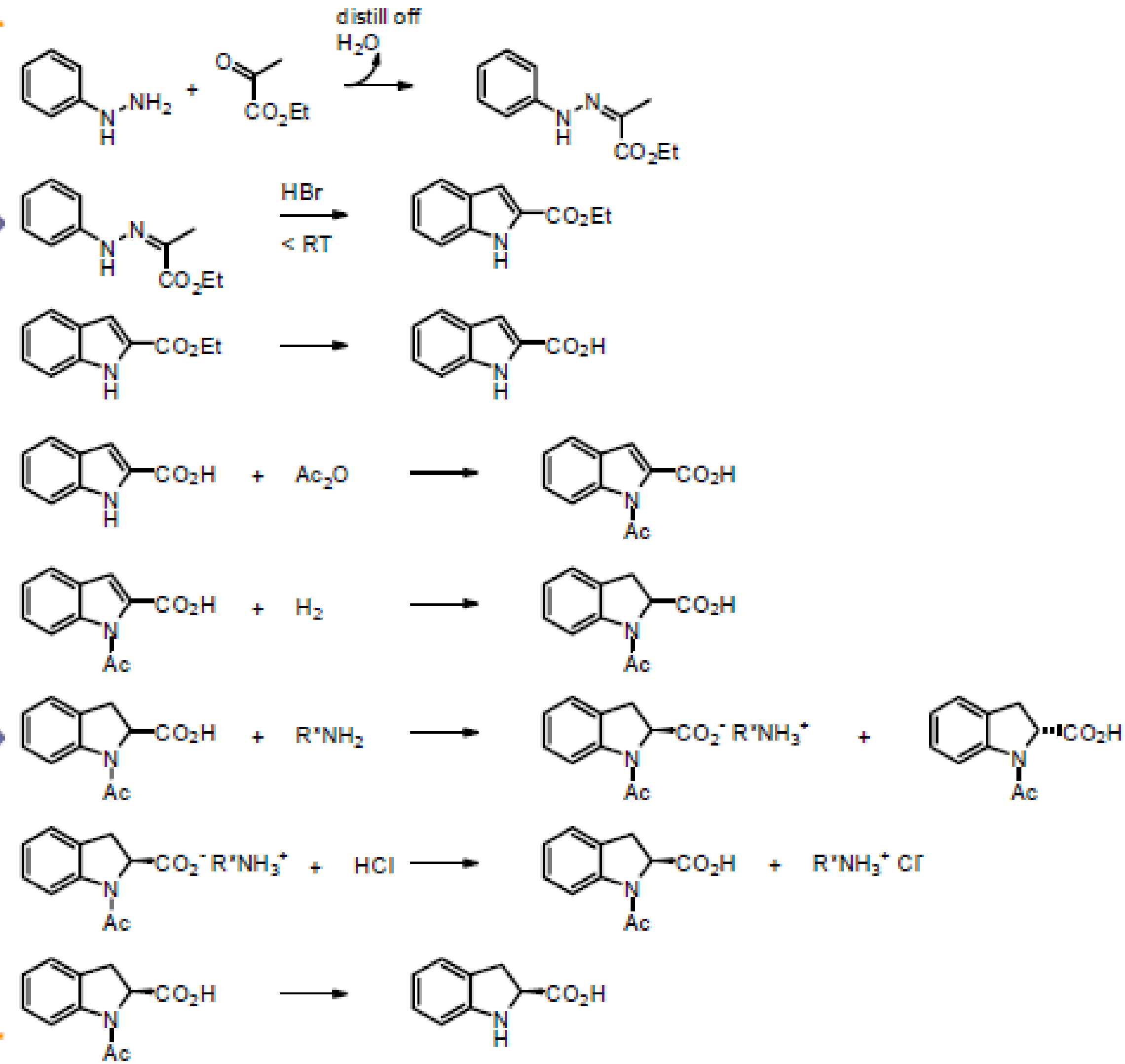
Perindopril

INDAC: 最早的合成(EP 937714)

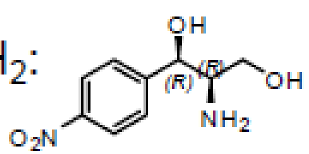
Fischer indole synthesis:

Steps:
1 catalytic,
7 stoichiometric

Racemate resolution:

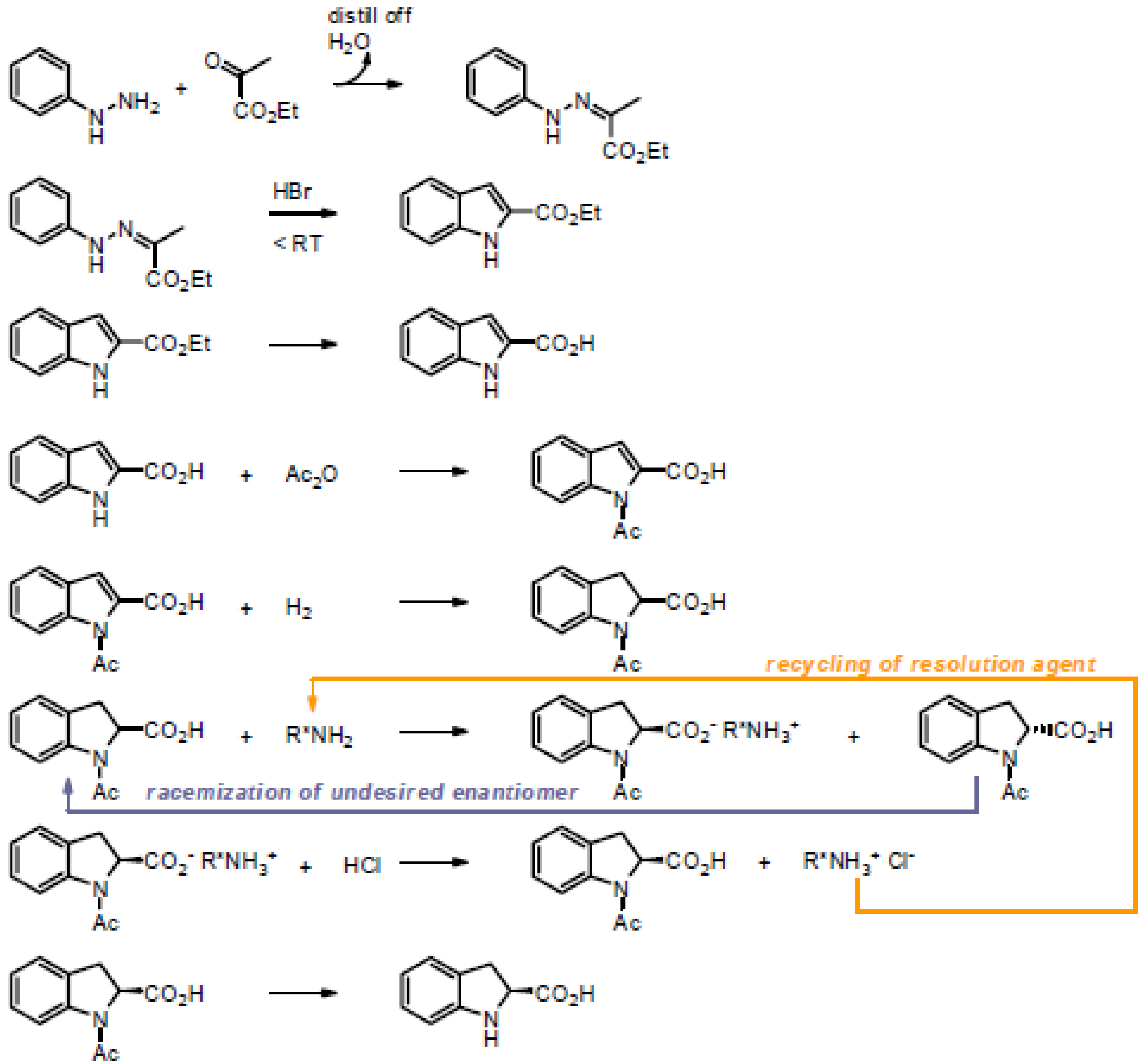


R*NH2:



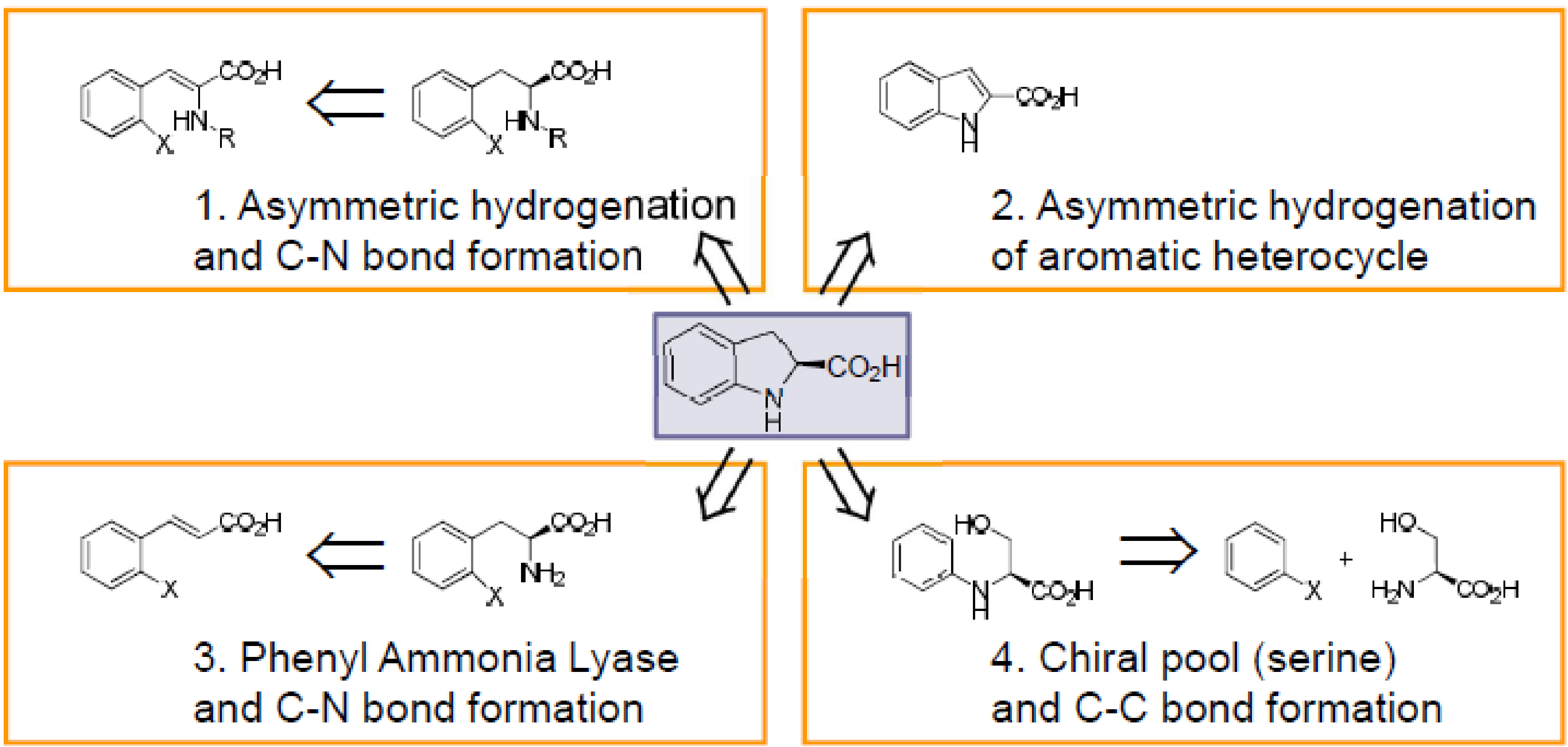
INDAC: 同一合成中提高产率和减少废料

But leading to an increase in the number of steps:



INDAC: 以绿色化学为出发点的合成路线

Bio- or chemo-catalysis is key!

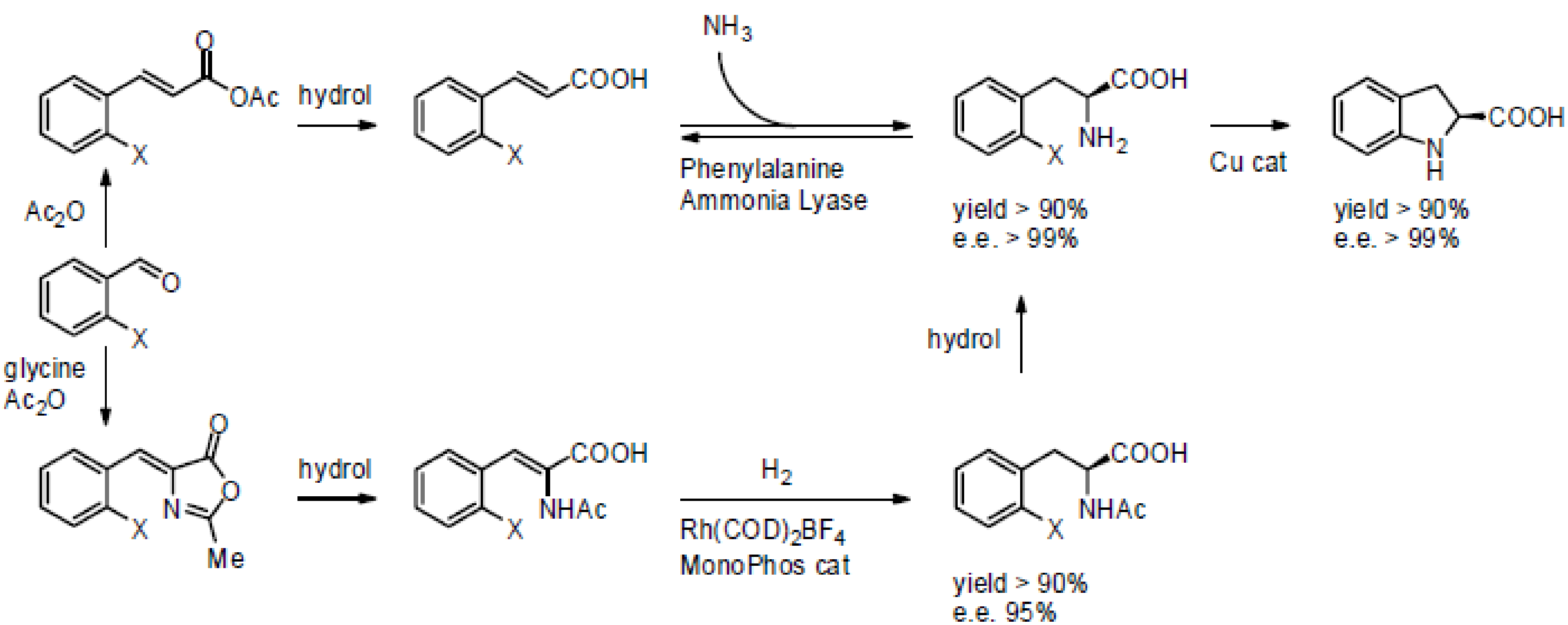


INDAC: 路线对比

- Number of steps
- Amount of new breakthrough technologies
- Availability (costs) of starting materials
- Estimated chance of success
- Cost estimations at maturity assuming the required breakthrough
- Adherence to the green chemistry principles!

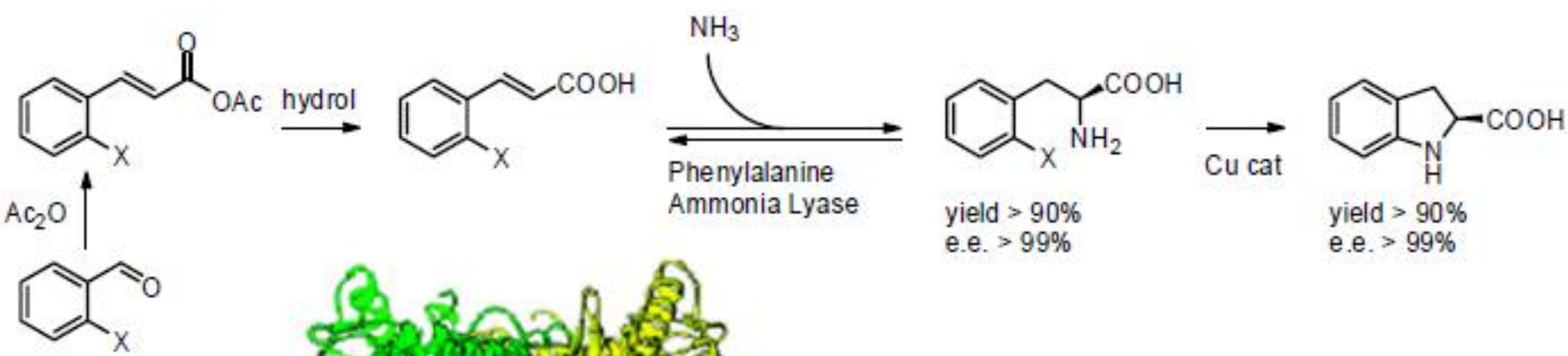
INDAC: 两条潜力路线

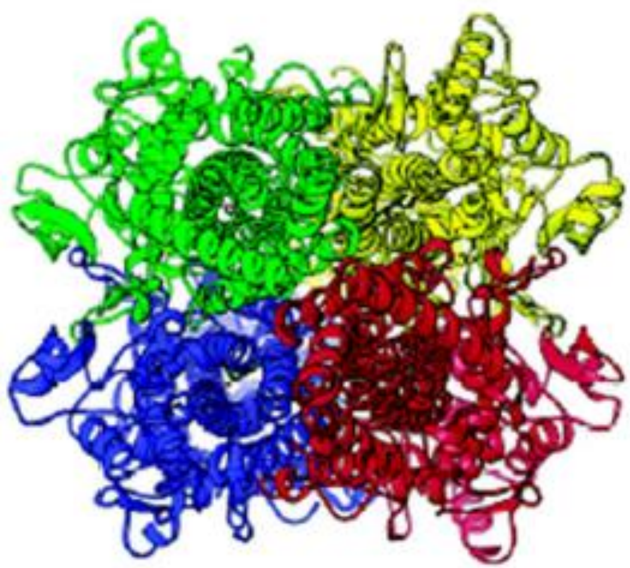
Which one is the winner?



INDAC: 第二代商业合成路线

The PAL route: *ChemCatChem* **2011**, *3*, 289

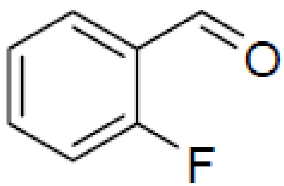


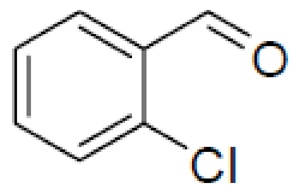


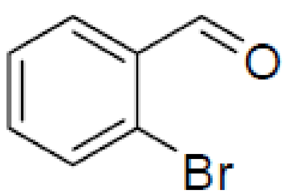
- Structure of *R. glutinis* PAL is known: Calabrese *et al*., 2004
- No cofactor required
- *(S)*-specific
- “Standard” literature conditions: 10% NH_3, pH 10
- Broad substrate scope

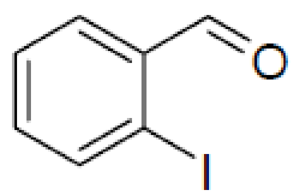
INDAC: PAL 路线里的 2-卤-苯甲醛

Which halogen to choose?







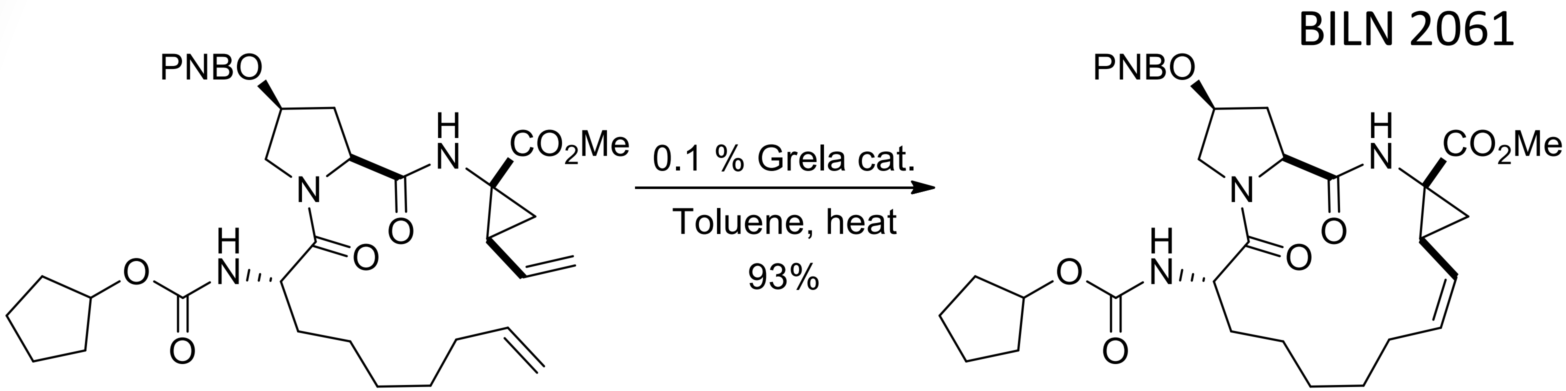


INDAC: 各个卤素的优缺点

Which 2-halobenzaldehyde should be selected for large-scale use in PAL route?

Substrate	Pro	Con	Conclusion
2-F	Low MW	Expensive, unreactive, toxic fluoride waste	Not selected
2-Cl	**Cheap, widely available, moderate MW, non-toxic**	**Modest reactivity but higher Cu loadings**	**Selected, best balance**
2-Br	Widely available, highly reactive so low Cu loadings	High MW bromide salt waste	Promising but second choice
2-I	Highly reactive so low Cu load	Not widely available, expensive, very high MW, and iodide waste	Not selected

关环双键置换反应用于大环丙肝抑制药



Original process:

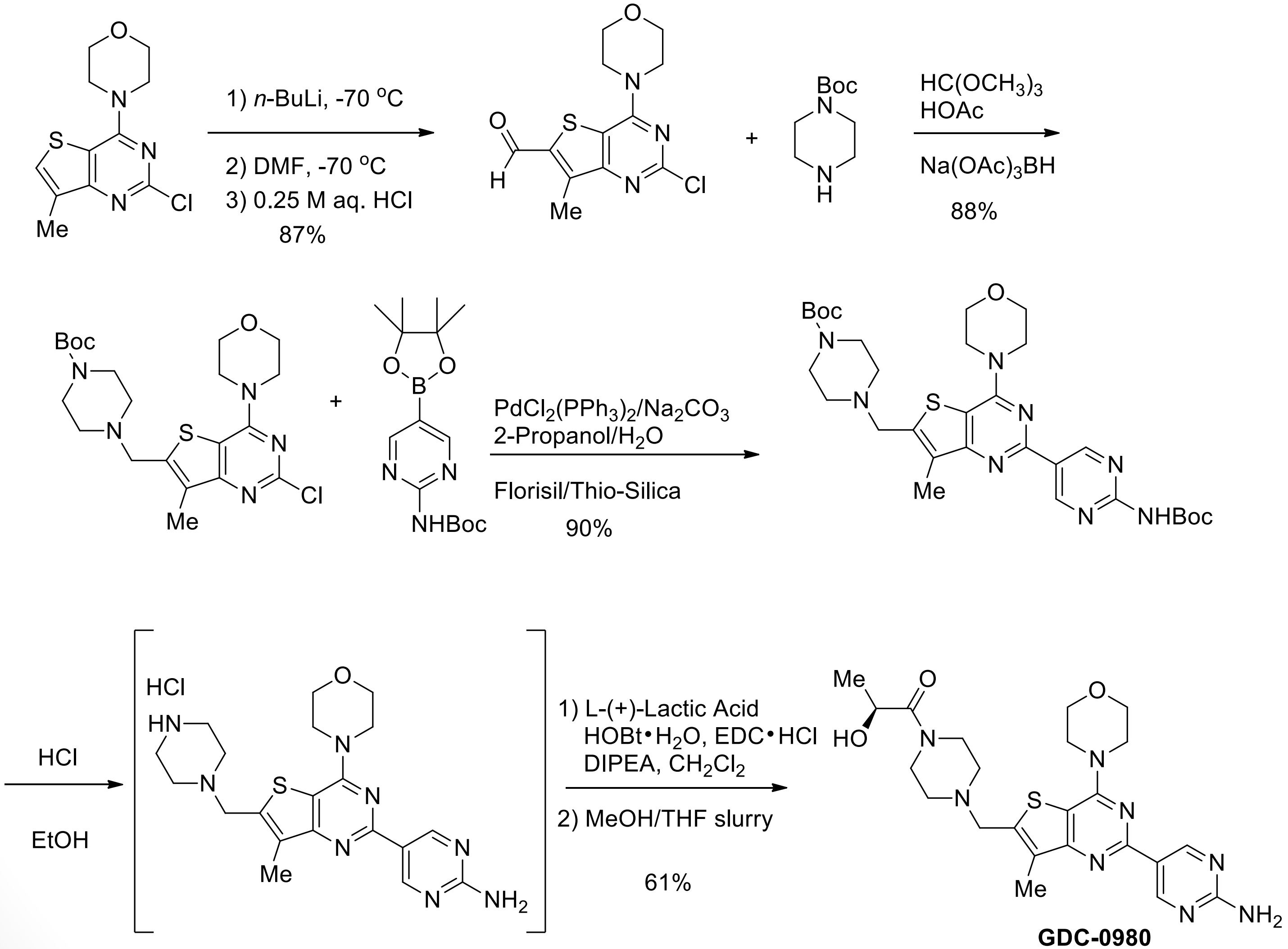
- high dilution (0.01 M DCM)
- high catalyst load (3 to 5 mol%)
- E-factor = 370
- Plan to build dedicated plant

New ***Greener*** Process

After detailed understanding and optimization of the reaction conditions

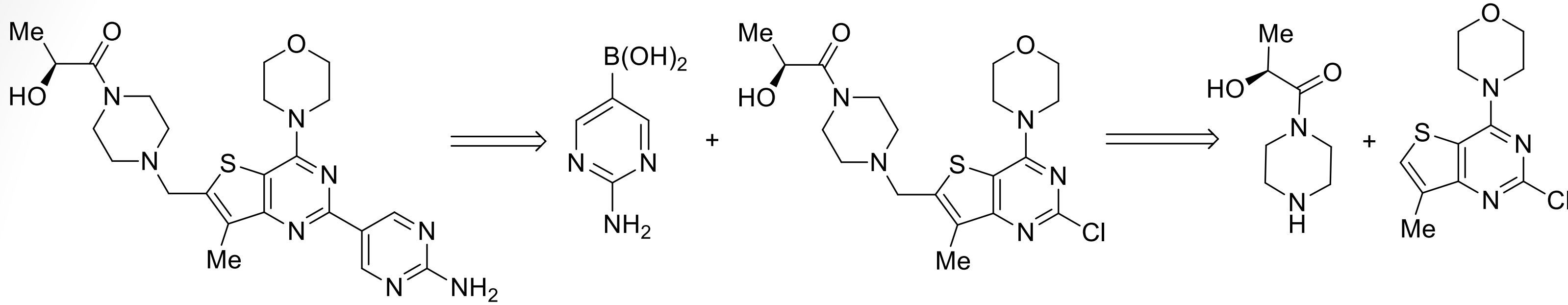
- High concentration (0.2 M in tol)
- Low catalyst loading (0.1 mol %)
- E-factor = 52
- Investment in new technology

GDC-0980 路线一

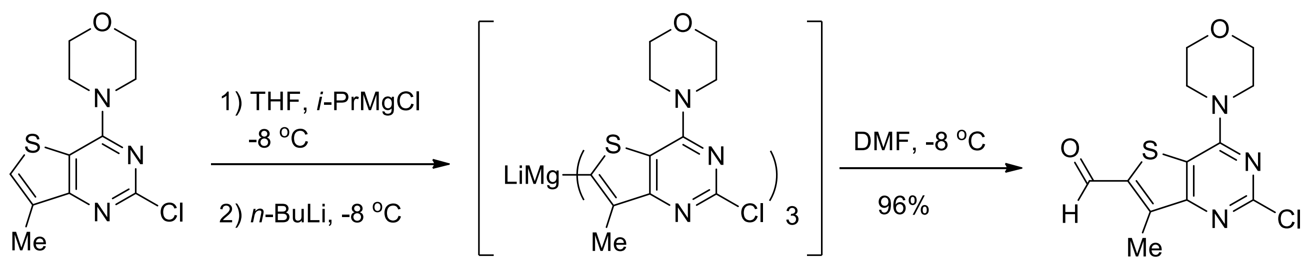


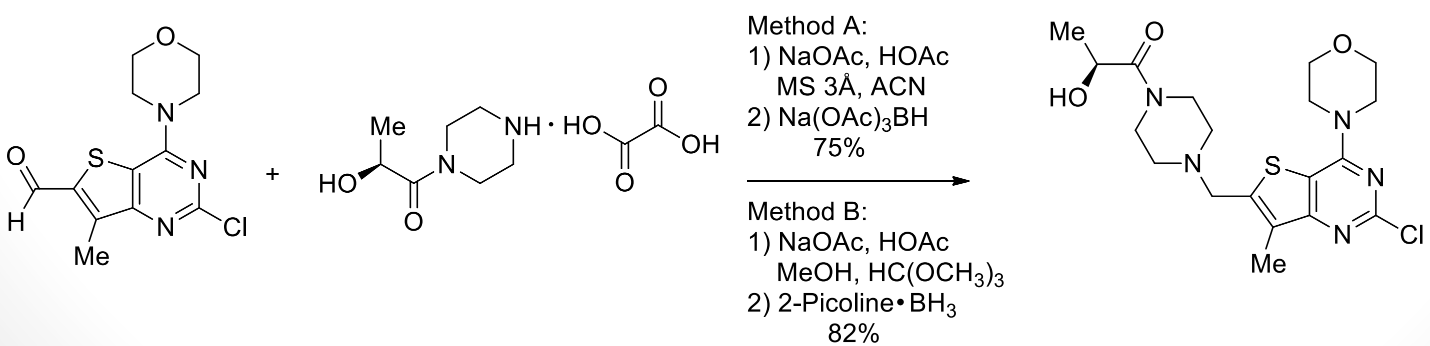
Tian, Q. et al. *Org. Process Res. Dev.*, **2013**, *17*, 97–107.

GDC-0980 路线二



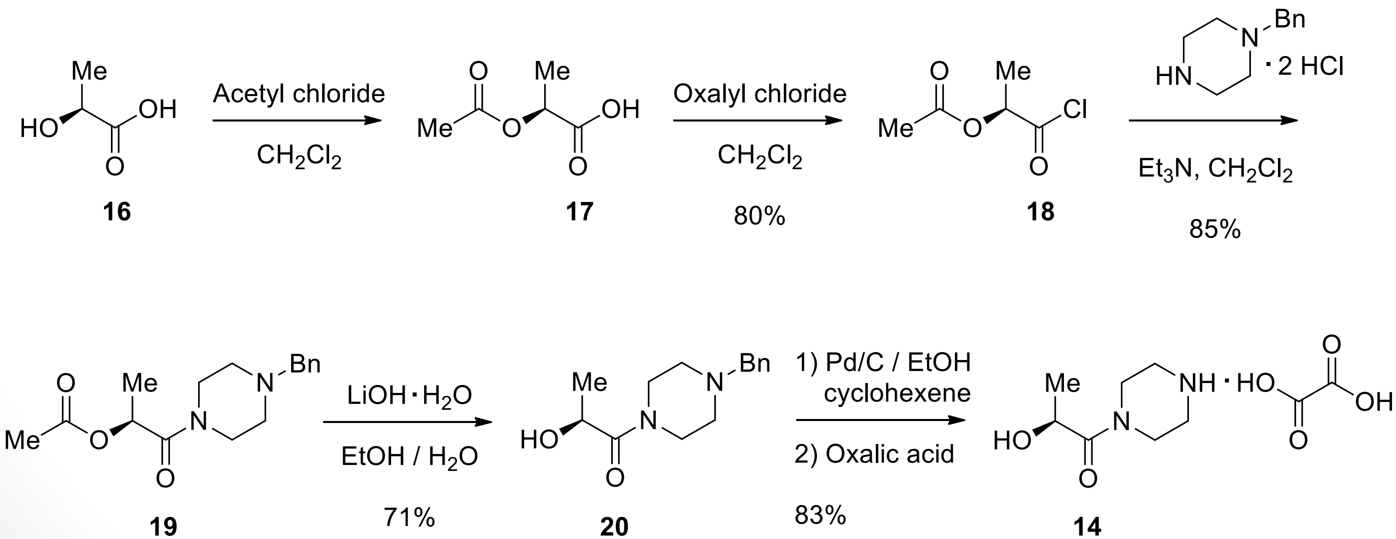
GDC-0980





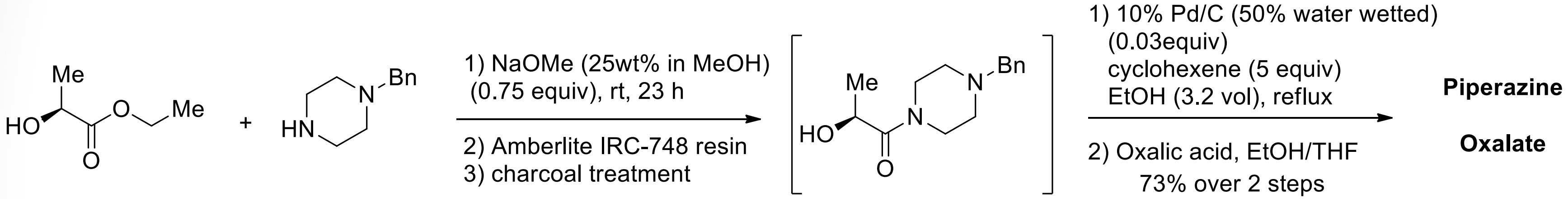
GDC-0980: Piperazine Oxalate 1

- First generation route:
  - utilizes many non-value adding steps (protection / deprotection)
  - requires undesirable conditions (DCM)
  - generates large amounts of waste, including benzene (from cyclohexene)
- 5 steps, 40% overall yield

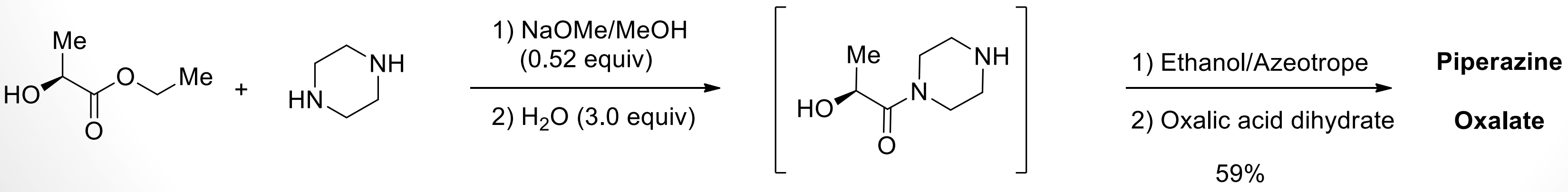


GDC-0980: Piperazine Oxalate 2

- Second generation route multi-step process but telescoped
- 73% overall yield but material-intensive

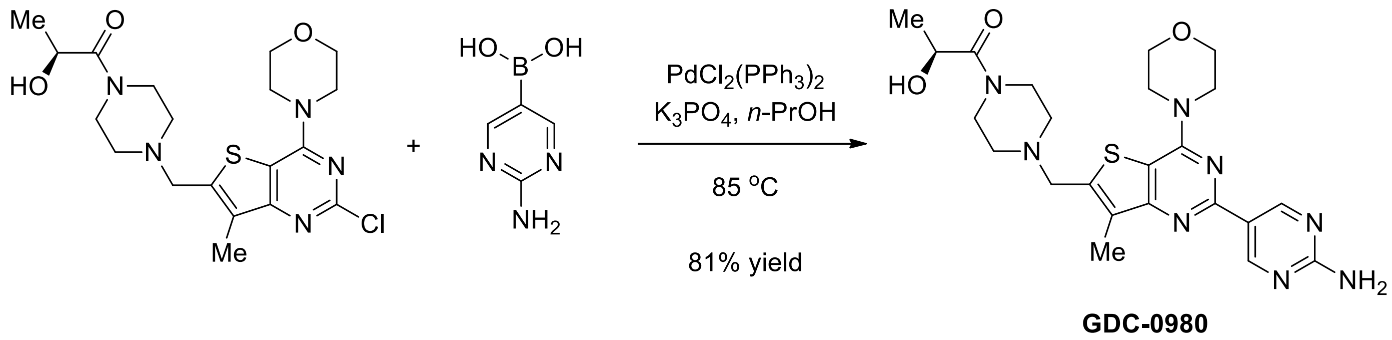


- Third generation route avoids protecting groups, auxiliary materials, and metal catalysts
- Final route utilizes sustainable chemicals and gives 59% yield

