About OMICS Group

OMICS Group International is an amalgamation of Open Access publications and worldwide international science conferences and events. Established in the year 2007 with the sole aim of making the information on Sciences and technology 'Open Access', OMICS Group publishes 400 online open access scholarly journals in all aspects of Science, Engineering, Management and Technology journals. OMICS Group has been instrumental in taking the knowledge on Science & technology to the doorsteps of ordinary men and women. Research Scholars, Students, Libraries, Educational Institutions, Research centers and the industry are main stakeholders that benefitted greatly from this knowledge dissemination. OMICS Group also organizes 300 International conferences annually across the globe, where knowledge transfer takes place through debates, round table discussions, poster presentations, workshops, symposia and exhibitions.

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About OMICS Group Conferences

OMICS Group International is a pioneer and leading science event organizer, which publishes around 400 open access journals and conducts over 300 Medical, Clinical, Engineering, Life Sciences, Phrama scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

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Globalization of Green Chemistry Within the Pharmaceutical Industry – Advancements and Opportunities



Ingrid Mergelsberg

Merck Process Chemistry, Merck & Co., Inc., Whitehouse Station, NJ, USA

International Summit on Past and Present Research Systems of Green Chemistry
August 25-27, 2014, Philadelphia, PA, USA

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What Is a Sustainable Future?



Social



Economic



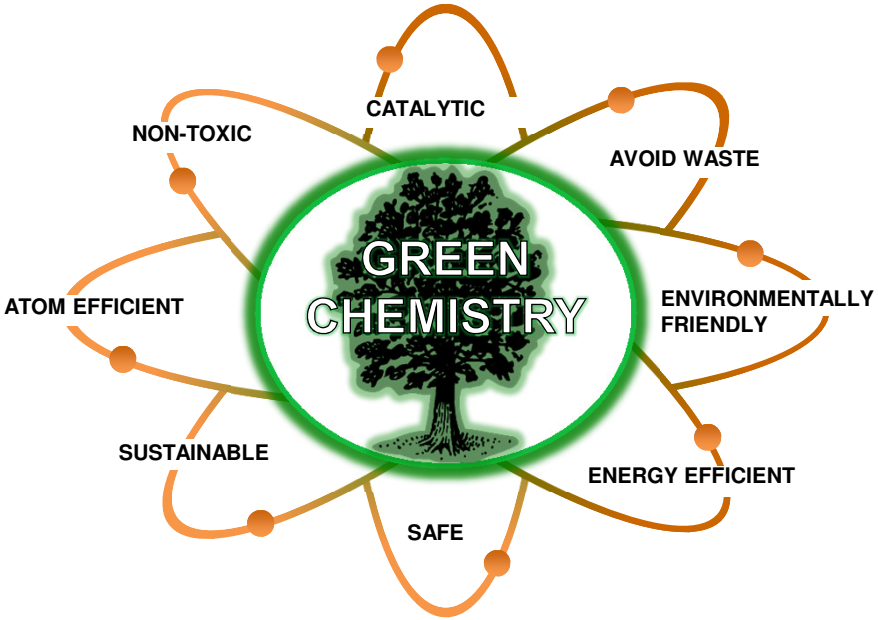
Environmental

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

Balance Social, Environmental and Economic Needs
Globally and Across Generations

What Is Green Chemistry?

It is the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances/wastes, create inherently safer processes, and increase process efficiency while – overall – minimizing the environmental footprint and impact.



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

If we focus on developing the ***best chemistry***, then almost always, this leads to the lowest cost and ***greenest*** process.

Source: City University of Hong Kong

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Education



The Green Chemistry Track in the Chemistry PhD Program at UMass Boston was established in 2002. It is the first such program in the world. Students obtaining a degree from this program will be prepared for conventional chemistry jobs in industry, government and academia. Green chemistry involves an ecologically sustainable view of chemical research, development, and manufacture. Toxicological understanding and environmental fate are necessary components to understanding the entire "molecular life cycle" of any commercial endeavor. The unique complement of chemistry, EEOS and biology department faculty has allowed the University of Massachusetts Boston to create such a program.

http://www.umb.edu/greenchemistry

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Communication, Awareness, and Benchmarking

ACS GCI Pharmaceutical Roundtable

Current membership (August 2014):



No endorsement or approval by the ACS GCI Pharmaceutical Roundtable has been received or is in any way implied.

