

Mastering Change in Inhalation Drug Delivery

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Introduction

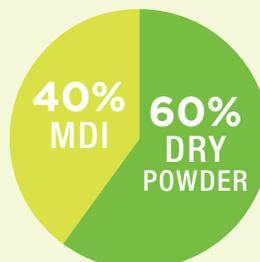
The first evidence of humans smoking *Atropa Belladonna* as a cough remedy can be dated back over 4,000 years. Fortunately, technology and expertise in inhalation drug delivery have improved significantly since then, offering better predictability, efficacy and safety of today's widely used inhalation devices.

The technology as we know it truly came into existence almost 60 years ago, when the pressurized metered dose inhaler (MDI) was invented. Today, these products are primarily used to treat COPD and asthma, but they are also suitable for many other therapeutic areas, including nasal drug delivery.

Currently, \$39 billion of the inhalation market is divided between MDIs and dry powder inhalers (DPIs), which make up 40 and 60 percent of sales value, respectively. With 940 million devices sold annually, pharmaceutical companies have big opportunities for their inhalation products, but they also face big risks—from generic competition, changing regulatory environments, and much more. This paper will explore some of the common changes that impact the inhalation market, as well as how pharmaceutical companies can position themselves for success in the face of these challenges.

INHALATION MARKET SALES REVENUE

\$39
BILLION
market sales



940
MILLION
units sold annually

Change is unpredictable by its very nature, but by examining the broad themes of change that have affected the industry in the past, pharmaceutical executives can gain some insight into what may come next.

“The only constant is change.”

- Heraclitus, 534-474 BC

3M™ Integrated Dose Counter, manufactured by 3M Drug Delivery Systems



Learning from the Past

Change is unpredictable by its very nature, but by examining the broad themes of change that have affected the industry in the past, pharmaceutical executives can gain some insight into what may come next. A review of some of the changes that have taken place in inhalation over the past 30 years may help illustrate how dramatically the climate has shifted for these products.

Environmental concerns have, of course, become globally prominent in recent decades, leading to the Montreal Protocol of 1989, which had a dramatic impact on inhalation technology by requiring the phase-out of CFCs. This led to the introduction of innovative new delivery methods and propellants for inhalers, including HFA propellants, and the first DPI.

Tighter dose and extractable requirements have also come into effect in recent decades. Additionally, the importance of patient compliance has grown, and the FDA is paying more attention to human factors in device design. This has increased the need for patient-friendly features like dose counters, which are now strongly recommended by the FDA and regulatory bodies in Europe.

Financial pressures have contributed to industry-wide consolidation. Mergers and acquisitions in the pharma industry have resulted in moves to and from out-sourcing; blockbusters are losing patent protection and generic competition is ever increasing. As a result, players in the industry are forced to be faster and leaner.

As these examples show, change has been unpredictable over the past 30 years, and it will remain so into the future. For players in the inhalation market, the best strategy for coping with this will be to manage their businesses so that they are proactively ready for change. In fact, companies that position themselves to drive change will be in an even better situation.

The following pages will explore some of the areas in which change can be expected. By considering how they might respond to changes in these areas, pharmaceutical companies can begin to put themselves on a strong footing to cope with whatever the future brings.



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Managing the Need for Material Changes

Sometimes what seems like a small change can snowball into a situation with a much greater impact. When CFC propellants were phased out, many initially thought of the situation as a simple material substitution. However, the change to HFAs had an impact on almost every aspect of drug delivery, and required teamwork across the industry to arrive at a satisfactory solution.

Examples like this show that it can be dangerous to underestimate the effects of material changes. Even a seemingly simple material substitution can result in significant challenges. Because the pharmaceutical industry uses many materials in relatively low volumes compared to other industries, pharma can be disproportionately affected by what may seem like a small change. For example, the polymers used in sealing rings are used in quite high volumes in other industries. If these other players require a design change or make a switch to an alternative product, the impact on the small volumes of polymers used in inhalation can be dramatic. In a case like this, either the cost of the material increases significantly, or the inhalation manufacturer must re-qualify the new variation to ensure it remains compliant. In some cases, inhalation companies will see both increased costs and the need for re-qualification.