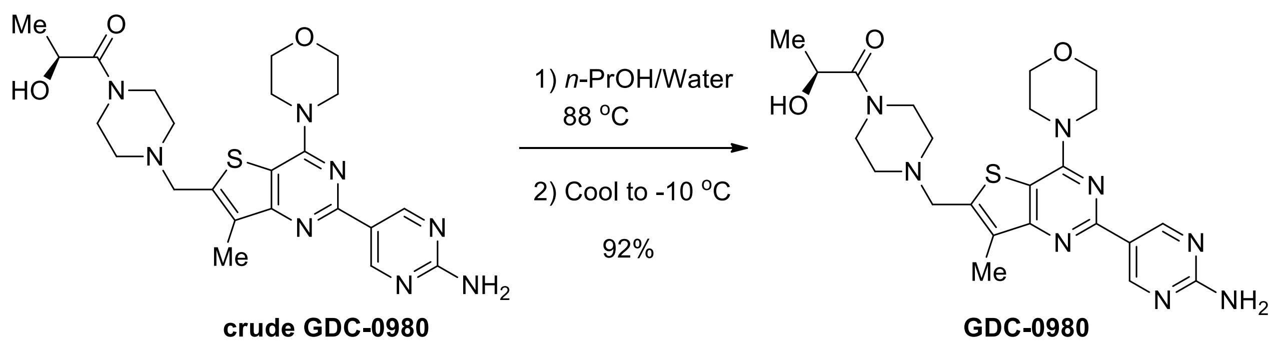


GDC-0980: 优化最后一步

- Protecting group-free Pd catalyzed C-C coupling



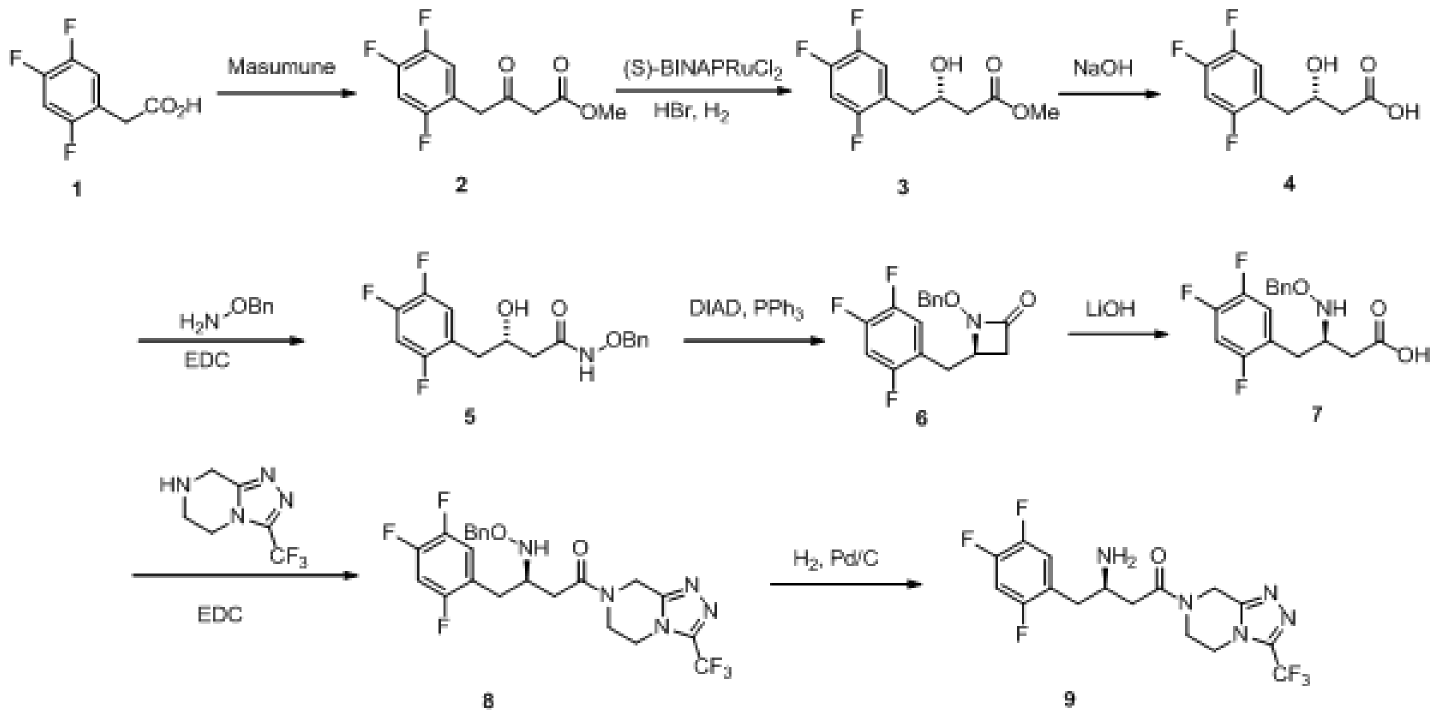
- Crystallization sufficient to control impurities (Pd content)



GDC-0980: 经验总结

- Catalysis (streamlines a synthesis - known) and can be conducted on scale with unprotected coupling partners
- Renewable building blocks can be incorporated efficiently
- Regulatory starting materials can be made more sustainably
- Protecting groups can be eliminated
- Cryogenic conditions can be avoided
- Auxiliary materials (filtration agents, molecular sieves, transition metal scavengers) can be removed

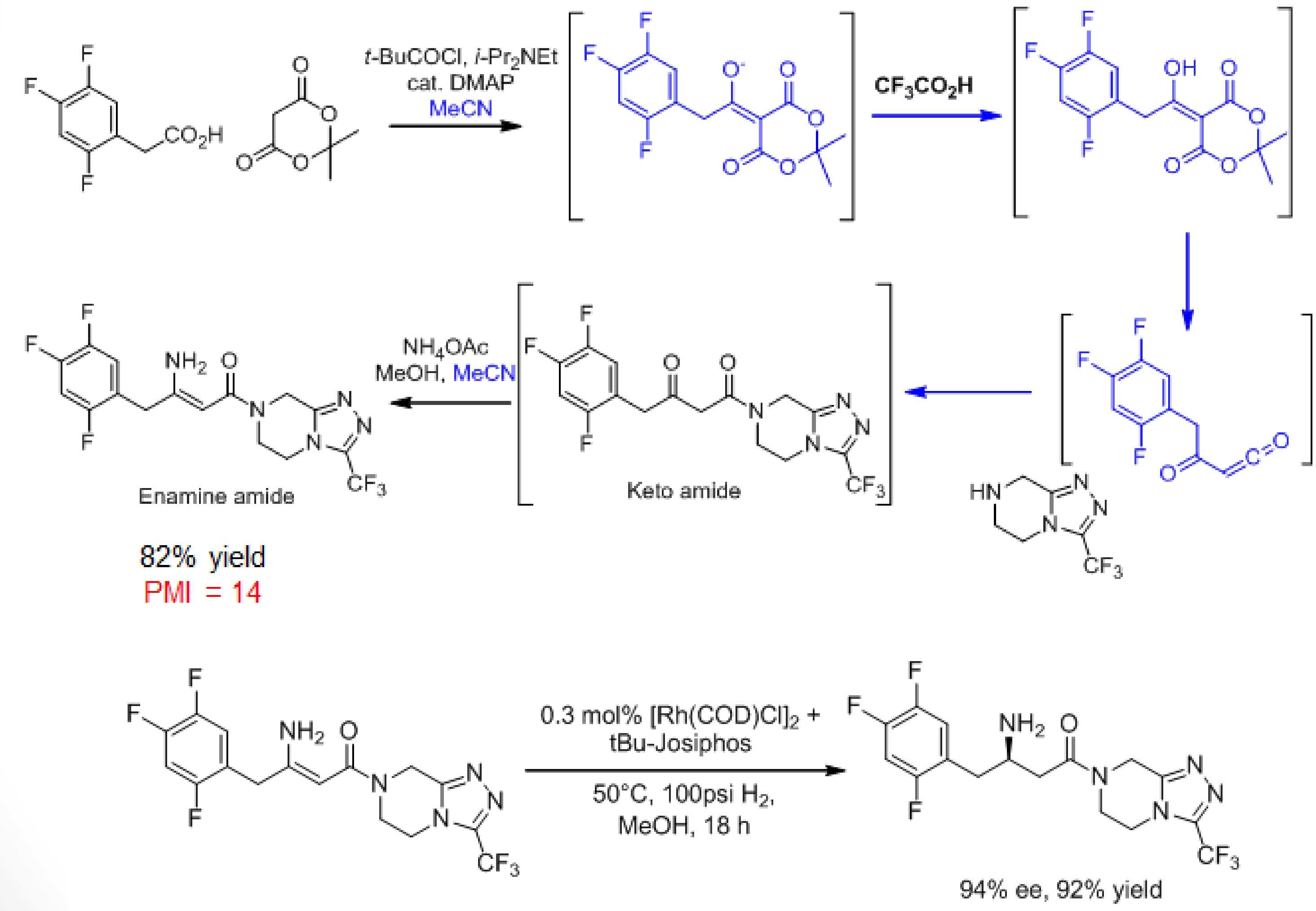
Sitagliptin 第一次路线更新



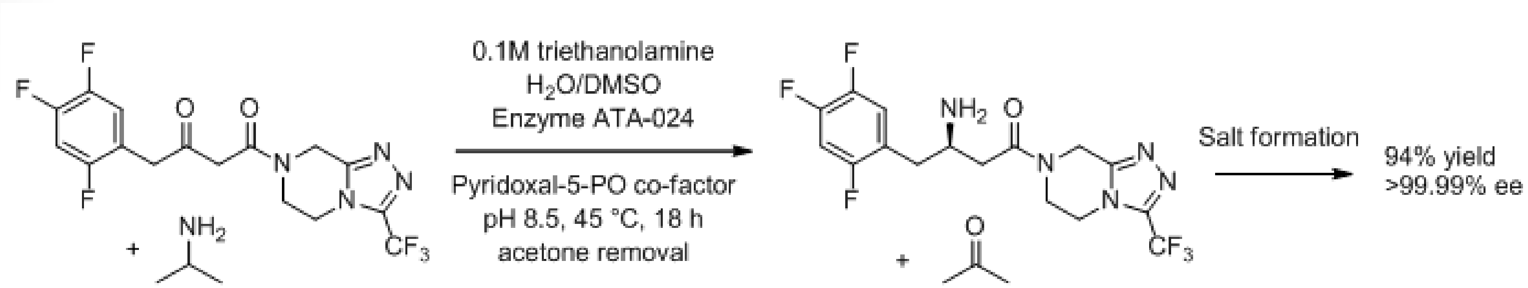
- >100 kg manufactured, 52% overall yield - 8 steps from acid 1
- 3 productive bond-forming steps **(38% desired)**
- 5 functional group manipulations **(62% undesired)**

Can we do it in only 3 steps?

Sitagliptin第二次路线更新

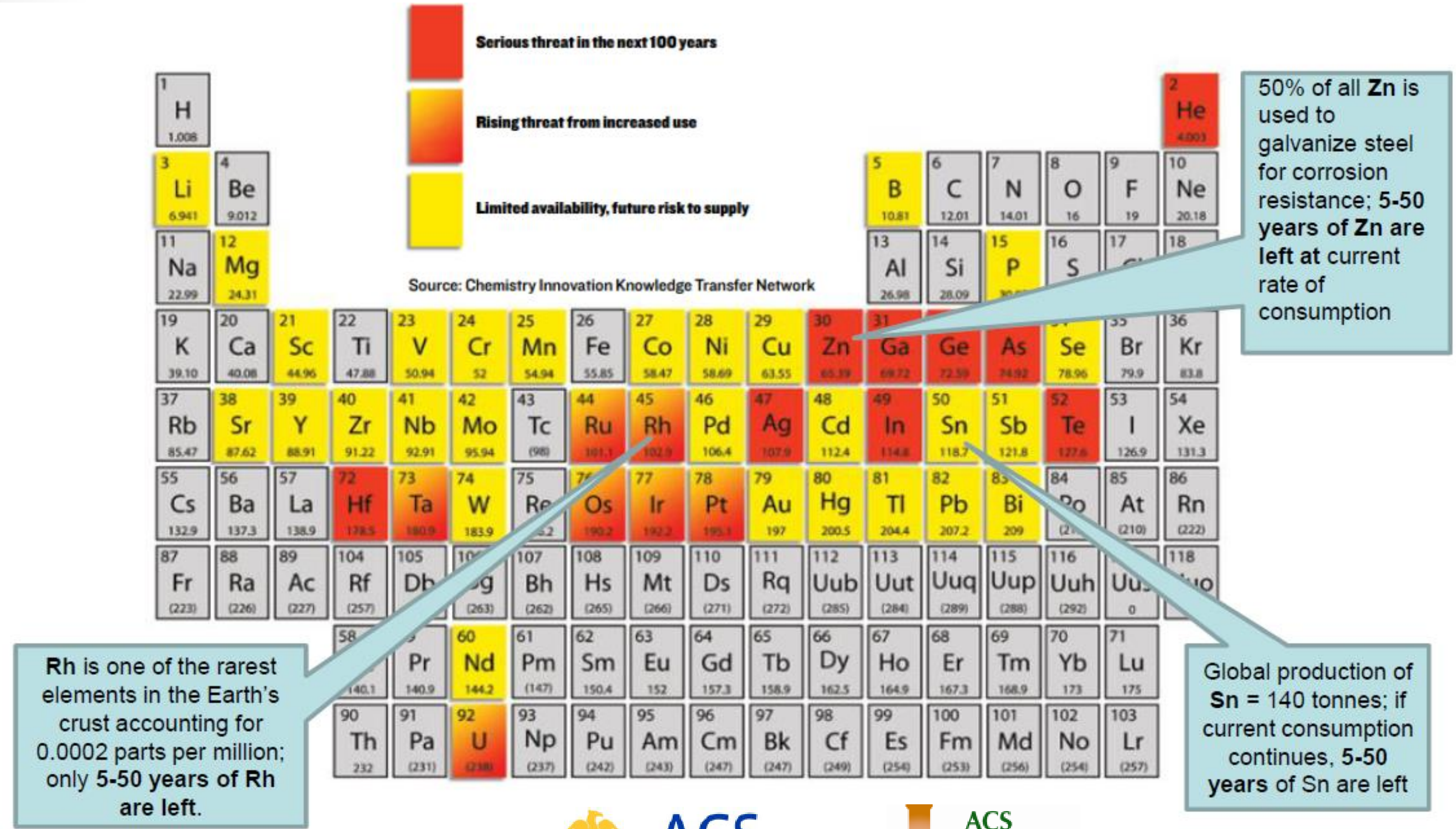


Sitagliptin 第三次路线更新



- 2010 EPA-Presidential Green Chemistry Challenge Awardee
- Uncovered after multiple rounds of enzyme evolution
- Reduces PMI from 30 to 23
- Avoids enamine intermediate, high pressure H_2 reaction as well as precious metal catalyst
- Saves multimillions in annual costs and helps make the medicine available to lower-income countries
- Green synthesis is lower in cost, hand-in hand with PMI

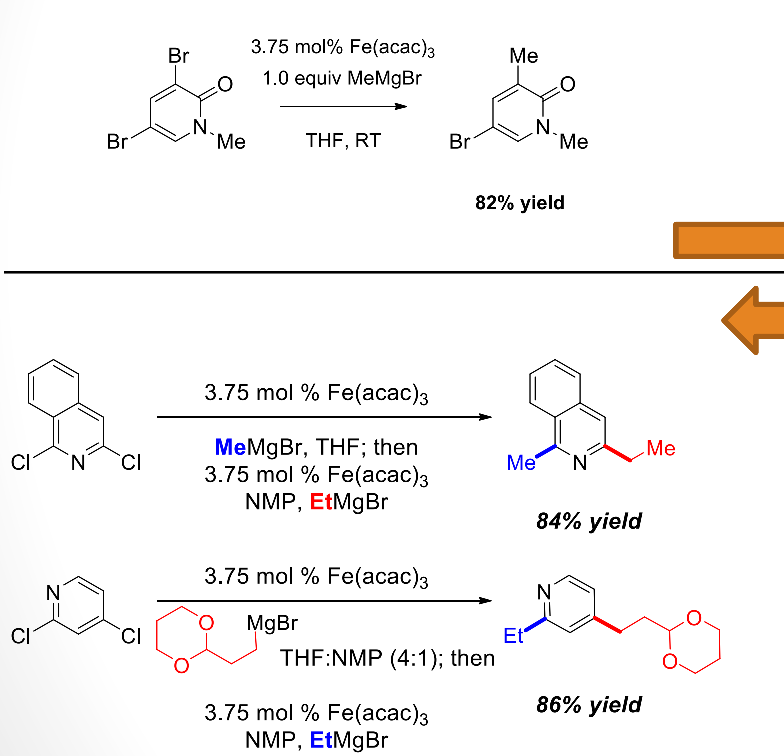
关键元素供应:不可持久

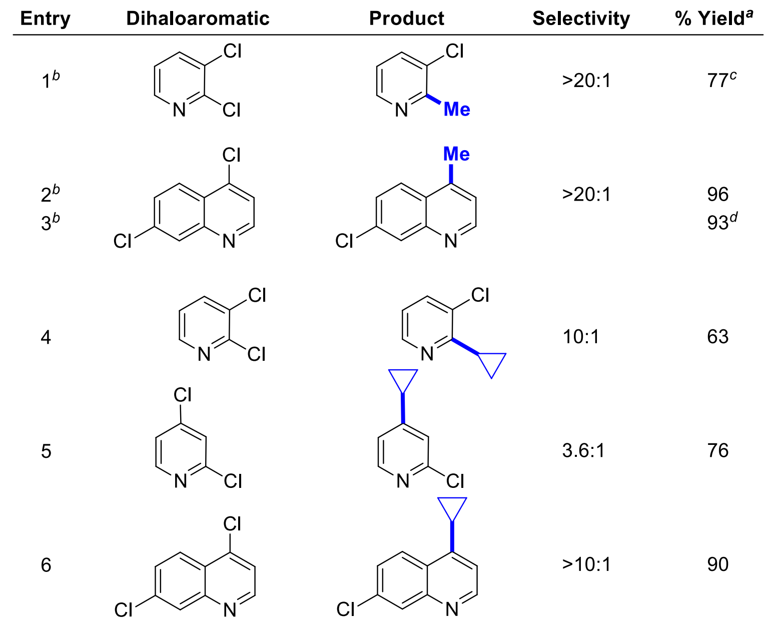


American Chemical Society
ACS Green Chemistry Institute®

研究铁催化

- Chemoselective Kumada-type coupling on dihalo heterocycles w/ $Fe(acac)_3$





a) Isolated yield of major product only from reaction in THF.
b) Reaction in THF:NMP (4:1). c) Volatile compound. d) 20 mmol scale.

Malhotra , S. et al. *Org. Lett.*, **2013**, *15* (14), pp 3698–3701

投资新技术

- Continuous processing is an enabling green technology
- Numerous environmental, safety, quality and economic advantages:
  - Superior mixing and heat transfer
  - Higher concentration reduces waste
  - Small quantities of reagents are reacting in any given time
  - Hazardous batch chemistry is made safer (example: azide chemistry)
  - Processes run under steady state control
  - Minimized batch to batch variation – potentially fewer reworks
  - Smaller footprint, waste and emissions

流动反应类型

- **PFR (Plug Flow Reactor)**

  - Ideal for rapid homogeneous single- phase reactions

  - Higher heat and mass transfer rates

  - Possibility of 100% liquid filled systems

  - Lower complexity and cost of reactor

- **CSTR (Continuous Stirred Tank Reactor)**

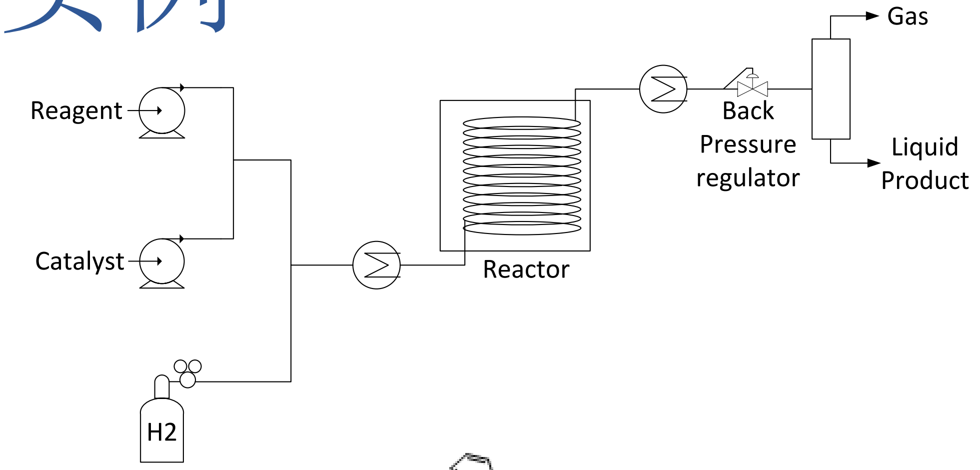
  - Ideal for reactions where solids may form / can be used for crystallization

  - Works well with bi-phasic systems

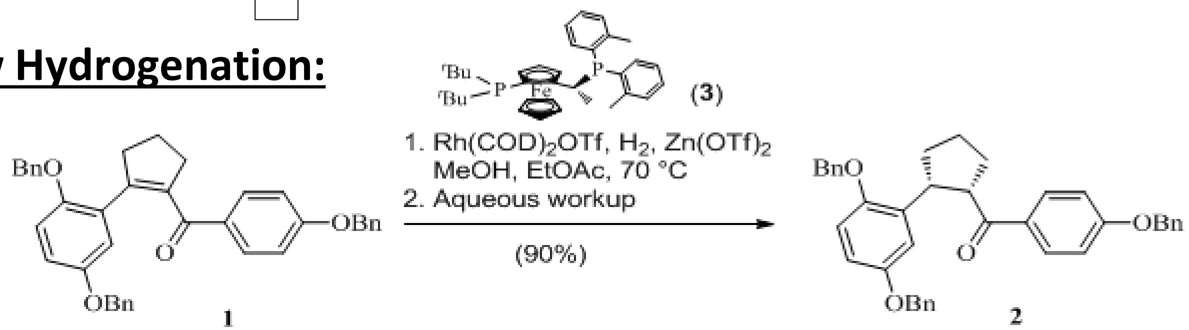
  - Ability to Operate at end of reaction conditions

  - Robust buffering capability to tolerate flow rate changes / disruptions.

PFR 实例

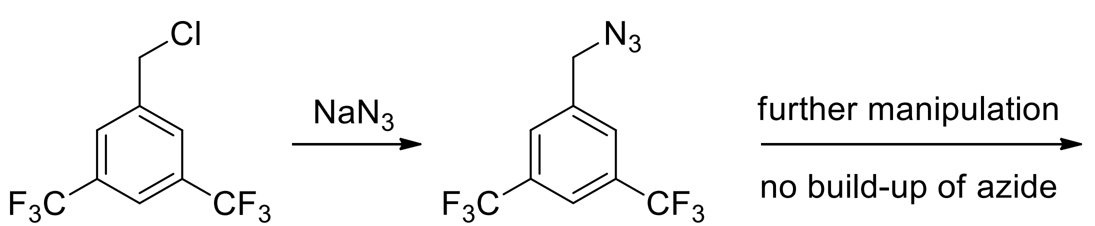


Flow Hydrogenation:



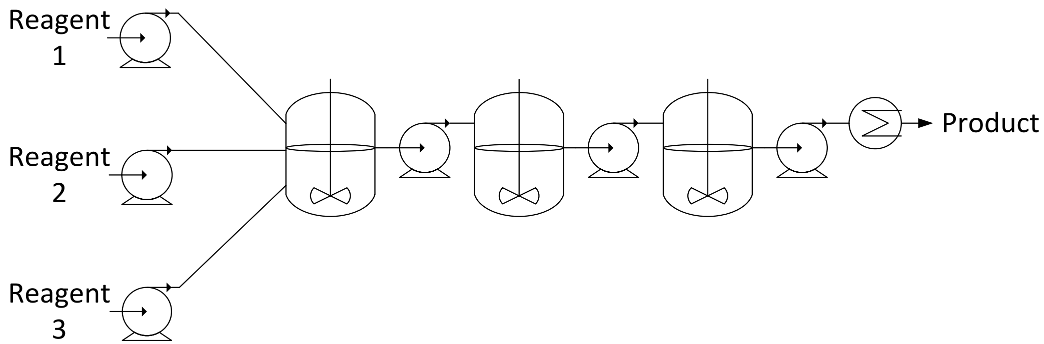
May et. al. *Org. Process Res. Dev.* **2012**, 16,1017−1038.

Flow Azide:

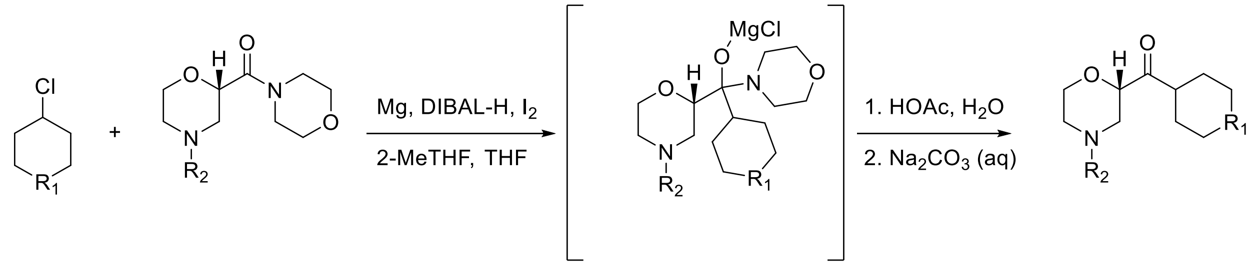


Kopach et. al. *Org. Process Res. Dev.* **2009**, 13, 152-160.

CSTR 实例

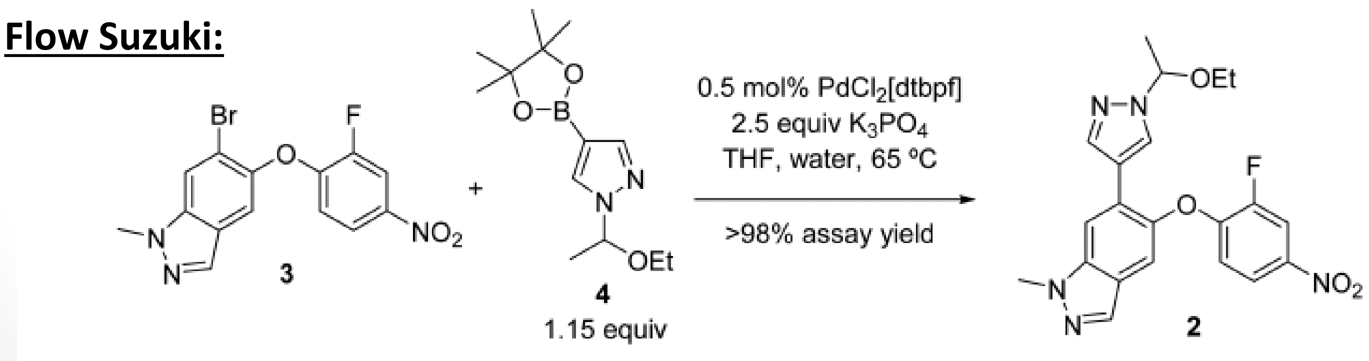


Flow Grignard / Barbier:



Kopach et al. *Green Chemistry* **2012**, 1524.

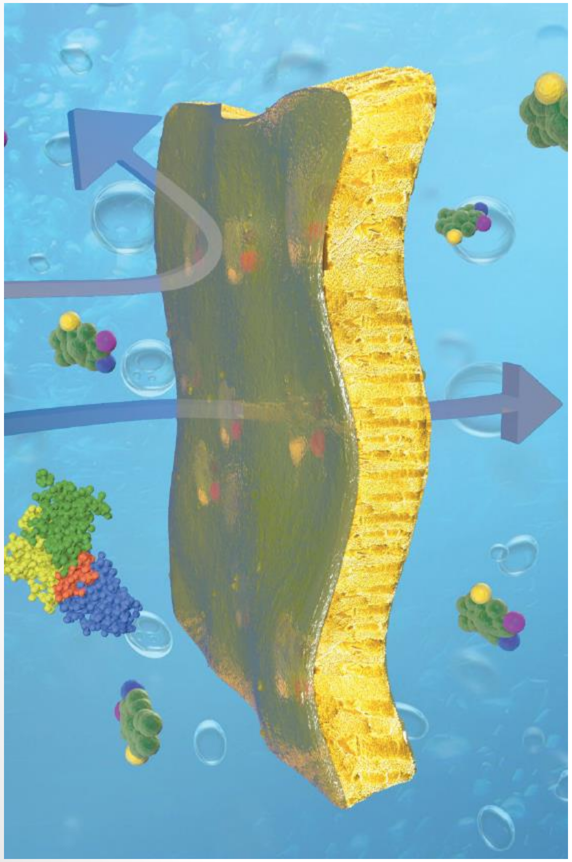
Flow Suzuki:



Cole et. al. *Org. Process Res. Dev.* **2016**, 20, 820.

投资新技术

- Organic solvent nanofiltration (OSN) could replace energy-intensive distillation processes:



- Low energy requirements, solid waste generation and labor intensity
- Straightforward scale-up and mild conditions
- Stability in harsh environments allowing wide flexibility (pH, T, solvents)
- Easy solvent swap from high to low boiling point solvents
- Simultaneous removal of solutes from different chemicals

- BUT benefit most obvious at larger scales

Livingston, A. G. et al. *Green Chem.*, **2014**, *16*, 4440–4473.

文献中的绿色化学

- Several journals in the field (*Green Chemistry*, etc.) though excellent work is reported in conventional top tier journals as well
- An established conduit is recurring "Articles of Interest" in *Organic Process Research & Development* – published 2 x / year: many different topics covering top areas of concern
- "Key Research Areas" article published in 2007 (*Green Chem.* **2007**, *9*, 411-420) with a follow-on article later this year to highlight progress and refocus the research community on challenges remaining
- Medicinal chemistry topics (*J. Med. Chem.* **2013**, *56*, 6007−6021):
  - Don't always need chromatography (precipitation, solid phase reagents)
  - Reactions can be telescoped in solution or as crude reaction residues
  - Try other metals for catalysis (Fe, Ni, etc.)

总结

- Chemists and Engineers – i.e. you – have enormous control of waste in synthetic processes by selection of routes
- The green chemistry principles are terrific guiding rules
- Catalysis, biocatalysis, continuous flow, nanofiltration, etc., are all valuable tools in the green arsenal
- Protecting groups, auxiliary materials, chromatography, etc., are often not necessary
- Green chemistry highlights are featured in literature for you
- Green chemistry is a triple win: cost-effective, better for environment and safer for employees

BREAK

ACS Green Chemistry Institute®
Pharmaceutical Roundtable

INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

绿色化学总结与展望

回顾

- Metrics

  - identification of areas of greatest need and opportunities to streamline chemical routes
- Solvents/reagents

  - sustainable alternatives to limit waste, create safer work environment and provide cost savings
- Synthesis

  - minimize (hazardous) materials and streamline construction of complex molecules

绿色化学原则1-6

- **Prevention**
  prevent waste instead of treating it after creation
- **Atom Economy**
  maximize incorporation of materials from process into product
- **Less Hazardous Chemical Syntheses**
  use / generate substances not toxic to humans and environment
- **Designing Safer Chemicals**
  design for desired function while minimizing their toxicity.
- **Safer Solvents and Auxiliaries**
  limit auxiliary substances (e.g., solvents, separation agents, etc.) when possible
- **Design for Energy Efficiency**
  minimize energy requirements; ideally, ambient temp and pressure

*Anastas, P. T.; Warner, J. C. Green Chemistry: Theory and Practice, Oxford University Press: New York, 1998, p.30. By permission of Oxford University Press.

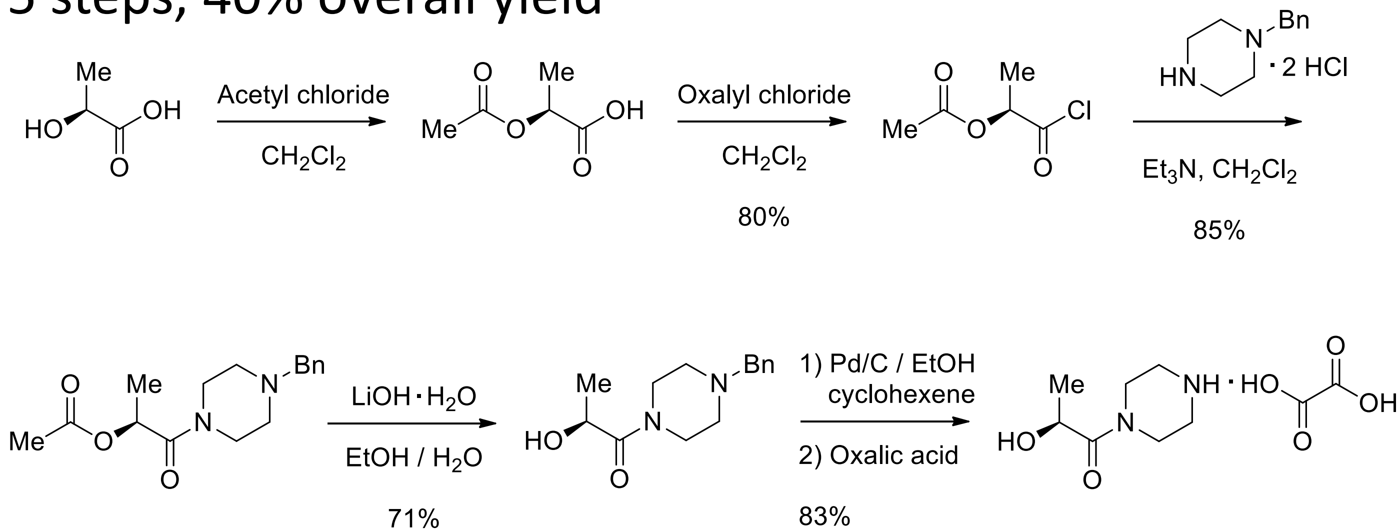
绿色化学原则7-12

- **Use of Renewable Feedstocks**
  raw material / feedstock to be renewable rather than depleting
- **Reduce Derivatives**
  minimize unnecessary derivatization to avoid additional waste
- **Catalysis**
  highly selective catalysts are superior to stoichiometric reagents
- **Design for Degradation**
  design chemicals no they do not persist in the environment
- **Real-time analysis for Pollution Prevention**
  use IPC methods to monitor / control formation of hazardous substances
- **Inherently Safer Chemistry for Accident Prevention**
  minimize potential for accidents, incl. releases, explosions, & fires

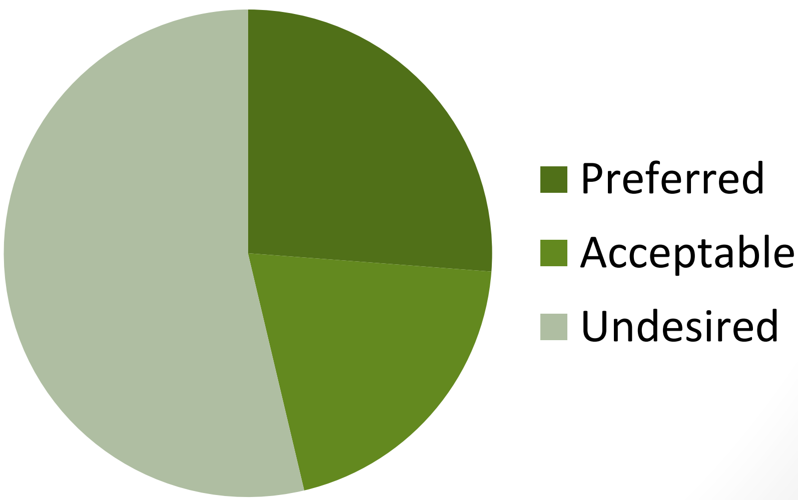
*Anastas, P. T.; Warner, J. C. Green Chemistry: Theory and Practice, Oxford University Press: New York, 1998, p.30. By permission of Oxford University Press.