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Strategic Priorities of ACS GCI Pharmaceutical Roundtable

- Award of research grants, partner in NSF grants
- Publication of key green chemistry and engineering research areas

- Strategic priority
- All activities of the RT are global wrt participation and influence
- 1 meeting per year outside of US
- Sponsor of research lectures at company sites in the EU and US



- Sponsor of workshops for undergraduates, graduates, teachers
- Co-author of Green Chemistry Articles of Interest to the Pharmaceutical Industry (published in OPRD)

- Solvent selection guide: www.acs.org/gcipharmaroundtable
- Reagents guide, green conditions for commonly employed transformations (eg, amide formation)
- Process mass intensity (PMI) calculator, www.acs.org/gcipharmaroundtable

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Additional External Collaboration Opportunities

IQ Consortium

- Green Chemistry Working Group (presentation sponsor)
- Engagement with FDA
- Sharing of best practices

Innovative Medicines Initiative (IMI)

- CHEM 21: €6.4m for improved catalytic and flow chemistry methods, novel biocatalysts, synthetic biology approaches to enable useful cascade reactions in cells, and improvements in education

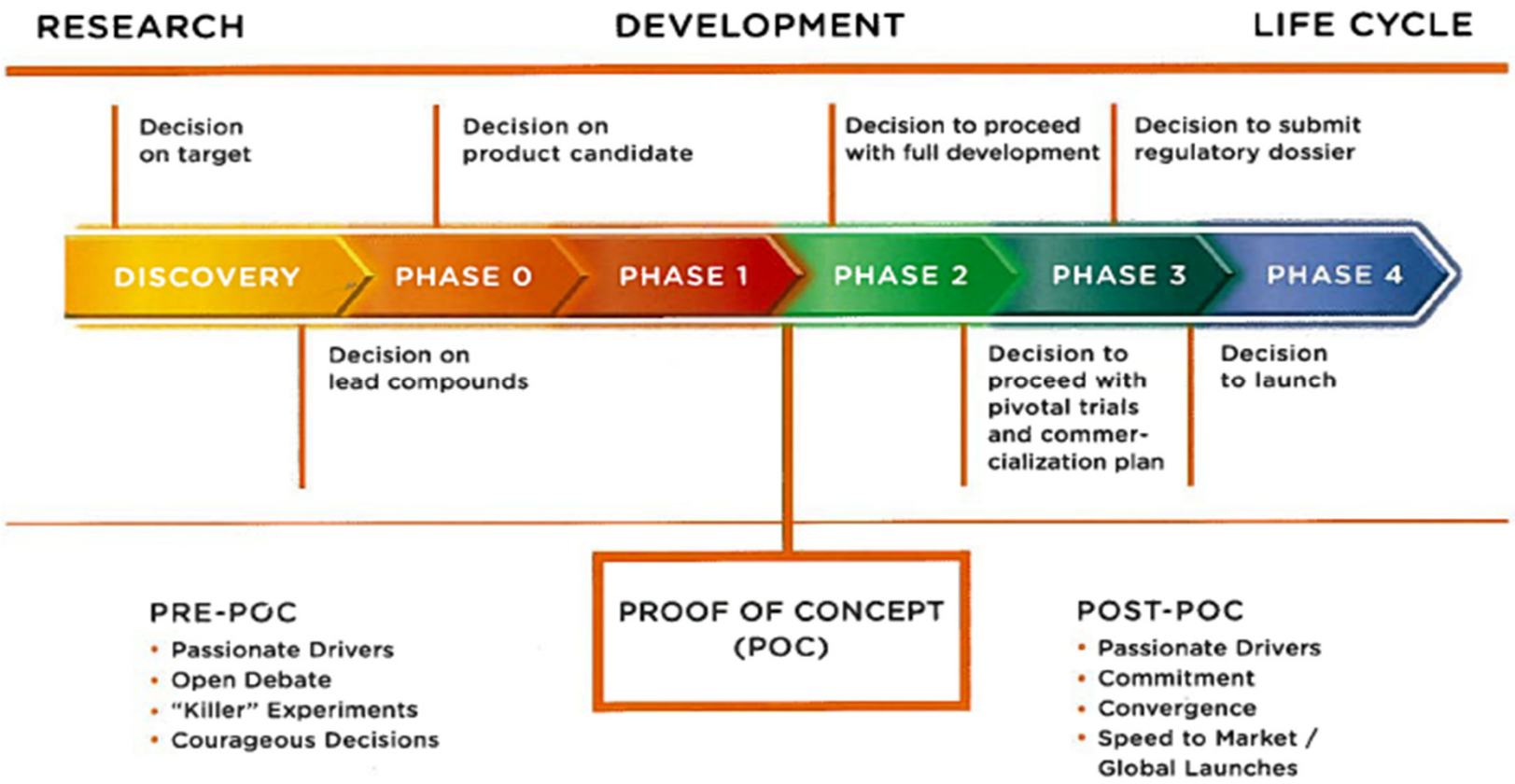
National Science Foundation

- Grant Opportunities for Academic Liaison with Industry (*GOALI*)
- eg, Prof. Maleczka at Michigan State
- "C–H Bond Activation and Functionalization Methods for Medicinal and Process Chemistry"

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When to Apply Green Chemistry?

- The idea is to integrate green chemistry throughout the life cycle of drug research and development and beyond
- **Early awareness can lead to large paybacks later**



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How Do We Calculate "Green"?

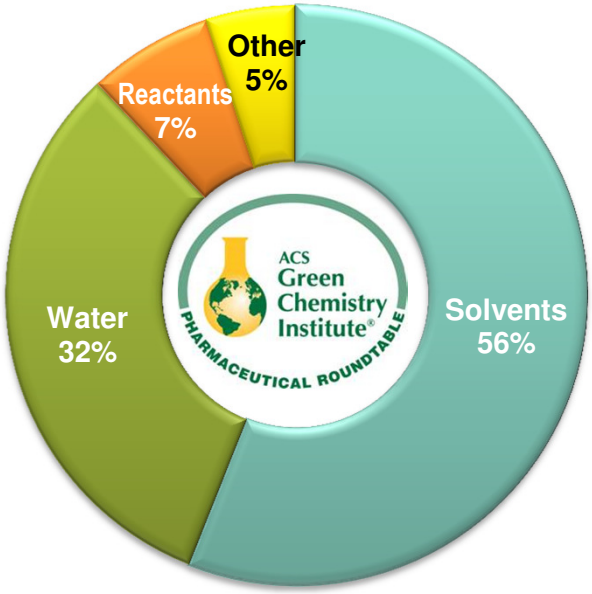
$$\text{Process Mass Intensity (PMI)} = \frac{\text{Quantity of raw material input (kg)}}{\text{Quantity of API out (kg)}}$$

- Includes all steps in the synthetic pathway from commonly available raw materials
- Raw materials are all materials including solvents and water used in synthesizing, isolating, and purifying the API

Typical discovery route >1000

Commercial process target <100

Composition of waste

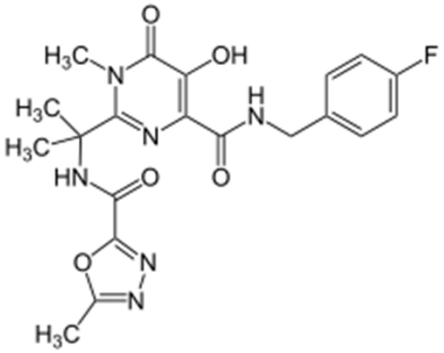


Process Mass Intensity Benchmark 2008

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Raltegravir – Significant Increase in Process Efficiency in Second Generation Process