Given the long list of components used in the 940 million devices produced annually, companies must be ready for nearly continuous change in order to support a product throughout its lifecycle. As coatings and polymers change, manufacturing processes are amended, and new sources for APIs enter the picture, it is vital for companies to have a plan in place for how to manage these conditions.

Working within a Highly Regulated Environment

Regulations have long played a role in driving change in the inhalation market. Today, the tight standards seen in the U.S. are becoming common around the world. As emerging markets begin to define their own standards, they frequently look to the U.S. and European Union as models. Therefore, as these very high standards become almost universal, patients can be assured of the quality of their products, but the costs for pharmaceutical companies to enter new markets will increase. These higher costs will ultimately impact the prices paid for inhalation products, particularly in emerging markets.

Many countries have put legislation in place mandating Good Manufacturing Practices, which not only enhances working conditions for those involved in manufacturing, but also improves the ultimate quality of the product. Of course, many contract manufacturers already maintain their own internal standards, such as Lean Six Sigma (LSS) manufacturing and process controls. Again, while legislation mandating quality-focused manufacturing processes ultimately results in better products, it can also mean more work and often means higher costs.

Managing Generics

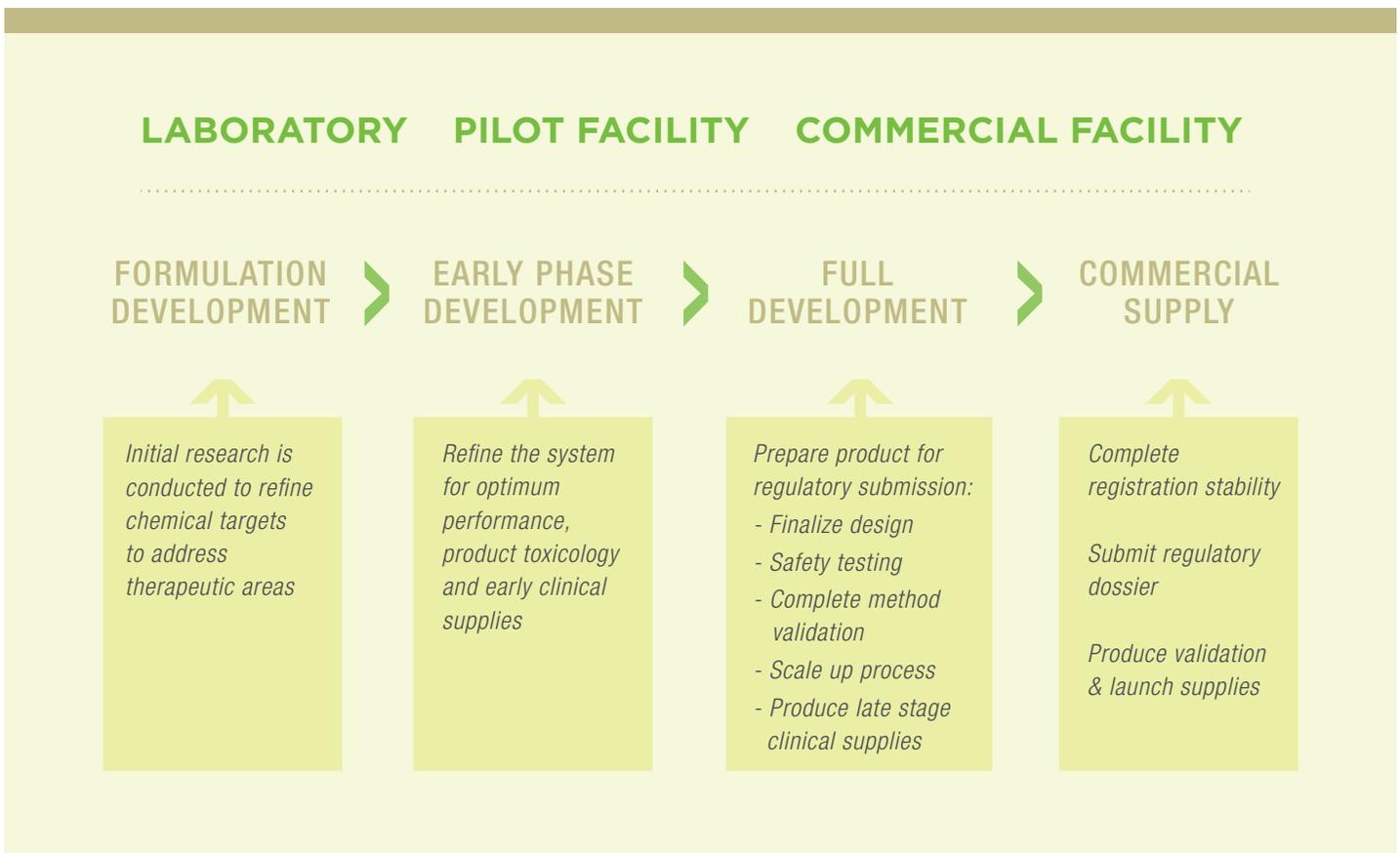
Patents on many blockbuster products are now close to expiring or have already expired. As this happens, regulators must determine how to control new generic versions of these drugs. Currently, the focus for generics is to achieve bio-equivalence of the innovator product, which is driving the demand for technologies that can analyze and replicate existing products. Regulators want to see that the new product compares precisely with the innovator and that it fits within the approved product specification.

