The Real Cost of Poor Data Integrity in Pharmaceutical Manufacturing

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The reliability and integrity of all data generated for pharmaceutical products across the entire product life cycle are both a fundamental requirements of the pharmaceutical industry regulations around the world, but are also key to the safety and efficacy of all pharmaceutical products. The potential and real impact of good manufacturing practice (GMP) deficiencies that may affect data reliability and confirmed data-integrity breaches on the pharmaceutical industry, in terms of lost sales of impacted products and remediation costs, is well documented.

What is less understood, however, are the costs resulting from regulatory actions, such as Warning Letters (WLs) and import alerts to the industry in terms of product-approval delays and overall industry profitability. The following document provides an overall analysis of the real costs of poor data integrity and presents the case for a proactive approach to the assessment of risks to data reliability and accuracy in the pharmaceutical industry.

The Importance of Data Integrity to the C-Suite

Every business faces risk. Broadly speaking, the primary categories of business risk are market, financial, execution, and regulatory. Successful companies have developed a core competency in managing these risks, turning risk management into a sustainable competitive advantage. For drug manufacturers, recent trends have underscored the importance of managing regulatory risk in order to remain a viable business. More specifically, these trends have raised the profile of data integrity (DI) as a business risk.

Figure 1 summarizes the major trends that have led to the rise in importance of DI in the eyes of the regulatory agencies. It is important to understand that DI scrutiny is applied across the product life cycle, from development to market to product cessation. Most DI (and GMP) enforcement actions to date have focused on products in the market, but it is our assessment that the same scrutiny is now being applied to products in development, and this focus on the entire pharmaceutical product life cycle will only continue to increase.

The Challenges and Costs of Not Doing It Right

To be clear, ensuring that data is generated and maintained in a way that determines its reliability and accuracy is a continuous challenge, and getting DI systems and controls right requires a concentrated, continuous effort to develop and maintain the policies, culture, and discipline required to avoid regulatory issues. The challenges and costs to the pharmaceutical industry of NOT doing it right, however, are far greater. The time, hard costs, opportunity costs, and strategic distraction of fixing a DI regulatory deficiency significantly outweigh the investment of time and energy to create appropriate DI systems and controls. It is our opinion that appropriate DI systems and controls afford a company a sustainable strategic advantage.

The Regulatory Basics

The basics of the new DI regulatory environment can be found in the following four elements:

Who does it apply to?

In today's regulatory environment, GMP compliance and DI are expected from the entire pharmaceutical supply chain. This includes companies responsible for clinical trials, research, manufacturing, testing, and distribution. For the US Food and Drug Administration (FDA), import alerts and other market actions, as well as delaying the review of, or rejecting, New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs), are the tools of choice to enforce compliance.

Key focus areas

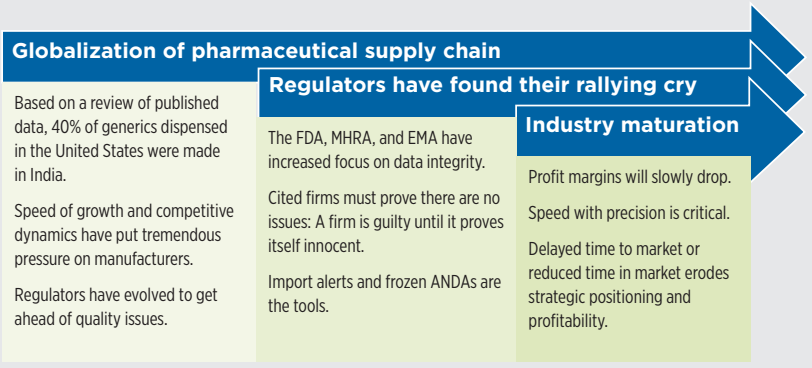
Regulators in the United States, Europe, and the United Kingdom recognize the growth in complexity and scale of the pharmaceutical industry and the contract service providers and global manufacturing partners that support it. Based upon multiple public presentations, regulators are increasing global inspections, as well as the focus of those inspections, to get ahead of product problems that may impact patient safety, product efficacy, and marketplace interruptions. Any laboratory or manufacturing data used to support regulatory approval or commercial product release is a constant focus for regulatory inspection. More specifically, the FDA and the Medicines and Healthcare products Regulatory Agency (MHRA) have both announced that they will continue to focus regulatory review and inspections on the integrity of data of all types.