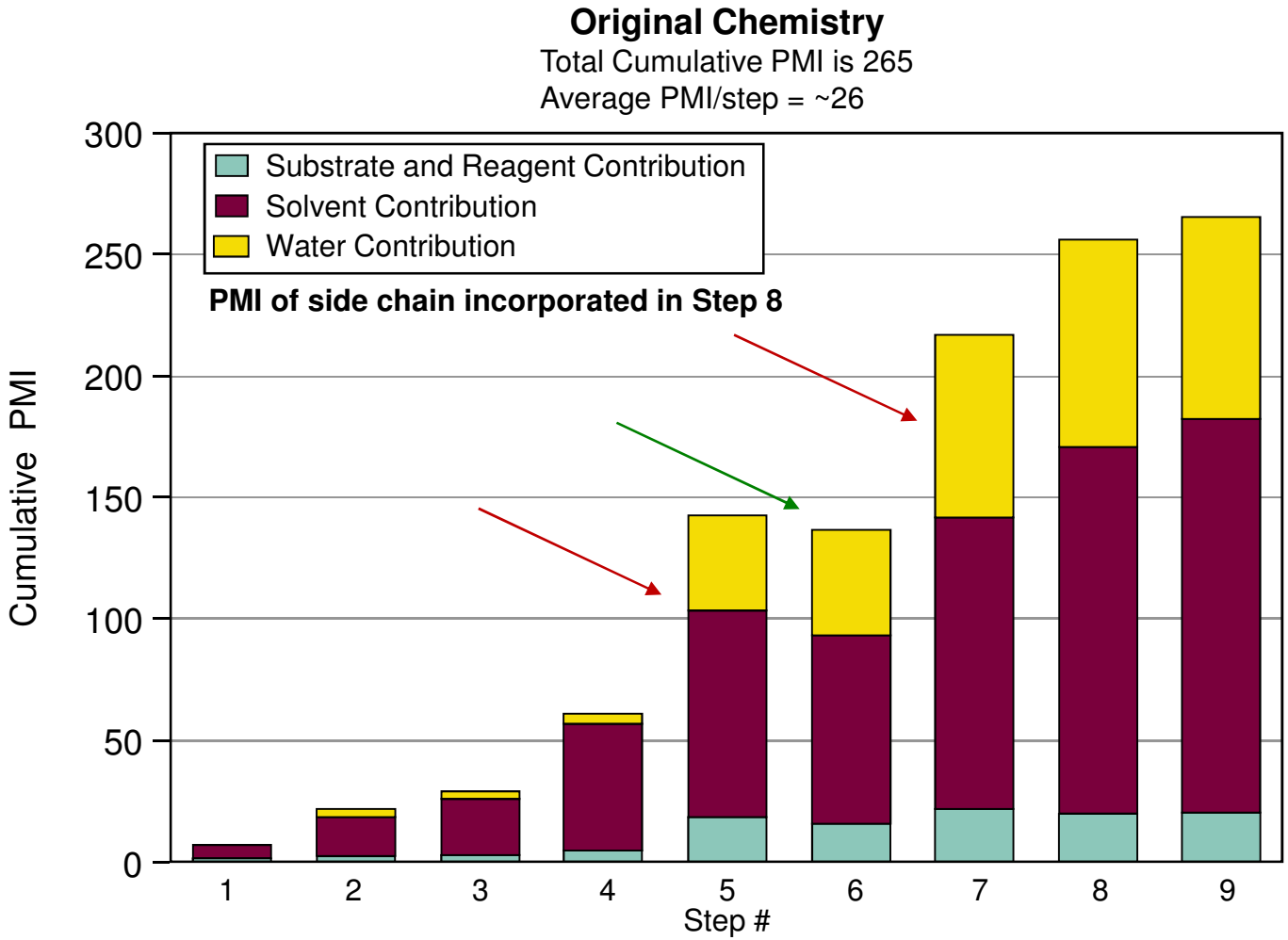
ISENTRESS
raltegravir film-coated tablets 400 mg



ISENTRESS® is a prescription human immunodeficiency virus (HIV-1) medicine used with other HIV medicines to treat adults with HIV-1 infection. HIV is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).

