Patheon
Performance the World Over

Recognizing Key Attributes of High-Quality Pharmaceutical Manufacturing:

Mitigating Risk, Maximizing Compliance in Outsourcing Relationships

Risk is intrinsic to most commercial enterprise, but few industries need to manage risk as closely, or assure quality as diligently as the pharmaceutical industry. With the advent of the Food and Drug Administration's (FDA) current Good Manufacturing Practices (cGMP) science and risk-based regulatory doctrine more than a decade ago, pharmaceutical manufacturers have been tasked with creating quality regimes within their production settings that assure quality through rigorous understanding of process and its intended outcome: safe, effective and affordable drugs.

Over the ensuing years, both the industry and its regulators have worked to introduce and refine the application of cGMP principles in pursuit of quality. Already well regulated, the pharmaceutical industry was guided quite directly to embrace and implement advances in all aspects of manufacturing excellence, from contemporary process and analytical technologies to the latest operational and administrative methods and practices. In the long march toward compliance, pharmaceutical companies accepted, adapted and implemented cGMPs into their operations with varying degrees of success. For many companies, compliance was problematic because implementing cGMPs across aging facilities with outdated, obsolete processes and operational procedures proved to be both economically and technically challenging to even the most prominent, financially healthy organizations.

At the 2013 ISPE annual meeting, FDA's CDER director Janet Woodcock offered this to attendees in her keynote: "The industry has to deliver quality, seeking dedication to quality from the shop floor to the executive suite." Perhaps easier said than done; creating a culture of quality often requires more from an organization than simply dictating its quality systems processes, polices and procedures to employees and expecting them to follow its precedents.

This gap between understanding cGMP concepts and actually implementing them in the production setting has manifested itself across pharma in a number of ways, but indicated most prominently in the steady rise in FDA's inspection tempo and the corresponding 483s and other regulatory sanctions mostly attributed to cGMP-based violations.

Number of FDA Investigators FY 2008 – FY 2012

Fiscal Year (FY)	Number of Investigators*
FY 2008	1,412
FY 2009	1,760
FY 2010	1,904
FY 2011	1,848
FY 2012	1,668

*Includes both domestic and foreign investigators

Number of FDA Investigators FY 2008 – FY 2012 cont'd

Fiscal Year (FY)	Domestic		Foreign	
	# of Inspections*	# of 483s	# of Inspections*	# of 483s
FY 2008	1,777	749	461	277
FY 2009	1,873	893	637	347
FY 2010	2,142	1,050	665	401
FY 2011	2,214	1,071	741	421
FY 2012	2,120	1,047	813	437

* These numbers include drug pre-approval, cGMP, and bioresearch monitoring (sponsor/monitor, clinical, non-clinical and institutional review board) inspections.

Although the industry is perceiving it's being exposed to increased regulatory pressure and a major uptick in violations, FDA statistics reveal that from 2008 through 2012 there has not been a dramatic leap year-over-year in the number of inspectors, the number of inspections and the number of 483s issued as a result. What the statistics do reveal is that the FDA is fielding a sustained and consistently strong inspection effort. Looking at it another way, however, in over five years there have been more than 10,000 inspections and nearly 5,000 483s issued domestically, and slightly more than 3,000 inspections and nearly 2,000 483s for overseas firms. This occurred with a relatively stable number of inspectors. It's apparent that in many cases pharma is struggling to truly understand and field operationally the technological and functional intricacies of cGMP.

Woodcock also perceives a disconnect: According to industry media reports in the wake of her ISPE appearance, "To my knowledge, there's no detailed common understanding within the United States about what GMP compliance exactly means," admitting perhaps controversially, that "In fact, the effectiveness of our inspection programs is unknown — even to me." She commented that there are not many written standards, and when they are written, they're high-level. "As a result, they don't tell you whether your operations are going to make the grade or not," she said, adding that the vision for 21st century pharmaceutical manufacturing industry encompasses, "A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight."

