Sustainable Drug Development: More than Being “Green”

A systems-based approach to optimizing for quality, safety, and environmental impact

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1. Introduction

Today’s pharmaceutical companies have a lot of “X” factors they need to optimize. In a highly regulated environment, they need to optimize for quality and safety, hence the concept of Quality by Design (QbD). But replace quality with an X (XbyD), and we can drop in any number of equally important objectives. There’s profitability—how can organizations get new drugs to market as quickly and cost effectively as possible? And, in part prompted by compliance demands, while in part prompted by economics and consumer expectations, companies are also seeking to optimize for sustainability.

But what does sustainability really mean? A smaller carbon footprint? Fewer toxic byproducts? Less hazardous synthesis? Cutting down on waste, engineering drugs that use safer chemicals and ingredients, and following more energy-efficient processes are all worthy goals, but each goal, in and of itself, is not necessarily sustainable. All too often, sustainability is viewed solely through a “green” lens – i.e., how much carbon is being produced by this process or that production facility? But this view of the issue can be shortsighted. While shrinking energy consumption can fall under the sustainability umbrella, optimizing for quality, safety, efficiency and environmental impact is a far more complex endeavor than optimizing for green alone. It involves trade-offs. The question is, how can drug companies best determine which trade-offs need to be made? How can they put themselves on a path to long-term sustainability that enables eco-friendly, productive and profitable practices for years to come? And what’s the role of emerging R&D technologies in making this happen?

2. “The whole is different than the sum of its parts”

To shine some light on the complexity involved in optimizing multiple parameters over a complex system, one can consider the ongoing sustainability debate in agriculture. In his writings on “Ecology-Based Agriculture and the Next Green Revolution”1), entomologist P. Larry Phelan argues that agricultural sustainability depends on bringing both reductionist and holistic approaches to agricultural management together. While reductionists are concerned with the individual components of a system—for example, addressing a specific challenge like low yield or destructive insects through the application of a chemical fertilizer or pesticides—the holistic camp looks at the entire ecological picture and seeks to understand how the multiple, complex components of agricultural ma-

nagement impact each other. How, for instance, do pesticides endanger the populations of spiders or birds that are beneficial to the agricultural ecosystem? What role do fertilizers play in the health of the local water supply? What if a short-term goal like stamping out a destructive aphid infestation has a broader long-term impact on the soil?

Addressing agricultural challenges solely at the component level can have (and has had) numerous unintended negative consequences, such as water pollution, or the creation or “super-pests” that are resistant to chemical insecticides. At the same time, the technological improvements driven by research done at a molecular level have led to big advances in crop yield and agricultural production—an important consideration in a world where an ever-growing population needs an ever larger supply of food. Phelan suggests that the reductionist and holistic camps need not be at odds, however, and instead argues that “reductionism and holism should be viewed as complementary rather than contradictory.” He goes on to say that for complex systems, the common phrase, “the whole is greater than the sum of its parts” may more accurately be stated as, “the whole is different than the sum of its parts,’ in that the result of component interactions may produce a state qualitatively different from its components.” In other words, agricultural researchers seeking to build a more sustainable industry need to think at a systems-level that balances component and holistic solutions. A systems-level approach can help them address the host of challenges they face, which include improving yield, long term productivity and food quality (as inexpensively as possible), as well as protecting the health of the soil, ecosystems and human communities that agriculture supports.

A parallel can thus be drawn between sustainability in agriculture and sustainability in the pharmaceutical industry. Pharmaceutical companies need to be able to efficiently and cost-effectively bring compelling new drugs to market. They also need to address the impact of their actions on the earth’s ecology, on members of society, and on their own ability to remain productive and profitable in the future. This means balancing a host of challenging (and sometimes competing) objectives on both a micro and macro scale.

3. Striking the right balance

When it comes to sustainability in drug development, improving processes and solving issues at the component level is important. Can the amount of hazardous byproduct produced by a chemical reaction be reduced? What are some ways that a processing plant can shrink its carbon footprint? Equally important, however, is understanding the bigger, systems-level, picture. What if a processing plant designed to significantly reduce toxic chemical byproducts also generates increased levels of CO2? In this case, a calculation needs to be made. Which action is more meaningful to an organization’s long-term sustainability goals? Using the plant and thus reducing the waste that may be put out into the environment? Or minimizing the amount of carbon that is produced? The less “green” approach may actually be more eco-friendly in the long run. True sustainability requires not only understanding the trade-offs that need to be made in these types of situations, but also understanding that it’s not a straight ahead trajectory. An organization may take one or two actions that positively impact sustainability only to have to take a step back in order to move forward again.