Planning for Lifecycle Management

Experienced pharmaceutical professionals—whether in research and development, purchasing/ procurement, business development, or marketing—understand that there is no “typical” situation for a product lifecycle.

If generic competition doesn’t threaten a product, its life can still be shortened by new developments in the market or changes in regulatory requirements as demonstrated with the CFC to HFA transition.

When a new drug is being developed, the initial research phase can take one to three years, or even longer in order to refine the chemical targets to address particular therapeutic areas. Next is the development stage, during which the drug is taken through a series of phases to test its safety, efficacy, and other attributes. These steps are necessary to prepare the product for regulatory submission and approval, and can add an additional seven to ten years to the timeline. Once the product hits the market, it has six to 10 years of patent protection before generic competition becomes a threat. After this, the product can remain on the market for any length of time, though it will typically face growing competition.





Metered Dose Inhaler (MDI), manufactured by 3M Drug Delivery Systems

One real-life example of how this works can be seen in GlaxoSmithKline's blockbuster Seretide[®] which is also known as Advair[®], Adair[®] and Viani[®] in different markets. This product was first approved in 1998 and marketed in 1999. Its patent in the U.S. expired in 2010, and in the EU in 2013. There are currently no generic MDI products for Seretide[®] MDI in the US market. So, after the research and development time invested in this product, it has now been around for 15 years, and can continue on for some time. The launch of a generic can be expected, and will likely affect volumes and pricing for the product in time. With this example, it is easy to see how the long business cycle for an inhalation product, from concept to withdrawal from the market, can stretch upwards of 30 years.

Will products like Seretide[®], having 15 years of market success, remain common in the inhalation marketplace of the future?

It may depend on how carefully pharmaceutical companies consider lifecycle management for their products. Generic competition is impacting an endless list of treatments, and it takes real differentiation and an ongoing commitment to research and development to protect product market share.

The fact is, the investment required to lead the pack and fend off generic competition is just one of the costs of doing business today. In any industry, there are countless ways for competitors to mimic attractive products, so innovators must keep forging ahead.

IV Considering Patient Expectations

Integrating product features that take into consideration both patient expectations and ease of use from the beginning stages of development can be a very effective way to help products remain competitive in the face of cheaper generics.

