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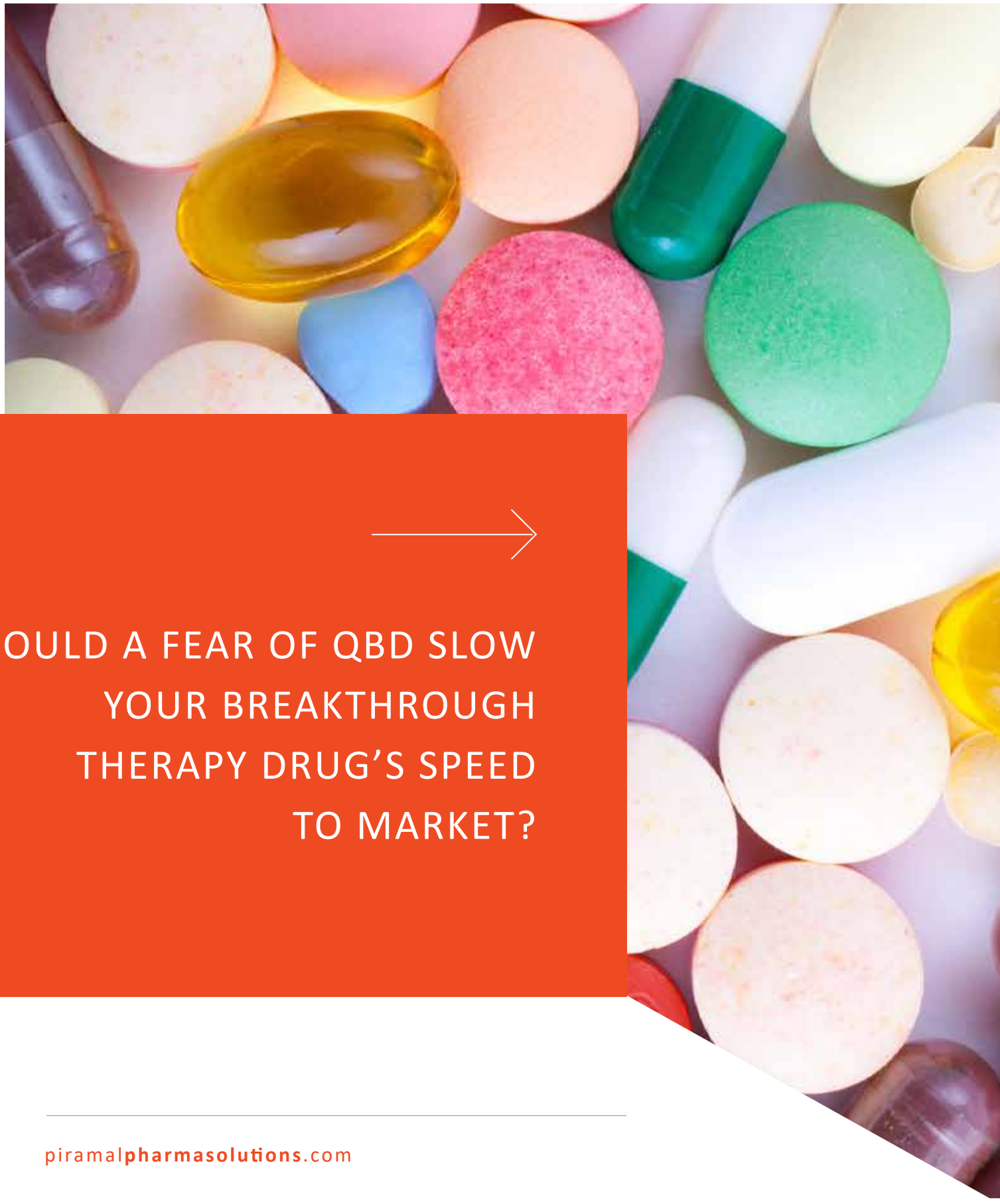

# COULD A FEAR OF QBD SLOW YOUR BREAKTHROUGH THERAPY DRUG'S SPEED TO MARKET?

# INTRODUCTION

The pharmaceutical industry's evolution from one that relies on the high revenue of blockbuster drugs to one that focuses on the unmet needs of smaller patient populations has changed the paradigm of drug development. It has also driven a rise in innovation over the past several years, due to the advances in technology that have generated new opportunities in the laboratory and in the body. Scientists learn more and more each day about how to produce products that can transform patient care.

The breakthrough therapy drug designation (BTD) made possible by the FDA's Safety and Innovation Act in 2012 creates even more potential for the treatment of many diseases. Its "fast-track" status paves the way for novel drugs to make it to market more quickly, giving renewed hope to those waiting on medications that could mean the difference between life and death. However, while the review process is expedited for a BTD, the expectation of the FDA remains unchanged when it comes to safety and efficacy. Proof of a drug's "profound clinical effect" must be accompanied by a development and manufacturing strategy that can deliver a consistent level of quality in the face of any market demand.

An approach well known for its emphasis on process understanding, process control, and risk mitigation is Quality by Design (QbD). While there are many benefits to QbD, there is longstanding skepticism about applying its tools and principles to drug development. This is due to not only the time and financial commitment required for successful implementation but also because of an industry that is well known for being risk averse. Nonetheless, as pharma continues to evolve, the drive to pursue new cutting-edge drugs will become even greater. For those companies competing to push the boundaries of innovation, a fear of implementing QbD might end up being the biggest threat in its race to the finish.