Striking the right balance demands that companies deploy informatics tools that help improve decision-making and data analysis. First, they need a systematic way of capturing, sharing and using R&D data across various scientific disciplines and departments. Second, they need advanced modeling and simulation tools that can help them better understand the fundamental “molecular” aspects of sustainability and then use this knowledge to predict sustainable (or adverse) outcomes before a great deal of time and expense has gone into experimentation. And third, they need to be able to facilitate streamlined, repeatable and sustainable processes up and down the product design-test-manufacture pipeline. All of these needs point to the importance of an “end-to-end” system that captures processes and fundamental science to create a “Learning Organization” that supports ongoing sustainability.

4. Creating a learning organization

In many R&D enterprises, individual departmental goals and an ever expanding organizational structure can get in the way of true knowledge sharing. The global reach of today’s pharmaceutical companies means that critical “learning” can easily get trapped in departmental, system and geographic “silos.” The chemists don’t share enough data with processing engineers, the processing engineers don’t communicate with procurement specialists, regulatory experts aren’t brought into drug design early enough, and so on. This disjointed information environment not only negatively impacts innovation—leading to errors, re-work, redundant experiments, and missed insights—it can also negatively impact sustainability efforts.

Research discoveries need to translate into drug therapies that are safe, cost-effective to source and manufacture, and commercially and ecologically viable. For example, just because something works in a microvial or on a test animal doesn’t necessarily mean it can sustainably (or profitably) be produced in thousand- ton quantities in 12 locations around the world. Having a better understan-
ring, as early in the R&D cycle as possible, of which compounds are going to be viable in a large-scale production environment, is just the type of insight critical to the trade-offs that need to be made in sustainability, such as cost vs. eco-friendliness, or quality vs. manufacturability. This requires greater information sharing and collaboration, particularly between early research contributors and the development and manufacturing side of the house.

Also important, especially considering the need to mitigate regulatory risk, is being able to document everything. Who did which experiment? When? What was the outcome? Systematically and consistently capturing organizational knowledge (whether experiments, processes or decisions) is one piece of this. Today there are a host of informatics technologies, like electronic laboratory notebooks (ELNs), as well as chemical and biological registration systems that enable organizations to better document and track R&D data. To create a more effective “learning organization” overall, this captured information also needs to be accessible and usable to stakeholders across the entire R&D enterprise—from chemists and biologists on up to project managers, research directors and top-line executives—regardless of where it originated. Thanks to the advent of platform solutions for scientific informatics that utilize web services and more flexible IT infrastructure, this is now possible. Web services facilitate the data and process integration that allows knowledge to cross disciplinary and departmental boundaries. Imagine capturing disparate information sources—such as data from chemical, biological and materials databases or ELN and LIMS systems—then feeding this data into modeling and simulation computations to gain additional insights, and finally publishing this information across various organizational departments. Armed with a tool that makes organizational knowledge easy to access and use, scientists, engineers, and project/product teams can make better, faster and smarter decisions that have a direct impact on sustainability.

5. The role of modeling and simulation

Today’s pharmaceutical and biotech companies are continually challenged to find new substances that have novel targeted therapeutic effects in a very crowded and competitive market. The requirements to have efficacy without adverse interactions or environmental impact are difficult to satisfy, and many of the simplest solutions have already been identified. In such a complex environment, computational models are useful in helping organizations better understand all the variables that can impact a potential drug’s viability as a profitable and sustainable product. For example, are there substitutes for a key compound ingredient that’s rare and difficult to source? Can we determine how much byproduct a chemical reaction is going to produce?

Software-enabled scientific modeling and computational techniques make it possible for researchers to design and test potential drug leads in silico. Instead of running multiple experiments in a lab, researchers can take advantage of simulations to virtually explore a broad range of candidates and better understand the trade-offs in terms of safety, environmental impact, performance, etc.—before doing any actual chemical synthesis or live testing. For example, computational models can leverage existing data sets (again, efficient and integrated information access is critical here) to predict the upstream and downstream behavior of various compounds, allowing researchers to narrow down their field of candidates to those that offer the greatest chance of being safe, stable and sustainable. The advantages of virtual approaches are several. First, the ability to virtually design and screen lead drug candidates means less time, expense and resources will be spent in the lab. Second, fewer non-viable candidates will be pushed forward into development, potentially saving millions in wasted efforts. Finally, greater insight into how pharmaceutical materials might behave in the plant on a large scale, enable more streamlined and sustainable production processes. What’s key is that in silico techniques can be deployed to more closely integrate the discovery processes surrounding target and lead candidate selection with testing, scale-up and manufacturing, combining both the small-scale, component approach of research with the bigger holistic picture.