Guilty until proven innocent

The FDA's stated policy is to not waste resources reviewing applications where there is a question of reliability. If the FDA feels that an applicant's processes, adherence to processes, or compliance history are not pristine, additional evidence in the form of supporting documentation and increased regulatory oversight to ensure compliance and the reliability and accuracy of data are required. Many market actions are now based on "lack of assurance" of GMP, as opposed to the specific finding or direct evidence of product defects.

For drug manufacturers, recent trends have underscored the importance of managing regulatory risk in order to remain a viable business

Figure 1: Key generic drug trends[1]



Aggressive data forensics

Regulatory investigators apply forensic investigative techniques to search for common deficiencies that may directly impact DI, including a lack of:

1. GMP knowledge
2. Understanding of regulatory expectations
3. Management interest in compliance reporting
4. Escalation of internally detected DI problems to management
5. Continuous improvement techniques
6. Mature and knowledgeable QA oversight
7. Strong electronic record controls

Recent Regulatory Environment

The United States FDA provides notice of regulatory deficiencies in a Form 483; when a firm's responses to this notification are not acceptable, the agency issues a WL. A review of publicly available information indicates that in the first 10 months of 2015, the FDA issued 16 WLs, of which 12 were DI specific, up from 10 in 2014 and six in all of 2013.

The FDA is not alone in its heightened focus on data integrity. The UK's MHRA report on inspections in 2013 highlighted an increase in DI issues while announcing the agency's heightened awareness in searching for such issues.[2] Of 630 GMP inspections in 2013, 216 showed major or critical deficiencies. According to the MHRA report, DI issues have been the key reason for the growth of critical deficiencies since 2013.

James G. Davidson and Stephen C.Mahoney, Senior Director, Global Quality & Compliance, Genentech, Inc., chat during a break at the Data Integrity Workshop.

From recently published information in Europe, the European Medicines Agency (EMA) conducted 50% more GMP inspections globally in the first half of 2015 than the same period in 2014. Its inspectors have also revised their approach to inspecting DI, becoming more aggressive and focused on detecting vulnerabilities in this critical area.

Impact of Regulatory Deficiencies on Profitability

With the rapid growth of the market for generic pharmaceuticals, economic and regulatory pressure on pharmaceutical manufacturers is increasing. In this environment, time to market has become even more critical to

shareholder value creation and sustainable profitability than it was before. However, speed without precision leads to compliance issues, particularly DI issues. With the frequency that DI is being cited in regulatory deficiency statements, DI problems are fast becoming the biggest threat to profitability for the pharmaceutical manufacturer, particularly generics. Market removal or delayed market entry could wipe away significant profits. Generic atorvastatin, for example, earned more profits in the first 180 days than in the subsequent 3.5 years.[3] In addition, market removal or delayed market entry significantly impacts project internal rate of return (IRR) along with the company's return on capital employed (ROCE) and cost of capital.

Certainly, regulatory actions will stress profitability, but this only adds to current market-driven pricing pressures expected over the next few years. Margins on products sold to the United States will be squeezed as reduced insurance reimbursement and higher deductibles are passing a larger percentage of drug costs onto the consumer. In addition, generics competition is increasing across most drug categories. To wit: The number of new market entrants grew by 7.7% annually from 2010 to 2015[4] (Figure 2).

Cost of Market Removal

Receiving a WL or other notice of regulatory deficiency will have longstanding financial impacts on a company. These impacts go beyond the profitability of the period in question (the annual loss of revenue and increase in costs); they continue to drag on profits over the long term by reducing a company's strategic options. Impacts such as lost pricing leverage by being late to market, increased costs of capital, a lower market cap, and employee and customer distrust all make it more expensive to do business. The scale of these impacts will vary based on a firm's product and manufacturing facility differentiation, along with access to other markets and access to capital. For example, a global firm with a strong product portfolio will weather the storm far better than a company with few product or facility options. To illustrate the impact of market removal due to regulatory action, case studies from four high-profile generics manufacturers are summarized in Table A. Along with regulatory highlights, the impact of regulatory action on revenues, expense, and opportunity costs are estimated based on publicly available information.

