Regulatory Strategies to Enable Green Chemistry

The International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) is a technically focused organization of pharmaceutical and biotechnology companies interested in advancing science-based and scientifically driven standards and regulations for pharmaceutical and biotechnology products and processes worldwide. A key leadership group within IQ is the Active Pharmaceutical Ingredient Team which has multiple initiatives, including the promotion of Green Chemistry within the pharmaceutical industry. In support of this effort a working group for Green Chemistry was created within the IQ Consortium.

Initial discussions of the IQ Green Chemistry working group brought to light that much has been accomplished toward Green Chemistry in the pharmaceutical industry over the last decade. This has resulted in many marketed products and processes receiving EPA Presidential Green Chemistry awards. Sitagliptin, Lipitor, Taxol, Emend, Januvia, Sertraline, and others have established the reality that Green Chemistry principles incorporated into drug development have a major and positive impact upon the environment, process safety, and upon the economics of pharmaceutical processing.

Green Chemistry Delivers Enhanced Environmental, Economic, and Safety Related Performance when Applied to Pharmaceutical Processing.

When one considers principles of Green Chemistry, it's not surprising that they deliver environmental, safety, and economic benefits as the environmental drivers inevitably exist symbiotically with favorable economics and enhanced safety.

	Environmentally Thinking	Economically Thinking
Atom Economy	Minimal by-product formation, ***reduced environmental burden***	More from less – incorporate total value of materials **reduced cost**
Solvent Reduction	Less solvent waste, ***reduced environmental burden***	Higher throughput, less energy, **reduced cost**
Reagent Optimization	Catalytic, low stoichiometry, recyclable reagents minimize usage, ***reduced environmental burden***	Higher efficiency - higher selectivities **reduced cost**
Convergency	***Reduced environmental burden*** due to increased process efficiency	Higher efficiency – fewer operations **reduced cost**
Energy Reduction	***Reduced environmental burden*** from power generation, transport, and use	Reduced energy reflects increased efficiency, shorter process, mild conditions **reduced cost**
In-situ Analysis	Reduced possibility for exposure or release to the environment	Real-time data increases throughput and process efficiency, fewer reworks **reduced cost**
Safety	Non-hazardous materials reduce risk of exposure, release, explosions and fires	***Worker safety*** and reduced down time, Reduced time on special control measures. **reduced cost**

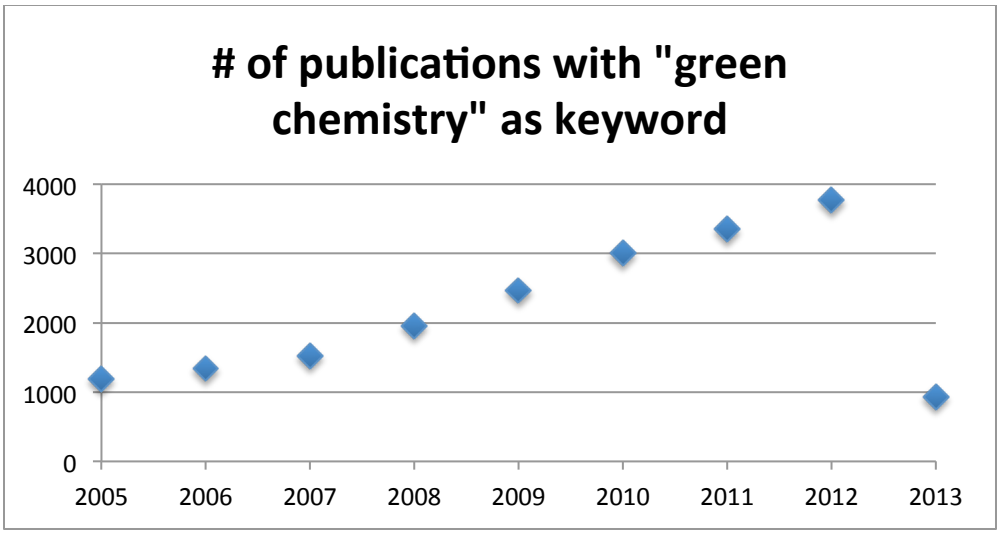
In addition to the demonstrated practical benefits of Green Chemistry application, the innovations and advances in synthetic methodologies and engineering inspired by Green Chemistry principles have spurred Nobel prize winning scientists to espouse Green Chemistry as a path to future sustainability. Professor Ryoji Noyori stated that "***Green chemistry is a creative, prosperity-bringing and responsible science. Indeed, our ability to devise straightforward and practical chemical syntheses is indispensable to the survival of our species*.**" Professor Robert H. Grubbs stated that **"*If approached in the right way, the present (sustainability) crisis provides a major driver for New Science and Technology…Green Chemistry.*"** Roald Hoffman, a champion for Green Chemistry reiterates concerns for chemicals and the environment when he states that "***Real, smart, normal, thinking and feeling people are concerned about where science is going, what it is doing to people's lives.*"** The father of atom economy, Professor Barry Trost proclaims that **"*Green Chemistry addresses our future challenges in working with chemical processes and products.*"**