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Raltegravir – Significant Increase in Process Efficiency in Second Generation Process



Guy R. Humphrey et al. *Organic Process Research and Development* 2011, *15*, 73-83

Raltegravir – Significant Increase in Process Efficiency in Second Generation Process

New Chemistry

Overall PMI reduced from

265 to 156 after route improvement

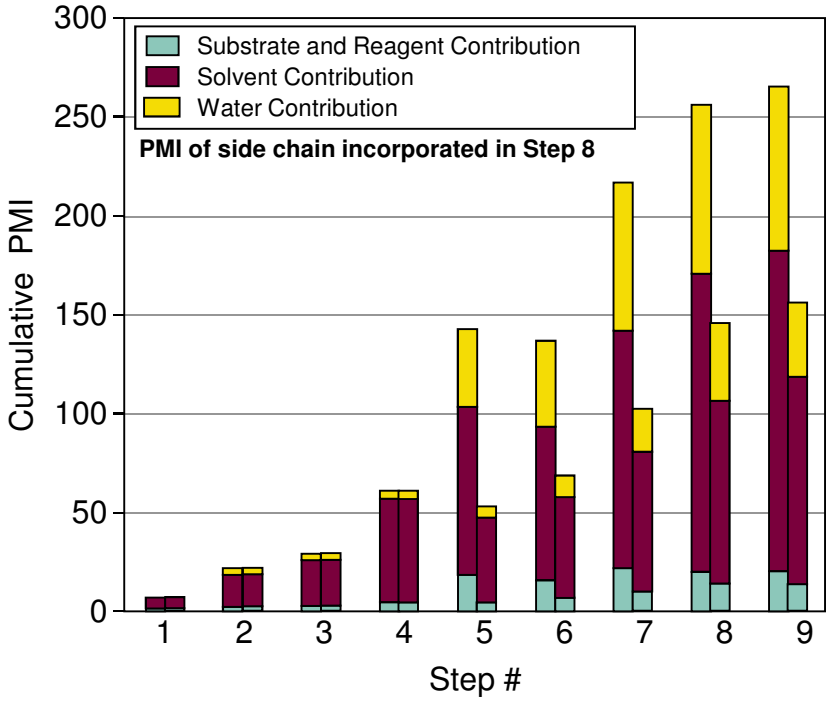
– About 40% improvement in mass efficiency

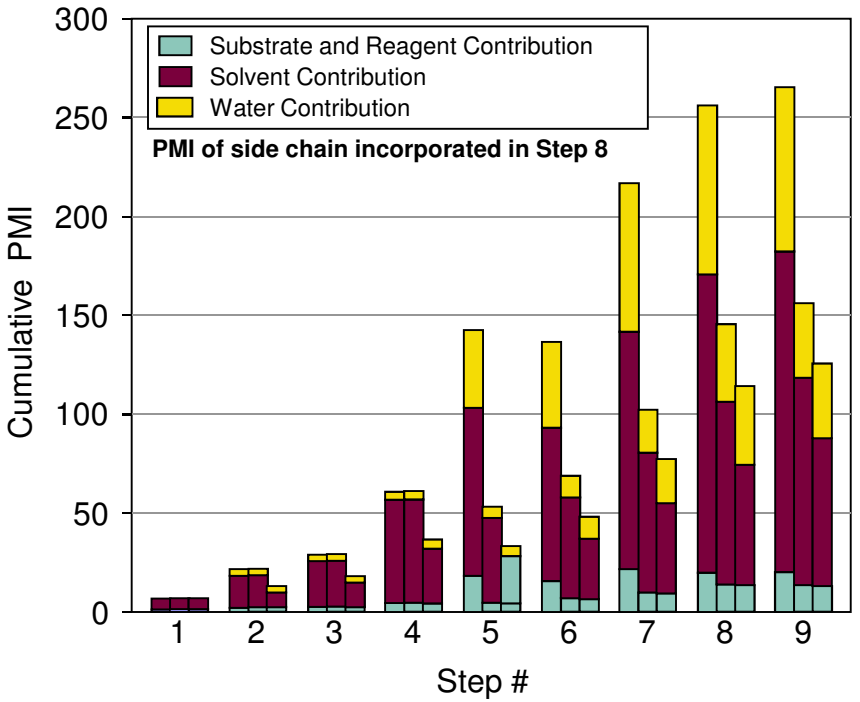
New Chemistry and Solvent Recycle

Further reduction in PMI from 156 to 126 after implementing solvent recovery programs