GDC-0980: Piperazine Oxalate 1

- 5 steps, 40% overall yield



- Atom economy of 53.4%
- >50% undesirable solvent:

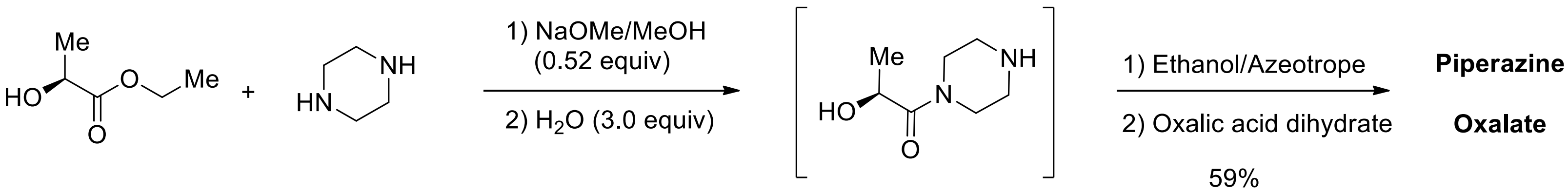


- Process Mass Intensity:

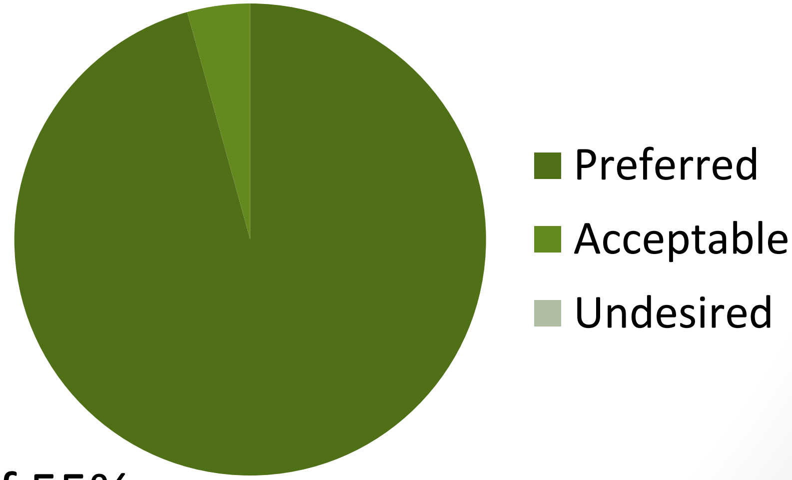
  98 kg waste / kg product

GDC-0980: Piperazine Oxalate 2

- Final route avoids protecting groups, auxiliary materials, and metals; utilizes sustainable chemicals in one-pot: 59% yield



- Atom economy: 75.2% – an improvement of 41%
- Solvents: > 95% preferred, 0% undesired
- Process Mass Intensity: 44.7 kg / kg – improvement of 55%



绿色化学的经济效益

- Green chemistry improvements usually track with financial improvements

51% E-Factor Reduction → **>65% Cost Reduction**

CP 1.0

Step	Yield	E-Factor
1	73%	93
2	81%	66
3	92%	11
4	82%	61
Total	45%	*231*

CP 2.0

Step	Yield	E-Factor
1	68%	30
2	92%	22
3	86%	23
4	87%	33
5	96%	24
Total	45%	*132*

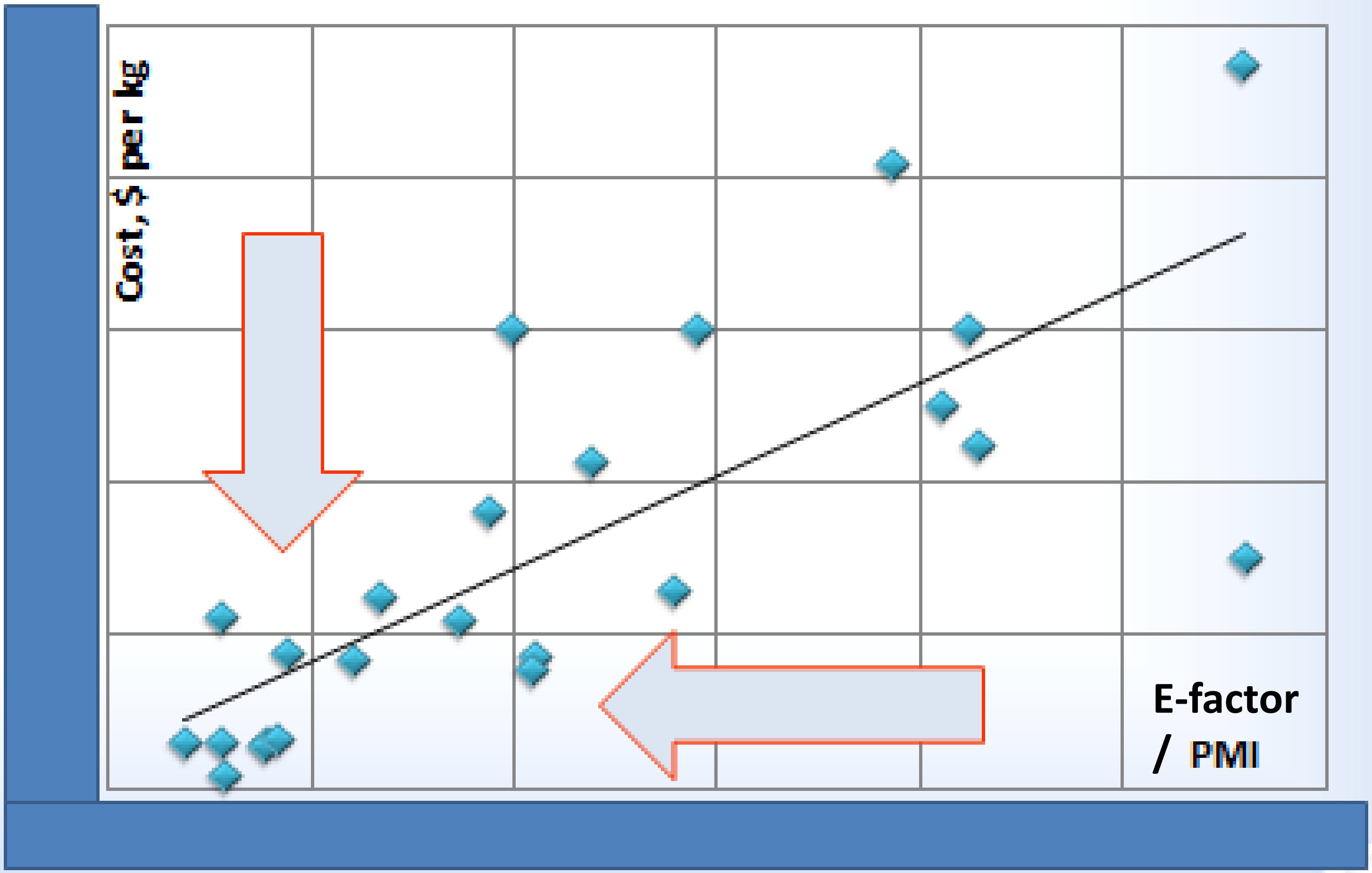
CP 2.1

Step	Yield	E-Factor
1	98%	17
2	89%	21
3	86%	23
4	87%	30
5	95%	23
Total	62%	*114*

E-Factor represents kg waste produced during manufacture of 1 kg of drug substance

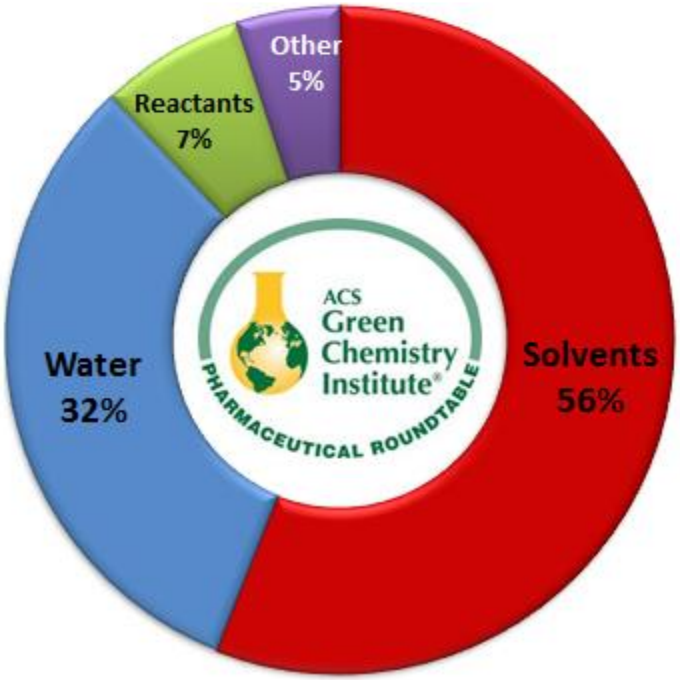
Cost and Metrics: Green Drivers

Late stage development compounds and marketed products



溶剂与试剂指南

- Multiple selection guides available
- Solvent selection guides
  - ACS GCI Pharmaceutical Roundtable (free of charge)
    - Considers safety, health and environmental impact of solvents
    - www.acs.org/gcipharmaroundtable
- Reagents guide
  - Green conditions for common transformations (e.g. amide formation, oxidation, etc.)
  - GSK (*Green Chem*. **2013**, *15*, 1542-1549 DOI: 10.1039/c3gc40225h)
  - ACS GCI Pharmaceutical Roundtable (free of charge) reagentguides.com



Process Mass Intensity Benchmark 2008

总结

- Chemists and Engineers have enormous control over manufacturing processes by selection of synthetic routes
- The 12 green chemistry principles are terrific guiding rules
- Catalysis, biocatalysis, continuous flow, nanofiltration, etc.
- Solvent and reagent selection guides, coupled with metrics and life cycle analysis can help make routes more sustainable
- Green chemistry is a triple win: cost-effective, better for environment and safer for employees

致谢

- ACS Green Chemistry Institute Pharmaceutical Roundtable (GCI PR)
- International Consortium for Innovation and Quality (IQ) in Pharmaceutical Development, Green Chemistry Working Group

- Stefan Koenig
- John Tucker
- Barry Dillon
- Mike Kopach
- Ingrid Mergelsberg
- Frank Roschangar

LUNCH

生命科学行业通风过滤系统设计经验概述

康斐尔过滤设备（昆山）有限公司
产品应用工程师　陈鑫
2016年9月

- 空气过滤行业应用概览
- HVAC系统空气过滤器选型与优化
- 洁净室末端送风系统与现场验证
- 安全排风箱体设计理念
- Q&A

通风用空气过滤器选型与优化

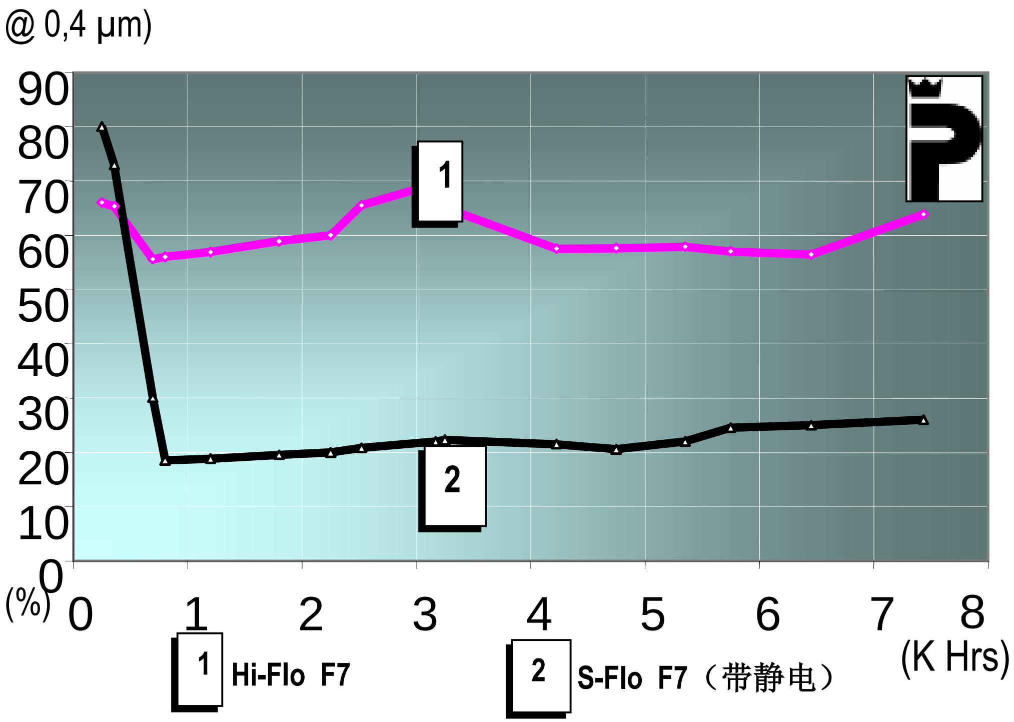
EN779:2012过滤器分级

分组	过滤器等级	测试终阻力（Pa）	人工尘平均计重效率Am %	对0.4μm粒子的平均效率 Em %	对0.4μm粒子的最低效率 %
Coarse	G1	250	50≤Am<65	-	-
	G2	250	65≤Am<80	-	-
	G3	250	80≤Am<90	-	-
	G4	250	90≤Am	-	-
Medium	M5	450	-	40≤Em<60	-
	M6	450	-	60≤Em<80	-
Fine	F7	450	-	80≤Em<90	35
	F8	450	-	90≤Em<95	55
	F9	450	-	95≤Em	70

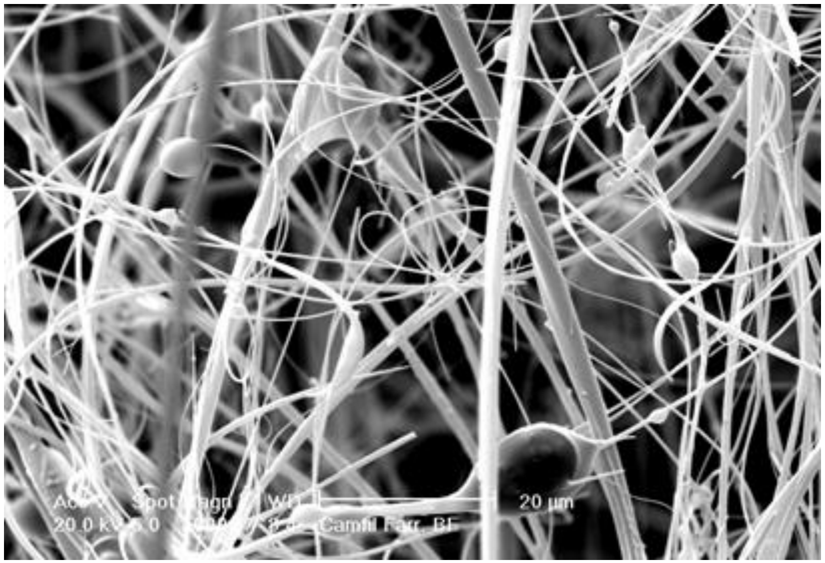
SP测试

- SP作为欧洲公认的第三方测试机构，采用实际运行测试的方法，对两种标签等级F7的过滤器进行了历时一年的比较测试。

- 测试表明一化纤过滤器携带的静电会在实际运行过程中很快衰减，效率会降到到原来的1/4 ~ 1/3。

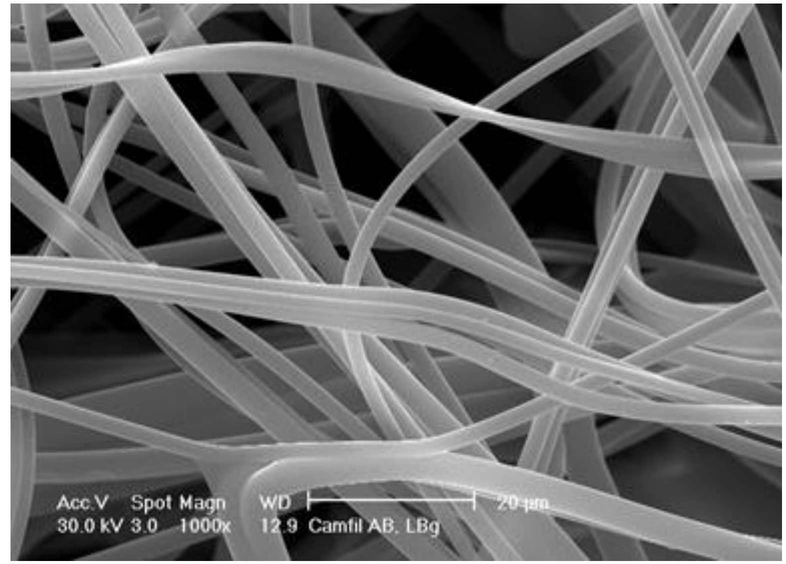


材料微观结构的不同决定了性能的巨大差异



1000 X

玻璃纤维滤料 F7
（大量的细纤维，纤维表面积大。）



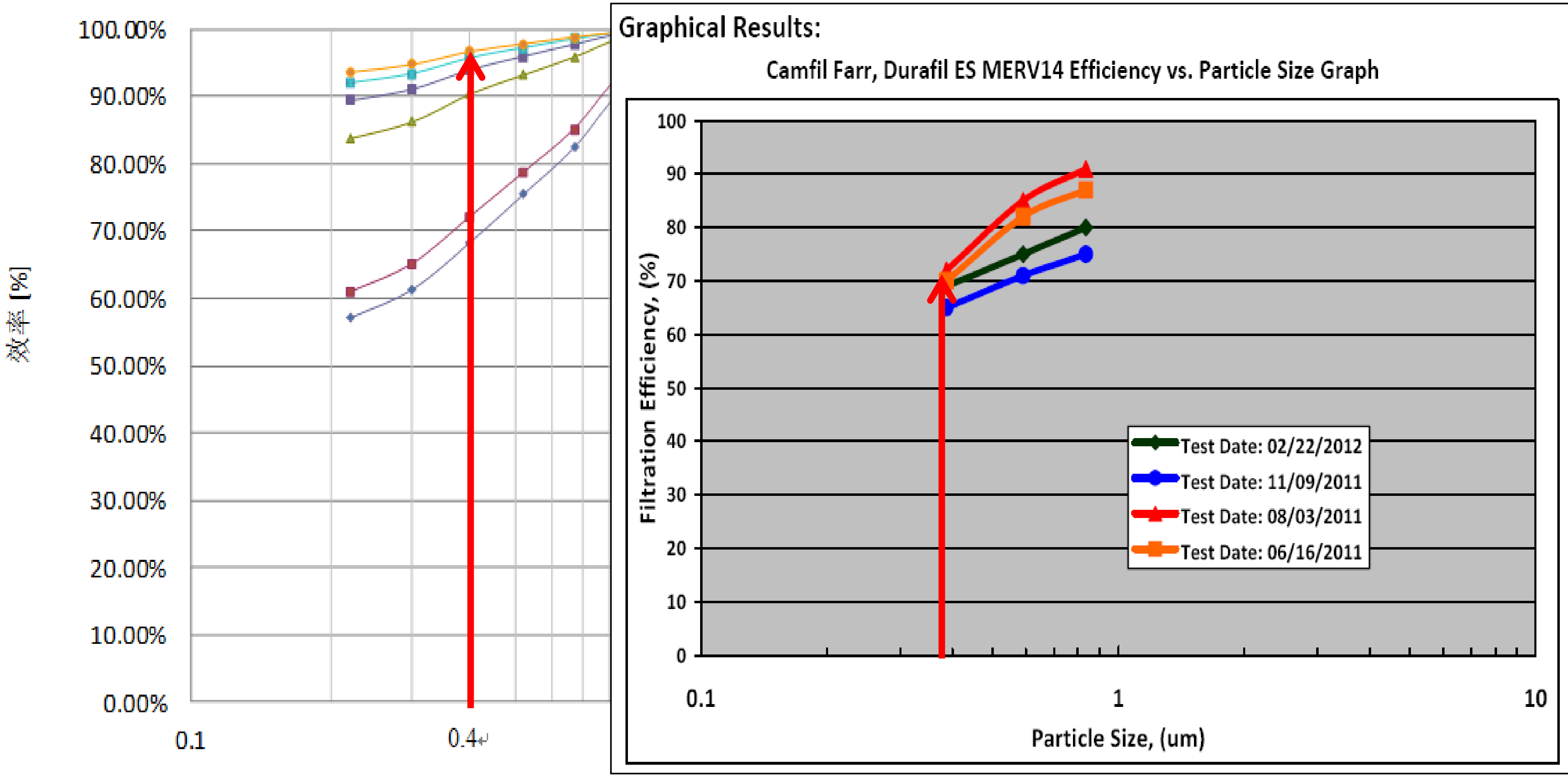
1000 X

化纤滤料 F7
（少量的粗纤维，表面积小。带静电，新过滤器依靠静电捕捉灰尘。）

EN779:2012过滤器分级

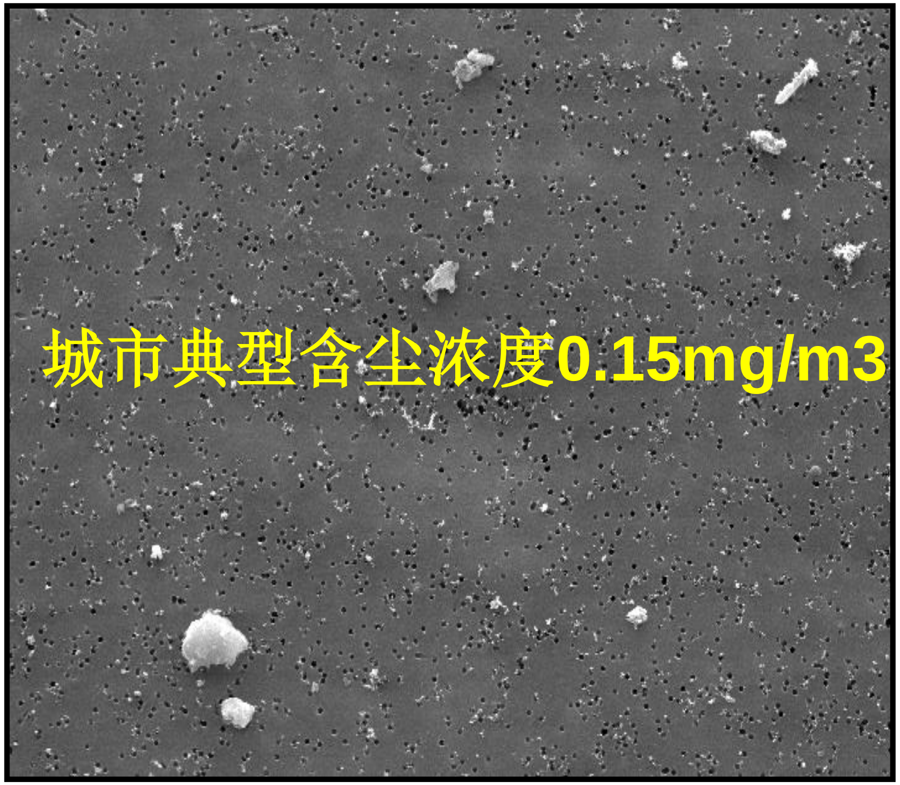
分组	过滤器等级	测试终阻力（Pa）	人工尘平均计重效率Am %	对0.4μm粒子的平均效率 Em %	对0.4μm粒子的最低效率 %
Fine	F7	450	-	80≤Em<90	35
	F8	450	-	90≤Em<95	55
	F9	450	-	95≤Em	70

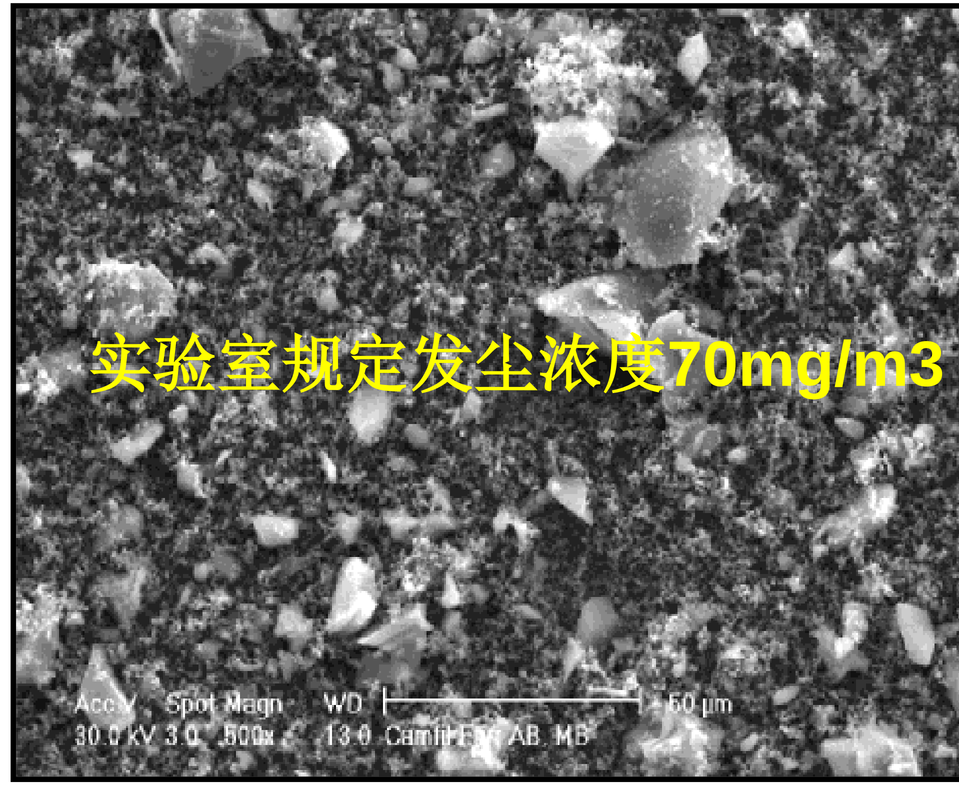
为什么实验室测试与现场测试差异巨大？



实验室测试 → 现场测试

大气尘和人工尘（ASHRAE人工尘、DEHS气溶胶）





室外大气尘
（很少有大于1um的颗粒）

ASHRAE负荷尘（ 72%亚里桑那道路尘，23%碳黑，5%棉绒，很少有小于1um的颗粒）

如何降低空气过滤器运行成本？

更好的空气 更低的成本

Life Cycle Cost (寿命周期成本)

每购买一台过滤器，至少要再付出4倍以上的成本才能得到洁净空气！

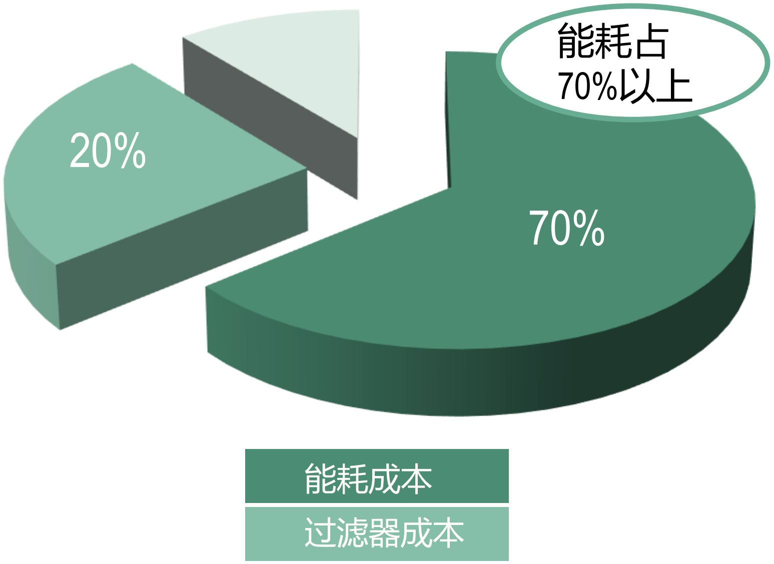
LCC=过滤器购买**成本**

+ 能耗

+ 维护更换

+ 系统清洗

+ 废弃处理



camfil

每年节约运行成本20%以上

LCC 成本(康斐尔)：80746 CNY

30/30® M8 2" (康斐尔)
HI-FLO M7 (康斐尔)

- 过滤器：9500 CNY（11.77%）
- 过滤器能耗： 69546 CNY（86.13%）
- 人工：1700CNY（2.11%）
- 废弃处理：0 CNY（0%）
- 新硬件：0 CNY（0%）

通风系统的寿命周期成本LCC减少20%

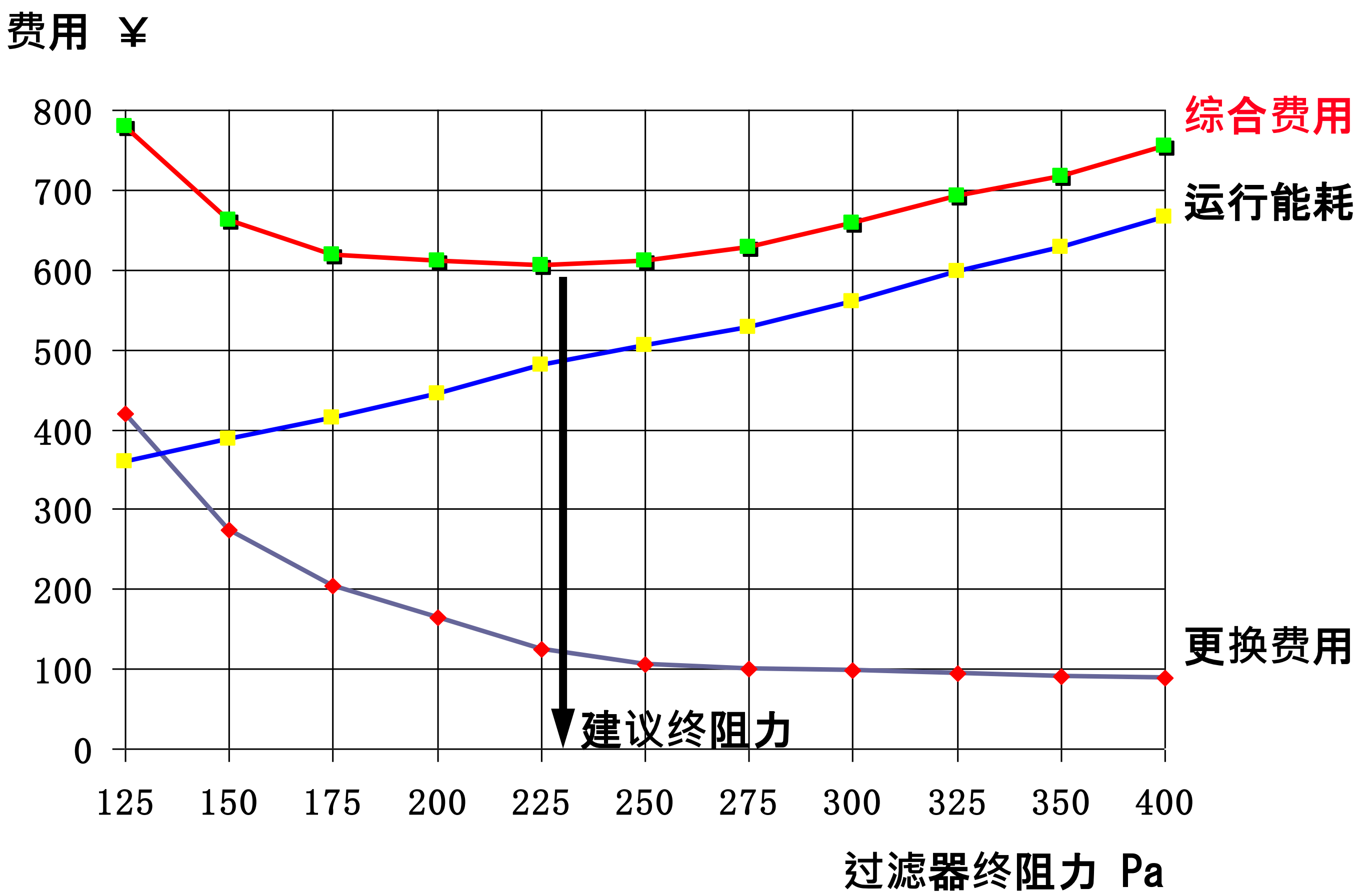
过滤器是空调系统可改进的成本最低部件

LCC 成本(康斐尔)：106380 CNY

OLD-AEROPLEAT® III M8 2" (康斐尔)
S-Flo A7-M6-592x592x600 (康斐尔)

- 过滤器：24100 CNY（22.65%）
- 过滤器能耗： 77380 CNY（72.74%）
- 人工：4900 CNY（4.61%）
- 废弃处理：0 CNY（0%）
- 新硬件：0 CNY（0%）

空气过滤器终阻力与运行费用



不同的更换条件下的过滤器使用情况对比：

G4

F7

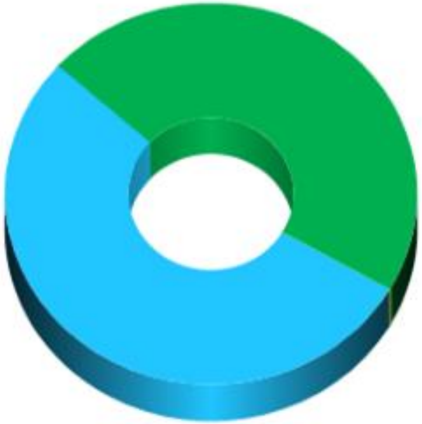
LCC费用（方案 1）: 30880 CNY

HI-CAP -66 (Camfil Farr)
HFGS-F7-0592/0592/0635-10 (Camfil Farr)

- 过滤器: 11000 CNY (35.62%)
- 能耗-过滤器: 19880 CNY (64.38%)
- 人工: 0 CNY (0%)
- 废弃处理费用: 0 CNY (0%)
- 新硬件: 0 CNY (0%)

LCC费用（方案 2）: 29038 CNY

HI-CAP -66 (Camfil Farr)
HFGS-F7-0592/0592/0635-10 (Camfil Farr)



- 过滤器: 15500 CNY (53.38%)
- 能耗-过滤器: 13538 CNY (46.62%)
- 人工: 0 CNY (0%)
- 废弃处理费用: 0 CNY (0%)
- 新硬件: 0 CNY (0%)

LCC费用（方案 3）: 28446 CNY

HI-CAP -66 (Camfil Farr)
HFGS-F7-0592/0592/0635-10 (Camfil Farr)

- 过滤器: 10100 CNY (35.51%)
- 能耗-过滤器: 18346 CNY (64.49%)
- 人工: 0 CNY (0%)
- 废弃处理费用: 0 CNY (0%)
- 新硬件: 0 CNY (0%)

为什么我们需要空气过滤器？

效率不合格

下游浓度增加1倍，HEPA寿命缩短一半

阻力上升快

寿命短，能耗高，LCC高

由于市面在售过滤器性能差异较大，如何选择正确的空气过滤器？既要效率稳定可靠，又要运行成本低。

过滤器分级效率基于EN 779:2012

通过现场测试手段验证其性能

通过Eurovent认证

洁净室末端送风系统与现场验证

Clean air solutions

camfil

GMP与洁净室

●GMP的目标是确保建立科学的、严格的无菌药品生产环境、工艺、运行和管理体系，最大限度地消除所有可能的、潜在的生物活性、灰尘、热原污染，避免交叉污染，避免混药，生产出高品质的、卫生安全的药物产品。GMP是质量保证体系的重要组成部分。

●洁净室和污染控制技术是保证GMP成功实施的主要手段之一。

●GMP没有详细说明洁净室的设计、建造、测试等方面的内容。详细内容还要参照相关的Fed 209D, ISO14644, ISO14698, IEST, 国标GB/T, EN1822等标准。

● GMP也没有详细对空气过滤器和相关FAT&SAT作出明确的技术要求，具体要求要参照EN1822、IEST、国标、ISO14644、洁净室施工验收规范、FDA等相关内容。

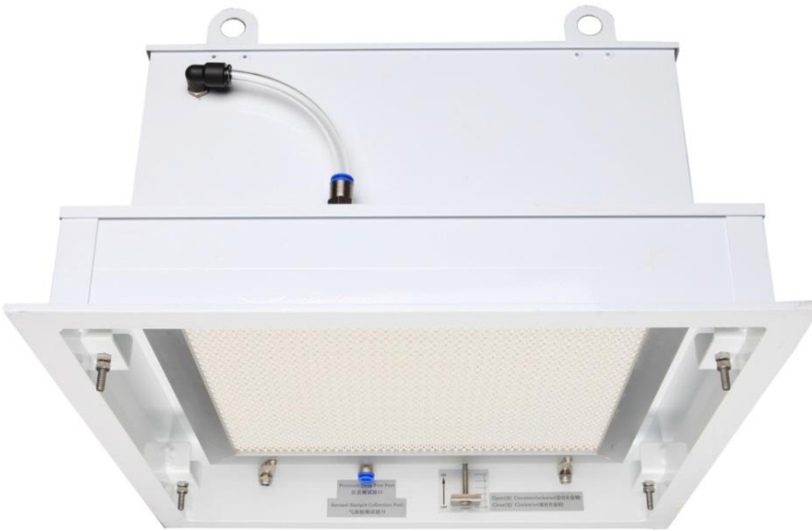
●药品在全球范围的销售要求制造商不但要符合自己国家的GMP规范，还要符合国际标准EU/GMP, FDA-cGMP的要求。

●GMP还要求我们充分利用现有技术，保证生产的药品达到最高质量标准。

SAT-末端送风HEPA 的原位“检漏”测试：(光度计手动扫描法)

依据标准：	美国IEST-RP-CC034.2	ISO14644-3	洁净室施工及验收规范GB50591-2010
测试条件：	风速0.45±0.05m/sb 气溶胶浓度10-90ug/L **上游气溶胶的一致性和稳定性** 方形探头最大扫描速度不高于5cm/s； 扫描探头离过滤器25mm	设计风速±20% 气溶胶浓度20-80ug/L **采取适当的措施验证加入的气溶胶与送风混合均匀；对系统第一次测试时就测定气溶胶是混合充分的。** 使用3cm*3cm方探管进行扫描时，其速率不应超过5cm/s；	设计风速的80%-120% 气溶胶浓度20-80ug/L 上游气溶胶均匀混合
评定标准：	渗漏指认水平为0.01%	上游气溶胶浓度的10^{-4}	探头静止不动时的标准透过率<=0.01%