Environmental benefits, economic benefits, enhanced safety, and no less than "the philosophy of the future of science" all point to Green Chemistry embodying our path to future sustainable and innovative pharmaceutical science.

The realization of the many benefits of Green Chemistry application presented the IQ team with a difficult challenge in postulation regarding why Green Chemistry principles are not the first concern and highest priority of every pharmaceutical scientist and leader. What has been impeding the full commitment and incorporation of Green Chemistry principles into every pharmaceutical endeavor?

Scientists Believe in Green Chemistry.

Upon reflection, it may have been scientists themselves impeding Green Chemistry incorporation in the past, exhorting that "Green Chemistry is too expensive" or "Green Chemistry is too time-consuming". Even suggestions that "Green Chemistry is just good chemistry", and that no new efforts should be required or are justified. Misguided attitudes such as these existed, but they have been soundly debunked in the last decade *via* numerous literature examples of green, superior science and award winning industrial processes exemplifying Green Chemistry as a more efficient (and cost-saving) path to the best chemical processes(vide supra?). Green Chemistry has been demonstrated to provide a unique framework of principles that guide process development and produce the best chemistry from an environmental and economic perspective as opposed to chemistry that's simply "good enough". This is a sea change in scientists' perception of Green Chemistry, and is apparent when one considers the significant acceleration in literature focused upon green principles, metrics, and technologies in peer reviewed publications.



Note: 2013 data not yet available

Chart provided by the Yale Center for Green Chemistry and Green Engineering.

What is Impeding Green Chemistry Commitment?

This begs the question; who or what is impeding the broad and committed application and incorporation of Green Chemistry principles into every chemical process throughout the devlopment and manufacturing lifetime of pharmaceuticals?

After much discussion, the IQ team identified two "perceived" regulatory hurdles that could be impeding Green Chemistry application and investment. The first concern involved 2nd generation manufacturing route development, and the second pertained to manufacturing route development pre-NDA filing, simultaneous with on-going Phase III clinical studies.

2nd Generation, Green Manufacturing Processes.

Consider potential replacement of an early generation, inefficient synthetic route to create a drug substance with a new, green, 2nd generation route. After a significant investment in development of this theoretical green route, a pharmaceutical company must then decide if it will file the route with FDA for use during drug manufacture. Upon re-filing of a new CMC section with FDA, it is possible that the original approved filing may be reviewed not only with regard to considerations about the new synthetic route, but also with re-examination of the current approved route as well. This might include additional questions regarding previous clinical outcomes or data. It may include a re-examination of the current manufacturing process with potential identification of new specific concerns (an example might be the re-classification of a by-product or intermediate as of genotoxic concern). This could theoretically lead to the loss of already approved status on a marketed medicine. This is a staggering "perceived" risk to a marketed product and is endured while attempting to improve efficiency and adopt a green manufacturing route. This perception of regulatory risk colors the decisions regarding when or if some firms will invest in green, 2nd generation manufacturing routes.

Consider an imaginary medicine that has 4 billion dollars in annual revenue. Assume a fictitious cost of manufacture at approximately 10% of total sales, 400 million dollars in manufacturing cost. Further anticipate that the 2nd generation, green synthetic route can eliminate significant waste and the cost of manufacture is reduced by 50% as compared to the existing manufacturing route…200 million dollars can be saved. If a hypothetical senior pharmaceutical executive examines the potential risk to a 4 billion dollar product upon re-filing (the bird in the hand), he or she must decide if 5% of that amount, 200 million dollars savings (the bird in the bush), is enough to justify the "perceived" risk of re-filing.

Each company/leader has a different tolerance for this level of regulatory risk. Some firms will re-file with FDA to incorporate a greener, more efficient route[i] (reference to Dunn paper here) , but other firms are hesitant to put a "bird in the hand" program at risk for the relatively small potential "bird in the bush". This results in stagnation of chemical route development, and it becomes little surprise that generic firms may have superior manufacturing routes when compared to the original inventors of the medicine at the end of patent protection since no further process development has occurred due to "perceived" regulatory risk.

