2018 Green Chemistry Challenge Award Winners

In 2018, the American Chemical Society's Green Chemistry Institute (ACS GCI) sponsored the awards. The winners of the 2018 Green Chemistry Challenge Awards are listed below under each award category.

To view the winners from all other previous years, please visit the EPA website.

Greener Synthetic Pathways Award

Merck & Co. and Merck Research Laboratories

A Sustainable Commercial Manufacturing Process for Doravirine from Commodity Chemicals

Innovation: Doravirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI) for the treatment of HIV, utilizes a novel synthetic strategy to produce the pyridone core and the

N-methyltriazolinone heterocycle through the use of continuous processing, without the use of expensive transition metals, and using only inexpensive commodity chemicals. Overall, the synthesis is optimized for reduction in waste, conducting several steps in tandem without workup or isolation.

Benefits: Compared to the benchmark process used for early clinical supplies, this innovative new synthesis reduces PMI by 81% (1,009 to 190), increases the overall yield from 23% to 52%, and reduces raw material costs by 67%. Life cycle assessment reveals the carbon footprint and water usage were reduced by 88% and 90%, respectively.

Summary of Technology:

Central to the development of green and sustainable pharmaceutical manufacturing is the design of efficient synthetic routes. Retrosynthetic logic and forward planning are foundational to achieving the best synthetic strategy while meeting broader sustainability goals. This logic is reinforced by principles of green chemistry and engineering which articulate the importance of resource efficiency, waste prevention, and the use of less hazardous chemicals. Too often the failure to define an appropriate and consistent synthesis starting point prevents an objective, comparative assessment of the effect of synthetic innovation on achieving sustainability goals. Chemists have come to rely on readily available, low-to-moderate cost compounds, and forget the vast majority of these materials have an environmental impact which is not always very transparent. Therefore, the overall negative environmental, health and safety impacts of pharmaceutical manufacture can be underreported. With the implementation of a 100

USD/mol requirement as the starting point for calculating green chemistry metrics, the field is evolving toward a more holistic accounting of waste products from pharmaceutical manufacturing.

A Merck 2017 blueprint for how to guide process development from route design validation focused on the pillars of (a) Designing for Atom Economy, (b) Inventing New Transformations / Use of New Technologies, (c) Prioritizing and Selecting the Route and (d) Optimizing for Sustainability. This framework was strengthened in two additional ways for this nomination. First, by taking into account all materials back to inexpensive commodity raw materials when designing for atom economy, and second, demonstrating the powerful impact that chemical processing technologies can have in the invention of new chemical transformations.

Greener Reaction Conditions Award

Mari Signum Mid-Atlantic, LLC

A Practical Way to Mass Production of Chitin: The Only Facility in the U. S. to Use Ionic Liquid-Based Isolation Process

Innovation: Mari Signum Mid-Atlantic, LLC is commercializing a safe, environmentally friendly, low energy-demanding, and overall less costly process to produce chitin from seafood waste. The chitin obtained is of very high MW and higher quality than that produced through any other current processing method. No hydrolysis/degradation of the polymer occurs, allowing for effective control over the final product's physical characteristics such as crystallinity, purity, and polymer chain arrangement. Moreover, a high degree of acetylation is maintained, greatly expanding chitin's potential applications.

Benefits: The Mari Signum process is a zero-discharge process in which all components of the waste crustacean biomass are monetized, with water and ionic liquids recycled and reused.

Summary of Technology:

The vast opportunities for chitin polymer applications result in a projected global market of $2,941 million by 2027. However, the current chitin isolation process (pulping) from crustacean biomass is of high cost, energy-intensive and generates a huge quantity of waste resulting in no chitin producing plant in the U.S., due to environmental regulations.

The current process for obtaining chitin consists of demineralization to remove the calcium carbonate in a shell matrix (using acids, e.g., HCl), deproteinization to remove proteins (conducted using hydroxides, e.g., NaOH), and bleaching/discoloration (conducted with organic solvents or oxidation agents). Pulping is conducted at relatively high temperature (60 – 100 °C), and usually for prolonged times, generating a large amount of waste. Thus, production of 1 kg of chitin using pulping method requires 10 kg of biomass, 300 L of freshwater, 9 kg of HCl, and 8 kg of NaOH, utilizing overall 1.2 kWh of electricity.

Estimating that generated liquid waste is equal to the amount of input freshwater volume plus process water, the overall amount of waste per 1 kg of chitin exceeds 500 L. Emission of CO_2 is estimated to be 0.9 kg/kg of chitin. The harsh conditions used in isolation were found to decrease the quality of the isolated chitin, promoting deacetylation and depolymerization and resulting in a lack of reproducible high-quality polymer product.