– About 50% total reduction in mass requirements after process launch

– Average Step PMI dropped from ~26 to ~12





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From "No Activity" to Industrial Enzyme

www.sciencemag.org SCIENCE VOL 329 16 JULY 2010

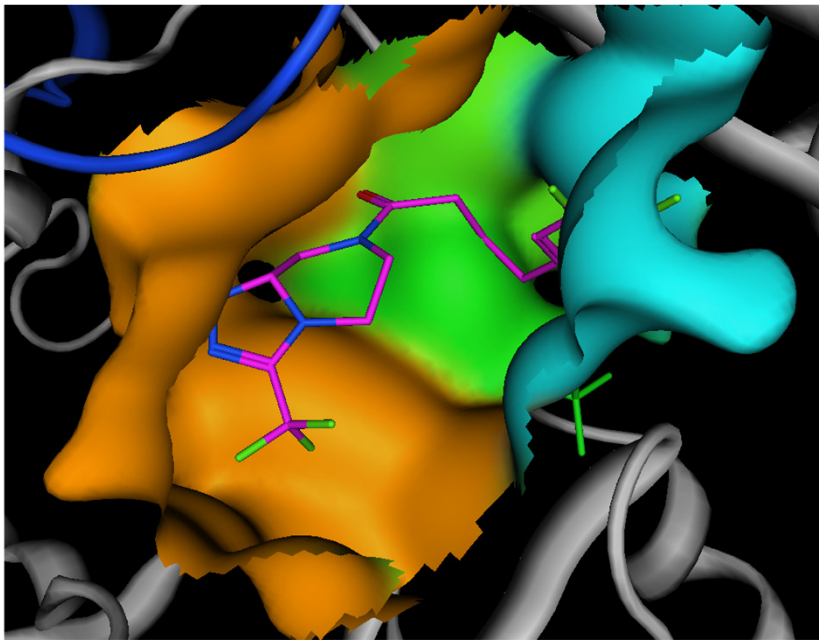
Biocatalytic Asymmetric Synthesis of Chiral Amines from Ketones Applied to Sitagliptin Manufacture

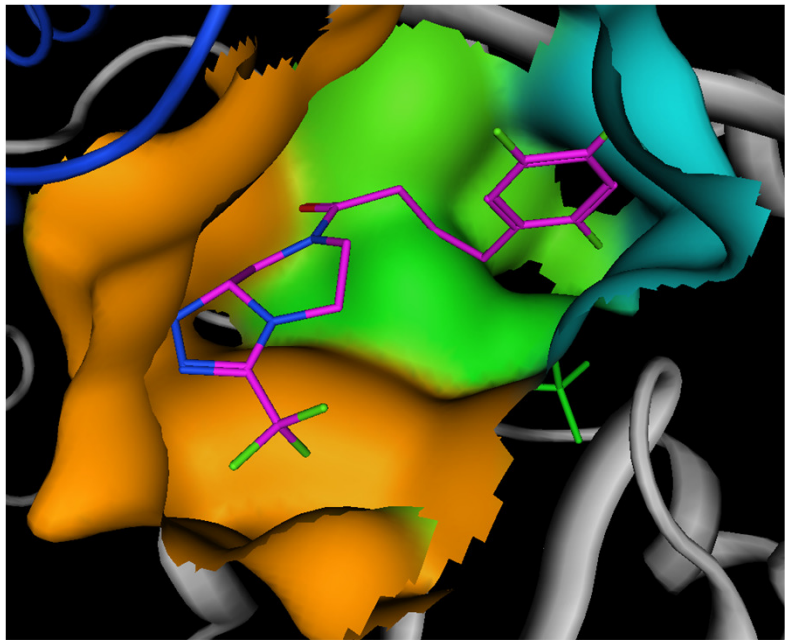
Christopher K. Savile,[1]* Jacob M. Janey,[2]* Emily C. Mundorff,[1] Jeffrey C. Moore,[2] Sarena Tam,[1] William R. Jarvis,[1] Jeffrey C. Colbeck,[1] Anke Krebber,[1] Fred J. Fleitz,[2] Jos Brands,[2] Paul N. Devine,[2] Gjalt W. Huisman,[1] Gregory J. Hughes[2]