6. Bringing it all together: a systems approach

A systems approach to sustainability demands that pharmaceutical organizations deploy technology solutions that help them get that holistic view of how every step in the drug development pipeline impacts sustainability. Beyond data integration, this also means being able to capture and automate “best practice” processes (whether focused on waste reduction, safety or product quality) that are consistent, predictable and repeatable. Furthermore, the highly specific, yet important, work done at the component level (a model that measures the process mass intensity of a chemical reaction) needs to be accessible and available beyond the few scientists who may have created it. This is why the end-to-end, enterprise foundation for scientific informatics described above is especially relevant when it comes to sustainability—such a solution can facilitate the data integration, process automation and information sharing required for better compound management, for virtualized science like modeling and simulation, for richer collaboration and a host of other activities.
Here’s a good example of better informatics and improved sustainability efforts in action: In 2005, a number of large pharmaceutical players, including Pfizer, Merck and Lilly, formed the Pharmaceutical Roundtable along with the American Chemical Society’s Green Chemistry Institute. The Roundtable’s goal is “to catalyze the implementation of green chemistry and engineering in the pharmaceutical industry globally.” But in this case, “green” doesn’t necessarily mean slashing carbon output (though that can be related benefit), it means cutting back on the use of hazardous solvents in chemical reactions, and thus reducing environmental waste. In order to do that, the participating companies sought to reduce the process mass intensity (PMI) ratio of chemical reactions involved in creating active pharmaceutical ingredients (APIs) (see Fig. 1).

The lower the ratio of chemical waste to API, the more eco-friendly the chemical process. One member of the group deployed an ELN to consistently and systematically track the PMI ratios of chemical reactions, capture models and experiments designed to identify less toxic solvent options, and build a tiered list of solvents (ranging from the least to most hazardous) that stakeholders throughout the organization can utilize. (see Fig. 2) The key here was having a solution in place that easily integrated data from multiple systems (such as chemical databases and modeling software) and that could easily be searched and leveraged by multiple ELN users. However, this important information should not be restricted to just ELN users. It should be accessible to anyone in the organization via web services orchestrated by an enterprise scientific informatics platform.

In another example, one of the largest pharmaceutical companies in the world is responding to increased regulation from Environmental Health and Safety organizations with an enterprise scientific informatics system that helps them assess the environmental impacts of their chemical manufacturing processes. Users of the system can enter a series of chemicals that are known byproducts of manufacturing, kicking off an automated workflow that retrieves data from a number of disparate sources. (The sources may include complex data types like chemical structures, biological sequences and even image-based data, and reside within corporate databases as well as public data repositories.) Once the data is aggregated, the in-

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2) [http://portal.acs.org/portal/fileFetch/C/WPCP_011424/pd/WPCP_011424.pdf](http://portal.acs.org/portal/fileFetch/C/WPCP_011424/pd/WPCP_011424.pdf)
This risk analysis system integrates data of multiple types from several locations and employs advance computations to assess the risk associated manufacturing a product depending on the initial components and intermediates.

When it comes to drug development, true sustainability comes in more than just the shade of green. Sustainable R&D practices help companies address environmental concerns, yes, but they should also help them mitigate regulatory and compliance risk, reduce costs, improve safety and turn out a high quality end product. Pulling all the right sustainability levers is a complex endeavor, but with the help of cutting-edge informatics, today’s drug companies can begin to make better and smarter decisions that take into account all the “X” factors involved.

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formatics system performs high-end statistical analysis and predictive modeling to assess the environmental hazards and risks. The results are then published to an interactive web-based report that anyone in the organization can use. The solution has allowed the organization to automate a highly complex and previously manual workflow, enabling it to provide deep insights into environmental safety risks (and hence sustainability) in a far more efficient manner. Multiple sites worldwide are now using this solution.

7. Concluding remarks

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Figure 3

This risk analysis system integrates data of multiple types from several locations and employs advance computations to assess the risk associated manufacturing a product depending on the initial components and intermediates.