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A QbD Implementation Roadmap for the Generics Industry

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The passage of H.R. 3962, the Affordable Health Care for America Act of 2009, has changed the healthcare landscape forever, kicking up dust in the U.S. pharmaceutical marketplace. One beneficiary of this legislation will be the generics industry. Generics got a boost from the Hatch-Waxman act in 1984, leading to a substantial increase in the number of filings and approvals of generic drugs. According to the Generic Pharmaceutical Manufacturers' Association, generics already comprise nearly 70 percent of all prescriptions written in U.S. market, and the portent for growth in generics will be tremendous once the new legislation is enacted.

The question that looms before us is this: will the major generics manufacturers, such as Teva, Mylan, and Watson, seize this opportunity to turn to more sophisticated tools like Quality by Design (QbD) and PAT to drive a wedge between themselves and the competition?

Innovators within the brand-name pharmaceutical marketplace have been debating the merits of ICH Q8, Q9 and Q10 since they were first issued more than five years ago. While big pharma and biotech have grappled with leveraging risk and quality, generic pharma has had limited discussion on the merits of pursuing ICH Q8 and Q9. Their reticence to embrace the principles of QbD revolves around the current business model for generic manufacturers in the U.S.

Unlike brand-name manufacturers that invest upwards of $1 billion and spend, on average, ten years to bring a new drug therapy to market, generic developers and manufacturers operate on a much more limited development timeframe. Their focus is on two critical business metrics: they must demonstrate clinical bioequivalence to the innovator drug and be the first to file their Abbreviated New Drug Application (ANDA) for review and approval.

Depending upon the type of ANDA filed (paragraph IV vs. paragraph III), first-filers can be granted 180 days of market exclusivity. Such metrics change the paradigm completely when it comes to product development. A generic pharma company will have months, not years, to reverse-engineer the performance of a brand product and demonstrate its bioequivalence.

The framework for proving bioequivalence is very tightly regulated by the Office of Generic Drugs (OGD), to the point where the Agency may actually define what specific assay or dissolution method is to be used by the generic company to demonstrate product performance.

Generic companies can enjoy the same double-digit profit margins as brand-name pharmaceutical companies without the large investment in development. Given this business model, what would possess a generic firm to contemplate a leading-edge approach such as QbD as a platform for its product development?

For both types of companies, the challenges facing the business process are actually very similar, but are presented in very different timeframes. Thus, the QbD opportunity can be distilled to a few simple questions. Is

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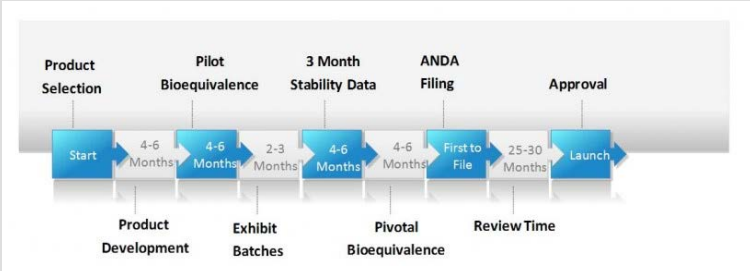
there a strategic advantage to developing a robust regulatory filing as quickly as possible? And if the stability and robustness of a process can be established at the product design stage, is there a tangible business advantage? I believe the answer is yes to both questions.

The QbD Opportunity

Despite the temptation to pursue business as usual, the generic industry has sought to implement operational excellence philosophies such as Lean manufacturing to speed TTM and increase profit. Other, more intensive approaches such as Six Sigma have struggled to gain a foothold, perhaps due to the more rigorous nature of the methodology and to the protracted time and difficulty in measuring its benefits. This reluctance may speak to the core issue separating brand from generic. Beyond clinical efficacy and safety, brand-name pharmaceutical companies primarily focus upon Time to Market (TTM) and ongoing Cost of Poor Quality (COPQ). The two metrics have an enormous impact on the near-term and long-term profitability of a new therapy. These considerations are no different for the generic industry.