根本保证 （1）-可靠的产品设计



✓**箱体/压力梯度界面满焊；**

✓**气溶胶注入口、气溶胶&压力采样口、风阀调节均采用快速气密设计；**

✓**HEPA与箱体之间标配为液槽密封，具有对常用消毒剂的抗老化兼容性。**

根本保证 （2）-精湛的制造工艺

Clean air solutions

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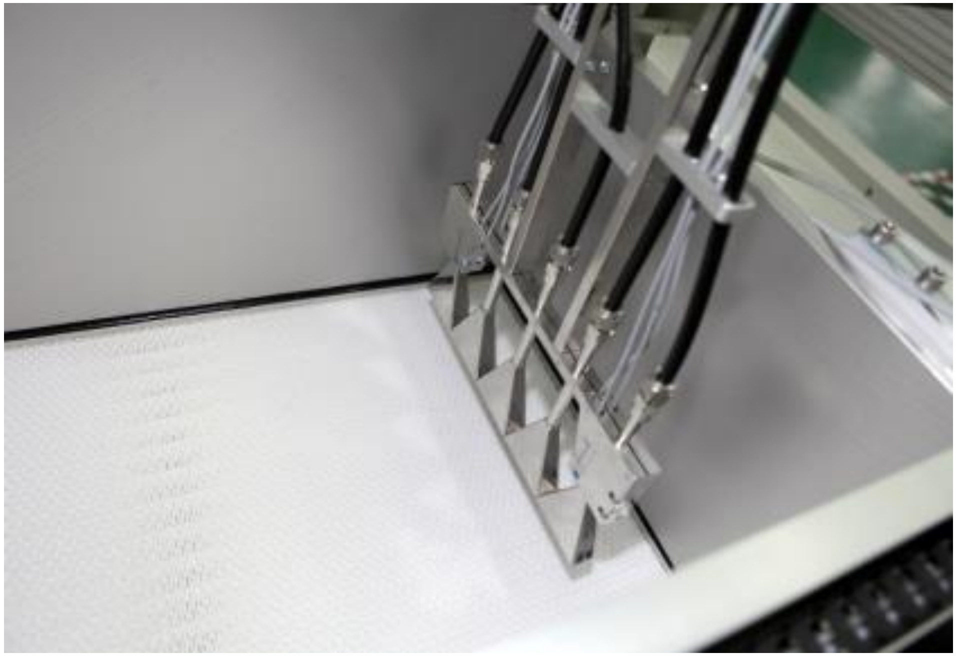
根本保证 （3）– 严格QC测试



- ✓ 严格按照EN1822,IEST标准
- ✓ 自动逐点MPPS穿透率激光计数扫描
- ✓ 过滤器风速均匀性自动扫描测试 （acc. to ISO14644-3)
- ✓ 全过程计算机自动控制
- ✓ 在风量300~5000m3/h范围内自动调节和精密控制。
- ✓ 三台设备满足生产线的100%逐台测试(年测试能力>20万台）
- ✓ 提供逐台逐点的MPPS扫描测试报告，QC连机控制。

根本保证（4）-按照使用工况正确选型

为什么会出现头疼的“渗血”现象？

1) 过滤器出厂前根本没测试；
2) 工厂QC采用的测试气溶胶粒径大于原位扫描用气溶胶粒径；
3) 工厂QC采用的测试风速小于实际使用风速；
4) 选用的过滤器效率等级过低。

按照实际工况选型，才能避免“渗血”现象！

“>0.01%局部渗漏指认”

HEPA的物理破损 → 严格的QC测试

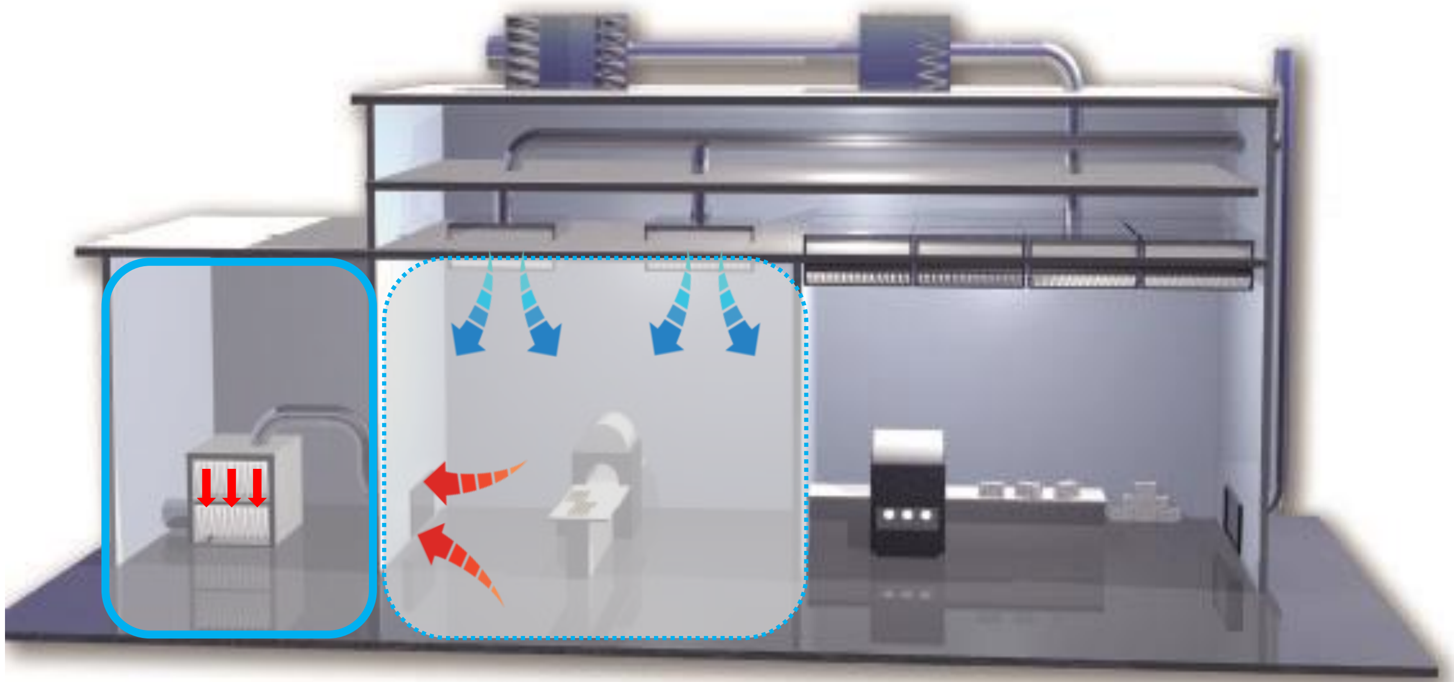
HEPA与箱体的密封不良 → 可靠的产品设计

箱体上游到下游的泄漏 → 精湛的制造工艺

“渗血现象” → 正确的产品选型

安全排风箱体设计理念

安全排风箱体应用



CamSafe 3 – 主要应用行业

制药车间

- 疫苗生产环境排风
- 疫苗车间动物房送排风
- β-内酰胺类药品生产环境排风
- 激素类、细胞毒素类药品生产环境排风
- 高活性化学药品生产环境排风
- 抗癌制剂生产环境排风
- 隔离器设备送排风

生物安全实验室送排风

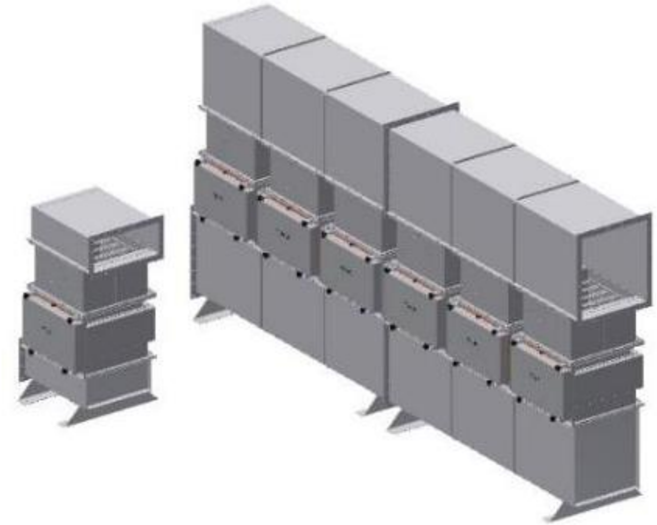
医院负压隔离区排风

- 负压手术室和负压病房
- 试验动物房

工业危险气体排风（化学）

CamSafe 3-丰富的功能选择

- 高效过滤 99.99% 99.999% （H13 或 H14）
  - ✓ 可单级或双级
  - ✓ 可配预过滤：G4~F9
- 多种风量： 1600 ~ 20400 CMH@ 250Pa （单级高效）
- 专业级过滤器免接触安全更换BIBO
- ClampSafe 过滤器100%安全压紧装置
- 原位检漏：电动/手动
  - ✓ FAT过滤器逐点扫描测试
  - ✓ FAT过滤器密封界面扫描测试
  - ✓ FAT箱体气密性试验
- 现场气溶胶（PAO/DEHS）原位发尘、注入、均匀混合
- 原位消毒（可选配）
- 气密隔离阀（可选配）
- 压差检测（可选配：仪表防护系统和压差信号传输功能）



Q&A ?

PSCI

PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

ACS Green Chemistry Institute®

Pharmaceutical Roundtable

DEKRA Insight

BREAK

THE CAMFIL GROUP

Potent Compound Containment Concepts and applications

by

Jianwei Qi, Camfil APC

Clean air solutions

camfil
AIR POLLUTION CONTROL

CAMFIL GROUP

A Swedish, family owned organisation and one of the world's largest air filter companies

Comfort

Clean Processes

Power Systems

Air Pollution Control

Containment

Industrial

Camfil APC Overview

- Camfil APC (Air Pollution Control) 业务部门是康斐尔集团迅速成长的部门
- **制造工厂坐落于**U.S, U.K, Germany, Czech and China
- **英国的**Heywood UK –Gold Series **除**尘器**的生**产
- **德国的**Tuttlingen – **油**雾除尘器以及湿**式除**尘器的生产
- 宽广的产品范围以及全球的服务体系
- **制**药市场是康斐尔集团重要和迅速增长的业务

Agenda

- 制造生产环境中粉尘的收集和粉尘的处理以及粉尘收集系统的设计
- 粉尘收集时的遏制和抑制措施
- 制药工业中的遏制和抑制措施
- Camfil APC 遏制抑制选型
- 替代产品测试Surrogate Testing
- 操作员工的培训Operator training
- 未来的需求Future requirements
- 新产品的开发 – Quad Pulse QPP-PX1

The Role of Dust Collectors in Pharma Manufacturing

- **Removes dust from the workplace**

  - 保护员工的健康和环境。
  - 预防爆炸和火灾的危险。
  - 保护设备的安全。
  - 提高产品质量，减少污染物。
  - 减少卫生的清洁，提高生产力。

- **Compliance with EU and country specific health and safety laws and environmental legislation**

  遵照欧盟和国家规定标准，安全健康法规和环境立法

  – ATEX
  – Emission Limits
  – Exposure limits (OEL's)

Dust Collection – Basic Principles

Dirty Air Ductwork 管道

Fan Set 风机

Gold Series
Dust Collector
除尘器

Capture Hood /
Machine Extract Point
粉尘抽吸

HEPA Filters
精过滤

camfil
AIR POLLUTION CONTROL

Designing an Effective Dust Collection System

- 应用合适的吸收罩设计/**机器吸收点来收集粉**尘气**体而且不影响生**产流程。

- 设计吸收管道来提供一个风量的平衡，**保**证必要**的**风速使得粉尘不会积在管道中，**全部吸入除**尘**器中**。

- 计算确定合适的除尘器的气布比，**保**证除尘系统**能**够有效的运行。

- 计算确定滤芯的材质来保证需要的过滤效率并且**保**证除尘器压差保持恒定，这样滤芯能提供一个**合理的运行寿命来减少生**产停机需要的设备维护维修时间。

Why is Containment in Dust Collection so Important?

1. **有毒粉**尘的完全防护措施是必不可少的，**以保**护工人免受直接接触或吸入**粉**尘，**防止急性或慢性健康**问题

2. **良好的**卫生管理是必需的，**以防止**积聚在工作环境中的灰尘，**不**仅保护工**人的健康**，**而且**还防止二次粉尘爆炸的可能性

3. 细尘颗粒会影响电气和机械部件，导致过早失效和潜在的火灾风险

4. FDA cGMP（现行良好生产规范）**要求遏制粉**尘，**防止交叉**污染，**以确保最**终产品的纯度

5. **法律要求**满足OEL / OEB职业性有害因素接触限制值/**等**级来设定每个产品**的**处理

Where Can Dust Escape?

- **如果除**尘系统设计不当，**灰**尘会从产生灰尘**的地方逃逸。解决方案**，**聘**请专家在除尘收**集系**统设计。

- **劣**质的或不当的安装管道和/**或除**尘器，**粉**尘组件接头处泄漏。**解决方案**，**聘**请有经验的**管道承包商和可靠的除**尘器生产厂家。

- **关于粉**尘/**气体爆炸事件。解决方案**，设计除尘器时采用适当的爆炸预防和保护系统，对**于空气中含有的粉**尘和气体/**溶**剂中具体定义**定性来**设计合适方案。

- **集**尘箱设计。**解决方案**，**安全防**护系统

- **初效或**二级（**高效**）过滤器更换。**解决方案**，**安全防**护系统

Containment – **Exposure Control**

System	OEB	OEL	W	Hazard-dousness
Isolators, Drum Containment System, split valve system Big Bag discharging and filling	5	< 1 µg/m³	< 0,1 mg/day	Highly hazardous
Container with cone, split valve, Big Bag discharging and filling	4	1 - 10 µg/m³	0,1 - 1 mg/day	hazardous
Container with cone, split valve, Big Bag discharging and filling	3	10 - 100 µg/m³	1 - 10 mg/day	Mildly hazardous
Systems with increased seal for discharging and filling barrels and Big Bags	2	100 - 1000 µg/m³	10 - 100 mg/day	Almost non-hazardous
Open systems with local aspiration	1	1000 - 5000 µg/m³	> 100 mg/day	Non-hazardous

OEB - Occupational Exposure Band
OEL - Occupational Exposure Limit
W - API content

除尘器控制解决方案通常是采用当**OEB指定**为4级或以上。这是制药厂家**的**责任承担，进行适当的风险评估，**确定他**们处理的各个产品**OEB的**职业**危**险接触等级。

Camfil APC Containment Solutions – Gold Series Camtain

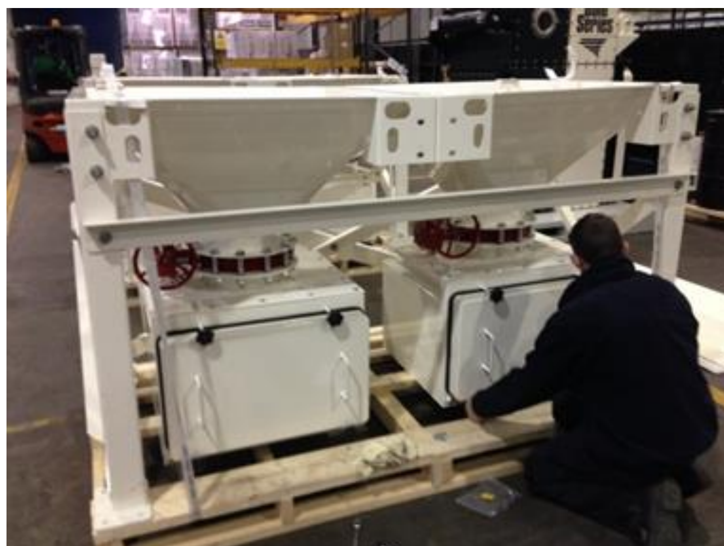
- Camtain除尘器是专为在制药行业的严格要求根据ATEX和安全防护法规
- 许多全球制药制造商和世界各地的制造商的首选吸尘器
- 提供了一个安全、简单的碧波安全更换过滤器的操作
- 使用已验证的过滤器替换的遏制解决方案
- 为了帮助FDA cGMP法规提供了完整的操作和培训文档
- 用在广泛的医药制造业的应用包括涂料、压片、制粒、干燥、混合

camfil AIR POLLUTION CONTROL

Camfil Pharma Solutions – **Dust Discharge Options**

Safe Change BIBO Options

- Continuous liner with Dual Valve 双联阀
- 35L BIBO Bin 袋进袋出收集桶
- BIBO Drawer 袋进袋出收集装置



camfil
AIR POLLUTION CONTROL

Camfil APC Containment Solutions - Gold Series High Vacuum Camtain

- **高真空Camtain使用相同的袋**进袋出为标准Camtain单元
- **一个独特的遏制**单位的应用程序，**包括中央真空清**洁，**平板印刷机和包装机**连接
- ATEX标准并采用遏制粉尘排放的选项包括**双**阀系统

Camfil APC Containment Solutions – Surrogate Testing

- **用于遏制性能**验证的安全防护测试集尘系统
- 试验采用的ISPE规范指南”评估制药设备替代颗粒**遏制性能**测试协议。
- AIHA认证的实验室，**法国国**际检验局进行检验，**提供独立、公正的**测试结果。
- GS camtaintm**可以包含高度有效的**，**毒性或**过敏的OEL≥0.46μg/m3**的**时间加权平均的化合物（TWA）**与最大**测试OEL 0.67μg/m3
- **完整的**测试报告数据可根据要求提供。

Camsafe – **HEPA Containment Solution**

- Camsafe–**落地安装袋**进袋出高效系统。
- **作**为一个安全系统的“**安全警察**过滤器”，**以确保危**险的灰尘过滤从干净的空气，**如果有一个不当的密封或破裂的**滤筒（**非常罕**见的发生）。
- **也确保了最**优秀的亚微米级的灰尘颗粒，**可以通**过主过滤器也收集
- H14 HEPA过滤效率99.995% @ 0.3**微米**
- **可**获得ATEX Camsafe**版本**

Operator Training

- **一个安全防**护系统制造商的供应包中一个重要组成部分
- **一个安全防**护系统，**只有操作**员良好的操作规范可以确保安全的程序
- **操作**员的培训应始终包括在调试包中，**以确保一部分关**键的生产和维修人员了解所有的**系**统组件和操作。

Dust Collection Containment – Future Requirements

- **原料**药的正变得越来越细，**更具有活性**，**所以关**键的工艺设备，**包括除**尘器**必**须适应新的要求
- 对初级过滤器和高效过滤器的过滤效率**要求的影响**，H14**以上**
- 对于防爆有更高的要求的ST3**粉**尘收集**器系**统的影响（KST 300 + bar m/s）
- OEL/ OEB**和安全防**护系统设计的影响。更细的灰尘，**通常是更具有活性**，**更有毒的**，**更强**调安全防护系统的有效性。

Dust Collection Containment – Future Requirements

随着越来越多的全球制药企业实施这一变革，从传统的批量生产制造过程中，变成持续的制造过程

- 与较小规模的生产运行配套
- 可靠性是一个关键问题，因为生产停机时间和维修维护时间必须保持在最低限度

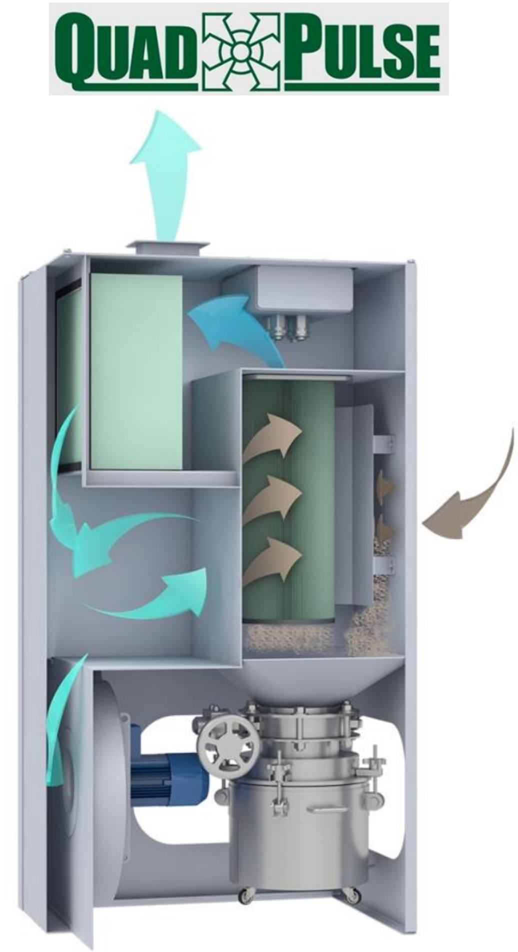
➢单台设备配套单台制药机器/工艺

➢在线粉尘清灰处理/集尘桶的安全更换

➢延长过滤器滤芯的使用寿命以减少耗时更换滤芯需要的时间

Camfil APC Containment Solutions – Quadpulse QPP-PX1

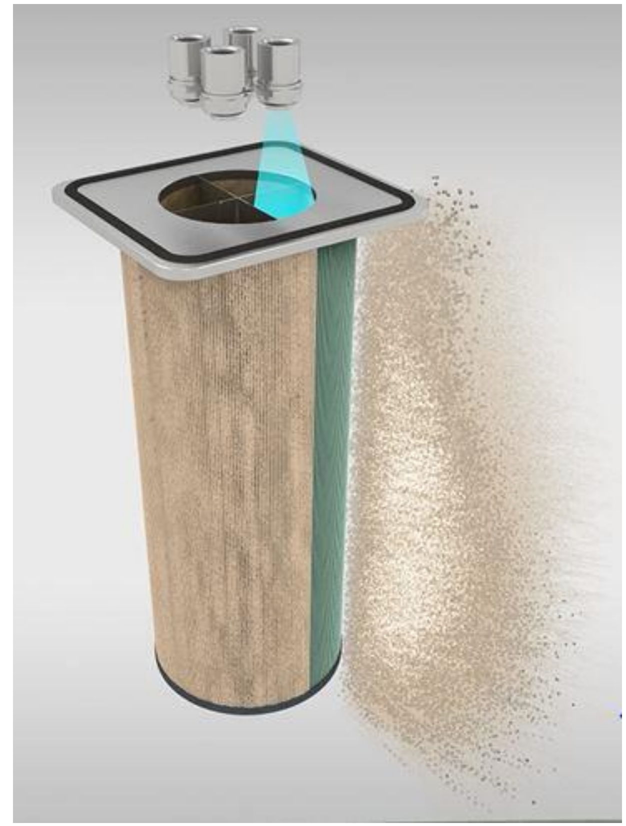
- **在制**药制造行业给当前和未来的需求提供革命**性**设计
- **一个**紧凑的，**集成的**单元，**可以安装在最**拥挤**的房**间内
- **采用Camtain安全更**换措施，**用于初效和HEPA高效**过滤器更换滤芯操作
- **安全更**换35L**集**尘桶、风机集成或落地安装，**适用于**简便安装和操作的防爆系统
- **在工**艺中如压片，**包装**，**制粒和真空吸**尘的理**想解决方案**
- **取代非**ATEX标准和非安全防护便携式除尘器和**真空**机组



camfil
AIR POLLUTION CONTROL

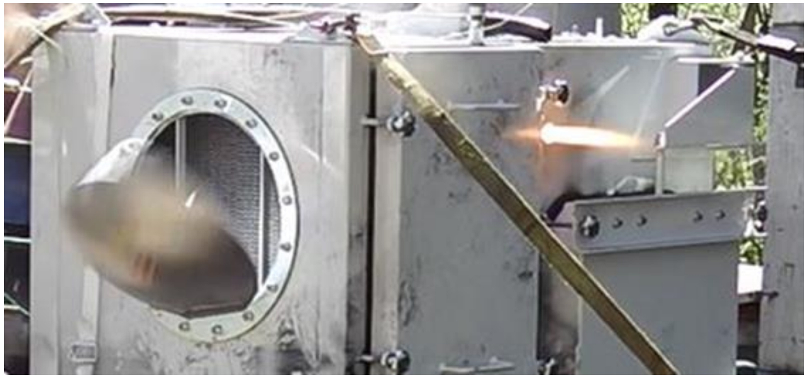
QPP Features and Benefits – QuadPulse System

- **独特的**过滤器清洗设计（专利）为了提高粉尘释放和增大过滤器使用寿命
- 过滤器使用一个内锥从而使干净空气均匀分**布整个分段部分**
- **通**过清洁个别分段的过滤器单元，**空气流量的**变化，**以**维持风管的速度
- **清**洁空气量可以降低机械过程和脏空气管道**的空气流量和**压的力稳定
- **使用**单一过滤桶，过滤器更换将变得简单



QPP Features and Benefits – ATEX

- QPP**已做了大量的爆炸**试验证明其安全性的概念
- 测试制度，**包括初效**滤筒的失效测试和HEPA**的防火潜力**
- **安全概念的基**础是避免点火源
- **通**过所有金属部件的接地
- 滤筒和袋进袋出使用抗静电材料



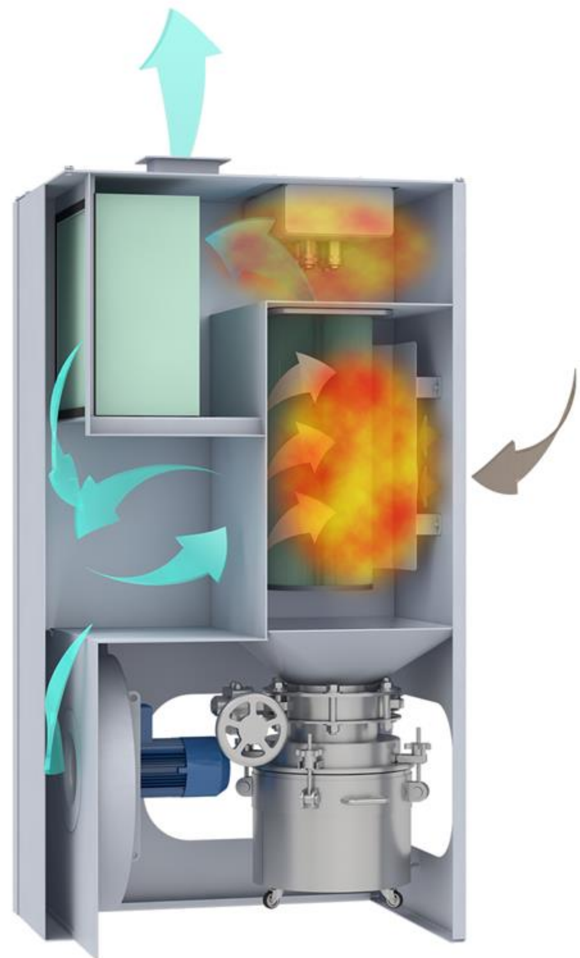
QPP Features and Benefits – ATEX continued…

❑ **第二**层的保护是在爆炸的情况下避免任何危险的**后果**

❖ 该设备可以承受的压力降低，**如果在**压力过大产**生爆炸的情况下**，**而**不需要使用泄爆阀。**入口关**闭（**出口打开**）。QPP**是非常灵活的**，**它可以安装在空**间狭小的地方。

❖ 该设备也可以在高效空气过滤器后使用泄爆板，这将减少污染工艺房的安全防护风险

❖ 对于高KST值和一些混合物（**气体和**尘埃）**将采用化学抑制**



QPP Features and Benefits - Containment

- **市**场领先的安全更换袋进袋出操作、**HEPA高效**过滤器和**35L粉**尘集尘箱
- **安全地包含在**标准操作过程中的有害粉尘和过滤器的安全更换，**以达到于工人高水平的安全防**护对和交叉污染的预防
- HEPA过滤器的测试能力

QPP – Typical Applications

- 对于小型的制药生产过程机器，产生中等浓度的爆炸物和/或有害的灰尘。例子包括：

- 压片
- 压缩
- 制粒/铣
- 包衣
- 灌装/包装

- 一般的制造工艺 ：

- 混合/混料
- 研发/试点工厂

QPP Technical Data

Item	
Air capacity 流量	Nominal 1000 m^3/h (500 – 1200 m^3/h)
Motor 电机	4 kW Ex 3D
Suction capacity 压差	5 kPa (higher fan pressure available using remote mounted fans)
Filter media 材质	eXtreme Carbon or Durapleat PTFE membrane antistatic
Filter area 滤芯面积	16.7 m^2 / 12.7 m^2
HEPA 精过滤	ATEX 99.995% at MPPS (H14) 22.5 m^2
Maximum reduced P	0.6 Bar
Dust 爆炸指数	KST : 299 Bar m/s PMax 10 Bar (ST3 dust and / or gases / solvents can be handled using Chemical Suppression)
Rated shock pressure	1 Bar
ATEX Rating	Ex II 2/3 D IIIA, IIIB, IIIC, T=125 C

Further Product Developments

- ❑ 高压QPP

  - 更换现有的便携式真空机组数以千计没有ATEX防护和控制
  - 单台工艺除尘，制药机械使用50mm或80毫米的连接–例如压片机机提取，中试规模的包衣等

- ❑ QPP-PX2

  - 下一代产品
  - 研发重点重点

QPP - Summary

- **一个完全集成的，**紧凑的除尘器专为具有挑战性的制药制造环境

- **独特的安全功能，包括：**

➢ **全密封保**护工人安全和**OEL的依从性**

➢ **无需泄爆所以QPP可以方便、安全地安装符合ATEX**标准

- **正在申**请专利的quadpulse过滤器清灰操作，**生**产过程控制、**能源效率和改**进的滤芯清灰**系**统可以提高使用寿命较长

- **短周期供**货周期**-在英国制造，**针对欧洲市场

- 进一步的产品开发...

Pharmaceutical Industry Focus

Thank you for your attention

How can we help?

THE CAMFIL GROUP

Dust Combustability and design of protection systems

by

Junchang Yang, Camfil APC

Clean air solutions

camfil
AIR POLLUTION CONTROL

目录

- 简介
- Part 1 - ATEX 指令
  - ATEX 理论
  - ATEX 分区和分类
  - 爆炸预防措施
  - 除尘收集设备基本原理
  - 粉尘爆炸 – 爆炸如何／哪儿 发生?
- Part 2 – 工业防爆技术要求
  - ATEX 和除尘设备
  - 具体工业案例
  - 总结

ATEX – 爆炸话题

什么是 ATEX?

- 法语‘ **AT**mosphères**EX**plosibles ’
- **欧盟关于工作**场所预防爆炸的法律框架
- Started in 1999 but compliance required from 2003
- Relates to new equipment and processes as well as existing equipment and applications
- A legal requirement for EU member states but also widely used across many non-EU countries for best practices
- NFPA – American equivalent

ATEX 指令 – 遵循3个指令

- **2014/34/EU (替代 94/9/EC) – 潜在爆炸**环境下使用设备和保护系统， 这个指令同样适用于除尘设备。

- **1999/92/EC – 覆盖工作场所安全，危险分区标示及保护措施**

- **2006/42/EC 机械指令** – 这个指令主要适用于没有包含在 94/9/EC 指令 的内容. "机床设计和建造必须避免任何机床产生的或者机床使用的爆炸性气体， 液体， 粉尘，蒸汽导致的爆炸性风险 ."

2014/34/EU 指令

- 1994年3月23日， **欧洲委**员会采用了“**潜在爆炸**环境用的设备及保护**系**统”(94/9/EC)**指令**。这个指令覆盖了矿井及非矿井设备，它包括**了机械**设备及电气设备，把潜在爆炸危险环境扩展到空气中的粉尘及可燃性气体、可燃性蒸气与薄雾。即现行的**ATEX防爆指令**。2014/34/EU **是**94/9/EC **替代指令**， **内容一**样，立法架构有更新。

- 设备分两大类. **第一**类针对矿用设备， **第二**类针对非矿用设备.
- **根据安装**设备的保护水平将设备划分为三个类别：
- (1) 1类（ Category 1）— **非常高的防**护水平
- (2) 2类（ Category 2）— **高防**护水平
- (3) 3类（ Category 3）— **正常的防**护水平
- **也可以按照气体和粉**尘分类，他们要求的安全措施不同。

Clean air solutions

camfil AIR POLLUTION CONTROL

指令 2014/34/EU – 设备选择

- 设备供应商必须确保出售合适的设备用在适当的用途，这意**味着**设备供应商需要从客户那儿获得足够的信息。
- 这些基础信息包含:

  - **粉**尘的爆炸性参数：爆炸指数 KST, **最大爆炸**压力 PMax, **最小点燃能量**MIE, **粉**尘层最低着火温度 MIT
  - ATEX **分区**
- **爆炸指数** KST **和最大爆炸**压力PMax **数**值用于防爆设施选型。
- **最小点燃能量**MIE **用于** 电气元件和防静电滤筒或布袋选型 。
- **粉**尘层最低着火温度MIT **用于**电气元件主要是电机选型 。

1999/92/EC – 工作场所指令

- 该指令规定了雇主的责任, 对危险的评估和对爆炸性粉尘存在的区**域**进行分区。
- **爆炸性区域分区和粉**尘爆炸性浓度出现的概率相关。
- **如果粉**尘爆炸性浓度经常或者频繁出现，则该区域爆炸性分区可**确定**为20**区**（**爆炸性气体**则为0**区**）。
- **如果粉**尘爆炸性浓度在正常工况下不经常或者不频繁，则该区域**爆炸性分区可确定**为21**区**（**爆炸性气体**则为1**区**）。
- **如果粉**尘爆炸性浓度很少或者偶尔在极端情况下出现，则该区域**爆炸性分区可确定**为22**区**（**爆炸性气体**则为2）。
- **越高的概率出**现粉尘爆炸性浓度则必须使用越安全的设备。

ATEX 分区

Dust EN 61241-10	Gas EN 60079-10	Details
Zone 20	Zone 0	A place in which an explosive atmosphere is continually or frequently present (more than 1000 hrs p.a)
Zone 21	Zone 1	A place in which an explosive atmosphere is likely to occur occasionally in normal operation (more than 10 hrs but less than 1000 hrs p.a)
Zone 22	Zone 2	A place in which an explosive atmosphere is not likely to occur in normal operation, but if it does it only occurs for short periods (more than 0.1 hrs but less than 10 hrs p.a). Alternatively if an explosive atmosphere can occur in case of a failure (e.g. if a cover opens or a bag is dropped)

指令 1999/92/EC

工作场所指令：

- 车间须配备爆炸保护计划，包含分区图及风险评估
- 车间须确保在此区内仅使用了适宜的被认可的设备
- **此保**护计划须为动态文件，须更新及维护
- 员工须接受适当的培训

脉冲频率及分区

- So in a dust collector running 8 h per day 300 days / year pulsing 50% of the time 4 times per minute and 1 s per pulse you would get一台集尘器每天运行8小时，300天/年，加上50%
- 300*0.5*8*60*4 秒 = 140 小时 = **Zone 21**

- **我**们离20**区极限**值还有很远距离，即使每天三班制**运行也达不到**1000**小**时。若三班制运行，连续脉冲，则可能归于20**区**。**若**查看实际粉尘数量，此假设存**在疑点**。

ATEX 基础 – 什么是粉尘爆炸?

