Green chemistry can deliver enhanced environmental, economic and safety-related performance when applied to pharmaceutical processing. Here, the IQ Green Chemistry Working Group addresses a number of reasons why companies may show reluctance to adopt this approach, and asks the FDA for its response.

**It’s Easy Being Green**

Green chemistry and green engineering as research topics

When one considers the principles of green chemistry (1), it is not surprising that this approach claims to deliver numerous advantages – environmental drivers inevitably exist symbiotically with favourable economics and enhanced safety (2). One need only look at the accelerated rate for upcoming scientific endeavours for proof of this. Environmental, economic and safety benefits all point to green chemistry embodying the industry’s path to future sustainable and innovative pharmaceutical R&D and commercial manufacturing.

This begs the question: who or what is impeding the broader and committed application and incorporation of green chemistry principles into every chemical process throughout the development and lifecycle of pharmaceuticals (3)?

Two perceived regulatory hurdles holding green chemistry investment back have been identified. One is the risk associated with second-generation manufacturing route development, and the other pertains to improvements to manufacturing routes prior to new drug application (NDA) filing.

**Second-Generation Processes**

Replacement of a synthetic process with a more efficient, greener, second-generation route should be considered. Upon resubmission of a new chemistry, manufacturing and controls (CMC) section with the FDA, the original approved filing may be reviewed not only with regard to the new synthetic route, but with a re-examination of the current approved route as well (4). This could theoretically lead to the loss of already approved status on a marketed medicine, but is extremely unlikely – yet, surprisingly, it is commonly cited as a risk. This perception of regulatory risk can prevent the design and implementation of greener manufacturing routes.

A new approach has been introduced to encourage firms to invest in green, second-generation chemical routes – removing the perceived risk of re-filing through clear communication. With the safety of patients paramount, the question now becomes: can the FDA communicate its intention to limit re-filing reviews to the new CMC section only? If so, the FDA could remove companies’ concerns over an existing programme and nudge the industry towards development of greener pharmaceutical manufacturing processes.

**Keywords**

Perceived risk
New drug application
Chemistry, manufacturing and controls
Second-generation route
Environmental sustainability
regarding expectations for streamlined toxicological approaches – such as bridging toxicology studies – that enable product equivalence (or substantial equivalence as with medical device approval) to be determined analytically, rather than clinically, will further prompt investment in new route development for existing products.

**FDA Response:**

Typically, companies try to improve the process, efficiency and yield of marketed drugs for economic and safety reasons. Guidance on post-approval changes for an already approved drug is available on the FDA website. In the case of a drastic change in 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 ensure that the changes will have no serious impact on patient safety or on the efficacy of the drug action.

It is recommended that more serious deviations from the original process can be expanded upon within a new document, and a meeting may be requested to discuss the expectations of the FDA with specific queries as to its relevancy to an approved drug. The FDA typically grants these kinds of meetings and responds to a company’s questions. The advice received at such meetings can help ease the pathway to adopting green chemistry processes.

Reviews of new chemistry generally focus on changing to a different process from a previously approved synthetic route. It would be a very rare case where the evaluation of new chemistry would give rise to concerns over already approved chemistry. 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 Development**

Another opportunity for the FDA to inspire green chemistry incorporation exists pre-NDA filing, in parallel with Phase 3 clinical studies.

At the conclusion of Phase 2, a final route is selected and used to manufacture the material required for Phase 3 clinical trials. Once this has been accomplished, the Phase 2 manufacturing route is ‘locked’; and development halts in anticipation of filing this route with the NDA. During this period, novel methodologies, technologies, catalysts and so on will continue to be developed by the scientific community, and the ‘locked’ Phase 2 route can potentially regress into technological irrelevance.

The key to ‘unlocking’ this route for further development is the demonstration of comparability of a drug manufactured via the new green route, versus a drug used in the clinic that was produced using the original Phase 2 route. This is a similar concept to the comparison of drugs created by a generic firm making use of altered methodology, as opposed to a drug manufactured using the established patented and filed routes. Patient safety is, of course, immutable, so clarification on the FDA’s expectations regarding the demonstration of product equivalence and patient safety analytically (rather than clinically) can further encourage and justify 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 manufacturers make use of new synthetic methodology to produce an active pharmaceutical ingredient, establishment of equivalence is expected with regard to physiochemical properties, specifications, stability and impurity profile. If new impurities above set limits are introduced by the new chemical route, bridging toxicology may allow for 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.

**Why Go Green?**

It is worth asking: why should the FDA concern itself with green chemistry at all? A glance at the FDA website’s ‘What We Do’ section explains: “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” (5).

The FDA’s promotion of green chemistry could enable the achievement of greater public safety and healthcare, enhanced process efficiency, and potential reduction in
the cost of medicines. It could also spur on innovative ideas required for evolving industrial practices towards increased sustainability. The FDA is uniquely positioned to serve as an important catalyst for this realisation.

The FDA has two significant opportunities to greatly encourage green chemistry in the pharma industry, while still ensuring patient safety:

- By limiting the review of second-generation synthetic routes to new CMC sections only, and by clarifying expectations for the analytical equivalence of a drug substance (or substantial equivalence, as with Section 510(k) of the Food, Drug and Cosmetic Act regarding medical device filings), the 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, the FDA can enhance the development of greener processes pre-NDA. A path to equivalence will encourage green chemistry investment by pharma firms during Phase 3 clinical studies, ensuring that greener technology is increasingly used for drug manufacture.

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

FDA Response:

The FDA recognises 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 the marketed lifetime of drugs. It is the FDA’s intent to dispel misconceptions regarding perceived regulatory hurdles and to support and encourage the pharma industry in adopting green chemistry practices, while ensuring drug efficacy and patient safety.

References


5. Visit: www.fda.gov/aboutfda/whatwedo

Acknowledgements

The authors would like to thank the FDA team for their contributions to this article: Christine Moore (christine.moore@fda.hhs.gov), Ramesh Raghavachari (ramesh.raghavachari@fda.hhs.gov) and Jane L Chang (jane.chang@fda.hhs.gov).