Quality Systems

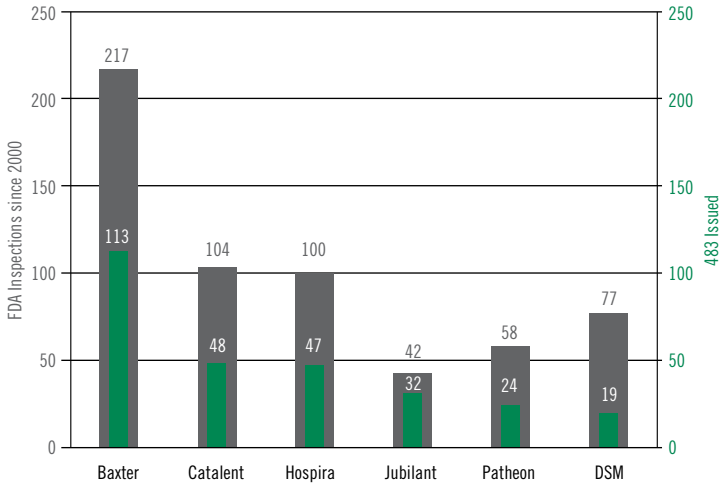
Regulators require pharmaceutical manufacturers to define and clearly articulate the quality systems it implements to support product quality. FDA regulations dictate that pharmaceutical quality systems include Standard Operating Practices (SOPs), adequate personnel and training systems, and an adequate system for recordkeeping. Fundamental controls that are institutionalized and codified to administratively assure drug quality is maintained as defined by a broad range of appropriate metrics and other relevant measures and standards. According to the International Conference of Harmonization (ICH) Q10 Pharmaceutical Quality System Guideline, effective quality systems are designed to be used throughout each stage of the product lifecycle and consist of four key elements:

1. Process Performance and Product Quality Monitoring
2. Corrective Action and Preventive Action (CAPA)
3. Change Management
4. Management Review of Process Performance and Product Quality

For the most part, a robust quality system spans laboratory control, production process, facilities and equipment, materials and packaging systems.

At the 2013 ISPE annual meeting, Woodcock also called for the industry's leadership to work harder to create a "culture of quality" and institute robust quality systems. Some argue that the industry has had at least 10 and more like 15 years to integrate cGMP and QbD doctrine into operations, reach a common ground with regulators, and create substantive, constructive

FDAzilla number of inspections and 483 letters since 2000



relationships with them to achieve compliance. Statistics from the FDA on the amount of warning letters leading CMO companies have garnered over the last five years reveal a commonly used yardstick of operational excellence in the face of tremendous regulatory and competitive pressures — and that some are doing better than others in attaining the operational excellence Woodcock's vision suggests and cGMPs mandate.

A Better Measure of Quality Performance

As noted, regulatory pressure over roughly the same period has been consistently strong. Recent data from FDAzilla.com reveals that since 2000, the increased scrutiny correlates well with the overall number of 483s issued to major global CMOs. Granted, for several, regulatory activity is par with peers, with a simple ratio along the lines of one letter per every two inspections, the trends show that companies with lower inspection rates also have fewer 483s overall, pointing to those organizations having a well-aligned and constructive relationship with regulators. But those numbers reveal only so much when it comes to making relative judgments on a given CMO's quality infrastructure and corresponding operational excellence.

A December 2013 sort of the inspections/483s data in FDAzilla.com's database reveals perhaps a better, more relevant metric with which to make comparisons. Because the major CMOs have a varying number of sites subject to inspection, a straight accounting of the total number doesn't really provide the apples-to-apples measure of a given manufacturer's

483 Issuance Rate 2000-2013

	# of Sites	Average annual ins.	483 Issue Rate %	Total Insp. 00-13
Jubilant	6	3	76	42
Baxter	48	15.6	52	217
Hospira	19	7.2	47	100
Catalent	19	7.5	46	104
Patheon*	12	4.3	41	58
DSM*	18	5.6	25	77

Source: FDAzilla.com database sort, December 2013
*This data reflect legacy Patheon and legacy DSM facilities prior to the formation of DPx Holdings B.V. and the realignment under the Patheon, DSM Fine Chemicals and Banner Life Sciences brand names.

quality performance and risk-management acumen. More appropriate perhaps is what FDAzilla.com identifies as the "483 Issue Rate," which is the ratio of the average number of annual inspections per year to the overall number of 483 observations since 2000.