Mari Signum Mid-Atlantic's process does not produce any waste as there is a complete recovery of all production substrates and by-products (i.e., chitin product, calcium carbonate and phosphate, and proteins are all monetized) including the ionic liquid solvent used in the process. Water and ionic liquid (the only two chemicals besides biomass used in the process) are separated for reuse back at the front of the dissolution cycle. The process produces no solid, liquid (other than water) or gaseous waste, including CO_2 emissions (as opposed to the current pulping process that produces 0.9 kg CO_2/kg chitin upon treatment of biomass with hydrochloric acid). The process for chitin extraction and solvent and water recycle uses 2 kWh/ kg of chitin, of which 54% is recovered, thereby reducing the energy-related CO_2 emissions. Mari Signum Mid-Atlantic's ionic liquid chitin extraction is also replacing hazardous chemicals used in pulping (i.e., HCl and NaOH) with the ionic liquid solvent alternative that belongs to the lowest toxicity category 5 according to GHS classification.

The Design of Greener Chemicals Award

Corteva Agriscience™ Agriculture Division of DowDuPont™

Rinskor™ Active – Improving Rice Production While Reducing Environmental Impact

Innovation: Rinskor active represents the latest member of the arylpicolinate family of chemistry, a unique and new class of synthetic auxin chemistry. Chemical substitutions resulting in the addition of an aryl ring to the pyridine-carboxylate auxin molecule resulted in significantly increased herbicidal potency and paved the way for a new generation of lower-dose-rate, synthetic auxin herbicides. In addition, the Rinskor active is formulated in a matrix built on carriers and non-hydrocarbon solvents that are predominantly plant-derived and renewable.

Benefits: The U.S. EPA granted Rinskor the Reduced Risk Pesticide Designation in rice and aquatics uses in 2016. Because Rinskor is displacing a number of existing products, it is expected to eliminate over 750,000 pounds of herbicide-active ingredient introduced into the environment and nearly the same amount of hydrocarbon solvents in 2018. Annually, the reduction will be well over one million pounds of active ingredient and hydrocarbon solvents at commercial maturity. These reductions will be further multiplied as Rinskor reaches farmers in other countries.

Summary of Technology:

Weeds cause more yield (as high as 80%) and quality losses than insects and diseases combined. Effective weed management is therefore critical to rice production, and over time, weeds develop resistance to herbicides or become less sensitive to means of control, requiring the introduction of new herbicides with differentiated or new modes of action to mitigate the development of weed resistance. Rinskor active represents the latest member of the arylpicolinate family of chemistry, a unique and new class of synthetic auxin chemistry within the Herbicide Resistance Action Committee's Group O category.

Rinskor clearly demonstrates a more favorable human toxicity profile than current market alternatives. The U.S. Environmental Protection Agency concluded that since there is no adverse toxicity found in any of the toxicity studies submitted to support Rinskor registration, no toxicity endpoints and points of departure (e.g., cPAD) are established for risk assessment.

In addition to a more favorable human health profile, Rinskor also has a favorable environmental profile because of its low persistence in soil, water and plants, and because of its low toxicity to other organisms like birds, insects, fish or other aquatic organisms. Rinskor's very low use rates (10-30 g of active ingredient per hectare) pose minimal risk to farmers, applicators, and to other non-target organisms (animals and plants) when used according to the label recommendations.

Small Business Award

Chemetry, Corp.

The eShuttle™ Technology for Propylene Oxide and Reducing CO2 Emissions in the PVC Supply Chain

Innovation: The novelty of the eShuttle technology lies in the elimination of chlorine as a chemical intermediate in the production of polyvinyl chloride (PVC), along with a chlorine-free route to the production of propylene chlorohydrin, a precursor to propylene oxide (PO).

Benefits: The eShuttle process provides a 20% reduction in cell voltage over state-of-the-art chlor-alkali membrane plants and conversion of these plants to the eShuttle process will reduce emissions by 10 million tonnes of CO_2 per year. The eShuttle process for PO reduces the power demand by 60% with respect to the conventional chlorohydrin process. In both cases, asbestos or mercury from the standard chlor-alkali and direct chlorination processes is eliminated, and the need for chlorine gas is avoided thereby removing the potential creation of hazardous chlorination products and by-products commonly associated with current commercial PVC or PO processes. For the production of PO, there is a reduction in total waste to 5 tonnes of water/tonne of PO. Further innovations in the PO process permits the recycle of the concentrated brine and allows the process to be run as a zero liquid discharge process.