- **当可燃物**为细小粉尘散布出来，暴**露于空气的表面增加1000倍**

- **若粉**尘着火，与空气大面积接触，**在高速条件下**发生燃烧

- **高速燃**烧释放大量能量，温度及压**力急速上升。冲**击波形成了。

粉尘爆炸五边形


Oxidant
Ignition source
Explosion
Combustible dust
Dispersion of dust
Confinement of dust

ATEX 基础 – 爆炸粉尘

- **食品工**业有机粉尘，如低筋粉，糖，
  茶叶， 调料，香料

- **合成有机粉**尘，如塑料研磨粉尘，粉
  末涂料， 肥皂粉

- **金属粉**尘-铝、镁、钛、 铬的细小粉尘，
  在特殊条件下， 细小未氧化的任意金
  属粉末， 甚至铁粉也会爆炸

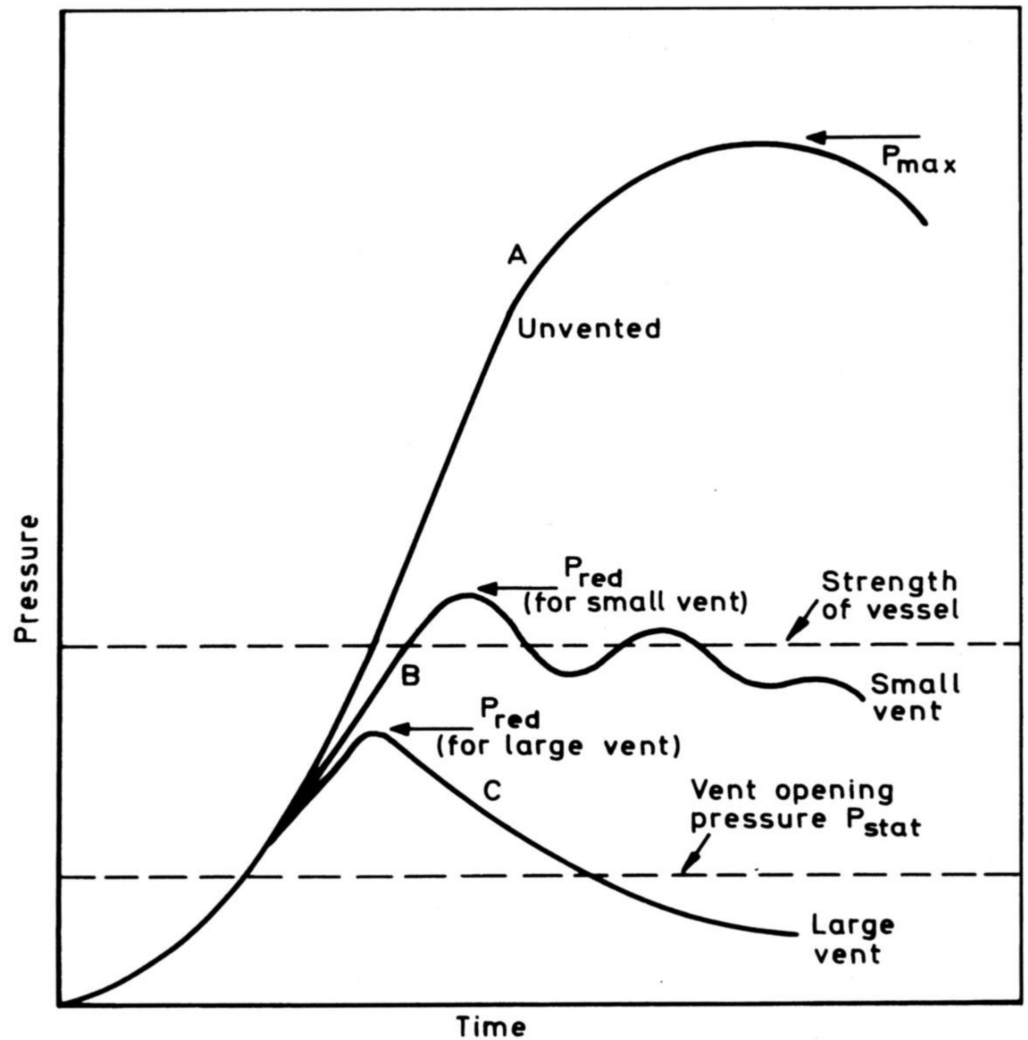
- 药物粉尘–**此行**业的大部分粉末都可爆

ATEX 基础 – 数据需求

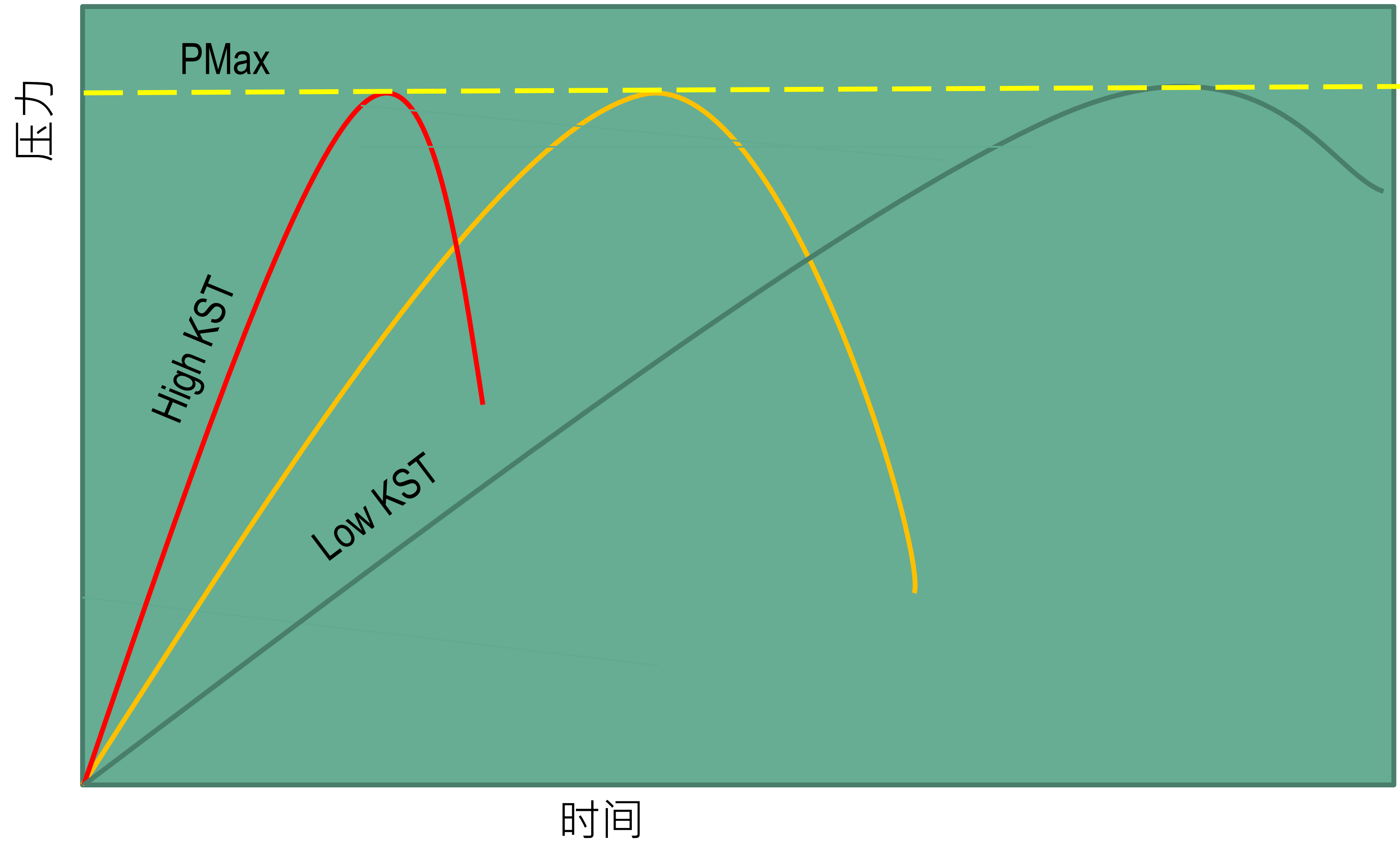
Kst值用于表示压力增加速度， 以Bar m/s为测量单位。

Pmax值是封闭容器中最佳浓度条件下的最大压力。

Pred是防爆门打开，降低**容器/集**尘器中爆炸压力时**的**压力减少值

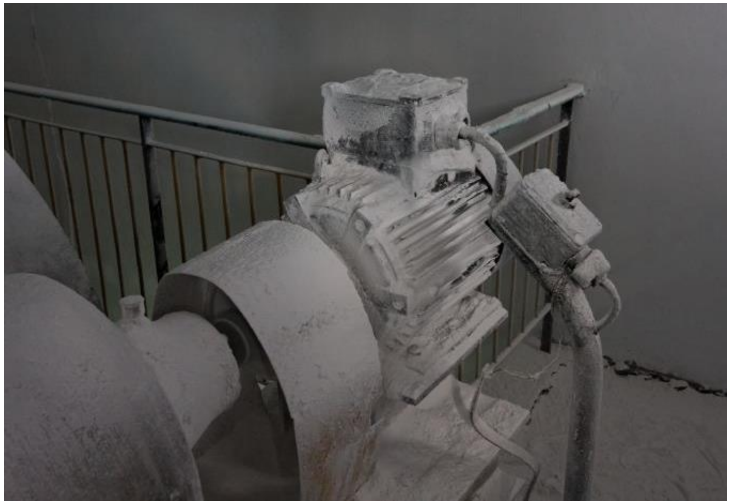


3 种具有不同KST值及相同Pmax值的粉尘



ATEX 基础 – 数据需求续...

- **最小点火能量**
- **引起粉**尘爆炸
- **温度是另一个重要因素。粉**尘可被灼热空气或灼热表面点燃。电动马达可**被粉**尘覆盖，需有极限表面温度。粉尘特性称为MIT Layer and MIT Cloud 。



ATEX 基础 – 火源

- 机械火花（研磨，撞击）
- 未经培训的维护人员
- 非导体静电（粉尘及气体的MIE < 3 mJ，我们将防护加至<10 mJ）
- 导体静电，如金属部件及防静电袋
- 灼热表面（马达，轴承）
- 火（意外或热加工）
- 自燃（有机物，一些金属）

着火统计

Type of ignition source	All 426 explosions	Silos/ bunkers	Dust collectors/ separators	Mills and crushing plants	Conveying systems	Dryers	Mixing plants	Grinding plants	Sleves/classifiers
Mechanical sparks	26.2	16.3	41.1	60.0	25.6	0	15.0	89.5	16.7
Smouldering nests	11.3	27.9	11.0	0	2.3	29.4	0	0	8.3
Mechanical heating Friction.	9.0	3.5	6.8	12.7	25.6	2.9	25.0	5.3	0
Electrostatic discharges	8.7	2.3	9.6	5.5	18.6	5.9	45.0	0	16.7
Fire	7.8	4.7	4.1	2	0	0	5.0	0	16.7
Spontaneous ignition (self-ignition)	4.9	2.3	2.7	0	4.7	14.7	0	8.3	
Hot surfaces	4.9	11.6	0	3.6	2.3	23.5	0	0	0
Welding/cutting	4.9	5.8	2	0	4.7	2.9	5.9	0	0
Electrical machinery	2.8	2.3	2	0	0	0	0	0	0
Unknown/Others	19.5	23.3	20.7	16.2	16.2	20.7	4.1	5.2	33.3
All	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**

ATEX 基础 – 粉尘等级

粉尘爆炸等级

- ST 等级专用于德国标准
- 三个等级：ST1, ST2和ST3
- ST1 1 – 199 Bar m/s
- ST2 200 – 299 Bar m/s
- ST3 300 – 无上限!

KG 和KST 类似，用于气体

- 气体防护跟粉尘通用
- 气体经常维持低浓度，仅为临时基础

ATEX分类

ATEX 分类	典型区域适用性
1G 1D	设备适用于0区 设备适用于20区
2G 2D	设备适用于1区 设备适用于21区
3G 3D	设备适用于2区 设备适用于22区

ATEX分组及分类

分类

1 – 最安全的设备。用于所有分区（不能提供）

2 – 21,22 / 1,2区安全

3 – 仅用于22/2区

使用特殊条件

ATEX 铭牌外观

II 2D3G/3D- X T=125 C

分组

I – 采矿设备

II – 非采矿设备

D – 粉尘

G – 气体

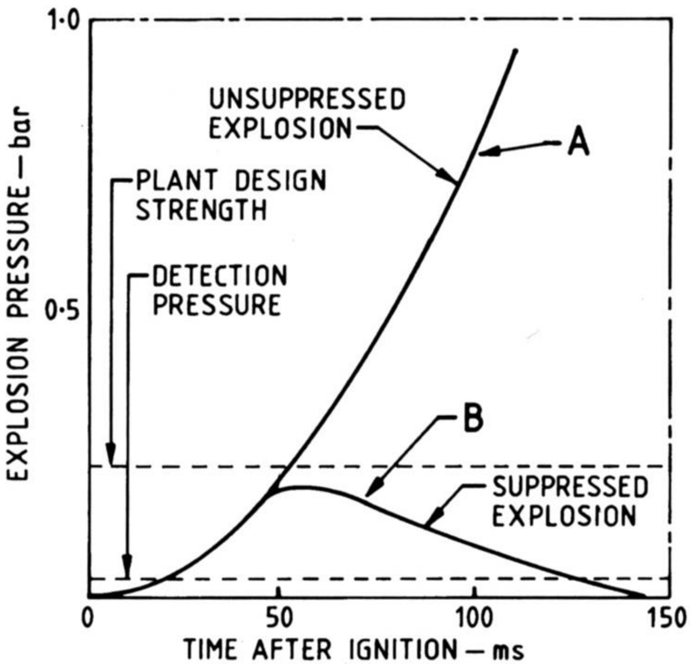
设备最高表面温度

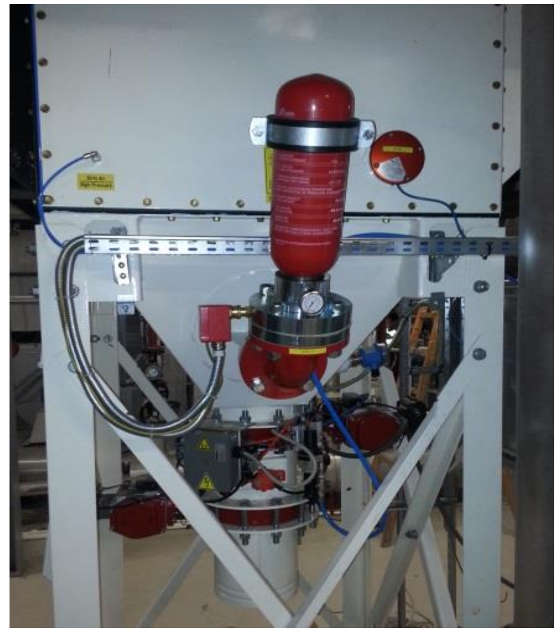
爆炸粉尘- 危险属性尺寸

- 燃烧发生在材料表面，细小材料每重量单位有更多表面，由此反应更强

- 大多数粉尘收集系统设计防止细小粉尘溢出。这意味着，集尘器中的粉尘通常比加工料更小

抑制-压制初期爆炸





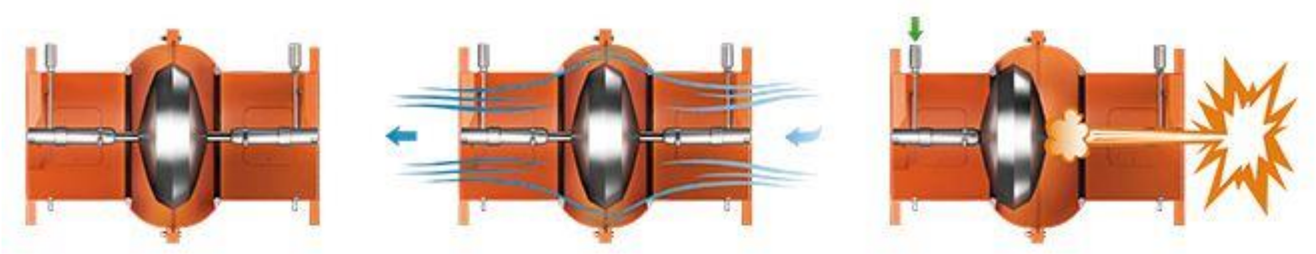
通常联合一个快速反应机械阀或化学屏障，**用以保**护脏污侧管道

出口隔离

- It may also be required to prevent an explosion from travelling through the clean side pipes. This can be done with an active valve or a passive Ventex valve还可用于防止爆炸通过洁净侧管道蔓延。可借助于
- 康斐尔已检测并证实， ISMF过滤器可用作有机ST1粉尘有效火焰屏障

Active flap valve蝶阀

VENTEX ESI-E/-D



总结

- **坏消息：粉**尘爆炸和火灾是造成死亡和破坏的主要潜在危害

- **好消息：爆炸及火灾可根据以下原**则进行安全管理：
  1. **采用好的管理流程**
  2. **了解粉**尘**-**对其进行检测，将给您省钱！
  3. **安装**设计良好的粉尘抽吸和收集系统，聘用经验丰富且**可信的**设计师、安装人员及供应商
  4. 选取适用的粉尘收集器/**湿式除**尘器
  5. **遵守ATEX指令，确保所供**设备的防护等级可将危险降至最低，**能提供一个安全且健康的工作**环境

Dust Combustability Pharmaceutical focus

Thank you for your attention

Any Questions?

PSCI

PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

ACS Green Chemistry Institute
Pharmaceutical Roundtable

DEKRA Insight

END OF DAY 2

PSCI

PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

ACS Green Chemistry Institute® Pharmaceutical Roundtable

DEKRA Insight

Conference: Day Three

PSCI

PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

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Pharmaceutical Roundtable

DEKRA Insight

Responsible Labor Practices
负责任的劳动力实践
——PSCI准则指引及中国供应商的挑战

Presented by

Roland Qin

Group Responsible Procurement Manager, China & Asia East

Novartis

Agenda

1 PSCI 原则指引（劳工部分）

2 中国供应商所面临的劳工方面的挑战

3 案例分享与讨论

Agenda

1 PSCI 原则指引（劳工部分）

2 中国供应商所面临的劳工方面的挑战

3 案例分享与讨论

PSCI原则 – 劳工部分

- 1. 自由就业 （**Freely Chosen Employment**）
- 2. 童工与未成年工 （**Child Labor and Young Workers**）
- 3. 非歧视 （**Non-Discrimination**）
- 4. 公平待遇 （**Fair Treatment**）
- 5. 工资、福利及工作时间 （**Wages, Benefits and Working Hours**）
- 6. 结社自由* （**Freedom of Association**）

**注：此次讲演不涉及此部分内容 / Remark: this section is excluded in this presentation*

PSCI原则 – 劳工 – 自由就业（和非强迫劳动）

- **原则： 供应商不得使用强迫、抵押、契约劳力或非自愿的监狱劳力。**

- **典型制度要素：**
- **了解并熟悉相关法律法规**
- **建立公正且合乎道德**标准的雇佣体系
- 订立平等自愿、合法合理的合同雇佣关系
- 专人负责执行的完整且一贯性的雇佣和解雇流程
- **提供相**应条件的工作（生活）条件以满足员工基本需求

PSCI原则 – 劳工 – 自由就业和非强迫劳动 – 法令

- **相关中国法律法规：**

❖ **《刑法》第244条** – 强迫劳动罪：用人单位违反劳动管理法规，以限制人身**自由方法**强迫职工劳动。。。

❖ 《劳动法》**第32、96条**：**不得**强迫劳动。。。

❖ 《劳动合同法》**第二章（第**7、8、9、10、17**条）**劳动合同订立；**第**31、32**条**，严禁强迫劳动； **第四章（第**37,、38**条）**劳动合同解除与终止。。。

PSCI原则 – 劳工 – 自由就业 – 管理系统要点

- **建立良好的雇用系统：**

✓ **委任**专门的人员和团队来负责管理该系统；

✓ **透**彻理解相关法律法规；并且具有完整清晰的政策文件和被完全执行的流程

✓ **用工**审查和按需招聘 – **被管理和控制的招聘途径**

✓ **留存完整的**应聘人员档案

✓ 针对自身状况而制定的格式或非格式合同

✓ **充分、透明以及一致性的沟通**

✓ **由高**阶管理层领导的定期监督和审查机制

PSCI原则 – 劳工 – 童工与未成年工

- **原则： 供应商不得使用童工。要雇用 18 岁以下的未成年工，必须仅让其从事非危险性工作，并且该工人年龄高于国家法定就业年龄或完成义务教育所达到的年龄。**

- **典型制度要素：**

➢ 对任何童工行为的零容忍

➢ **明确最低年**龄要求和入职年龄审查

➢ 预防使用童工及纠正措施（应急管理）

➢ **未成年工的**识别与（申报）管理

➢ **未成年工的**岗位设置与工时管理

PSCI原则 – 劳工 – 童工和未成年工 – 法令

- **相关中国法律法规 – 童工：**

❖ 《**刑法**》 **第244条 – 使用童工罪**：违反劳动管理法规，雇用未满十六周岁的未成年人**从事超强度体力**劳动的，或者从事高空、井下作业的，或者在爆炸性、易燃性、放射**性、毒害性等危**险环境下从事劳动。。。

❖ 《劳动法》**第15条**：**禁止用人**单位招用未满十六周岁的未成年人；

❖ 《**未成年人保**护法》**第28条**：**任何**组织或者个人不得招用未满十六周岁的未成年人，**国家另有**规定的除外。

❖ 《**禁止使用童工**规定》

- **相关中国法律法规 – 未成年工：**

❖ 《劳动法》**第58条**：**未成年工是指年**满**16周**岁未满**18周**岁的劳动者； **第64条**：**不得安排未成年工从事**矿山井下、有毒有害、国家规定的第四级体力劳动强度的劳动和其他**禁忌从事的**劳动； **第65条**：**用人**单位应当对未成年工定期进行健康检查。

❖ 《**未成年人保**护法》**第28条**：**任何**组织或者个人不得招用未满十六周岁的未成年人，**国家另有**规定的除外。

❖ 《**未成年工特殊保**护规定》

PSCI原则 – 劳工 – 童工和未成年工 – 管理系统要点

- **建立良好的未成年工管理系统：**

✓ **必**须清楚的研判是否有招聘和使用未成年工的迫切需求

✓ **定**义能够使用未成年工的岗位，并适时更新；涉及工作环境、强度、时长和性质

✓ **委任**专门人员负责该系统，必须透彻理解相关法律法规

✓ **制**订相应的管理文件和操作流程；确保和用人部门之间的良好沟通

✓ **至少每半年一次**对所有现有的未成年工进行状况审查

✓ **关注未成年工的身心**发展，鼓励进一步完成学业或职业技能培训

PSCI原则 – 劳工 – 非歧视

- **原则： 供应商应提供没有骚扰和歧视的工作场所。不能容忍基于种族、肤色、年龄、性别、性取向、民族背景、残障、宗教、政治信仰、工会身份或婚姻状况之类的歧视现象。**

- 典型制度要素：
- ➢ **正式的**书面化的非歧视政策与制度
- ➢ **多元化工作**场所的建立（Diversity）
- ➢ **内部**报告机制，预防潜在的歧视性问题
- ➢ **不会依据**员工的生育状况进行测试或评估，并将此作为雇佣条件
- ➢ 员工之间的薪水或其它福利差异不被用作歧视手段

PSCI原则 – 劳工 – 非歧视 – 法令

- **相关中国法律法规：**

❖ **《就业促进法》 第三章　公平就业**

第27条（性别和婚姻状况）国家保障妇女享有与男子平等的劳动权利。
用人单位招用人员，除国家规定的不适合妇女的工种或者岗位外，不得以性别为由拒绝录**用**妇女或者提高对妇女的录用标准。用人单位录用女职工，不得在劳动合同中规定限制女职工结婚、生育的内容。

第28条 （民族背景）各民族劳动者享有平等的劳动权利。用人单位招用人员，应当依法对**少数民族**劳动者给予适当照顾。

第29条（残障）国家保障残疾人的劳动权利。用人单位招用人员，不得歧视残疾人。

第30条（艾滋病）用人单位招用人员，不得以是传染病病原携带者为由拒绝录用。但是，经医学鉴定传染病病原携带者在治愈前或者排除传染嫌疑前，不得从事法律、行政法规和**国**务院卫生行政部门规定禁止从事的易使传染病扩散的工作。

第31条（户籍）农村劳动者进城就业享有与城镇劳动者平等的劳动权利，不得对农村劳动者进城就业设置歧视性限制。

PSCI原则 – 劳工 – 公平待遇

- **原则： 供应商应提供没有骚扰和不人道待遇的工作场所，这些不良待遇包括对工人进行任何性骚扰、性虐待、体罚、心理或生理上的强迫、言辞辱骂，并且不得威胁采取上述任何手段。**

- 典型制度要素：
- **正式且**书面化，并被有效传达的公平待遇政策与制度
- **建立基于“正激励”的**纪律管理系统
- **确保**员工熟悉了解并认同纪律管理体系；并清楚申诉的渠道
- 员工仅因为**“明知故犯”而受到**规劝、警告、降职或开除
- **不将扣留或扣押薪酬和其它**应得福利作为一种纪律处分措施

PSCI原则 – 劳工 – 公平待遇 – 管理系统要点

- **建立**纪律管理和激励系统：

✓ 纪律管理系统的目的
✓ 执行人员的培训
✓ 员工的受知及反馈
✓ **透明的**处理结果和申诉反馈机制
✓ **由高**阶管理层领导的定期监督和审查机制

PSCI原则 – 劳工 – 工资、福利及工作时间

- **原则：供应商应依照相关的法律向员工支付工资，包括最低工资、加班工资以及法定福利。供应商应适时向员工解释他们的工资标准。供应商还需要向员工说明是否需要加班以及加班所能获得的薪水。**

- **典型制度要素：**
- ➢ **制**订合法合理的薪资标准；包括法定福利
- ➢ **建立完整且可追溯的工**资支付体系
- ➢ **制**订完整且细致的工时制度
- ➢ **建立良好的工**时追踪和管理系统
- ➢ **确保法定休假和**带薪休假制度

PSCI原则 – 劳工 – 工资、福利及工作时间 – 法令

- **相关中国法律法规 – 工资福利：**
- 《劳动法》**第五章：工资 - 国家**实行最低工资保障制度； **工**资应当以货币形式按月支付给劳动者本人
- 《劳动合同法》
- 《**最低工**资规定》
- 《**社会保**险法》

- **相关中国法律法规 – 工作时间：**
- 《劳动法》**第四章 ：工作**时间和休息休假
- 《**国**务院关于职工工作时间的规定》
- 《**企**业职工带薪年休假实施办法》

PSCI原则 – 劳工 – 工作时间 – 管理系统要点

- 工时管理系统：

✓ **基于不同**岗位和生产需求设置的工时制度
✓ **准确并且可被**验证的工时记录
✓ **加班需求**评估
✓ 强制性的（固定）**休息**时间
✓ **基于生**产能力而设定的生产计划*
✓ **由高**阶管理层领导的定期监督和审查机制

Agenda

1 PSCI 原则指引（劳工部分）

2 中国供应商所面临的劳工方面的挑战

3 案例分享与讨论

中国供应商面临的劳工方面的挑战 - I

- **新入职员工的管理：**
  - 合同签订
  - 入职培训
  - 试用期管理
  - 押金问题及其他

- **可能的解决方案：**
  - 1.
  - 2.
  - 3.

中国供应商面临的劳工方面的挑战 - II

- **学生工的管理：**
- ❖ 学生工的定义
- ❖ 模糊的相关法律法规
- ❖ 勤工俭学？
- ❖ 三方协议问题及其他？

- **可能的解决方案：**
- ✓ 1.
- ✓ 2.
- ✓ 3.

中国供应商面临的劳工方面的挑战 - III

- **员工沟通：**
  - 单向？双向？
  - 员工沟通的话题和目的？
  - 反馈和解决？
  - 其他

- **可能的解决方案：**
  - ✓ 1.
  - ✓ 2.
  - ✓ 3.

中国供应商面临的劳工方面的挑战 - IV

- **加班管理：**
- ❖ **依据**生产计划还是生产能力？
- ❖ **加班**审批权限？
- ❖ 员工主动要求加班？
- ❖ **加班**所引发的的其他问题

- **可能的解决方案：**
- ✓ 1.
- ✓ 2.
- ✓ 3.

Agenda

1 PSCI 原则指引（劳工部分）

2 中国供应商所面临的劳工方面的挑战

3 案例分享与讨论

案例分享和讨论 - A

- **背景：**

某供应商与所有新入职员工在入职三个月后才签订劳动合同；并且所有员工必须缴纳人民币**1000元作**为制服和生产工具押金

- **其中的问题以及原因思考：**

- **我们怎么样可以做的更好？**

案例分享和讨论 - B

- **背景：**

某供应商和员工约定，将在员工春节返回公司后（3月底）， 支付1、2月份的工资及前一年度的生产奖金。

- **其中的问题以及原因思考：**

- **我们怎么样可以做的更好？**

案例分享和讨论 - C

- **背景：**

某供应商与与所有员工签订自愿加班协议，规定每月休息一天，每天可**以最**长工作**2个班次（每班次8小**时）。。。多劳多得，奖金不封顶。

- **其中的问题以及原因思考：**

- **我们怎么样可以做的更好？**

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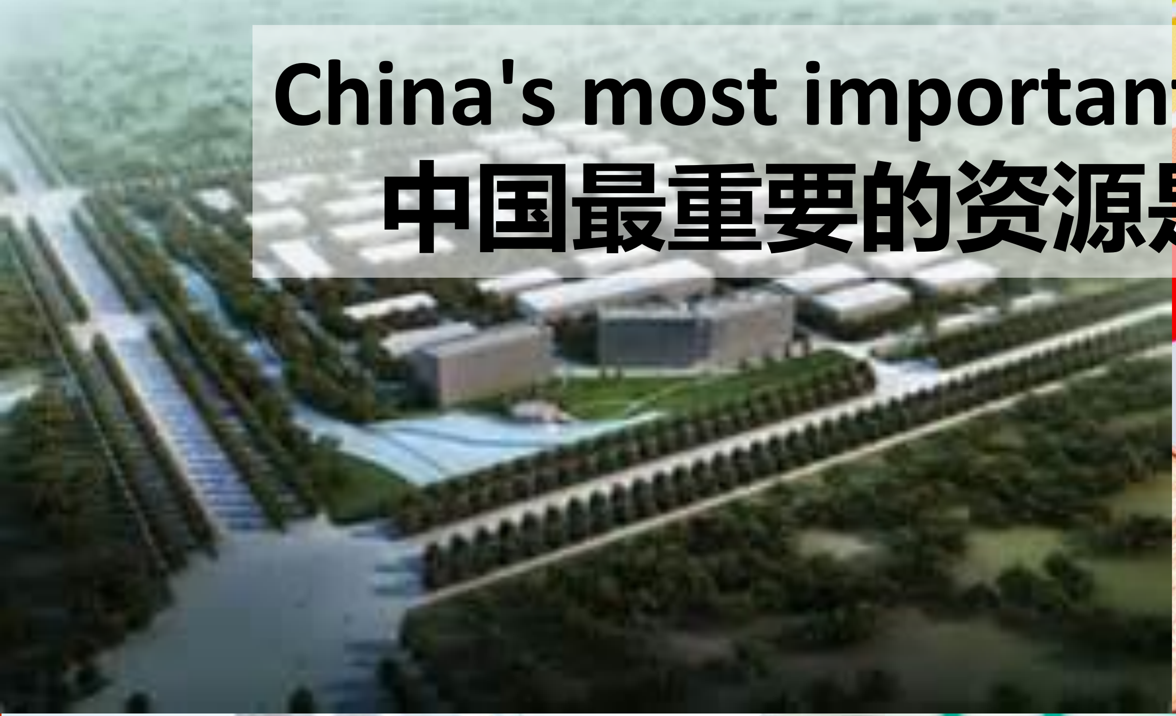
working well project

Tristan Edmondson, Senior Partner, Carnstone
高峰，高级合伙人，凯嵘咨询
Dave Zhao, General Manager, ELEVATE
赵勇，上海办公室总经理，达岸咨询

carnstone
凯 嵘 咨 询 asia

ELEVATE
Business Driven Sustainability

China's most important Resource?
中国最重要的资源是什么？



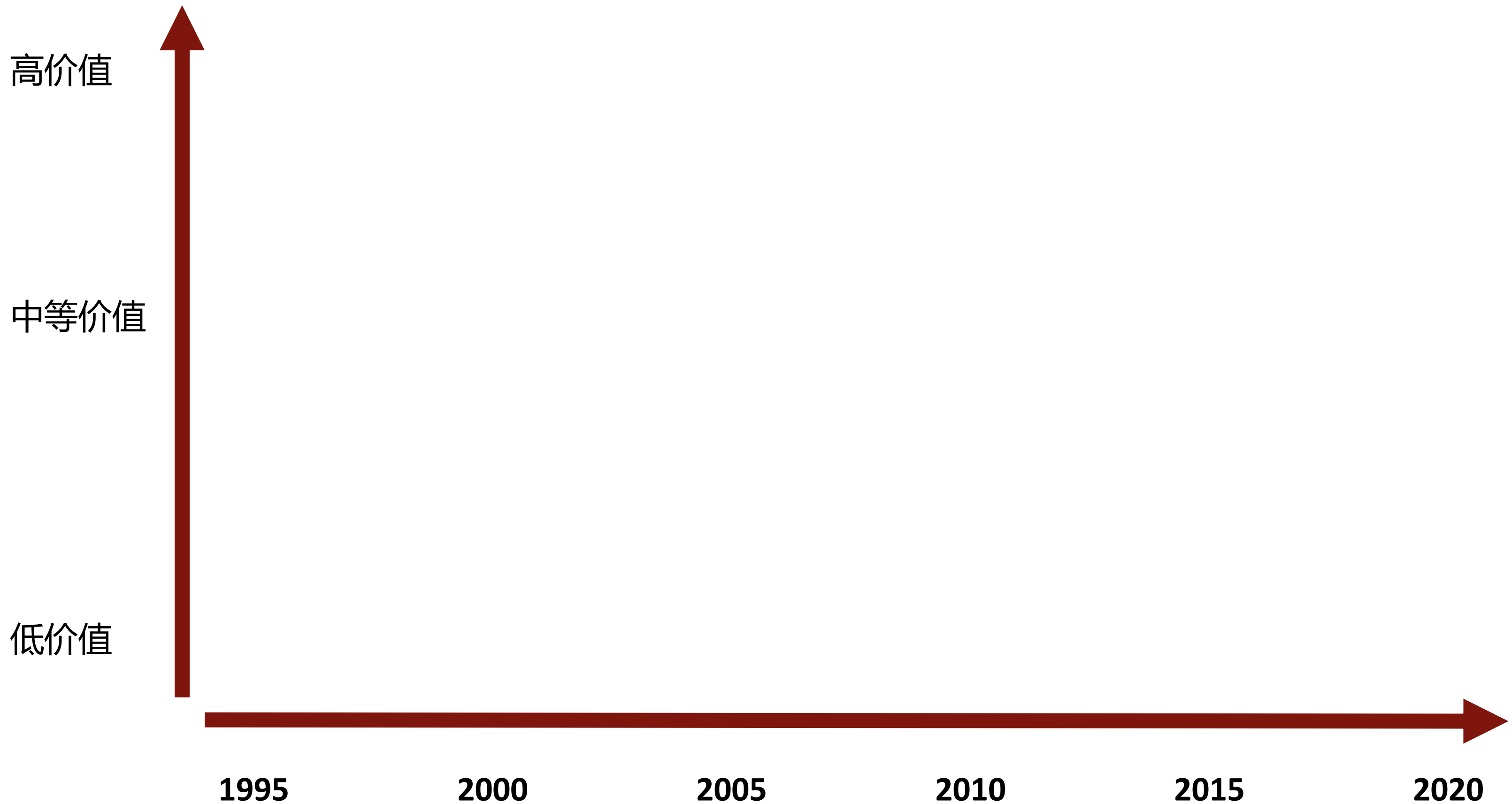

China's most important Resource?
中国最重要的资源是什么？
土地？


China's most important Resource?
中国最重要的资源是什么？
土地？
资本?

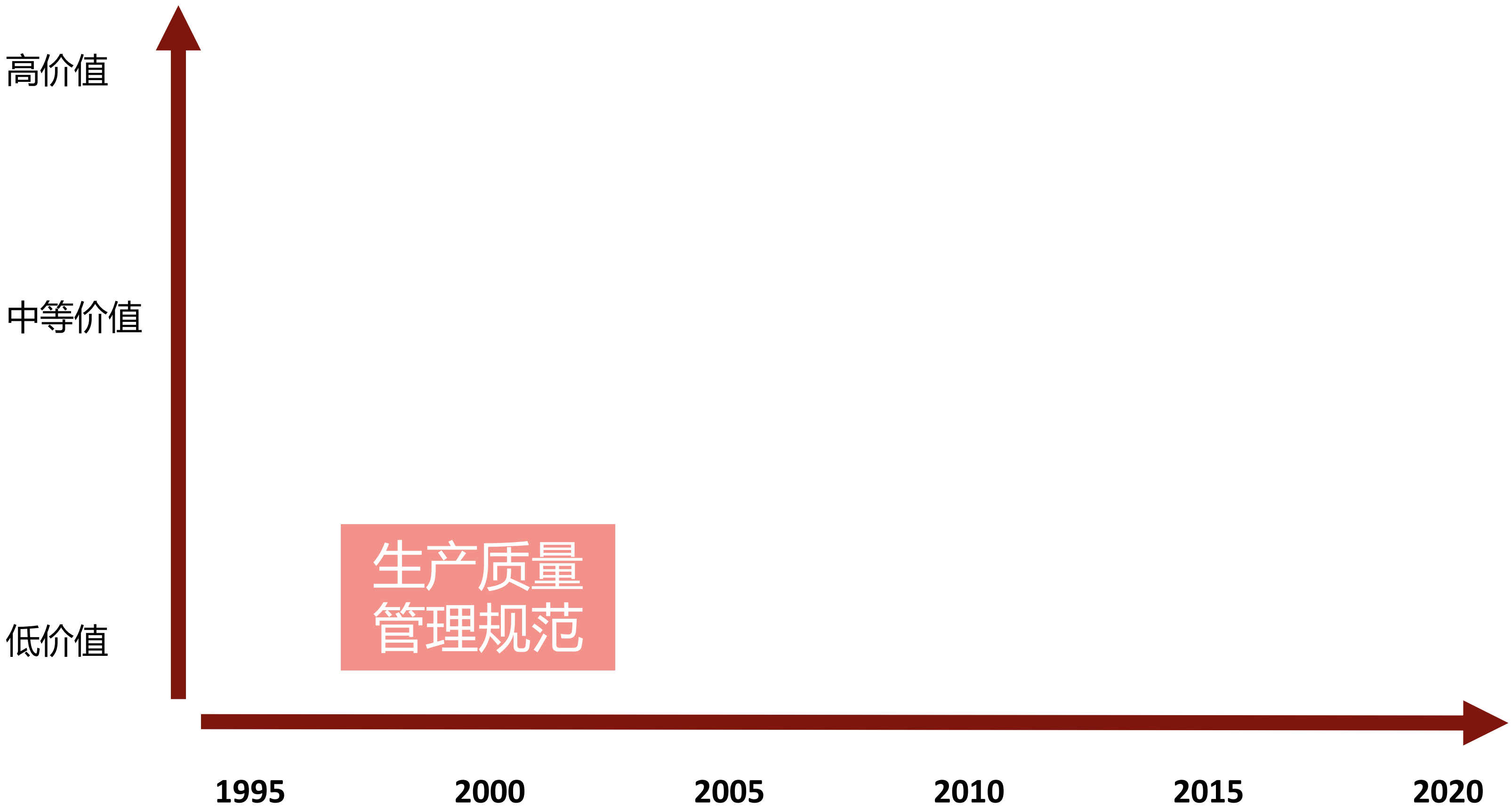

China's most important Resource?
中国最重要的资源是什么？
土地？
资本?
技术?

China's most important Resource?
中国最重要的资源是什么？
土地？
资本?
技术?
人!