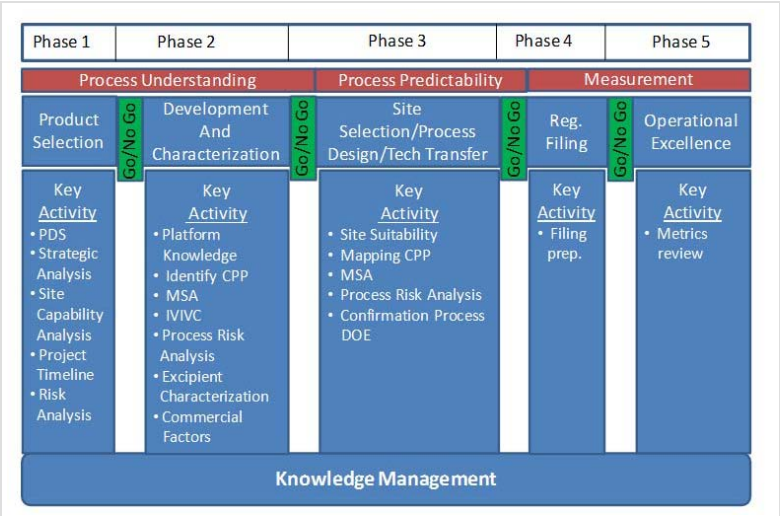
The typical product development roadmap for a generic drug is shown below.



The timing is generalized but the contrast between TTM for a generic drug approval and brand timeline of 10 years on average is noteworthy.

Creating the QbD Framework

The challenge facing R&D is the time allotted for development and characterization. To address this issue, a structured framework is required with clearly defined metrics and deliverables to minimize the risk of downstream failure. A proposed framework is shown here.



The framework consists of five phases that serve as stage gates or process review points within the development process. Each stage gate is intended to ensure that the elements required to minimize risk and

QbD Links

- Chemical Research, Development and Scale-up
- Design Space and QbD Blog
- dTC's Quality by Design Blog (Spanish)
- Emerson Global Life Sciences Blog
- FDA Homepage
- ICH Homepage
- Innovative Medicines Initiative
- International Pharmaceutical Quality
- Maxiom Group Blog
- Mining Drug Space
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- QbD Viewpoint

smooth the transition to commercial manufacturing are addressed adequately within the product development lifecycle. The framework is intended to address the core principles of QbD that we define as Process Understanding, Process Predictability and Process/Product Measurement. These three principles map directly to the four core principles of QbD: Product Design, Process Design, Process Performance and Product Performance.

Phase 1: Product Selection

This phase addresses criteria used for product selection. In addition to the primary principles associated with portfolio management, this phase proposes to add a component known as Site Capability Analysis (SCA). This ensures that the product design is compatible with internal or qualified Contract Manufacturing Organizations (CMO) capabilities, prior to the go/no-go decision. This is not to say that this consideration would outweigh the business opportunity of pursuing a new product, but it is one way to recognize that deviating from an organization's core capabilities will result in increased COPQ downstream and potential standard cost as well. As part of this exercise a Product Design Specification (PDS) should be developed summarizing the product's key attributes. Some product design elements, such as dosage form, strength, route of administration, identity, assay and content uniformity are expected to be constant during development. This is because there are regulatory requirements that must be the same as the reference listed drug or meet compendia standards. The PDS should include elements such as the recommended container-closure system if this is known, and information about pharmacokinetics and bioequivalence.

Any product risk analysis should be developed from a clinical perspective. This will frame the downstream process risk analysis and be the foundation for the process predictability and validation argument. Finally, a high-level project timeline should be developed for the program including anticipated regulatory approval. This can be used as one of the criteria for program performance at the end of the project.

Phase 2: Development and Characterization

The first five sections of an ANDA are the same as a Non-Disclosure Agreement (NDA). However, typically the level of understanding established in a generic development exercise pales in comparison to the innovator. This phase represents the largest opportunity for increasing overall business performance. To drive to better process understanding, a platform approach should be adopted for product development. By this I mean, most firms can lump their manufacturing expertise into broad categories, such as immediate release tablets, modified release tablets, modified release pellets in capsules, transdermal, liquids, creams and ointments or aseptic. Each product development represents a sum of unique knowledge gained in terms of process behavior and capability.