A path forward exists however that will encourage firms to invest in green, 2nd generation chemical routes, the key is to remove the "perceived" risk of re-filing through clear communication. With the safety of patients being paramount and immutable, the question becomes, can FDA communicate their intention to limit re-filing review to the new CMC section only (which appears to be the typical protocol)? If so, FDA could remove the "perceived" risk to an existing program (keeping the bird in the hand) and encourage the industry toward development of greener pharmaceutical manufacturing processes. Clarification and communication regarding expectations for streamlined toxicological approaches (such as bridging toxicology studies)that enable product equivalence to be determined analytically (rather than clinically) will further encourage the investment in new route development for existing products.

Encouraging 2nd generation routes with patient safety assured will make firms more cost-efficient, will reduce the environmental footprint of manufacture, has potential to reduce the cost of medicines, and is a cooperative path to advance pharmaceutical manufacturing toward the ultimate goal of sustainable practices. This path represents a rare opportunity for a significant benefit for the environment, pharmaceutical firms, for the FDA, and for the public, and will spur the evolution of sustainable science.

FDA Response:

Typically, companies try to improve the process, efficiency and yield of marketed drugs for economic and safety reasons. These kinds of changes for an approved drug are a subject of post-approval changes and guidance from Agency is available on the FDA website for anyone to follow. In case of a drastic change in the impurity profiles, these entities should be subject to a careful study. If these new impurities are shown to have structural alerts either by in-silico models or actual animal studies, then it is important to assure that the changes will have no serious impact on the safety of patients or on the efficacy of the drug action.

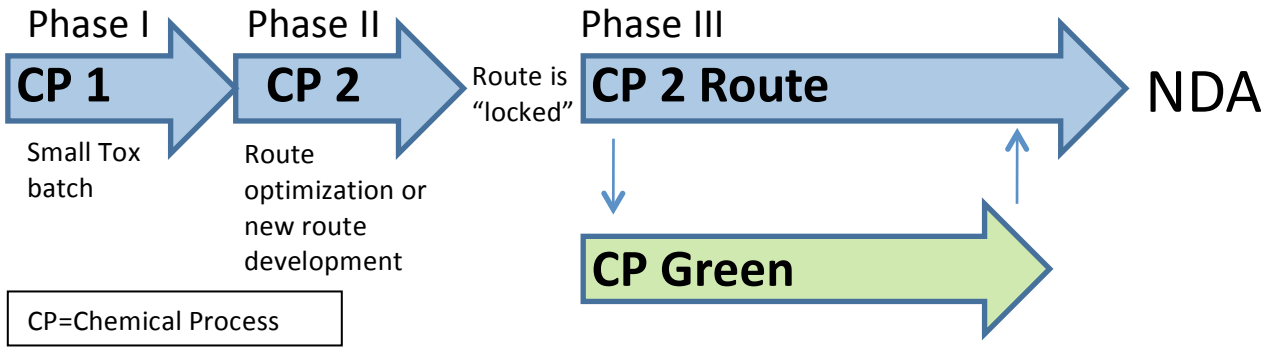
It is recommended that more serious changes to a process can be elaborated into a document and a meeting may be requested to discuss the expectations from the Agency with specific questions in the meeting package if relevant to an approved drug. The Agency typically grants these kinds of meetings and responds to the company's questions. The advice received at such meetings can help ease the pathway to adopt green chemistry processes.

Typically, review of new chemistry focuses on the changes from the previously approved synthetic routes. It would be a very rare case where the evaluation of new chemistry would give rise to concerns over already approved chemistry, including genotoxic impurities. We would like to point out that, regardless of a company's submission of a supplement, when new genotoxic impurities are discovered on existing products, FDA weighs the risk and when appropriate takes regulatory action. In such cases, the Agency will work with the manufacturers to ensure the continued supply of drug products, especially for medically necessary products. A change to the approval status of an approved drug product is extremely rare and is based on sound scientific evidence concerning the safety and/or efficacy of the drug product.

Pre-NDA Green Chemistry Development.

Another opportunity for FDA to inspire Green Chemistry incorporation exists pre-NDA filing, in parallel with phase III clinical studies.