2010 GREEN CHEMISTRY

Januvia™ (sitagliptin phosphate)

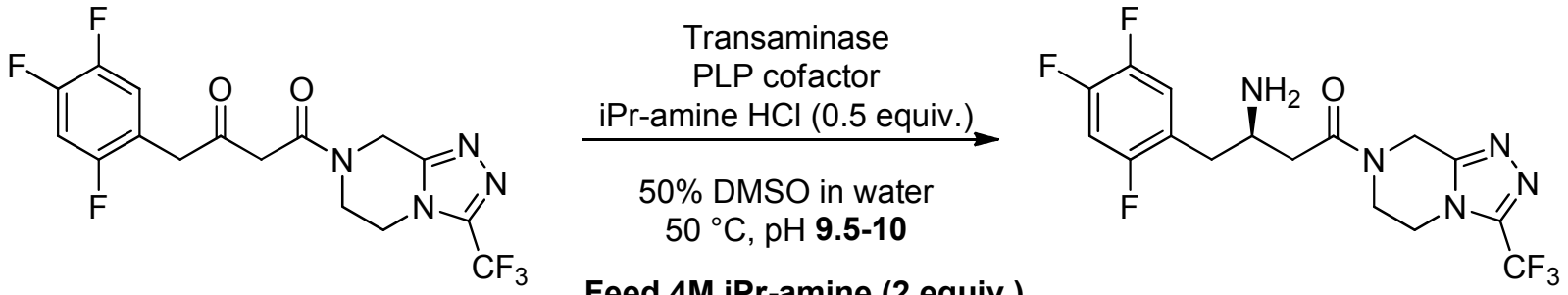
Janumet™ (sitagliptin/metformin HCl)





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Second Generation Januvia Process – Key Step



Isolation:

1) Extract product with 0.5X volumes IPA and 0.5X volumes IPAc
2) Filter off precipitated enzyme

- ~30% more productivity
- 10% Increase in overall yield
- No metals
- No special equipment needed
- >99.9% ee
- Lower cost
- Step PMI from 37 down to 26

www.sciencemag.org SCIENCE VOL 329 16 JULY 2010

Biocatalytic Asymmetric Synthesis of Chiral Amines from Ketones Applied to Sitagliptin Manufacture

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2010 GREEN CHEMISTRY

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Resource Productivity Innovation – Water Supply



- Lima, Peru lacks of adequate drinking water, but has high humidity
- Local university with declining enrollment installed billboard to advertise
- Innovative water condensing technology converts moist air into clean drinking water

Think Differently!

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Resource Productivity Innovation – 3D Printing

- Makes a 3D solid object by depositing successive layers of filament using a digital model
- Uses fewer raw materials: constructive vs reductive process
- Uses 41%-64% less energy than making products abroad and shipping to the US
- PLA filament made from renewable resources and can be reconstructed waste free
- Cheaper products: more efficient, no retail mark-ups or shipping costs



Think Differently!

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Resource Productivity Innovation – Closed Loop



- Levi Strauss WATER<LESS Jeans
- Uses 100% recycled water in its fabric dying and washing operations
- Reduced 770 million liters of water use since 2011
- Equivalent to supplying drinking water for 811,000 people for 1 year

Think Differently!

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Key Take Aways



- **Good science** is the key to sustainability, green chemistry, and low cost manufacturing across the globe
- If we focus on developing the best chemistry, then almost always, this leads to the lowest cost and greenest process
- **Education, collaboration** across industries, and innovation are the keys to advancing green chemistry and green engineering
- We must **think differently** in order to meet our future needs
- **Privileged position** to help patients, do great science, and minimize impact on the planet
- In the end, the sustainability of the pharmaceutical industry is dependent on the sustainability of our global population