For example, FDAzilla's data for DSM and Patheon just prior to the company's merger reveal both businesses had the lowest and second lowest 483 Issue Rates, respectively, among a self-selected peer group of CMOs. For example, legacy DSM's 18 sites had, since 2000, been inspected 77 times. During that period, the FDA issued 19 Form 483 inspectional observations resulting in an average of 5.6 observations per year and yielding a 25% issue rate over 13 years. Similarly legacy Patheon's 12 sites were inspected 58 times for the observed period, generating an average of 4.3 inspections per year and a 41% Issue Rate. Among competing CMOs ranked in this manner (see 483 Issue Rate Since 2000 chart), one firm generated a 483 Issue Rate of 76% across its six sites. The take-away is that both organizations brought legacies of quality performance and well-executed risk management strategy to the table, thus creating a strong foundation on which to support the critical operations of the post-merger Patheon going forward.

Devil's in the Data (Disconnect)

Pharmaceutical manufacturers institutionalize their quality systems in different ways, but few can argue that, however the approach, a sound quality system rubric can provide the means to manage risk effectively and provide

a path to continuous improvement and operational excellence. Certainly a robust quality system infrastructure is essential to administering quality effectively, but even though pharmaceutical manufacturers may be adept at demonstrating to regulators that these systems are in place and functioning, there continues to be a disconnect between how some CMOs administer quality and actually achieve it operationally.

Arguably, the 5,000 483s earned by the industry since 2008 do not so much point to gross negligence or even worse, some sort of upward-trending corporate malfeasance, but to something else — perhaps not as dark, but equally troubling if near perfect drug quality and subsequent regulatory compliance is to be achieved operationally.

A review of the top 10 observations that create 483 warning letters reveals that the violations producing regulatory action have more to do with 1) a pharmaceutical organization's inability to implement compliant procedures where they are prescribed by the FDA; 2) the ability to follow and execute well on its own quality regimes; and 3) not being able to document and deliver operational and process data that proves compliance to regulators.

Top 10 483 Warning Letter Observations

Rank	Observation	Total 2000-2013
1	211.192 Failure to Investigate Failure	232
2	211.100 (a)/(b) Inadequate Procedures to Assure Quality	184
3	211.160 (b) Inadequate Laboratory Controls	166
4	211.165 (a) Inadequate Testing Prior to Release	153
5	211.22 (d) Deficient QC Unit	129
6	211.67 (a)/(b) Cleaning/ Maintenance SOPs Not Followed	125
7	211.188 Batch Production and Control Records	100
8	211.25 (a) Employee Training	86
9	211.68 (a) Calibration/ Checking of Equipment	82
10	211.110 (a) Control Procedures/ Process Validation	70

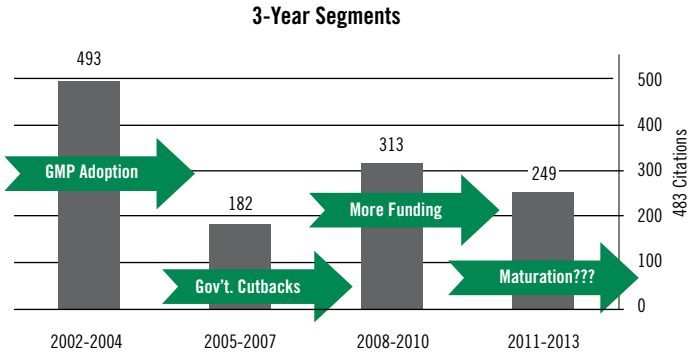
Consider the implications of the observation that has generated the most (232) 483 Warning Letters since 2001: 211.192 Failure to Investigate Failures. One, the nature of the observation points to a serious operational/quality administration disconnect. How can an organization claim operational excellence if their CAPA is not adequately investigating failures? Two, if the organization is not investigating failures, how is it ever going to adequately fix them? The company's shareholders might like to know as much as regulators.