One major theme that links patient expectations for the inhalation market is that of feedback and intelligent monitoring. A growing number of smartphone apps and other tools are helping to satisfy these demands, but inhalation manufacturers have the ability to provide more direct feedback mechanisms with their products. In recent years, companies have increasingly utilized dose counters and indicators to differentiate their devices.

In voice-of-customer workshops, patients have stated that they value having an accurate dose counter on their device, providing reassurance and improved control over their condition. This technology helps them confirm after use that a dose has been delivered, and also helps them keep informed of their remaining supply, reducing the risk that they will run out of medicine at an inopportune or even critical moment. In today's market, patients expect tools that help them stay informed about their treatments, and incorporating a dose counter on an inhalation device is an important way to meet this expectation.



This trend fits within the overall trend in the pharma industry toward promoting patient compliance by taking human factors into account. It has been estimated that non-compliance with medication costs the industry \$290 billion annually in additional costs as a result of complications with treatment, so addressing this problem can have significant benefits.

Partnering to Adapt

The task of preparing for change and responding to it is obviously multifaceted, and in most pharmaceutical companies, it may not be realistic for team members to tackle all these issues in-house. In these situations, working with a reliable outsourcing partner can go a long way toward helping a company prepare for the future while producing products that compete effectively in the current marketplace.

Pharmaceutical companies may look to outsource at various stages in the value chain, depending on their core strengths and the investment they are able to make in a program. It is becoming quite common for companies to outsource commercial manufacturing of products, as they realize that keeping this capability in-house requires considerable capital investment and infrastructure.

In the past, many companies looked to outsource manufacturing to emerging markets in order to contain costs, but recently many have turned to contract manufacturing organizations in the E.U. and U.S. These decisions are often made after a company has considered the total life cycle value of working with a manufacturing partner, rather than just the cost.

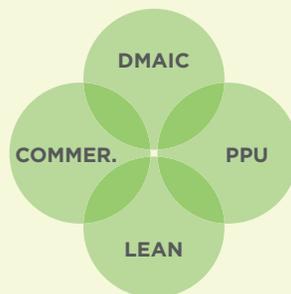
An experienced and broad-based manufacturing partner can help ensure that supplies are maintained reliably and with a high degree of quality, help manage regulatory hurdles, and work to solve other problems before they impact the program and sales. A strong manufacturer will also utilize Lean Six Sigma (LSS) or a similar process to maximize efficiencies, streamline operations and eliminate variation. Integrating the voice of the customer with established development and manufacturing processes helps give pharmaceutical companies a competitive edge while also enabling speed to market.

CONSIDERING PATIENT EXPECTATIONS

COMMERCIALIZATION

supports the NPI process in product development.

LEAN is a methodology that improves speed and reduces the cost of any value stream (process) by removing waste and eliminating non value-added activities.



DMAIC is a methodology that improves the performance of any process by reducing variation, decreasing defects and improving quality.

PRODUCT & PROCESS UNDERSTANDING is a methodology that aligns the voice of the process to the voice of the customer and promotes the transfer of that knowledge.



“It is not the strongest of the species that survives, nor the most intelligent that survives. It is the one that is the most adaptable to change.”

- Charles Darwin

VI Conclusion

It is vital for pharmaceutical companies to keep moving in today's inhalation market to stay on top of trends and the often daunting changes in the industry. The good news is that reliable partners who have experience with industry changes are available to help companies foresee and manage these trends and changes.

In searching for a partner, companies should look for one with a proven track record of delivering and adapting swiftly to new challenges. They should also look for a partner that has the stability and strength to ensure their own presence well into the future. By managing their businesses, being proactively ready for change, and building relationships with partners that will support them, pharmaceutical companies can confidently face the future, knowing that they have the tools they need to innovate and succeed.

3M: Experts at Commercializing Inhalation Innovation.

3M assessment of market value and volumes

3M research conducted in the USA and UK in 2008

Pharmaceutical Executive, June 2013

Seretide, Advair, Adoair and Viani are products and registered trademarks of GlaxoSmithKline.

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