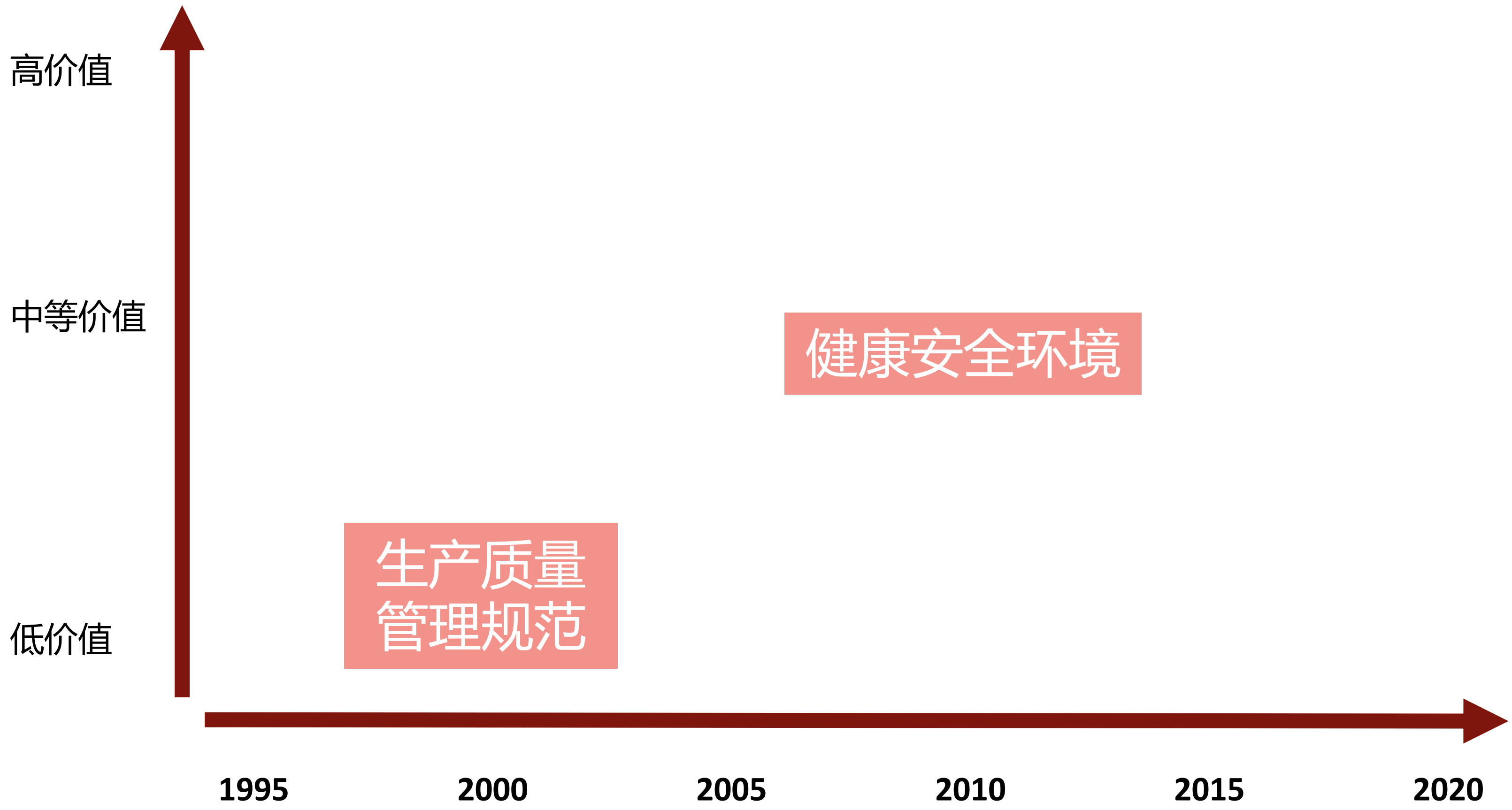
China’s pharmaceutical industry development
中国医药行业发展



China's pharmaceutical industry development
中国医药行业发展



China's pharmaceutical industry development
中国医药行业发展



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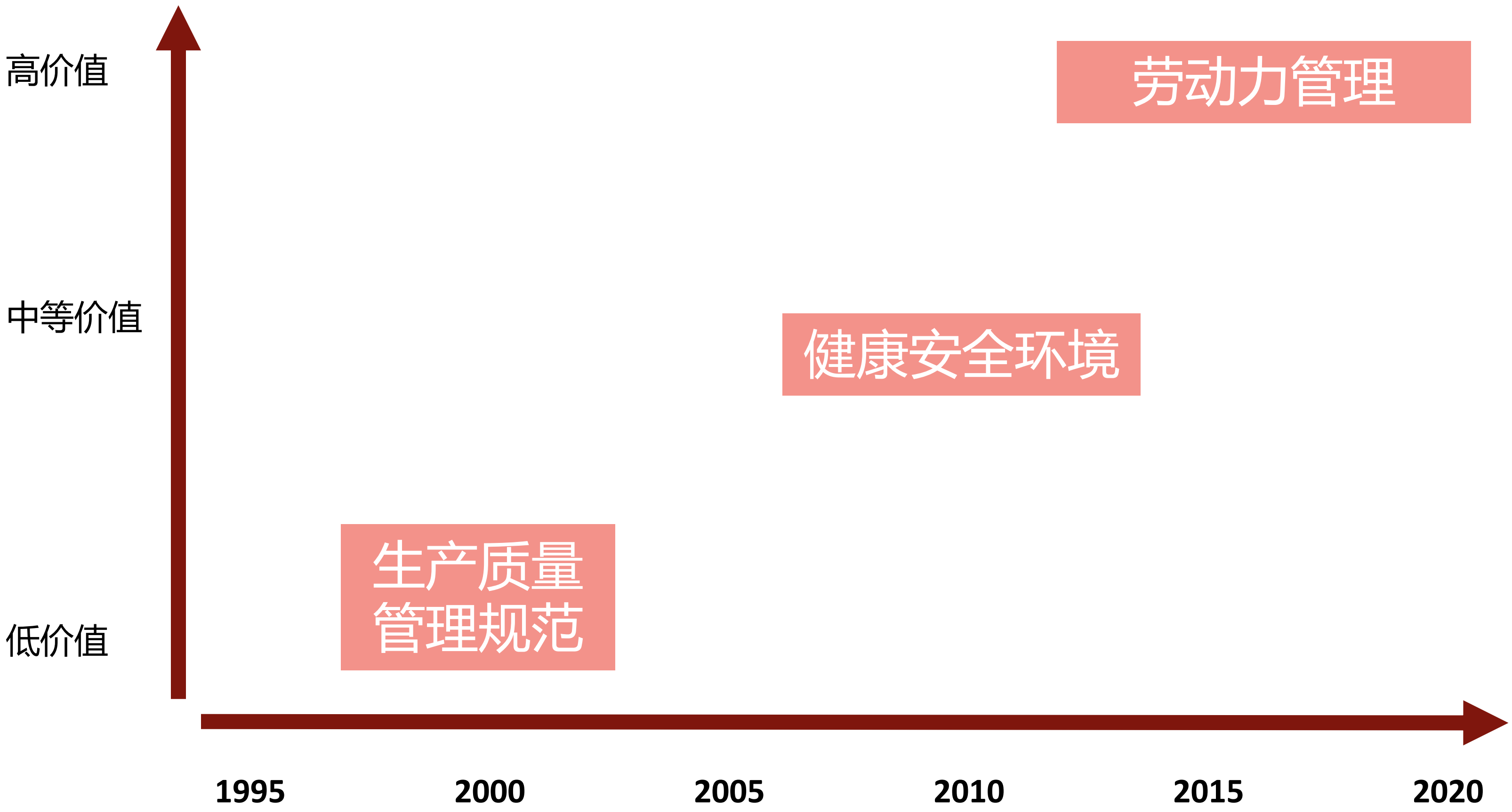
China's pharmaceutical industry development
中国医药行业发展



Why is this important?
为什么重要？

- **产品风险**

Why is this a problem?
为什么这是一个问题？

- **产品风险**
- **员工流失率高**

Why is this a problem?
为什么这是一个问题？

- **产品风险**
- **员工流失率高**
- **名誉风险**

Why is this a problem?
为什么这是一个问题？

- **产品风险**
- **员工流失率高**
- **名誉风险**
- **罢工及视察**

Project overview
项目概述

我们发现了哪些问题	工厂采取了哪些措施	结果
• 工时长 • 连续工作日长 (未能做到7休1) • 未依法支付工资 • 手工考勤 • 缺勤情况普遍 • 工资体系复杂缺乏透明度 • 缺乏有效的内部员工沟通体系 • 班组长缺乏沟通能力	• 研讨会培训 • 在线学习培训 • 现场培训 • 提交月度关键绩效指标 • 制定行动计划 • 实施行动计划 • 进行月度回顾和指导	• 第二次员工问卷中，19项问题里，有7项体现出显著改善，12项没有显著改善（即改善幅度小于+/- 5%） • 4家工厂体现了行动计划实施后的积极影响，3家尚未汇报情况 • 80%的工厂管理层愿意向别人推荐本项目（7家工厂作出回应）

Project timetable
项目时间表

月数		
0	项目准备	工厂参与
1		两次启动研讨会
2	项目基础	首次工厂访问
3		28项项目关键绩效指标
4		在线学习
5	行动计划制定	与工厂电话沟通
6		项目组和工厂共同决定优先处理的问题
7		提交行动计划
8	行动计划实施	第二次工厂访问
9		工厂培训研讨会
10		第三次工厂访问
11		与工厂电话沟通
12	项目结束	最后一次工厂访问

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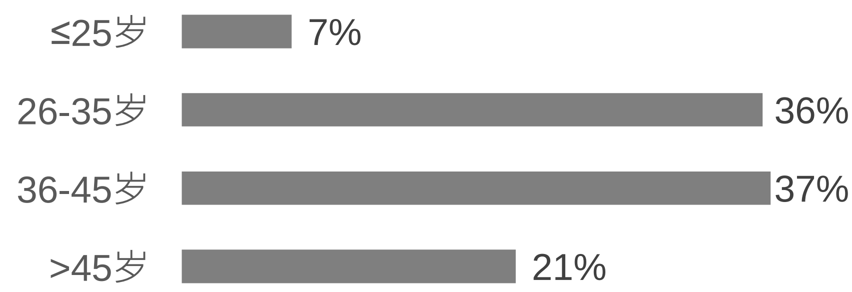
What we found – Summary
我们发现了哪些问题——总结

8家工厂
参与了基线问卷

834名员工
参与了基线问卷

年龄



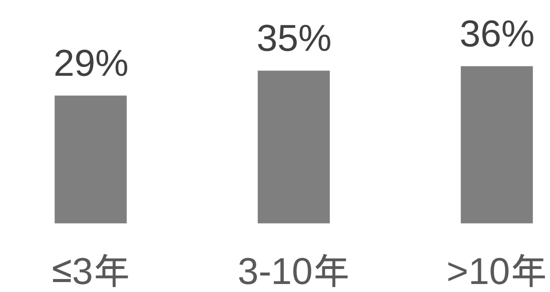
性别

女员工 **39%**

男员工 **61%**

工龄

平均工龄: 10年



What we found – Summary
我们发现了哪些问题——总结

8家工厂共同的问题

- 工时长
- 连续工作日长 (未能做到7休1)
- 未依法支付工资
- 手工考勤
- 缺勤情况普遍
- 工资体系复杂缺乏透明度
- 缺乏有效的内部员工沟通体系
- 班组长缺乏沟通能力

我们是如何发现这些问题的

- 工厂访问
  - 员工问卷调查
  - 和管理者面谈
  - 查阅文件
- 工厂每月提交的28项关键绩效指标，包含工时、休息天数、生产情况和员工反馈等数据

这些问题可能产生的影响

- 员工不满，降低生产积极性
- 因员工操作机器感觉疲劳引发生产事故的风险上升
- 对员工得到的激励减少，离职率上升
- 面临政府罚款或员工罢工的风险

What factories did – Summary
工厂采取了哪些措施——总结

作为这些问题的回应，Working Well项目中的8家工厂与达岸及凯嵘咨询公司合作，**接受实际培训，也实施了行动计划。**

实际的培训和指导

1. 理念转变研讨会
2. 项目培训研讨会
3. 工厂访问
4. 30多个主题的在线学习
5. 针对管理者的项目中期团队培训

行动计划实施

1. 工厂查阅了首次访问报告
2. 工厂提交了首次草拟的行动计划
3. 提出改善建议
4. 每个月和工厂通电话
5. 第二次工厂访问，回顾进度
6. 第三次工厂访问和最后的员工问卷调查
7. 最后一次工厂访问

2015年4月，工厂参加项目系统培训

What factories did – Action plans, 3 examples
工厂采取了哪些措施——行动计划，3个范例

	寿光	工厂2	工厂3
问题	1. 缺乏申诉渠道 2. 10%的员工不清楚工资是如何计算的	1. 手工考勤系统 2. 61%的员工不清楚工资是如何计算的 3. 没有收集员工反馈	1. 70%的员工不清楚工资是如何计算的 2. 75%的员工表示班组长没有认真倾听他们的问题
行动	1. 2016年3月对选出的班组长进行培训，提高他们和员工沟通的水平，再由他们培训其他班组长 2. 在员工培训材料中加入工资计算的部分，公示工资计算方式，制定培训现有员工的计划。	1. 对工时作数字化记录和分析，创建加班申请流程，培训负责人 2. 把三套工资体系优化为一套 3. 建立收集和记录员工反馈的系统	1. 开发工资计算方面的培训材料，公示工资标准，培训新老员工 2. 和工会及员工代表共同讨论，提高班组长能力，每月汇报反馈意见

The results – Summary
结果——总结

行动计划实施和员工反馈结果

在参与项目的8家工厂中

- 4家体现出可量化的积极结果
  - 超过半数以上的员工觉得工厂有进步
  - 4家工厂均改善了工资支付不足的问题
  - 减少了最长连续工作天数
  - 建立相应的内部沟通管理体系，跟踪和处理员工反馈

- 3家工厂启动项目晚，还在等结果
- 1家工厂因为商业原因退出了项目

The results – Worker survey
结果——员工问卷调查

领域	问题	首次问卷	第二次问卷	改变
工时	旺季员工每天工作**超过**8小时	65%	48%	- 17%
	淡季员工每天工作**超过**8小时	19%	13%	- 6%
	员工连续工作**超过**6天不休息	51%	44%	- 7%
	员工连续工作**超过**13天不休息	37%	13%	- 24%
沟通	员工认为班组长部分倾听或**不**倾听他们的担心	64%	53%	- 11%
	员工与班组长处得好	58%	70%	+ 12%
工资	员工认为自身工资公平	39%	45%	+ 6%
进步（仅第二次问卷）	注意到在过去12个月中取得进步的员工百分比		69%	-

The results – Action plans
结果——行动计划

	工厂1	工厂2	工厂3	工厂4	工厂5	工厂6	工厂7	工厂8
问题	1. 缺乏申诉渠道 2. 10%的员工不清楚工资是如何计算的	1. 手工考勤系统 2. 61%的员工不清楚工资是如何计算的 3. 没有收集员工反馈	1. 70%的员工不清楚工资是如何计算的 2. 75%的员工表示班组长没有认真倾听他们的问题	1. 77%的员工连续工作超过6天不休息 2. 46%的员工表示班组长没有认真倾听他们的问题	1. 40%的员工表示班组长没有认真倾听他们的问题 2. 44%的员工不清楚工资是如何计算的	1. 55%的员工不清楚工资是如何计算的 2. 47%的员工与班组长处得好	1. 前5%的员工,平均周工时为75小时 2. 74%的员工认为班组长没有认真倾听他们的问题 3. 只有95%的员工领到了法定工资	1. 70%的员工认为班组长没有认真倾听他们的问题 2. 51%的员工不清楚工资是如何计算的
结果	1. 每月平均收到9.5条员工反馈意见 2. 100%的员工清楚工资是如何计算的	1. 记录目前100%正确 2. 80%的员工不清楚工资是如何计算的 3. 每月平均收到7.3条员工反馈意见	未完成二次员工问卷	未完成二次员工问卷	工厂由于和项目发起人终止业务关系，而中断了项目合作	1. 48%的员工不清楚工资是如何计算的 2. 68%的员工与班组长处得好	1. 前5%的员工,平均周工时没有变化 2. 60%的员工认为班组长没有认真倾听他们的问题 3. 100 %的员工领到了的法定工资	未完成二次员工问卷

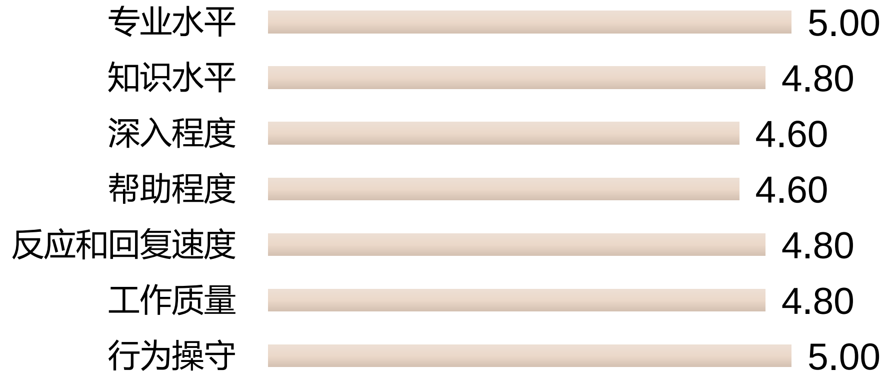
The results – Factory manager survey
结果——工厂管理层问卷调查

您在多长程度上会向别人推荐本项目？
（1代表不可能，10代表非常可能）

80%的管理者会向别人推荐本项目*

***给本项目打7分或7分以上的比例**

请从1到5打分，您怎样评价达岸和凯嵘公司在以下各方面的表现？（1代表非常差，5代表非常好）



您最喜欢本项目的哪些部分？

- “数据分析和展现”
- “员工管理上的新工具和新概念”
- “团队专业、流程标准”

7家工厂的管理者对问卷调查的平均回复情况

Project Challenges
项目挑战

这是中国制药供应商首次参加一个解决地方性劳工管理问题的项目，过程中出现了各种挑战。有些问题在项目期间被解决了，还有一些可以留待开展Working Well第二阶段工作时解决。

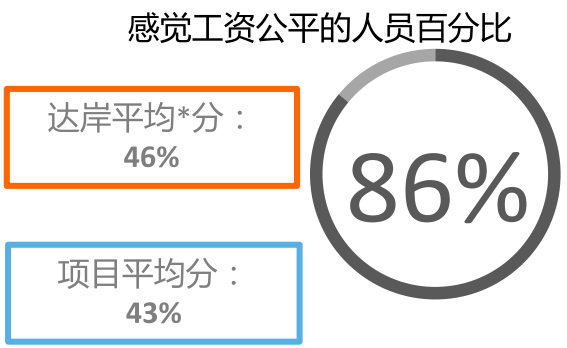
挑战
1. 工厂签约参加项目的进度慢，推迟了项目的结束日期
2. 制定可执行且高效的行动计划，是工厂面临的一项挑战
3. 工厂不是没有提交生产效率方面的关键绩效指标，就是没有用到这类指标
4. 工厂普遍没有提交质量方面的关键绩效指标

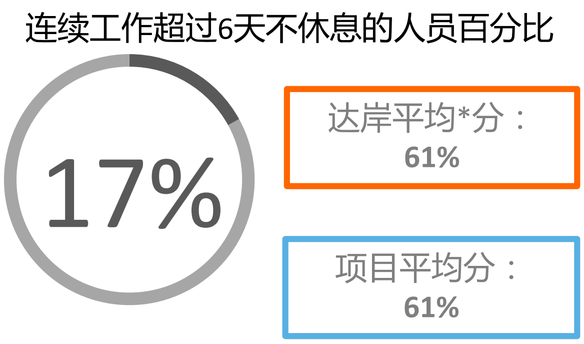
Annex 1: Factory 1 Case Study
附录1：工厂1案例分析

工厂概述

首次员工问卷调查：6月15日
关键绩效指标提交日期：6月15日至16日
二次员工问卷调查：6月16日
接受调查的员工总数：238
员工队伍的特征： • 以男性、本地员工为主 • 文化程度较高（将近100%的人都接受过高中或高中以上教育） • 员工队伍稳定，留厂时间长 • 员工队伍较资深，平均年龄30岁

工厂在哪些方面做的好？





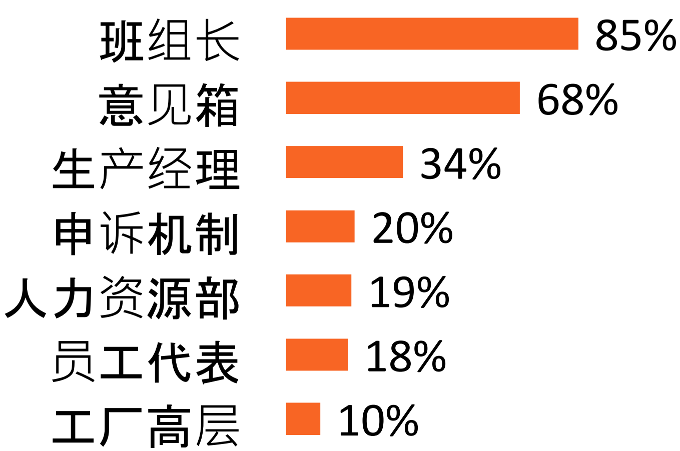
- **较高地管控着工时**
- **员工总体上对工资体系非常满意**

*达岸平均分是对不同行业各家工厂做问卷调查后汇总的结果

Factory 1 - First Worker Survey
工厂1 - 首次员工问卷调查

工厂在哪些方面可以做得更好？

员工有了问题会和谁说？



30%	在过去12个月中曾提出问题/建议。
在提出意见/建议的员工中	
13%	感觉自己的问题只有部分被认真对待或完全没被认真对待。
37%	感觉自己的问题只有部分被妥善处理或完全没被妥善处理。

31%

认为班组长部分倾听或是不听他们担心的问题

10%

不总是清楚工资的计算方式

Factory 1 – Action Plan Implementation
工厂1 - 行动计划实施

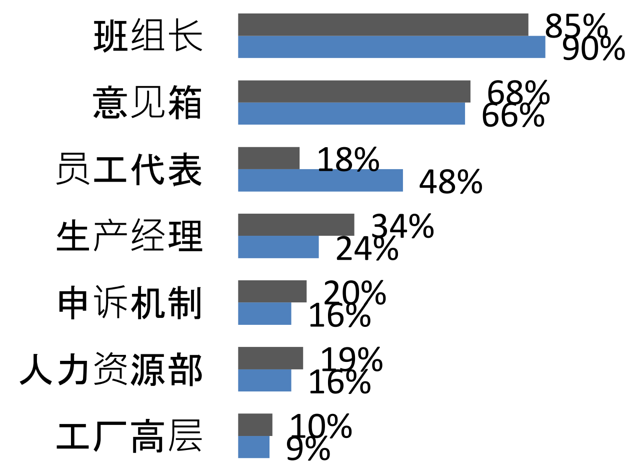
侧重领域	详情	进度和现状
工资说明	提高工资计算和支付方面的沟通水平	• 更新新员工培训材料，张榜公布工资计算方式； • 培训结束时，测试员工的了解程度。
沟通	创建有效的自下而上的员工反馈体系	• 建立正规申诉流程，并于2015年8月起实施。第一个月，收集到25名员工的意见。内容涉及餐厅服务、班组长态度以及机械维护。
班组长能力	提高班组长受理员工反馈的能力	• 2015年11月，对班组长进行员工管理方面的培训，重心落在工厂政策和规定上，让他们能解答好员工的问题。 • 利用提供的在线学习资源，给全体班组长做（沟通、员工意见处理、员工留任等）相关课程的培训。创建了9个在线学习账户，学了15门课。

Factory 1 – Survey Results & KPI Monitoring
工厂1 - 问卷调查结果和关键绩效指标监督

员工问卷调查结果

认为工资公平的受访者百分比 | **认为班组长部分倾听或是不听自己担心的问题的受访者百分比** | **不完全了解工资计算方式的受访者百分比**

员工有了问题会和谁说？



- 100%的员工都表示，他们完全清楚工资的计算方式
- 员工的态度比班组长更积极
- 我们发现，员工找员工代表谈话的意愿度有了很大的提升
- 现场查阅文件发现，在员工意见中占比很高的是建议，而不是申诉或投诉。

月度关键绩效指标数据结果

日期	15年6月	15年7月	15年8月	15年9月	15年10月	15年11月	15年12月	16年1月	16年2月	16年3月	16年4月	16年5月	16年6月
收集的员工意见数	0	0	25	23	13	8	9	10	7	5	0	2	3

Annex 2: About Carnstone and ELEVATE
附录2：凯嵘和达岸咨询公司简介

凯嵘咨询是一家总部位于上海的可持续咨询公司，隶属于Carnstone Partners LLP

- 凯嵘与Novartis合作四年，帮助其发展实施负责任采购项目。
- 凯嵘在经营多个产业网络方面，拥有丰富经验 http://carnstone.com/networks
- 领导本项目的Tristan Edmondson曾担任Novartis东亚区的负责任采购经理，现领导上海办事处的业务。详情请见www.carnstone.com。

一家全球专业服务公司，致力于提高供应链的社会、环境和业务绩效。

- 达岸咨询公司提供咨询、指导和班级培训，帮助工厂达到美国和欧洲为零售商制定的社会责任及环境标准。
- 达岸咨询公司现已完成300多家工厂的能力建设工作
- 达岸咨询公司与全球百强中20%的成员均有合作。详情请见www.elevatelimited.com。

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Establishing An
Effective Ethics & Compliance Program

建立有效合规体系

Marx Zhou

Agenda

I. 合规理论

- 合规要求从何而来？
- **法律要求是什么？**

II. 具体实务操作

- 合规部对内控提出了额外的要求？
- **政府的基本要求是什么？**
- **第三方管控体系**
- 供应商的合规风险管理

合规的前世今生

尼克松

田中角荣

克林顿

小布什

美国反海外腐败法的基本规定
THE BASIC REQUIREMENT OF FCPA

I. FCPA 适用于下属实体与外国官员的交往:

- **公众持有或私人所有的美国公司或**实体；
- **在美国境内**营业的公司或实体；
- **美国公民或定居者**；
- **在美国境内的非美国人.**

如下主体也有可能承担FCPA项下的法律责任：

- **上述**实体的合资合作方
- **上述**实体的非美国籍员工或代理商

II. FCPA的基本规定

美国公民或公司不得:

- **提供**、给与、**支付**、**允**诺支付或授权支付任何有价值之物给
- **任何外国官**员
- 诱使、**影响或**试图影响该外国官员。

美国反海外腐败法的基本规定
THE BASIC REQUIREMENT OF FCPA

III. 哪些属于"外国官员"?

- 任何非美国的
  政府、部门、机构、国有实体及政府间国际组织的官员或雇员。
  为政府、**部门、机关或国有**实体或代表其行使公共职能的个人。
- **国有**实体是指:
  - **国家所有或控制的**实体，包括国家控制的公司;
  - **也可能包括政府只占少数股份的公司。**

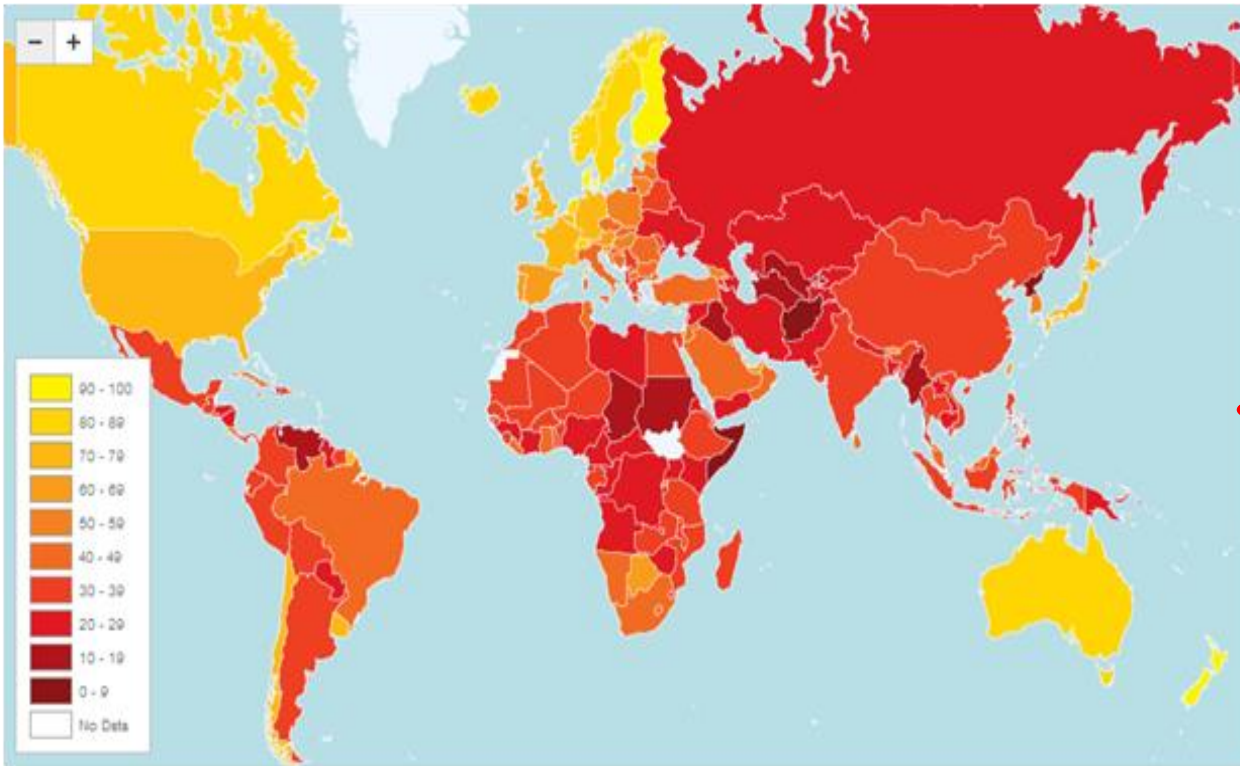
IV. 关于第三方（经销商、咨询公司等）的特别规定

相关公司的代理商也不得:

- **向任何其他**实体，如政府机关提供、给予、支付、承诺支付或授权支付任何有**价**值之物（无论有形或无形）
- **知悉全部或其中一部将被提供、**给予或承诺给予任何外国官员，以诱使、影响**或**试图影响该外国官员

"**不能雇佣一个代理商从事禁止的行**为，而明知该代理商会为你而为腐败之行为。"

- 透明国际上年度发布的CPI (Corruption Perception Index)。中国的排名从75位下降到80位，参加排名的总共约180个国家和地区



国家/地区	11年	12年
新西兰	1	1
新加坡	5	5
香港	12	14
日本	14	17
美国	24	19
台湾	32	37
南韩	43	45
马来西亚	60	54
中国	75	80
泰国	80	88
印度	95	94
印度尼西亚	100	118
越南	112	123
蒙古	120	94
菲律宾	129	105
俄罗斯	143	133
柬埔寨	164	157
缅甸	180	172
北朝鲜	182	174

美国反海外腐败法在医药行业领域的执法情况
The FCPA Enforcement on Pharmaceutical Industry

我们对于FCPA方面的关注和决心不会减退，并且我们将着重致力于清除你们行业的海外贿赂行为。”

- 美国司法部律师致医疗行业

FCPA反贿赂分则的犯罪构成要件

核心规定：
美国公民或公司不得：

➢提供、给与、支付、允诺支付或授权支付任何有价值之物给
➢任何外国官员
➢诱使、影响或试图影响该外国官员。

什么行为构成对FCPA的违反？
➢An Act By a Covered Person
➢In Furtherance of an Offer, Payment, Promise to Pay, or Authorization of Payment
➢Anything of value （**旅行、就**业机会？）
➢Directly or Indirectly
➢To a Foreign Official （谁是“**外国官**员”？）
➢Corruptly
➢For the Purpose of: Influencing Official Action or Decision, Inducing an Unlawful Act, Inducing Official Influence Over Government Action, or Securing Any Improper Advantage

具体实务操作

- Additional Requirement from E&C Team? 合规部对内控提出了额外的要求？

- What's the basic requirement from the government?政府的基本要求是什么？

- Third Party Management System 第三方管控体系

- TP Controls on meeting vendors, distributors and trade association 会务供应商、经销商及协会的风险管理

合规部对内控提出了额外的要求？

- Procurement 的范围:
- Raw Material
- 3rd party finish goods
- Capital project
- MRO
- Others

- Risks: Internal fraud, conflict of interest…
- Controls: vendor selection process, contractual obligation, job rotation, training, monitoring etc.
- 广义与狭义的合规
- 合规对于内控提出的额外要求

政府的基本要求是什么？

How Are Payments to Third Parties Treated?

The FCPA expressly prohibits corrupt payments made through third parties or intermediaries.[129] Specifically, it covers payments made to "any person, while knowing that all or a portion of such money or thing of value will be offered, given, or promised, directly or indirectly,"[130] to a

Because Congress anticipated the use of third-party agents in bribery schemes—for example, to avoid actual knowledge of a bribe—it defined the term "knowing" in a way that prevents individuals and businesses from avoiding liability by putting "any person" between themselves and

the foreign officials.[137] Under the FCPA, a person's state of mind is "knowing" with respect to conduct, a circumstance, or a result if the person:

- is aware that [he] is engaging in such conduct, that such circumstance exists, or that such result is substantially certain to occur; or
- has a firm belief that such circumstance exists or that such result is substantially certain to occur.[138]

Thus, a person has the requisite knowledge when he is aware of a high probability of the existence of such circumstance, unless the person actually believes that such circumstance does not exist.[139] As Congress made clear, it meant to impose liability not only on those with actual knowledge of wrongdoing, but also on those who purposefully avoid actual knowledge:

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政府的基本要求是什么？

transaction. Risk-based due diligence is particularly important with third parties and will also be considered by DOJ and SEC in assessing the effectiveness of a company's compliance program.

First, as part of risk-based due diligence, companies should understand the qualifications and associations of its third-party partners, including its business reputation, and relationship, if any, with foreign officials. The degree of

Second, companies should have an understanding of the business rationale for including the third party in the transaction. Among other things, the company should

Third, companies should undertake some form of ongoing monitoring of third-party relationships.[322] Where appropriate, this may include updating due diligence periodically, exercising audit rights, providing periodic training, and requesting annual compliance certifications by the third party.