The typical development cycle of most drugs involves the generation of a small toxicological batch of material at Phase I by any synthetic means possible. This material is then used to determine the toxicological profile of the drug and determine if advancement is appropriate. If the compound appears acceptable, Phase II development begins in earnest with examination of the early route used to make Phase I tox material with regard to process research and development concerns, such as raw material and reagent selections, robustness, safety, scalability, physical attributes, cost, etc.. This includes exploration into route optimizations, and frequently leads to new route development to replace the inefficient Phase I route with a manufacturing ready Phase II route.



At the conclusion of Phase II, a final route is selected and used to manufacture the material required for Phase III clinical trials. Once this has been accomplished, the Phase II manufacturing route is "locked"

and development halts in anticipation of filing this route in the NDA. The Phase III clinical studies then begin and can take years to complete. During this time, new methodologies, technologies, catalysts, etc. are being developed by the scientific community and the "locked" phase II route is potentially regressing in technological relevance. If on the other hand, a team of scientists would continue to develop superior, green methodologies for manufacture of this drug (a CP-Green route) it is possible that a far superior route from an efficiency and environmental standpoint could be included at the time of NDA filing. Like 2nd generation routes, this enhanced green chemistry development would raise the quality of synthetic routes being filed with FDA and used for pharmaceutical manufacture. This would again benefit the firm that invests in superior science for greater efficiency, would benefit the environment, and the public.

The key is to address the comparability of the drug manufactured *via* the CP-Green route with the drug used in the clinic and manufactured using the CP-2 route. This is in many ways akin to the comparison of drugs manufactured by generic firms using altered methodology and the drug manufactured using the established, patented and filed route. With the safety of patients being paramount and immutable, clarification on FDA expectations regarding streamlined toxicological approaches (such as bridging toxicology studies)that enable product equivalence and patient safety to be determined analytically (rather than clinically) will further encourage the investment in greener route development prior to NDA filing.

FDA Response:

Certainly, the above criterion fits well within the paradigm of the risk versus benefit analysis. As when generic drug manufacturerers make use of new synthetic methodology to produce an API, establishment of equivalence is expected with regard to physio-chemical properties, specifications, stability and impurity profile. If new impurities above set limits are introduced by the new chemical route, bridging toxicology may establish equivalence with no new clinical study requirements anticipated. Ultimately the proposed green chemistry changes should have no impact on the already established safety and efficacy of the final drug product.

One could ask, "why should FDA concern themselves with Green Chemistry at all?". A glance at the FDA homepage "what we do" section explains that *"FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs… FDA is also responsible for advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable"*.

FDA encouragement of Green Chemistry can enable the achievement of greater public safety, public health, enhanced process efficiency, potential reduction in the cost of medicines, and spurs the innovations required to evolve industrial practices toward ultimate sustainability. FDA is uniquely positioned to serve as an important catalyst for this realization.

A good example of the broad Green Chemistry impact that FDA encouragement can achieve is seen *via* Q-11: Development and Manufacture of Drug Substances. By enabling the use of, and defining advanced GMP starting materials as "a significant structural fragment" and "substance of defined chemical properties", FDA has directly encouraged continuous process optimization through greater chemical

route flexibility. Pre-GMP steps can be easily optimized without the need for additional regulatory filing, and equivalence and control are ensured through rigorous specifications at GMP starting materials.

Two significant opportunities exist for FDA to greatly encourage Green Chemistry in the pharmaceutical industry while ensuring patient safety.

- By limiting review of 2nd generation synthetic routes to new CMC sections only and clarifying expectations for analytical equivalence of drug substance, FDA can eliminate the perceived risk related to re-examination of existing marketed products and greatly influence the evolution of green manufacturing of pharmaceuticals.
- By providing clarification on a path to analytical equivalence with streamlined toxicological approaches, FDA can enhance the development of greener processes pre-NDA. A path to equivalence will encourage Green Chemistry investment by pharmaceutical firms during Phase III clinical studies to ensure the best technology and methodology is used for drug manufacture.

These two opportunities seized in tandem will enable Green Chemistry principles to be applied throughout the development and marketed lifetime of a drug providing a giant leap forward in our constant evolution toward sustainable pharmaceutical science.

FDA Comment:

The Food and Drug Administration recognizes the importance of environmental sustainability and the process of going green in chemistry. There are established paths forward to obtain approval of new chemistry during drug development activities and during the marketed lifetime of drugs. It is FDA intent to dispell misconceptions regarding perceived regulatory hurdles and to support and encourage the pharmaceutical industry to adopt Green Chemistry practices while ensuring patient safety and drug efficacy.

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