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Questions

Some are green by nature…



Others need…





Back-up Slides

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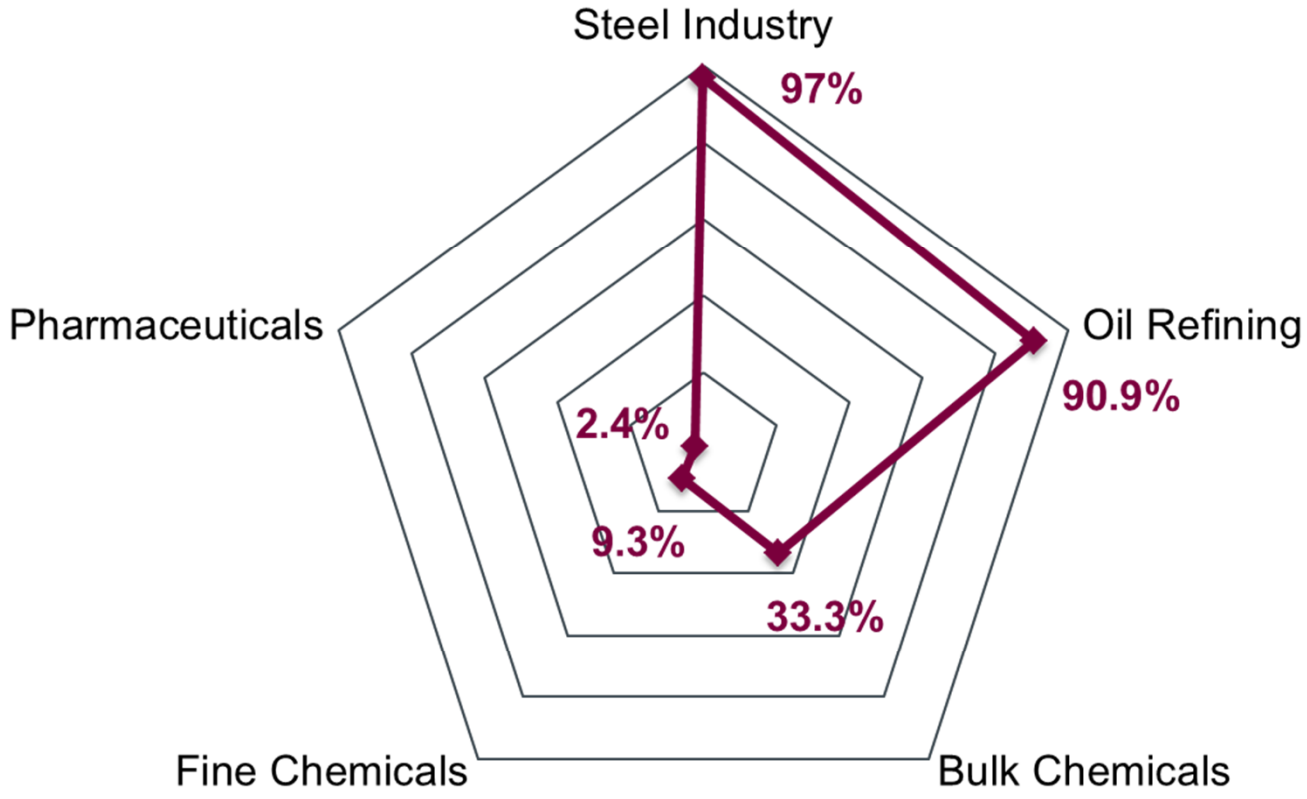
PMI and Material Efficiency

$$\text{PMI} = \frac{\textit{total kg process inputs}}{\textit{kg product output}} \qquad \text{Material Efficiency} = \frac{\textit{kg product output} \times 100}{\textit{total kg process inputs}}$$

Name	Product	PMI	Material Efficiency
JANUVIA®	sitagliptin	75	1.3%
COZAAR®	losartan	112	0.9%
ISENTRESS®	raltegravir	156	0.6%
CLARITIN®	loratadine	175	0.6%
ZOCOR®	simvastatin	239	0.4%

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Material Efficiencies of Various Industries



Average material efficiencies derived from Sheldon, 1997.

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Material efficiency improvements can often help reduce product and waste disposal costs



Figuring out how to use less water is critical because we don't know where our future products will be made



Ambient reactions and thermally stable products will reduce energy needed to make, store, and transport our products

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Let Us Meet Again

We welcome you all to our future conferences of OMICS Group International

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