Summary of Technology:

Chemetry's eShuttle Technology for propylene oxide (PO) addresses the environmental challenges associated with existing commercial routes and shows superior process economics. Similar to the traditional chlorohydrin process for PO, wherein PO forms by ring-closing a chloro-propanol molecule with NaOH, the eShuttle process avoids the co-product liabilities associated with the use of organic peroxides. When compared to the reaction conditions used in the chlorohydrin route, the eShuttle reaction conditions have two environmental benefits. First, the eShuttle process produces propylene chlorohydrin without the use of chlorine (Cl_2) gas by using aqueous copper chloride as the oxidant. The co-products in the reaction are thus HCl and CuCl, which can be reacted with oxygen in a separate vessel to regenerate the aqueous $CuCl_2$. Regenerating $CuCl_2$ through chemical oxidation reduces the power demand of the electrochemical cells by more than 60% when compared with the traditional chlorohydrin process. Second, the eShuttle reactor allows for the reaction to be run in such a way as to isolate the chlorohydrin prior to the epoxidation step. This separation step reduces wastewater by almost 90% and allows the possibility of zero liquid discharge.

Chemetry's eShuttle process eliminates chlorine (Cl_2) as an intermediate in the production of ethylene dichloride (EDC). The eShuttle technology replaces chlorine gas with a circulating stream of aqueous copper chloride. Cupric chloride ($CuCl_2$) is contacted with ethylene where it reacts to form EDC and cuprous chloride (CuCl). The CuCl is then regenerated back to $CuCl_2$ in an electrochemical cell that co-produces NaOH and H_2. When integrated in this way, the eShuttle technology provides a straightforward replacement for the chlor-alkali/direct chlorination processes. In addition to eliminating the fugitive emissions and other human safety risks associated with Cl_2 gas, the use of aqueous $CuCl_2$ also reduces the GHG footprint of EDC. Converting the anode reaction to Cu(I) oxidation saves approximately 600mV of operating voltage in the electrochemical cell, which in turn reduces the power demand by almost 20%. Because the chlor-alkali process is electrically intensive, retrofit of existing EDC plants will save more than 10 million tonnes of CO_2 annually. The process economics, which are cost advantaged up to almost $100/tonne of NaOH, have been demonstrated at the pilot scale at Chemetry's facility in Moss Landing, CA.

Academic Award

Professor Frank Gupton and Professor Tyler McQuade

Virginia Commonwealth University

Increasing Global Access to the High-volume HIV Drug Nevirapine through Process Intensification

Innovation: Through the use of novel high atom economic transformations, use of compatible reaction conditions, and the introduction of continuous processing, the overall process yield increased from 53% to 91% while reducing waste generated from isolation and purification steps.

Benefits: The Process Mass Intensity (PMI), a ratio of the material used to produce the API versus the amount of API produced, was dramatically reduced from 56 to 4. The number of unit operations also decreased from 15 to 4, and the novel process produced an estimated 30-40% raw material cost savings. The process was transferred to the Clinton Health Access Initiative (CHAI) in 2016, which collaborated with two Chinese API manufacturers to commercialize the new method. The new process was implemented approximately six months thereafter, resulting in a 9% price reduction over the following 12-month period.

Summary of Technology:

Access to affordable medications continues to be one of the most pressing issues for the treatment of disease in developing countries. For many drugs, synthesis of the active pharmaceutical ingredient (API) represents the most financially important and technically demanding element of pharmaceutical operations. Nevirapine is the first non-nucleoside reverse transcriptase inhibitor approved for the treatment of HIV-infected patients and is a high volume component of HIV combination drug therapies. Two commercial processes have been reported, both of which construct the central diazapine ring system from two multi-functional pyridines, 2-chloro-3-amino-4-picoline (CAPIC) and a nicotinic acid derivative, as the registered starting materials. These processes provide moderate yields, but require multiple synthetic steps, solvent exchanges, and intermediate isolations that add to process complexity and waste generation.

Professors Gupton and McQuade, along with other researchers, have demonstrated that by adopting a set of core principles for API process development that includes (a) implementation of innovative chemical methodologies and new manufacturing platforms, (b) consolidation of high-yielding reactions into a minimal number of unit operations with common solvents and limited intermediate isolations, and (c) vertical integration of advanced starting materials prepared from commodity chemicals, significant yield improvements to API production costs and efficiency are possible.

Using these principles, the route to the API was streamlined by pinpointing conditions that minimize unit operations through the elimination of unnecessary isolation and purification steps. In doing so, the isolated yield of nevirapine was increased from 63% to 91%, while the PMI for the process was reduced from 67 for the first generation commercial process to 4 for the optimized process.