What the Top 10 list reveals, perhaps, is just how challenged some organizations have been in fielding efficient internal organizational and operational elements able to administer and manage the complexities of not only quality-system implementation, but also its application to actual production processes, quality controls and subsequent documentation. The type and total number of observations for each category over time support that conjecture and for several, show improvement. The aggregate numbers also reveal an interesting trend that speaks to both the industry and the regulatory community's ability, over the last 13 years, to 1) better understand what actually is the practical application of cGMP in the field and 2) how such a common understanding informs both parties on what cGMP compliance actually is.

The waxing and waning of the number of observations over 13 years point to trends of another sort. The chart "cGMP Compliance Macro Trends 2000-2013" pushes the numbers into three-year segments. The chart correlates the total number of warning-letter worthy observations with the introduction of cGMP, the impact of budget cuts on the FDA's regulatory activities, as well as the effects of better funding and the possibility that the receding number of observations reveals something positive: When it comes to delivering quality, as defined by the cGMP framework, the industry is maturing, both in its ability to physically comply via the adoption of technology and operational excellence paradigms internally, and in its ability to quantify and communicate said compliance to regulators.

Most operational managers can understand that aligning standard operating procedures and implementing quality controls through existing organizational structures across facilities, units and departments is a daunting task — one made infinitely more difficult when investment in information systems, process automation and other facilitating technologies isn't sufficient to support operational imperatives that drive quality and mitigate risk, not to mention compliance.

cGMP Compliance Macro Trends 2000-2013



That is why the 483 issuance rate should be considered a highly valuable decision-making metric in which to judge the quality performance of a prospective CMO. Often within highly complex manufacturing operations these gaps are exacerbated by poorly integrated or obsolete information systems which fail repeatedly to generate meaningful, actionable information on a timely basis, and thus unavailable to support continuous improvement (can't manage what you don't measure) and equally important provide objective data to prove compliance to regulators.

If one accepts that the 483 issuance rate is a measure of organizational efficiency and competence, and operational excellence as it relates to quality controls and compliance, then it follows that companies with a lower issuance rate are well structured to assure FDA mandated quality and will be excellent stewards of the risk ultimately shared by both parties but shouldered by the drug owner. Macro trends point to a maturing industry and that we are at a point where the cream is rising to the top, especially when it comes to the CMO industry. However, among its peers, companies with a lower 483 issuance rate may be particularly adept at delivering the highest levels of quality at the lowest levels of risk, and through proactive dynamic quality systems keep that 483 issuance rate relatively low across the its operations.

During the past 15 years of regulatory discovery and implementation by the industry, a number of (now) well-known economic and competitive forces have come into play, pushing the pharmaceutical manufacturing industry to respond in new ways to emerging market trends, political agendas and scientific advances. Increasingly, branded and generic pharma are migrating the functional, operational aspects of both research and development manufacturing to contract organizations. This behavior is justified in many ways, informed by financial, competitive and operational exigencies. It's also viewed as a logical, strategic response to the rising complexities of the pharmaceutical manufacturing industry, compounded by its global reach and the growing demand for the therapies it produces.

Quality Is the Driver

The ever-increasing importance of quality and compliance in the CMO selection process is well documented and recently highlighted in the Nice Insights Survey from December 2013: "Rank of Industry Drivers Section." One of the take-aways in the study is that among reasons driving a CMO selection, the number one reason cited is quality. Not necessarily a surprise there. Clearly, contract manufacturing organizations that have consistently achieved high rates of compliance in the post-cGMP era (as indicated by the issuance rate of 483s) have a better handle on quality control, and therefore are likely to make better manufacturing partners — both over the short- and long-term.

Patheon is proud of its compliance track record. The intent of this white paper, first in a series of three, is to help executives and managers assigned to provide due-diligence of prospective contract manufacturing partners a framework in which to make a solid, objective evaluation of its overall operational excellence as it relates to quality. The next white paper in the series is intended to offer decision-makers further guidance on evaluating prospective CMO partner operations, and weighing the relative and technical merits of more specific aspects of quality and contamination control, as well as product-segregation strategies to eliminate those and associated risks within multi-product production facilities. The third white paper in the series will cover emerging Quality Agreements regulation, their impact on partnerships, and how both drug owners and CMOs can align themselves for success within this new regulatory environment.

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