In addition to considering a company's due diligence on third parties, DOJ and SEC also assess whether the company has informed third parties of the company's

compliance program and commitment to ethical and lawful business practices and, where appropriate, whether it has sought assurances from third parties, through certifications and otherwise, of reciprocal commitments. These can

第三方管控体系

I. 签约前的管控
- Risk based DD/ 背景调查
- 通过内部审批流程

II. 第三方合同中的合规条款
- 一般性合规条款
- 审计条款
- 其他条款（涉及monitoring，定期报告义务等等）

III. 签约后的管控
- 放入TP inventory
- 第三方培训
- 定期审计
- Monitoring
- 年度合规证书
- Re-do the DD

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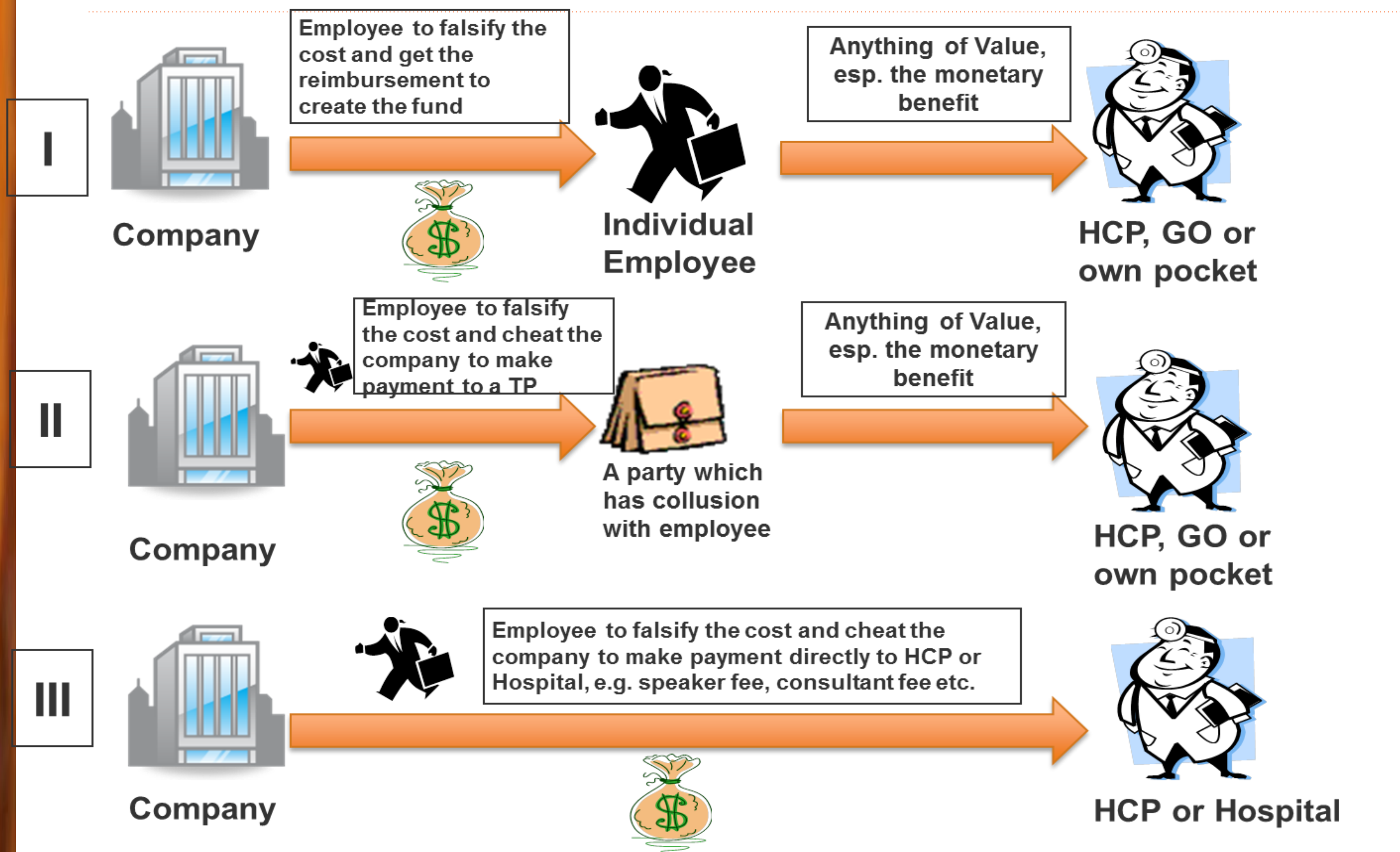
Trace the Money - 会务供应商、经销商及协会的风险管理



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供应商、经销商及协会的风险管理

- 针对会务供应**商的特**别管控：
  - **公司指定会**务供应商，缩减供应商数量；
  - **禁止向医院、**协会、学会指定的第三方打款；
  - **要求提交活**动的其他支持文件进行审核及比对；
  - 现场核查
  - **要求供**应商跟会确保活动的真实性；

- 针对学会、协会的特别的风险管理
  - **背景**调查
  - 项目风险管理计划及负责人的确定
  - **和管理**层的定期**Review的机制**

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Environmental Risks and Recommended Solutions For Pharmaceutical Manufactories in China:
中国制造型药企的环境风险分析以及建议的应对方案:

A lesson learned from an Indian Case and reflection from multiple stakeholders' perspective

Presented by

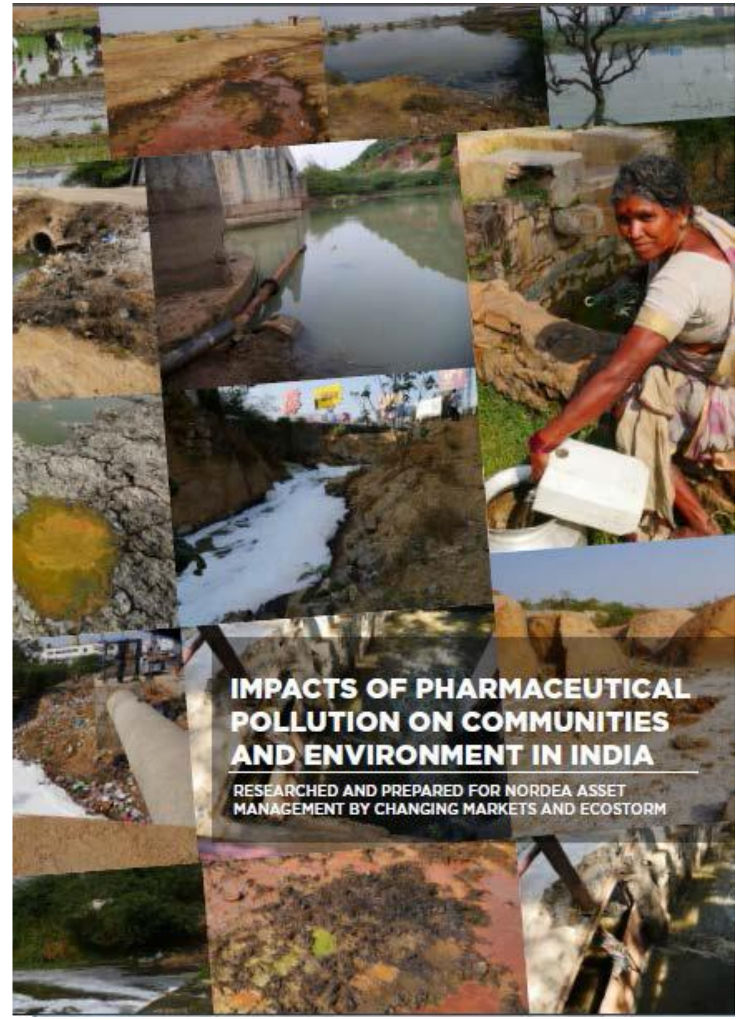
Takeda

[王文超]

[亚太区可持续采购负责人]

[Takeda Pharmaceutical]

药企十强，印度“药谷”水污染，北欧银行



五百强，上海，儿童，血铅中毒，政府媒体公众

http://www.wsj.com/articles/SB10001424052970204653604577248640436283030
http://finance.sina.com.cn/focus/mgjsgssxwr/

印中案例比较与反思

- 制药领域
- 本国（民营家族企业）
- 跨国银行（资本）介入
- 民众“默然”
- 尚无实质进展

- 工业领域
- 外资跨国公司
- 政府监管部门介入
- 民众检举施压
- 一年定论结案理赔

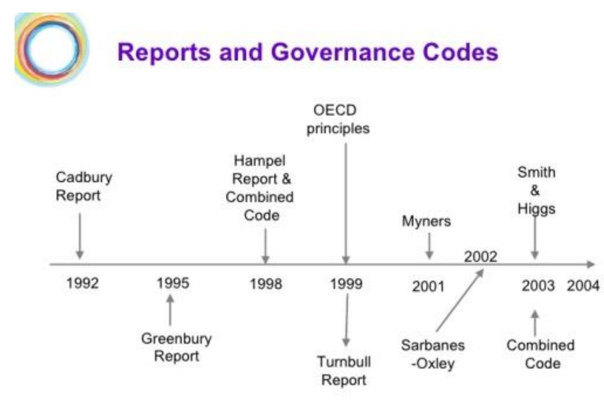
现代企业管理两大学术理论的辩论

School of Shareholder theory -股东理论学派

- Jensen’s agency’s theory
- **The sole objective of management is to protect the interests of shareholders (owners) by maximizing the value of the firm on their behalf**
- 所有PSCI会员单位都会有自己的风险管理或可持续发展管理委员，并直接汇报给董事会或管理团队

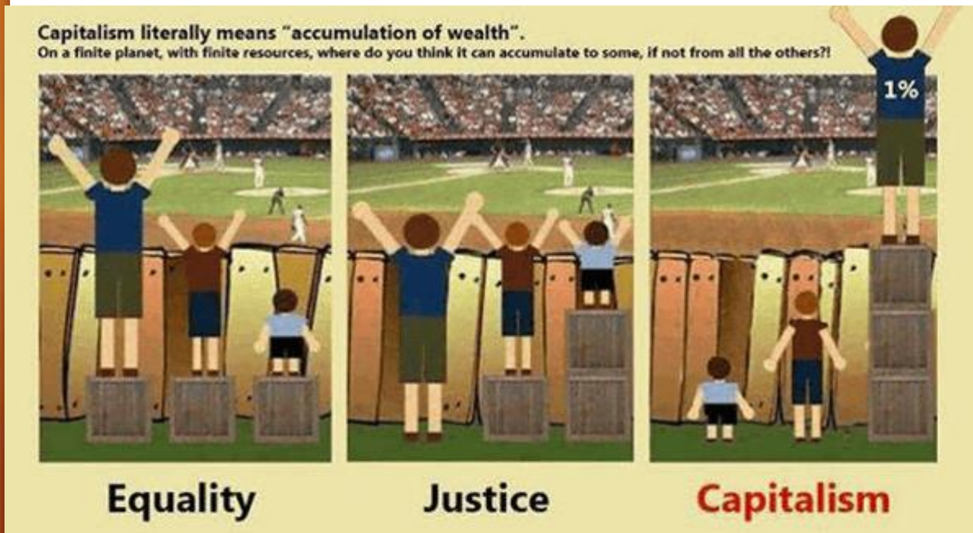
School of Stakeholder theory -利益相关方理论学派

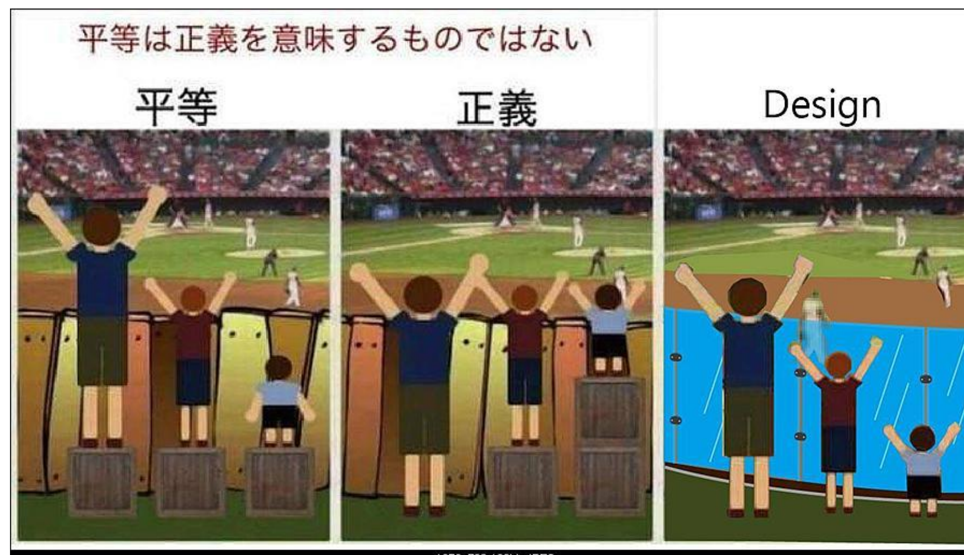
- The Hampel report on corporate governance (1998)
- **The board directors is responsible for relations with stakeholders; but accountable to shareholders**
- 不仅关注股东，而且关注所有利益相关方。几乎所有的跨国公司都会建立利益相关方模型来确保公司的健康可持续的发展以及风险管控



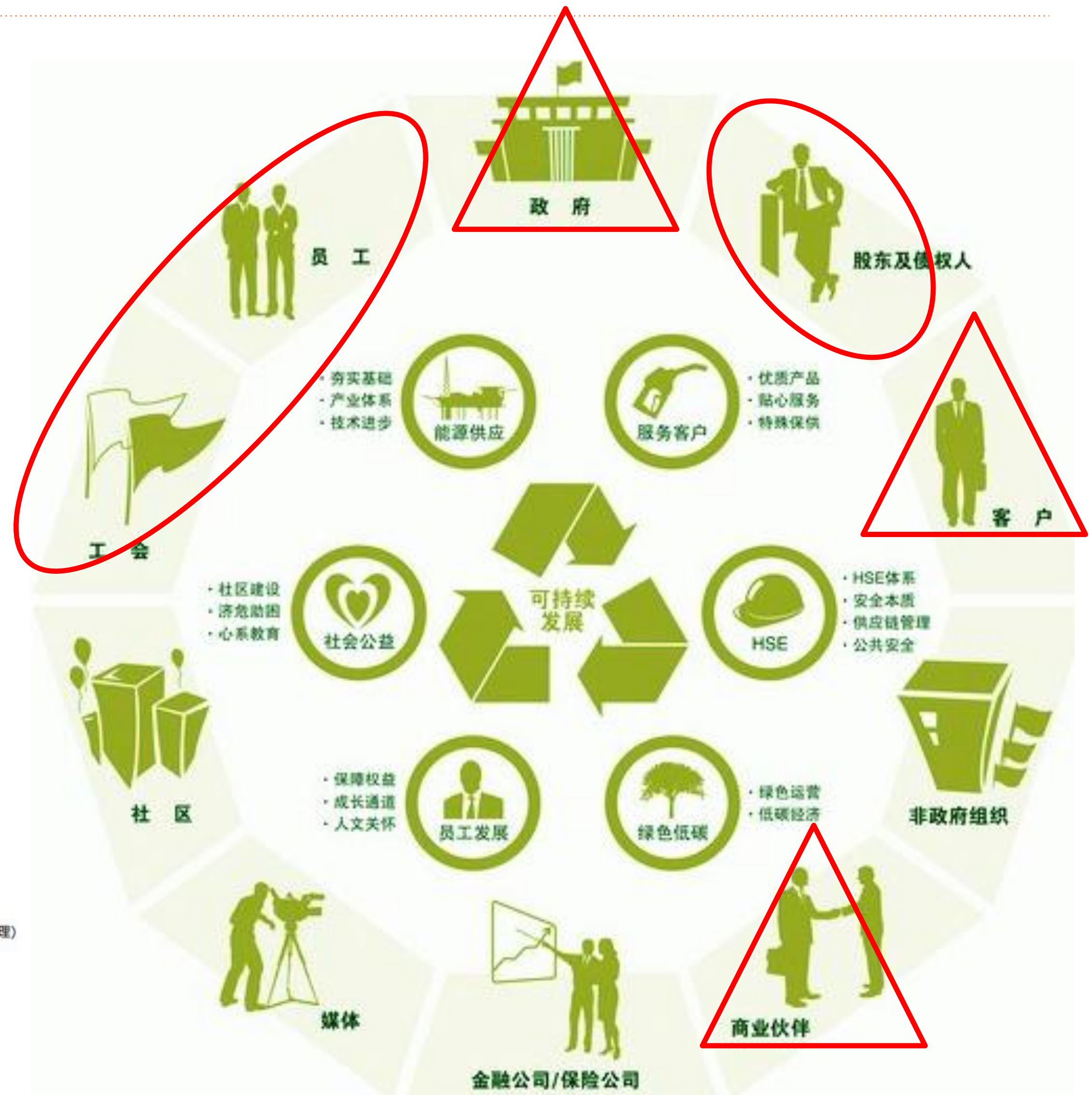
Significant recent reports and developments in corporate governance

两大理论争论的延伸


Capitalism literally means "accumulation of wealth".
On a finite planet, with finite resources, where do you think it can accumulate to some, if not from all the others?!
1%
Equality
Justice
Capitalism

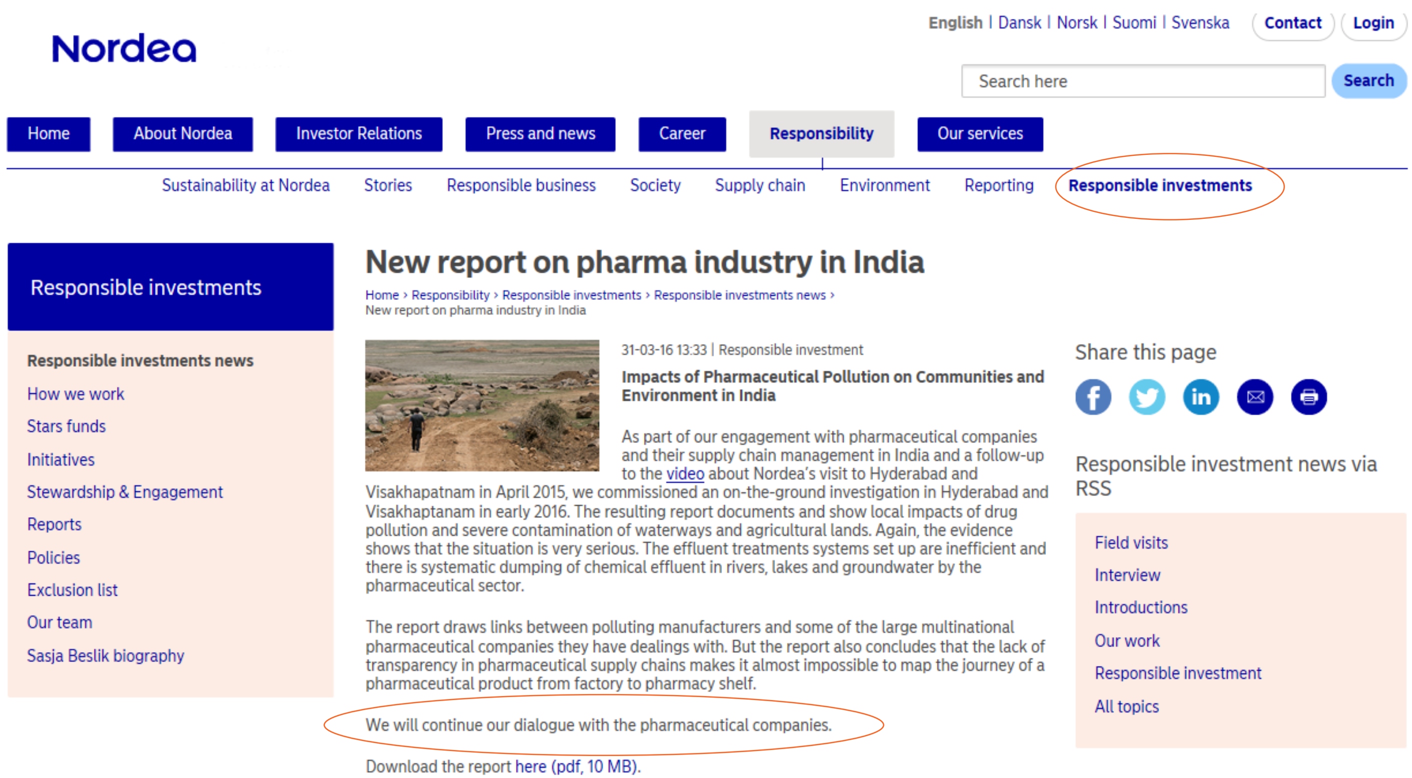

平等は正義を意味するものではない
平等
正義
Design
1373x766 122kb JPEG

善用利益相关方分析环境风险及解决问题



从股东层面分析 Nordea为何关注以及如何解决

- Nordea 关注印度制造型药企污染是本着利益相关方原则
- Nordea 通过对跨国公司药企施压是本着股东原则
- 跨国药企与印度制造型药企都是本着利益相关方原则里的关键直系合作伙伴关系通过敦促与被敦促，要求与被要求，帮扶与承诺提升达到最终解决问题的目的



Nordea

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Responsible investments

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- How we work
- Stars funds
- Initiatives
- Stewardship & Engagement
- Reports
- Policies
- Exclusion list
- Our team
- Sasja Beslik biography

New report on pharma industry in India

Home › Responsibility › Responsible investments › Responsible investments news › New report on pharma industry in India

31-03-16 13:33 | Responsible investment

Impacts of Pharmaceutical Pollution on Communities and Environment in India

As part of our engagement with pharmaceutical companies and their supply chain management in India and a follow-up to the video about Nordea's visit to Hyderabad and Visakhapatnam in April 2015, we commissioned an on-the-ground investigation in Hyderabad and Visakhaptanam in early 2016. The resulting report documents and show local impacts of drug pollution and severe contamination of waterways and agricultural lands. Again, the evidence shows that the situation is very serious. The effluent treatments systems set up are inefficient and there is systematic dumping of chemical effluent in rivers, lakes and groundwater by the pharmaceutical sector.

The report draws links between polluting manufacturers and some of the large multinational pharmaceutical companies they have dealings with. But the report also concludes that the lack of transparency in pharmaceutical supply chains makes it almost impossible to map the journey of a pharmaceutical product from factory to pharmacy shelf.

We will continue our dialogue with the pharmaceutical companies.

Download the report here (pdf, 10 MB).

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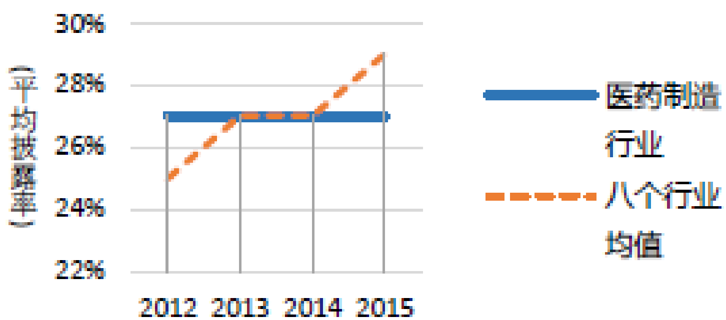
对股东负责：医药制造行业上市公司社会责任披露情况

医药制造行业沪深上市公司发布报告的平均披露率为 27%，略低于八个行业均值。



央企控股上市公司的披露水平最佳，平均披露率为 34%，其次为国有非央企，为 30%。

医药制造行业沪深上市公司对"推动和履行社会责任上的经济投入"指标的披露程度最高；对"机构产生和分配的直接经济价值"、"废气排放量及减排量"、"危险废弃物排放量及减排量"、"违反环境法规的次数及被处重大罚款金额""等七项指标的披露率保持逐年上升；所有 20 项关键定量指标均有企业进行了披露。

Source from: 商道纵横

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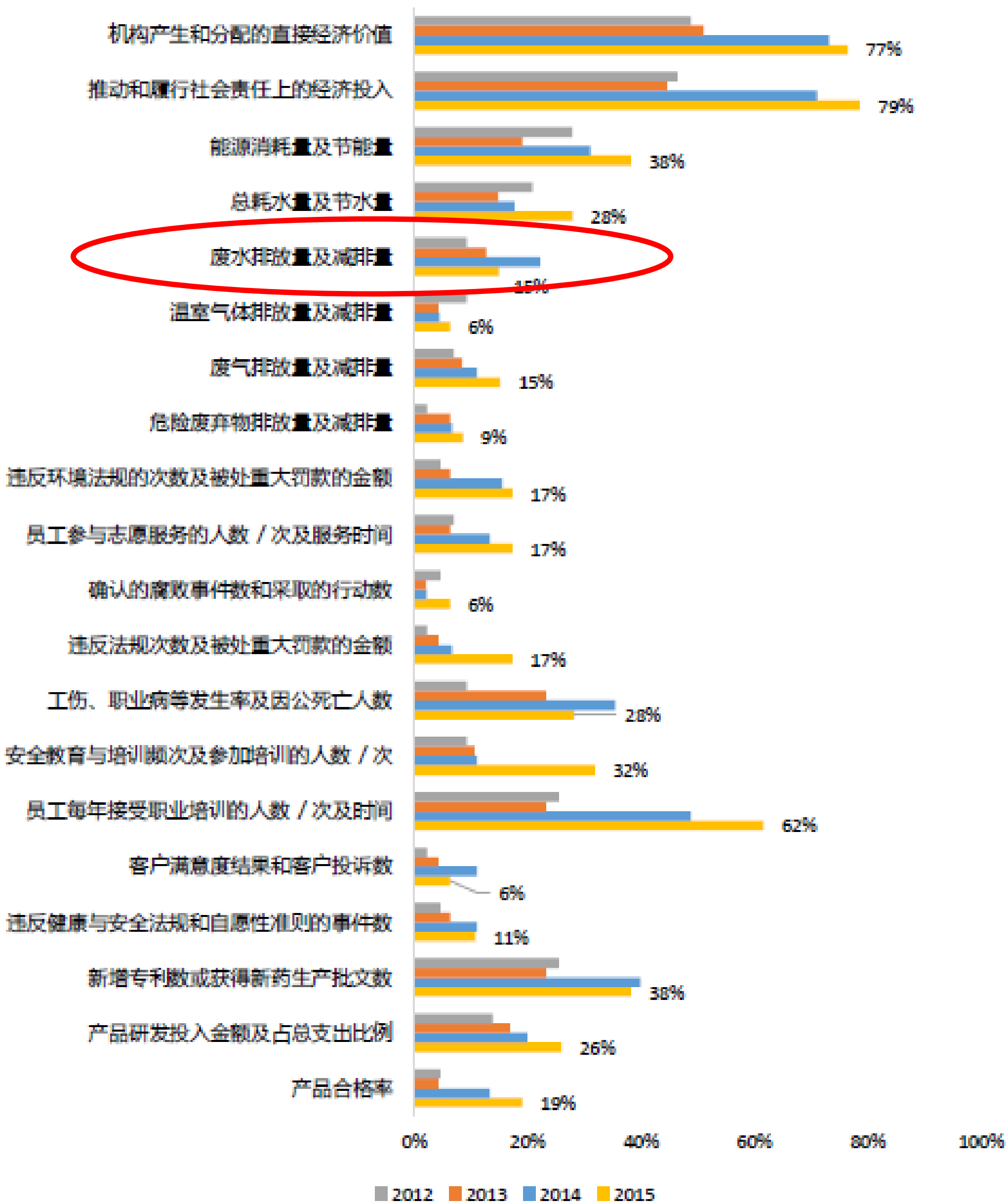

从内部员工EHS风险及企业内部关联管理说起

好的风险管理不单单包括反映在事后危机管理，也包含企业内部风控。好的风险**关联管理**体系往往也会反映在企业对员工人文关怀上

从外部利益相关方以及风险本身的特性看待中国制造型药企的环境风险

空气污染与G20“蓝”

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

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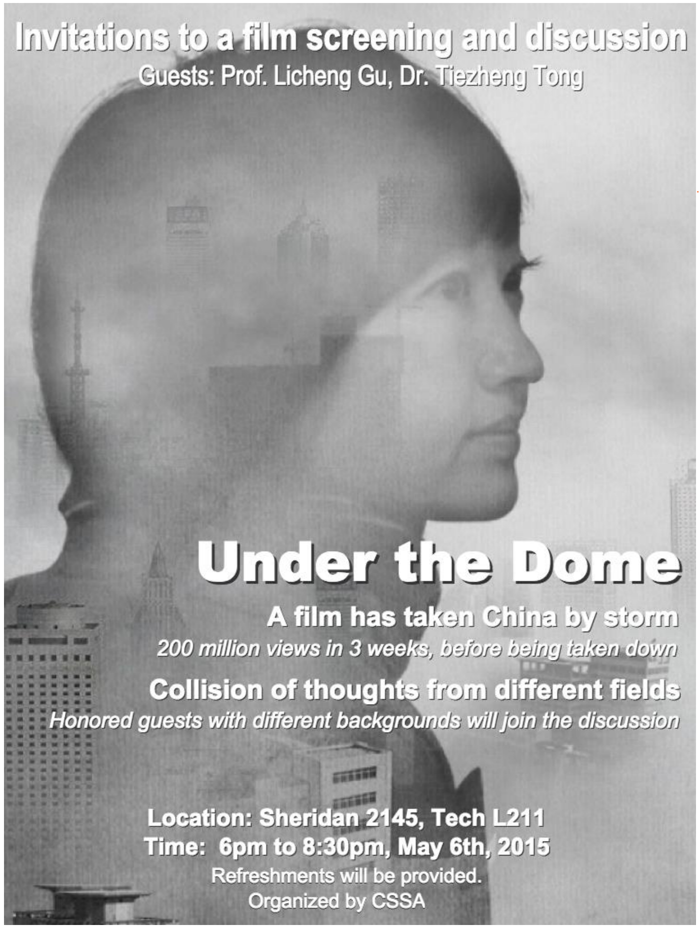
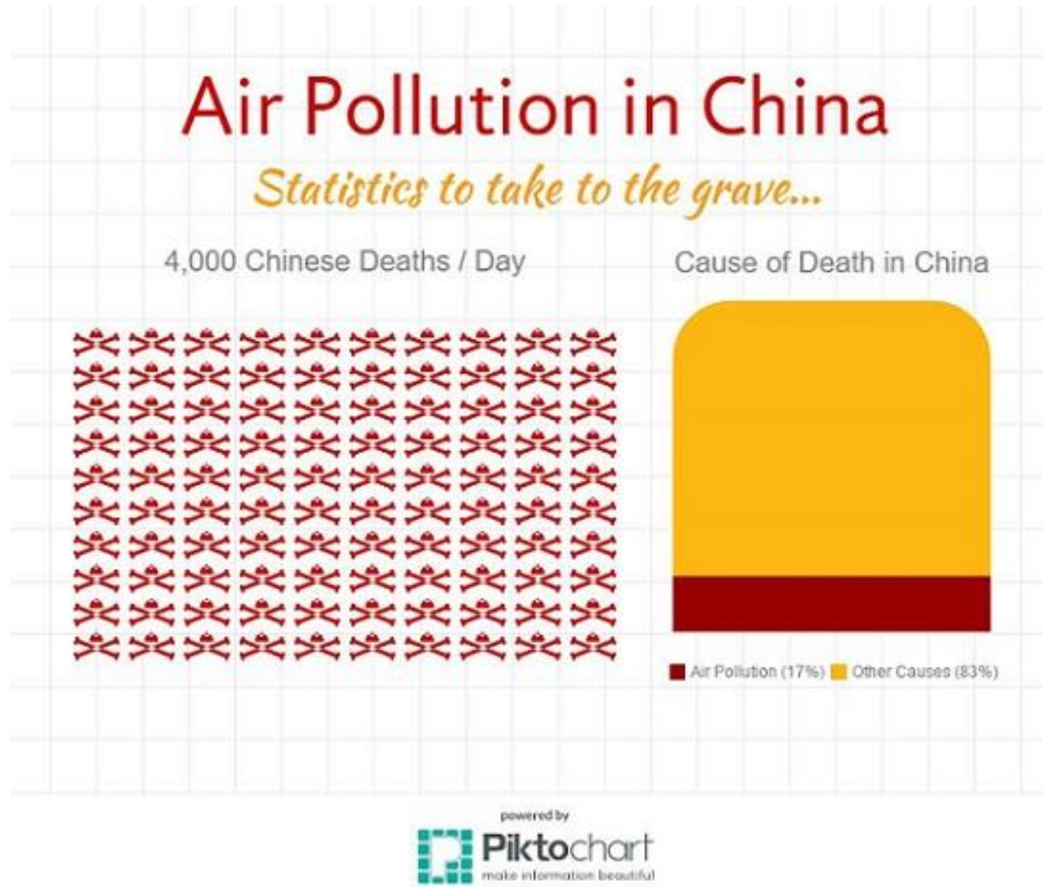




中国抗生素原料药厂污染频发，研究称世界知名药企助长危机

PSCI PHARMACEUTICAL SUPPLY CHAIN INITIATIVE | ACS Green Chemistry Institute® Pharmaceutical Roundtable | DEKRA Insight

TOP 10 TOTAL PHARMACEUTICAL MARKETS IN THE WORLD, 2005-16

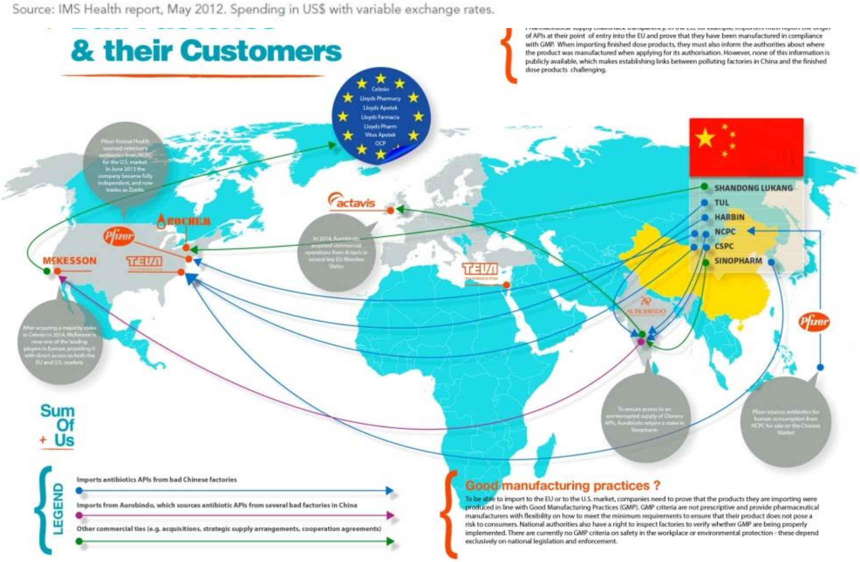
$Billion—all figures in US billion

	2005	2010	2016
Total	$496.1	$711.3	$812–$962
BRIC	$25.9	$96.6	$244–$284
BRIC %	5%	14%	30%

Rank (2005)	Size $B	Rank (2010)	Size $B	Rank (2016)	Size $B
1. USA	249.2	1. USA	322.0	1. USA	360–380
2. Japan	84.9	2. Japan	111.2	2. China (+1)	166–186
3. France	33.3	3. China (+8)	66.7	3. Japan (-1)	106–136
4. Germany	33.1	4. Germany	46.0	4. Brazil (+2)	42–62
5. Italy	21.3	5. France (-2)	41.3	5. Germany (-1)	39–49
6. UK	16.4	6. Brazil (+4)	29.9	6. France (-1)	32–42
7. Spain	16.1	7. Italy (-2)	28.6	7. Italy	23-33
8. Canada	16.9	8. Spain (-1)	22.7	8. India (+6)	24–34
9. China	14.1	9. Canada (-1)	22.4	9. Russia (+2)	23–33
10. Brazil	11.8	10. UK (-4)	21.6	10. Canada (-1)	19–29

Emerging markets　Placement movement

Source: IMS Health report, May 2012. Spending in US$ with variable exchange rates.