Similarly, the formulation knowledge gained from key excipient, binder and other functional excipient elements can serve as powerful starting point for all development activity. This platform approach allows all new programs to benefit from past development activity knowledge.

Before beginning product design and process design activities, the product risk analysis from Phase 1 should be used to compartmentalize risk in terms of the development choices made. If there is an In-Vitro-In-Vivo Correlation provided by the innovator, this can be used to steer the product design and characterization activity. As the formulation activity progresses, it is critical that all excipients be characterized along with the API so the baseline component variability is understood. The API's fundamental characteristics such as solubility, melt point, polymorphism, particle size distribution, bulk density and glass transition temperature should be captured as part of the development dossier. The same corresponding metrics should be applied to excipients being evaluated as part of the product design process.

A process risk analysis, such as a Failure Mode and Effects Analysis (FMEA), should be developed at this point with commercial equipment in mind. This will highlight key commercial considerations, such as environmental variables, storage conditions, etc., to be evaluated quickly and effectively at small scale.

Finally, a Measurement Sensitivity Analysis (MSA) should be used on all in-process and release tests used to steer and measure the process stability and product performance. This will ensure that the measurement tools being used to evaluate the process have the resolution to tell good from bad.

Phase 3: Site/Selection/Process Design/Tech Transfer

This phase is often one of the weakest because of the lack of process understanding during the development phase. However, after Phase 2 is completed, the equipment suitability decision as part of a site selection process should be much more robust. For example, if development work was performed in a 16-quart PK mixer and commercial production will take place in a 60-cubic-foot Gemco slant cone mixer, the critical process parameters (CPP) that drive mixing homogeneity should be better understood if the Phase development activity identified the CPPs that drive mixing efficiency and product content uniformity. This will allow the tech transfer process design to measure and compare process stability more effectively.

A commercial process FMEA should be repeated before initiating process design studies to ensure the critical to quality elements can be demonstrated at the commercial scale. The MSA should also be repeated after the

method transfer of any in-process and release test methods. Using the Phase 2 data, the process design should be able to establish a process capability metric before beginning the process tech transfer exercise that has a high probability of demonstrating process predictability.

Once these are completed, the process design exercise will be much simpler and have a maximum possibility for success.

Phase 4: Regulatory Filing
Having characterized the process and product performance, the limits filed within the ANDA and the batch record should represent a robust design space and control space which should not constrain the organization from setting performance metrics for the organization, process and product.

Phase 5: Process/Product Measurement
Process measurement will be a direct output from the structured development and process design activity. Monitoring and tracking the true CPP in addition to the products performance will allow the organization to intervene easily if the process begins to drift. More importantly, because of the detailed product design approach, the factors that drive the process drift will be understood, allowing a more focused investigation corrective action exercise. Finally, the business can use the organizations' performance at each stage gate as a continuous improvement driver for improved business performance, including metrics such as COPQ, Right the First Time, and compliance measurements such as the number of deviations and Corrective and Preventive Actions (CAPA) generated by each product.

Knowledge Management
The common element that will catalyze the greatest benefit throughout the development lifecycle is knowledge management. Establishing a structure which requires routine evaluation of past products and processes that are relevant to the product under development will simplify the development choices made. This can limit the risk profile of new products to those components and unit operations that are unique to the product.

Conclusion
For generics, the framework described may seem burdensome at first, but there are several elements that facilitate a faster TTM. Following a structured framework with clearly defined metrics at each stage gate will reduce any confusion and variability in the product development process. Integrating risk assessment tools is quick and will highlight opportunities that can easily be addressed cheaply early in the process. Establishing a knowledge management framework will move the organization to a broader and more comprehensive understanding of product and process design, breaking down the silo mentality that is rampant in most pharmaceutical companies. This change presents the biggest benefit for generic companies as it drives the organization toward a platform mentality that will simplify the development and commercial scale-up process. Finally, the structured approach allows the organization to measure and focus its continuous improvement activities upon those elements that have the largest potential to increase and sustain business performance.

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