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# THE ROCKY ROAD OF A BREAKTHROUGH THERAPY DESIGNATION

As pharma navigates this new era, a company developing one of these niche drugs may find exciting early promise in the preliminary clinical evidence. If these results demonstrate a dramatic impact on patients with serious or life-threatening disease, a company may submit evidence to the FDA that it has a potential "breakthrough" drug. If granted, this designation expedites the review and approval process for a drug that also demonstrates "substantial improvement over existing therapies on one or more clinically significant endpoints."1

As of March 2017, 505 total requests have been made to the FDA for BTD, with 170 of those requests granted. Approximately 55 of these breakthrough therapy designated products have been approved, likely transforming the lives of millions of patients.2 Nonetheless, navigating the development and manufacturing process for any drug on a "fast-track" status can be extremely challenging. This is especially true if you do not have the tools and resources in place to identify and control any possible risks to the safety and efficacy of your product along the way.

Even if clinical data supports the submission of a new drug application (NDA) or biologics license application (BLA), a manufacturer must be ready to present its chemical, manufacturing, and control (CMC) information to regulators. The FDA needs this before it can provide approval as CMC data ensures the appropriate regulatory compliant manufacturing capabilities will be in place to meet market demand. Receiving breakthrough status also requires information about the product's critical quality attributes (CQAs), critical process parameters (CPPs), validation and launch plans, and even a post-approval lifecycle management plan.

In a traditional development timeline, it takes approximately 88 months before a drug reaches market approval, while a BTD can take as little as 53 months or sooner.3 This significantly reduces the time a manufacturer can dedicate to completing CMC development activities, creating a formulation, and establishing a manufacturing process that can consistently deliver a safe and effective product. As Janet Woodcock, director of the Center for Drug Evaluation and Research (CDER), noted at the Well-Characterized Biotechnology Products (WCBP) symposium in 2014, demonstrating efficacy of a drug is

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not the biggest challenge in the breakthrough drug program; the biggest challenge is ensuring quality manufacturing and access to the necessary diagnostics. This is where QbD can serve as an extremely valuable approach. Pharmaceutical manufacturing is already complex, but when you add in the pressures of bringing a BTD to market, it can become even more challenging. Through this systematic approach to process development, manufacturers can have confidence that the safety and efficacy of their product will be maintained throughout production, regardless of the timeline it is on.

## QBD ON YOUR SIDE

Principally, QbD is a scientific, logical, and preemptive system that incorporates quality control into each and every step of the drug development and manufacturing process. Most often, it is deviations, such as out-of-range specifications/parameters, low yields, etc., that negatively affect a drug development timeline. This is due to not having control strategies and a proper design space— the multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality.4 When a company seeks to drastically shorten its development timeline, it puts itself at an even greater risk for error. However, through QbD, a company can gain a better understanding of the impact certain parameters can have on product quality and, as a result, build in controls at these critical points.

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With QbD, a target product profile (TPP) is defined at the initial stages of development, which describes the desired performance of a product based on specific criteria, such as:

- clinical aspects
- dosage strength
- delivery mode
- pharmacokinetics
- drug product quality criteria and
- container closure system

From there, the manufacturer defines the quality target product profile (QTPP) in order to define the design criteria for the product and to identify the critical quality attributes (CQAs). Through the application of various risk assessment methods (e.g., flowcharts, quality risk assessments (QRAs), failure mode effects analyses [FMEA]), the critical process parameters (CPPs) that could affect the CQAs are determined. The combination and interaction of these variables creates what is known as a product's design space. Other tools, such as design of experiments (DoE) and process analytical technology (PAT), can also be used in a QbD approach. While they are not necessary, these tools can shorten the development time if applied correctly and contribute to the development of the design space. A manufacturer can work with and make changes within the design space after a product has gone to market without seeking approval from regulatory authorities. This manufacturing flexibility is often touted as one of the key advantages of the QbD approach, although the agency has yet to clearly define how this can be used in to reduce regulatory change burdens in a practical way. Any changes made after approval that are outside the scope of the design space would initiate a regulatory post-approval change process.

After the process described above is complete, a control strategy is put into place to monitor it and to ensure a consistent level of quality is maintained. This can be accomplished through a heightened scrutiny phase (HSP) that occurs post approval. During this phase, process/manufacturing and release testing data are subjected to increased sampling and testing; the results of which are monitored and evaluated for any out-of-trend (OOT) results. If any are detected, adjustments within the design space can be made as needed. Once a preset statistically significant number of batches have been successfully completed during this HSP (i.e., all products produced meet the established specifications), then the design space should be expected to continue to produce quality product. At this point, the additional testing needed during the HSP may be removed or relaxed and more routine testing can be applied going forward.

Regardless of how simple or complex a manufacturer wants to make its approach, the main goal of QbD is to think about the entire manufacturing process ahead of time in order to reduce variability and defects in a product. It is this heightened focus on quality that puts QbD in such a favorable light with the FDA. While the agency has not required QbD in product filings, it may see processes designed with the approach as more reliable since the process helps assure quality specifications are met more consistently. By streamlining the manufacturing and approval processes, a company can have confidence it is

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delivering a safer product to market. In a breakthrough drug scenario where speed is a key factor, this assurance of quality is especially vital to the success of patient care.

1. FDA, Fact Sheet: Breakthrough Therapies - https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/FDASIA/ucm329491.htm

2. Friends of Cancer Research, Breakthrough Therapies - https://www.focr.org/breakthrough-therapies

3. ADC Review, Editorial: Utilization of Breakthrough Therapy Designation for Market Access - https://adcreview.com/articles/utilization-of-breakthrough-therapy-designations-for-market-access/

4. FDA, Guidance for Industry: Q8 (R2) Pharmaceutical Development - https://www.fda.gov/downloads/drugs/guidances/ucm073507.pdf

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