中国目前已经成为世界抗生素原料药最大的生产国和**出口国，供应全球90%的抗生素原料**药，全球原料药**市**场的三级供应链根植于中国，通过印度，再销售到**世界各地。**

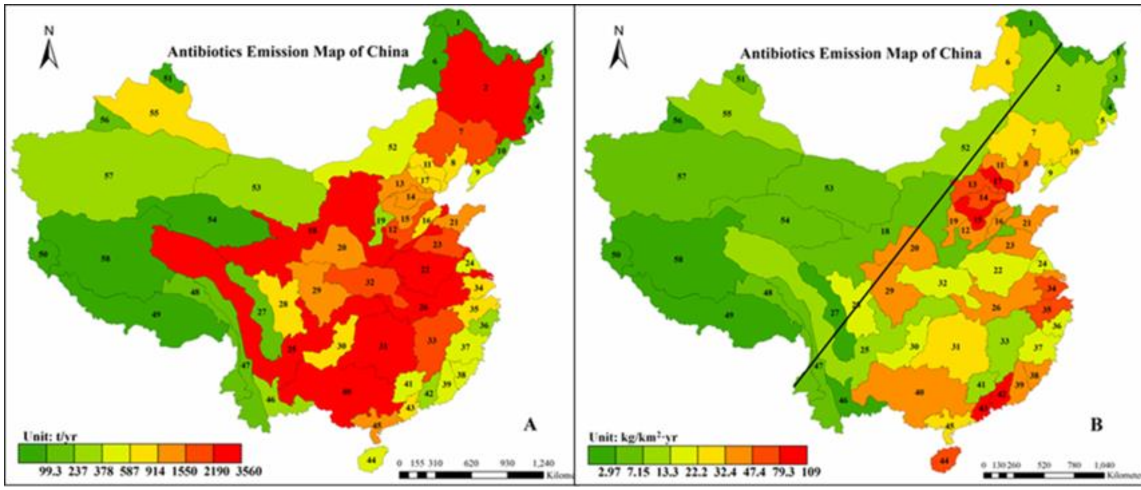
在2013年，中国抗生素产量达**12.12万吨，出口3.43万吨，，是中国原料**药出口规模最大的品种。与此同时，当年中国化学药品原料药制造利润总额为284.7亿**元，**利润率为7.45%，**同比增**长0.02%，**而行业**平均**水平**为10.13%。

而中国抗生素原料药制药工艺还在广泛使用的传统的**化学法，也**让其成为名副其实的“**双高**”（**高**污染、**高**环境风险）行业，如果发生非法排污现象，无疑会让细菌耐药性问题雪上加霜。

超级细菌一般指超级病菌，它是一种耐药性细菌，对绝大多数抗生素均不敏感，2010年，**英国媒体爆出印度**发现新型超级病菌——**新德里金属-β-内**酰胺酶1（简称NDM-1），**如果当地爆**发大规模的“**超级细菌**”传播事件，可能导致约**8万人死亡，抗生素**产生抗药性问题是医学界的“计时炸弹”。

中印是全球最大的两个抗生素生产商，只不过中国做**原料**药，印度做仿制药. **据外媒**报道，**很多印度制药厂的污水中，都检测出了“超级细菌”。它**们会通过水、**土壤、包括**动植物等感染途径进入人体。

抗生素归途：半随流水，
半入尘埃，中国首份抗生素污染地图



中国和发达国家抗生素使用量对比

国家	时间	总使用量(吨)	人用(吨)	兽用(吨)	千人抗生素日使用量
中国	2013	162000	77760	84240	157
英国	2013	1060	641	420	27.4
美国	2011/2012	17900	3290	14600	28.8

infzm.com

据澎湃新闻报道，复旦大学一项针对江苏、浙江、上海逾千名8至11岁在校儿童尿液检验研究显示，58%检出1种抗生素，1/4检出逾2种抗生素，有些样本甚至有6种抗生素。《生命时报》早前报道，北京儿童医院教授杨永弘说，在北京儿童医院，上世纪80年代的细菌耐药在10%以下，但是现在青霉素等耐药达到了70%甚至更高，非常惊人。

风险的定义与特性

RISK　　风险
危険

风=Wind
阝=Hill
佥=Sword

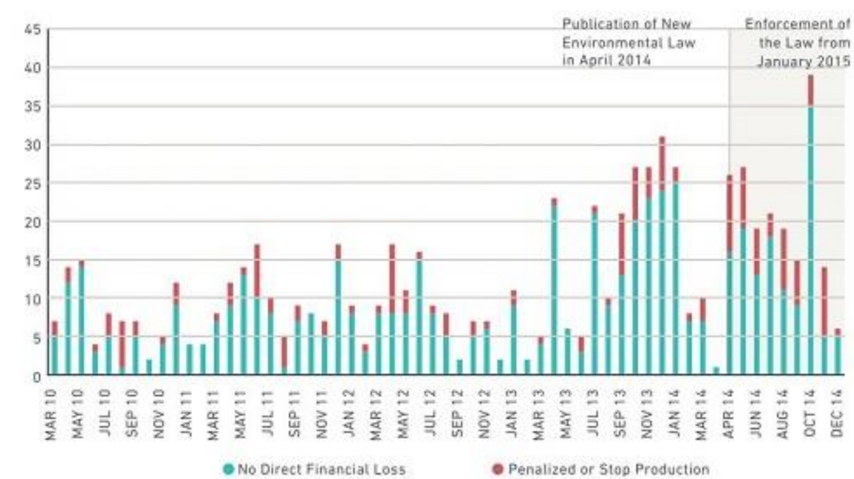
风 “Unpredictable” (what/when/how)
&
险 “Predictable”

风险性质 风险具有客观性、普遍性、**必然性**、**可识别性**、**可控性**、**损失性**、**不确定性**和**可转化性**。风险同时意味着机遇。

政府层面：日趋严厉的环保法规以及政府监管执法

- G20的天是蓝蓝的天；奥运会的天是蓝蓝的天 – 大量周边工厂被提前关闭歇业1-2个月
- 新的环境保护法严厉至极，环境执法日趋频繁严格
- 安全停业罚款往往与环保停业罚款相互关联

Environmental Regulatory Violations, 2010-2014

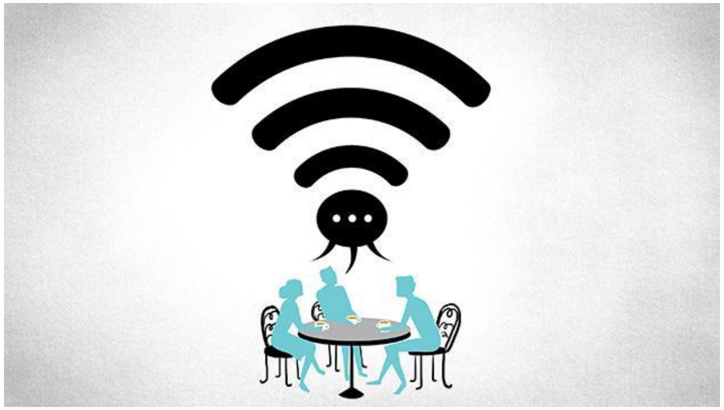


Scope: MSCI China Index constituents as of April 2015
Sources: MSCI ESG Research, Institute for Public and Environmental Affairs database

2015年因环保限产停产案件分布

消费者，社区，公众，媒体，NGO的高速进化，高度团结及高科技联姻

- 消费者，社区与公众角色的多重与互换性
- 媒体与NGO意识到以消费者，社区及公众利益为向导的重要性
- 广大民众对自身利益高度关注以及对相关领域知识的快速提升：PM10与PM2.5，PX项目
- 互联网的开放性与公正性：负面信息可以随时被检索和公开，并且不可去除
- 微博，微信以及手机软件应用被广泛应用，从而使得环保负面信息被实时，无缝，高速，几何级传播。



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- 认知-意识提高
- 数据-信息公开
- 追溯-源头透明
- 反应-联合抵制

五点如何更好的搭建“刹车装置”的建议

- **引进：**1. 主动引进国际资本或者积极推动国际合作（供应），从而学习强化国际环保标准和管理理念。积极引进先进生产设备和工艺理念，减低甚至去除污染，排放与高危化学品的生产与使用
- **推动：**积极推动内部高级EHS人才的招聘，培养和晋升，视EHS为高层高级管理人才，向高层直接汇报。推动全员参与EHS管理的理念
- **公示：** 积极公示EHS环保管理信息数据，组建CSR或者EHS风控委员会，撰写CSR报告，定期向股东回报，并接受全社会监督
- **沟通：** 积极与社区及周边民众互动，沟通，公示，加强民众监管以及管理参与
- **监管：** 加强对下游供应商的环保监督与管理，与符合标准和要求的供应商开展战略合作

- 对大型药企的新时代要求，价格不是唯一要求甚至也不应是第一要求。

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对于环境职业健康安全专业人才的几点建议

- HSE vs. SHE vs. EHS
- 确保环境合规的最低要求
- 分析理清自己所在企业基于产品生产及企业现状最大的环境安全风险是什么
- 改变自己的管理团队中所处的汇报层级，环境安全管理委员会应该直接向最高领导人一级汇报
- 清楚认知，环境职业健康安全问题不是一个人的问题和责任，需要调动全员意识形态的转变，全员互动参与
- 善用工具，会讲“故事”


thank you
danke
рахмат
謝謝
ngiyabonga
teşekkür ederim
Баярлалаа
спасибо
faafetai lava
mersi
barka
welalin
tack
dank je
misaotra
matondo
paldies
gracias
tapadh leat
mahalo
хвала
asante
manana
vinaka
blagodaram
kiitos
dankie
dhanyavad
hvala
maururu
köszönöm
bedankt
enkosi
dziękuje
chnorakaloutioun
gràcies
sulpáy
go raibh maith agat
mochchakkeram
djiere dieuf
mamnun
murakoze
sukriya
kop khun krap
obrigado
dėkui
mèsi
sagolun
najis tuke
kam sah hamnida
terima kasih
ありがとう
tanemirt
grazie
rahmet
arigatô
takk
dakujem
trugarez
shukriya
мерси
diolch
dhanyavadagalu
감사합니다
xièxie
ευχαριστώ
merci

PSCI

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BREAK

中国及亚太区 EHS 法规更新
PSCI Conference

2016-09-22

Presented By: Ellen Zhang,
资深EHS法规顾问,
亚太区客户关系经理

enhesa
Worldwide Compliance Intelligence

演讲者:

Ellen Zhang 张赟

- **超过10年EHS法**规咨询服务经验
- **大中**华区合规审核和其他项目**开展**经验

比利时鲁汶大学环境能源法硕士

中国律师执业资格

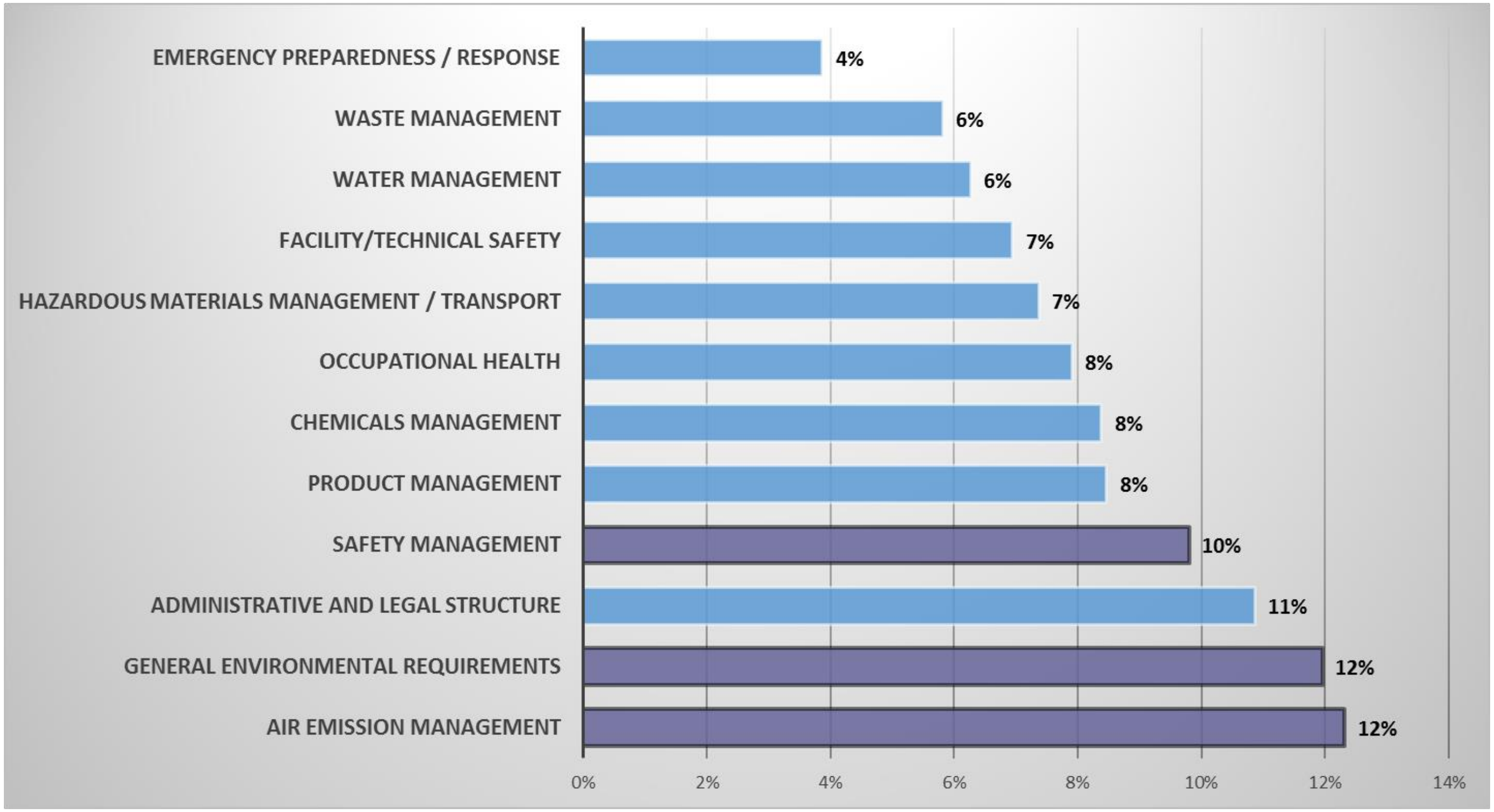
日程: 中国及亚太EHS法规更新

今天我们将讨论:

- 中国EHS法规概述
- **近期中国**环境法规更新
- **近期中国**职业健康及安全法规更新
- **相关法律法**规实施及执法情况
- 亚太地区法规更新

中国EHS法规概述

EHS及产品相关法规: 2011-2015走势



中国EHS法规概述

- 法律层级

Constitution

宪法(NPC)

Laws (法律：法)

(NPC & its Standing Committee)

Administrative Regulations

(行政法规：条例，规定) (State Council)

Local Regulations (地方法规)

(Local Government)

Rules (规章) (State Council Department Rules and Local Government Rules 国务院部门规章及地方政府规章)：管理规定，管理办法

Overview of China EHS Regulation

- 标准

中国的标准分为国家标准,**地方**标准以及行业标准。

标准有强制性标准，**推荐性**标准和自愿性标准。**自愿性**标准如果在强制性的法规中引用，**那么也**变为强制。

- **国家**标准批准发布公告**2016年第XX号**
- **生物工程**类制药工业水污染物排放标准 GB 21907-2008
- **上海市大气**污染物综合排放标准 DB31/933—2015
- **制**药企业职业危害防护规范 AQ/T 4255-2015

环境管理主要制度

- 环境影响评价
- “三同时”
- 试生产
- 建设项目竣工验收
- 总量控制
- 排污许可证
- 排污申报
- 排污费 – 环境税

中国EHS法规概述

安全生产方面的主要制度

- “三同时”
- 生产许可证
- 安全生产责任制
- 安全人员，安全委员会， 安全管理人员
- 培训

职业卫生方面的主要制度

- 三同时
- 职业病危害申报
- 职业病危害监控
- 体检

环境相关法律法规更新

环境保护法更新


CCTV 13
新闻
CNTV
山东临沂 打击环境违法·环保部督查行动
新闻直播间 半数抽查企业在线监测形同虚设
10:32 行后，顺利返回地球，落入太平洋。发射现场


CCTV 13
新闻
CNTV
山东临沂 打击环境违法·环保部督查行动
污染多发 偷排漏排情况严重


CCTV 13
新闻
新闻直播间


CCTV 13
新闻
CNTV
资料
山东临沂 打击环境违法·环保部督查行动
新闻直播间 北方焦化：漏洞百出的环保设施

环境保护法更新要点

综合并加强一系列环境保护制度

- **加强企业责任**
- **保护公众环境权利及利益**
- **强化环境相关违法的处罚**
- **改善环境保护制度**

环境保护法更新要点

- **加强企业责任**
  - 责任制: **需要明确**单位负责人和相关人员的责任
  - 对建设项目的要求：**没有**环评的后果

- **保护公众环境权利及利益** -
  - 环境公益诉讼
  - **公众参与 – 公众有**权利获得相关环境信息，**参加并**监督环境保护活动

环境保护法更新要点

- **改善环境保护制度**
  - 排污许可证制度
  - 排污费制度
  - 清洁生产制度
  - 减排制度

- **强化环境相关违法的处罚**
  - 每日续罚
  - 查封，扣押排放污染物的设施、设备
  - 限制生产或停产整治
  - 行政拘留

环境影响评价法更新要点

- **未批先建**处罚力度可能大大增加
  - **最高不超过20万** ⟶ **建**设项目投资额 1%-5%
- 环境影响登记表无需审批，**只需要**备案
- 删去对于涉及水土保持的建设项目需要对水土保持方案审查同**意的要求**

危险废弃物名录更新 – 2016版

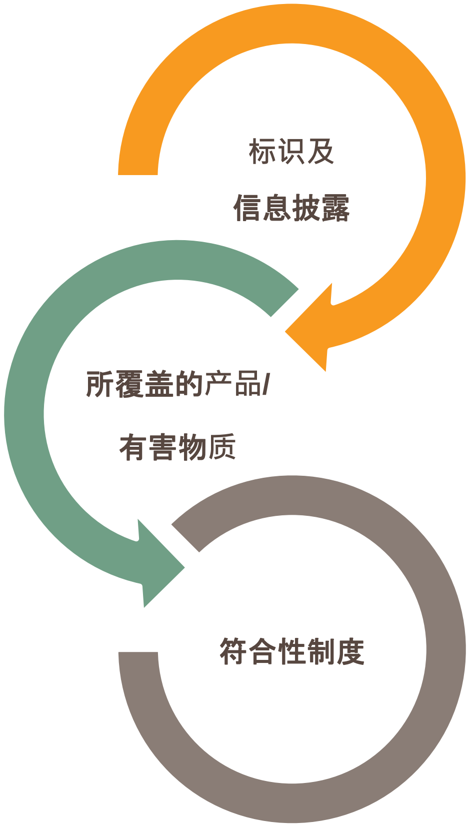
主要变化点:

- 危险废物调整为46大类别479种（其中362种来自原名录，新增117种）；
- 认定废弃的危险化学品即危险废弃物
- 生物制药废物方面的修改
- 增加了《危险废物豁免管理清单》

危险废物豁免管理清单

序号	废物类别/代码	危险废物	豁免环节	豁免条件	豁免内容
1	家庭源危险废物	家庭日常生活中产生的废药品及其包装物、废杀虫剂和消毒剂及其包装物、废油漆和溶剂及其包装物、废矿物油及其包装物、废胶片及废像纸、废荧光灯管、废温度计、废血压计、废镍镉电池和氧化汞电池以及电子类危险废物等	全部环节	未分类收集。	全过程不按危险废物管理。
			收集	分类收集。	收集过程不按危险废物管理。

- 电器电子产品有害物质限制使用管理办法 (China RoHS II)



FAQ

China RoHS II FAQ

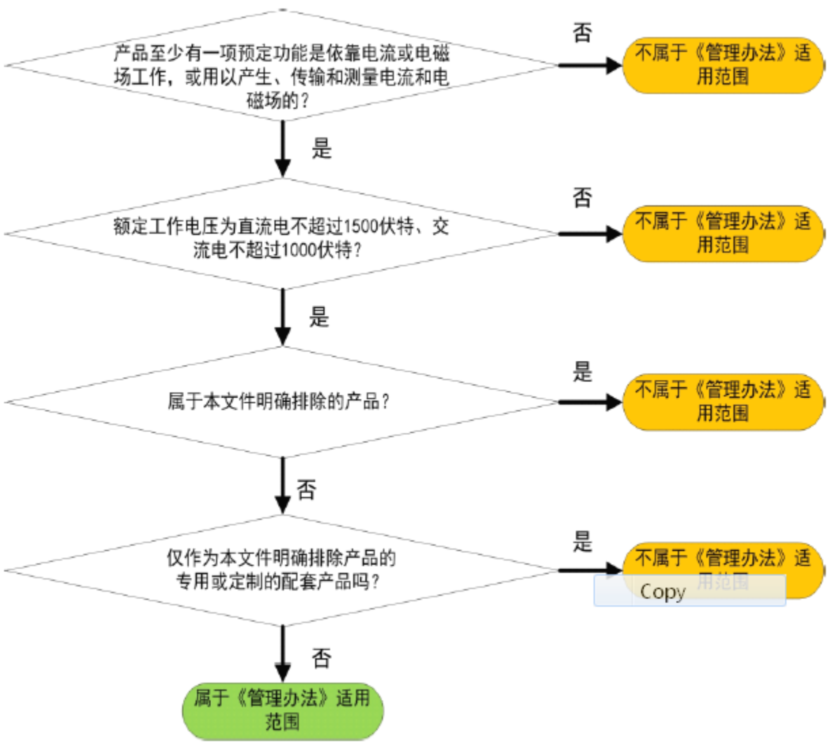
- 生效日期 – 2016年7月1日
  - 生产日期还是投放市场的日期?

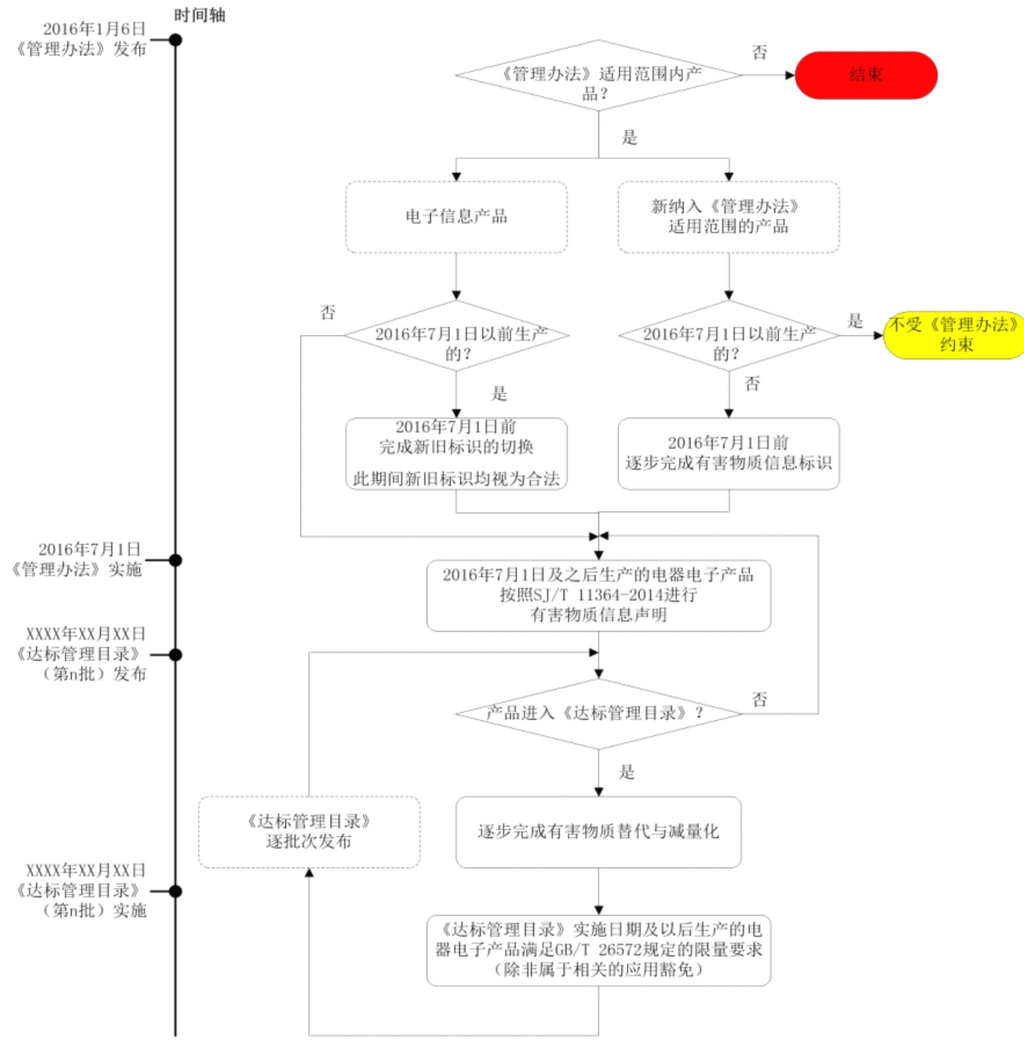
- **豁免范**围
  - **不在中国市**场销售的产品: **出口的**产品，仅供展览的产品，实验用途的产品，进口仅作修理的产品;
  - **用于**军事用途的电器电子设备
  - **在极端和特殊**环境下使用的电器电子设备;
  - **涉及**电能生产、传输和分配的设备，**如**发电厂、输配电站、**建筑物供配**电所**用的系**统及设备。

- 问题:

  海外母公司将电器电子产品转卖给在中国的子公司时是否需要满足《**管理**办法》**的要求**

China RoHS II FAQ





职业卫生安全法规更新

enhesa
Worldwide Compliance Intelligence

职业病危害治理“十三五”专项规划 （草案）

挑战

- 职业病危害依然严重（医药行业）；
- 职业病危害治理基础薄弱；
- **用人**单位职业病危害治理主体责任不落实
- 劳动者自我保护意识不强
- **老矛盾尚未解决**，**新**问题不断出现

Goals:

——职业病危害严重的行业领域用人单位职业病危害项目申报率达到85%以上。

——职业病危害严重的行业领域用人单位工作场所职业病危害因素定期检测率达到80%以上。

——职业病危害严重的行业领域劳动者在岗期间的职业健康检查率达到90%以上。

——职业病危害严重的行业领域用人单位主要负责人和职业卫生管理人员的职业卫生培训率分别达到95%以上。

——各级人民政府建立完善、专业的职业卫生监管执法队伍，建立职业病防治目标和责任考核体系。

主要任务

- **完善**职业卫生法规标准和政策体系.
- **健全**职业卫生监管体制
- **加强**职业卫生监管能力
- **提升用人**单位职业病危害防治能力
- **推进**职业卫生监管信息化建设;
- 强化科技创新和技术支撑体系建设
- **加强**职业病危害的源头治理

职业病防治法修正

- **新建**、扩建、**改建建**设项目和技术改造、**技**术引进项目**(下称建**设项**目)可能**产生职业病危害的，**建**设单位在可行性论证阶段应当进行职业病危害预评价，**但**职业病危害预评价报告不再需要审核

- **建**设项目的职业病防护设施设计应当符合国家职业卫生标准和卫生要**求**，**但不再需要得到**卫生行政部门审查同意

- **建**设项目在竣工验收前，**建**设单位应当进行职业病危害控制效果评**价。增加一款**，**作**为第四款：**医**疗机构可能产生放射性职业病危害的**建**设项目竣工验收时，**其放射性**职业病防护设施经卫生行政部门验收**合格后**，**方可投入使用;其他建**设项目的职业病防护设施应当由建设单位负责依法组织验收，验收合格后，**方可投入生**产和使用。**安全生**产监督管理部门应当加强对建设单位组织的验收活动和验收结果的监**督核**查。

近期法规实施执行情况

Worldwide Compliance Intelligence

安全生产监督检查随机抽查重点事项清单

- 此份《清单》提供了安全生产监督检查随机抽查的重点事项，以及相关法律、行政法规、部门规章及国家标准、行业标准依据。《清单》中包括
  - 安全生产随机抽查综合事项
  - 职业卫生随机抽查综合事项
  - 各种行业随机抽查重点事项

序号	抽查对象	抽查事项	抽查依据	抽查主体	备注
1	生产经营单位（下同）	安全生产责任制和安全生产规章制度、操作规程制定、执行和适时修改情况	《安全生产法》第十八条	各级安全监管部门	
2		安全投入及劳动防护用品经费、安全培训经费保障情况	《安全生产法》第十八条、第二十条	各级安全监管部门	
3		安全生产管理机构设置、安全生产管理人员配备情况	《安全生产法》第二十一条	各级安全监管部门	
4		从业人员安全生产教育和培训计划、实施及档案管理情况	《安全生产法》第十八条、第二十四条、第二十五条、第二十六条；《生产经营单位安全培训规定》（国家安全监管总局令第 3 号）、《安全生产培训管理办法》（国家安全监管总局令第 44 号）	各级安全监管部门	
5		特种作业人员持证上岗、培训及档案情况	《安全生产法》第二十七条；《生产经营单位安全培训规定》（国家安全监管总局令第 3 号）、《特种作业人员安全技术培训考核管理规定》（国家安全监管总局令第 30 号）《安全生产培训管理办法》（国家安全监管总局	各级安全监管部门	

建设项目环境保护事中事后监督管理办法(试行)

事中监督 - **建**设项目自办理环境影响评价手续后到正式投
入生产或使用期间:

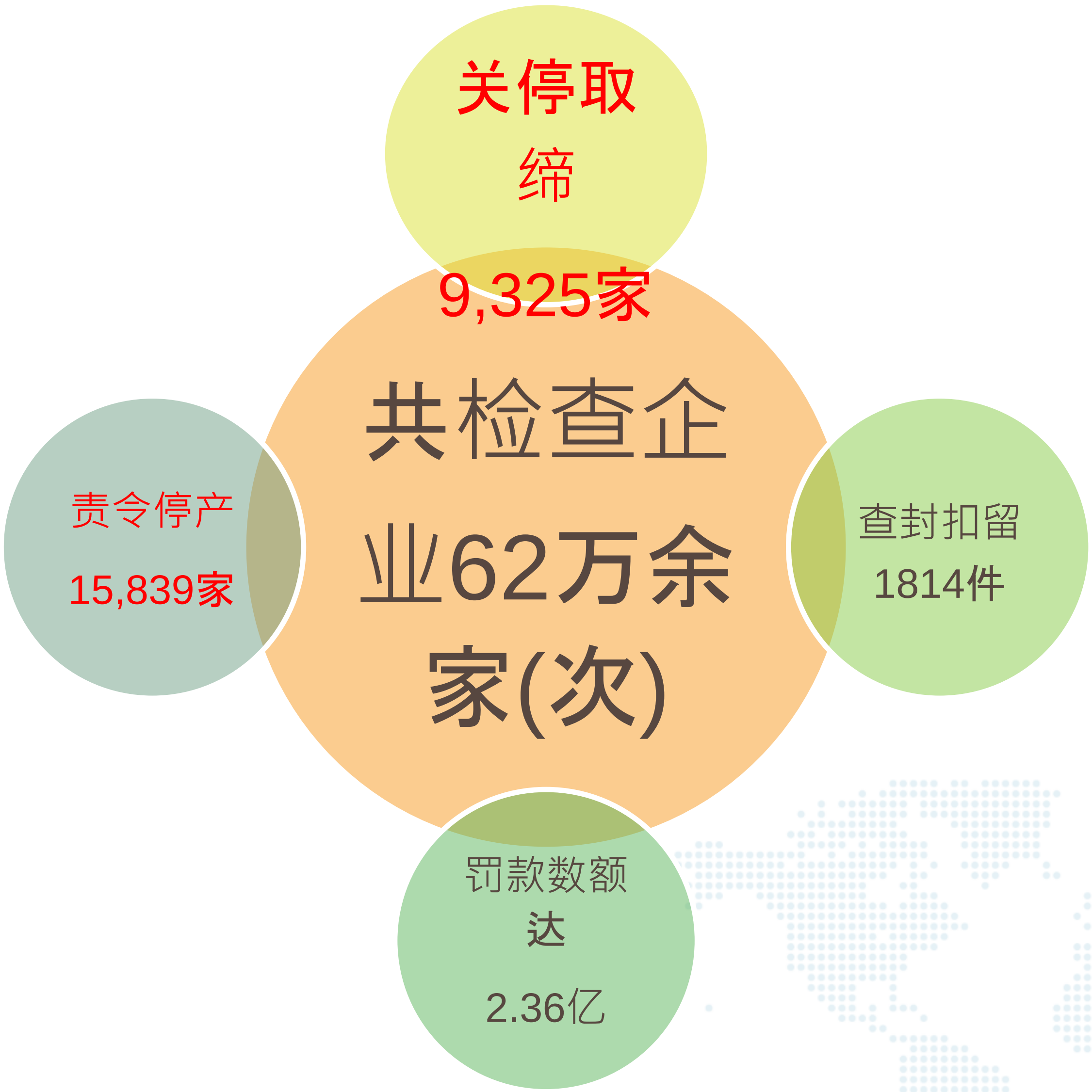
- 经批准的环境影响评价文件及批复中提出的环境保护措施落实情况和公开情况；
- **竣工**环境保护验收和排污许可证的实施情况；
- 环境保护法律法规的遵守情况和环境保护部门做出的行政处罚决定落实情况。

事后监督 -**建**设项目正式投入生产或使用后:

- **生**产经营单位遵守环境保护法律**、法**规的情况进行监督管理；
- 产生长期性、**累**积性和不确定性环境影响的水利、**水**电、**采掘**、**港口**、铁路、**冶金**、**石化**、**化工以及核**设施、**核技**术利用和铀矿冶等编制环境影响报告书的建设项目，**生**产经营单位开展环**境影响后**评价及落实相应改进措施的情况。

关于加强环境监管执法的通知

《环境保护法》修正后的法规执行情况 (2015上半年数据)



《环境保护法》修正后的法规执行情况 (2016年第一季度数据)

涉嫌环境污染犯罪案件265件

浙江
广东
福建

江西 河南 安徽
湖南 陕西 新疆

限产、停产案件共301件

扣押案件665件

罚款数额达1.15亿

最高人民法院关于审理环境侵权责任纠纷案件适用法律若干问题的解释

- **因**污染环境造成损害，**不**论污染者有无过错，污染者应当承担侵权责**任**
- **两个以上**污染者共同实施污染行为造成损害，**承担**连带责任
- **两个以上**污染者分别实施污染行为造成同一损害，责任承担按不同情**况判断**
- **两个以上**污染者共同或者分别实施污染环境行为造成损害，**需要确定**污染者之间责任大小的，**人民法院**应当根据污染物的种类、**排放量、危害性以及有无排**污许可证、**是否超**过污染物排放标准、**是否超**过重**点**污染物排放总量控制指标等因素确定。**因**污染环境造成损害的，污**染者以排**污符合国家或者地方污染物排放标准为由主张不承担责任**的，人民法院不予支持。**
- 污染者在生效裁判确定的期限内未履行环境修复义务的，**人民法院可以委托其他人**进行环境修复，**所需**费用由污染者承担

环境公益诉讼

《**最高人民法院关于**审理环境民事公益诉讼案件适用法律若干问题的解释》

案例 1

最高人民法院驳回6家化学品公司上诉，维持原判，责其承担1.6亿环境修复费用

案例 1


江苏城市
案件聚焦:高院院长亲审泰州...
400x300
高院院长亲审泰州天价环境公益诉讼案


江苏公共
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疯狂槽罐车 工业废酸偷排长江连续多年
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LIVE
《有一说一》播出时间：19：00—20:00 复播时间为00:35-01:35《有一


江苏公共
优酷
头 条
疯狂槽罐车 工业废酸偷排长江连续多年
LIVE

案例 1

环境修复费: 1.6亿人民币

环境责任: 污染者 v. 废酸处理厂商

污染者责任: 环境修复费用

案例 1

经过：

- 2012年1月至2013年2月，被告江苏常隆农化有限公司（以下简称常隆公司）、锦汇公司、江苏施美康药业股份有限公司（以下简称施美康公司）、泰兴市申龙化工有限公司、泰兴市富安化工有限公司、泰兴市臻庆化工有限公司等 6 家企业将生产过程中产生的危险废物废盐酸、废硫酸总计2.5万余吨，以每吨20-100元不等的价格，交给无危险废物处理资质的企业偷排进泰兴市如泰运河、泰州市高港区古马干河中，导致水体严重污染。泰州市环保联合会诉请法院判令 6 家企业赔偿环境修复费1.6亿余元、鉴定评估费用10万元。

判决情况：

2014年10月,泰州市中级人民法院一审判决6家公司承担1.6亿环境修复费

6家公司不服判决上诉到江苏省高级人民法院，江苏省高院维持原判；

2016年1月，中国最高人民法院终审判决维持原判

主要争论点：

环境修复费用如何确定？

泰州市环保联合会是否是适格原告？

这些化学品公司是不是造成污染的单位？

案例 2

按日续罚案例

经过:

2015年1月5日，临沂环保监测站在对临沂华龙热电有限公司进行环境监测时发现二氧化硫和氮氧化物排放超标。**1月9日**，临沂环保局做出处罚**10万元的决定。1月19日再次**检测时发现，**二氧化硫仍超**标排放。

处理结果：

1月23日，临沂环保局根据按日续罚的规定，对临沂华龙热电有限公司**做出**处罚100**万元的决定**。

案例 3

行政拘留案例

经过：

2015年1月27日，**深圳市**环保局对深圳市恒进五金制品有限公司进行了环境监察，发现其超标工业废水在没有任何处理的情况下直接排入市政污水管道。

处理结果：

公司被停产整治，罚款**20万元**，**排**污设施被查封、**扣押**。**同**时其直接负责的主管人员和直接责任人员面临最高**15日的行政拘留**处罚。

环境污染的刑事罪名

- **重大**环境污染事故罪
- **非法**处置进口的固体废物罪
- **擅自**进口固体废物罪
- **走私固体**废物罪
- 污染环境罪

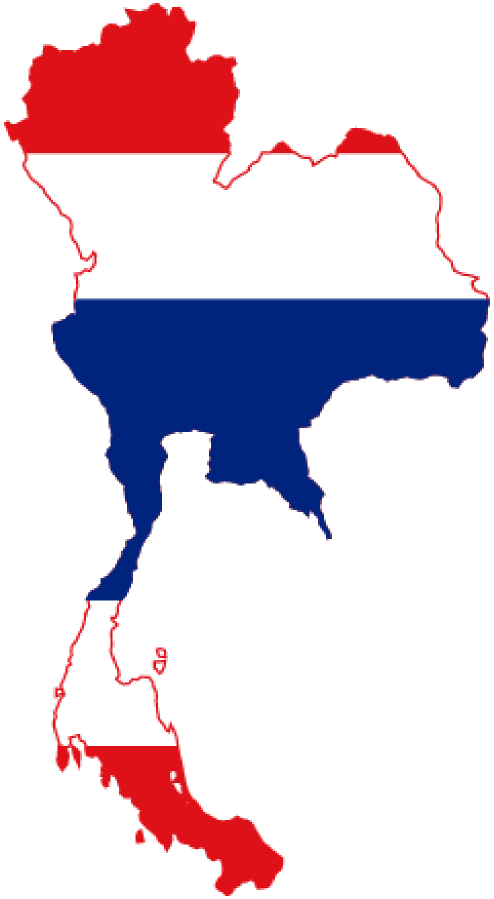
刑事责任

- **刑事责任的解释**
- **一个犯罪行**为同时触犯多项罪名时应按“**从一重罪**处断原则”,**即同**时构成污染环境罪、**非法**处置进口的固体废物罪、**投放危**险**物**质罪的,**依照**处罚较重的犯罪定罪处罚。

- **谁需要附刑事责任?**
- 单位犯罪的，对单位判处罚金，**并**对其直接负责的主管人员和**其他直接**责任人员判处刑罚

亚太地区法规更新

化学品管理：泰国



跨国化学品管理数据库

- 东南亚国家联盟 (ASEAN) – 日本化学品安全数据库 (AJCSD)
- 规管化学物质及危害
- 东盟信息共享

化学品管理：日本

综合化学品管理系统–chemSHERPA

- 主流法规及标准: 日本,美国,欧盟
- 涵盖5000个化学品的清单
- 2018年起全面实行

化学品管理：韩国

《韩国化学品注册与评估法案》(K-REACH) 对医药品的适用性：

- 2015年初，当K-REACH刚刚实施的时候，对于一些医药品原材料是否适用K-REACH的规定在医药企业内产生了很大的争论: 医药企业认为医药品原材料应该适用《药事法》，而非K-REACH.
- 2015年底，食品医药品安全厅与环境保护部以及食品和药品安全部进行了深入讨论 。2016年初告知医药企业被确认为原料医药品的中间体或有效成分出发物质的的医药品原材料不适用K-REACH

产品法规：印尼

- **关于清真**产品的法令 No. 33 of 2014 **要求在此法令生效5年后**需要药品也采用清真证书“Halal Certificate”。

- **至今**为止，**此**项要求非常有争议，对于药品的这个规定将非常难实施。

Q&A

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PSCI

PHARMACEUTICAL SUPPLY CHAIN INITIATIVE

ACS Green Chemistry Institute®
Pharmaceutical Roundtable

DEKRA Insight

The Pharmaceutical Supply Chain Initiative – Closing Remarks

Presented by

Julie Brautigam

Head of Procurement, Risk, Sustainability & Performance

Takeda Pharmaceuticals

Vice-Chair, PSCI

A lot has happened in three days!

We have learned many things about many topics on safety, environment, ethics and labor

We have had time to connect and network, ask questions….

Now it is time to take this investment and apply it at your sites; focus on continual improvement.

What we do together to improve our EHS, Labor, Ethics in our supply chain has an impact, for our business, our communities, and our patients

Together, we can make a difference.

Supplier Resources – After the event

Resource library

Our supplier resource library is available at

www.pscinitiative.org/resources

Training / capability-building events

We will be posting information about training/capacity building events on key issues for suppliers

Webinar

- On current topics impacting our industry (example, pharmaceuticals in the environment)

Supplier Conference

- To support technical capacity building

Watch our website for details

How can you get involved?

- Join PSCI and collaborate with us to further improve the pharmaceutical supply chain (for more information contact info@pscinitiative.org)
- Go to the PSCI website and use the tools in the Resource Library to make improvements
- Participate in upcoming supplier capability building events
- Give us your feedback on this event, so that we can improve future events

The Pharmaceutical Supply Chain Initiative

Thank you for active participation this week!

Need more information?

Visit: www.pscinitiative.org

Email: the PSCI Secretariat at info@pscinitiative.org

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END OF DAY 3