Cost of Delayed Market Entry

Analyses of historical performance data show that the bulk of generic profits are generated in the 6-month first-to-file exclusivity period. The average price point during exclusivity is 73% of the pre-generic high, while the average price point after exclusivity is 43% of the pregeneric high. This erosion grows with the number of market entrants for that drug.

The average number of manufacturers during the period of exclusivity has historically been fewer than two. Post-exclusivity, for drugs with over $100 million in combined annual sales among all manufacturers, there are at least seven manufacturers on average. Where the drug market size is around $40 million annually, there are just under five manufacturers on average.[7] The impact this has on pricing is significant (Figure 3).[8]

To illustrate this in the context of avoiding regulatory delay, consider a hypothetical generic drug product seeking a 180-day exclusivity entering a market where the branded price is $100 per unit. If the generic manufacturer has a $10-per-unit cost of production, the difference between achieving exclusivity and not (using averages) creates a difference of 19% gross margins. The bulk, if not all, of that gross margin goes directly to the bottom line. In an industry that averages just above 12% net margins, this is significant. Since regulatory action is based on the facility, and not the product, that effect could be multiplied across the products being produced at that facility.

When looking at opportunity costs associated with a market delay, these can also be significant. Figure 4 summarizes that analysis.[9]

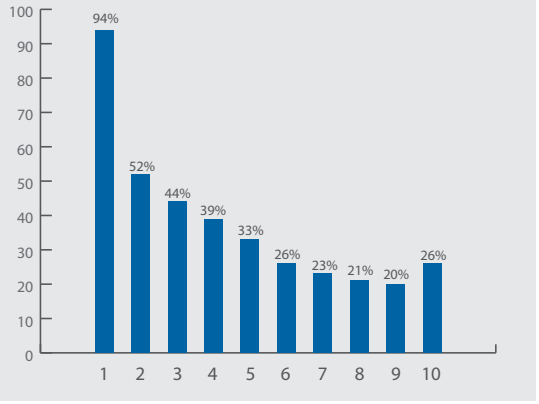
Diminished Strategic Options

Those who are familiar with regulatory action know that revenue and cost impacts are only part of the story. The longer-term impacts on strategy are several. Being forced from the market eliminates product leadership in that category and any price advantage such leadership might carry with it. The operational friction of response leads to inefficient allocation of management and line personnel, forcing decisions about which projects to focus on. The media attention causes embarrassment, which can impact employees, clients, and partners. Those same partners may renegotiate

Figure 2: Factors that affect profit margins

Branded generics	Branded pharmaceuticals leveraging manufacturing, regulatory, and distribution assets to continue production as branded generics.
M&A activity	Market concentration by larger players may increase pricing pressure on non-differentiated smaller players.
Fewer drugs coming off patent	Future off-patent cohorts will be smaller than in recent years, reducing opportunities for higher-margin generics. Drug R&D is generally being reduced or held steady due to investor and revenue pressures.

Figure 3: Generic price per dose by number of manufacturers in market



"It proved so successful, we kept the trial unit. The chemist and I wouldn't let it leave. We were able to achieve results that we weren't able to with the old system."

- Therapeutic products manufacturer

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Figure 4: Average opportunity cost of ANDA delay

$50,000: The average monthly opportunity cost of an ANDA delay.

This does not take into account expected profits on the drug once it goes to market, as that can vary considerably based on 180-day exclusivity, size of market, and company profitability.

Categories of Impact ↓

- Lower profits
- Disgorgement of profits
- Fines, regulatory burden
- Investor concern
- Lost opportunities
- Delayed time to market
- Partner friction
- Lost pricing leverage
- Increased cost of capital
- Lower IRR
- Reduced market cap
- Reduced M&A

terms to compensate for their increased risk. The reduction in cash to invest in the business, market products, or acquire assets hamstrings strategic-growth efforts. At the same time, the company's cost of capital is likely to increase as equity and debt become more expensive as the company risk profile increases. If a company is already in a poor cash position, equity dilution and uncomfortable loan covenants are possible. Finally, regulatory delays could reduce the attractiveness of the private company as an acquisition or merger candidate or make any terms very unpalatable.

For a generic drug manufacturer, the key levers to maximize time to profit for each product are in drug development, drug approval, and delivery to market. Managing regulatory risk through improved DI directly minimizes time to market by minimizing delays due to import alerts, remediation of compliance issues, and approval delays.

Strategies to Thrive

Of the 1,000+ generic pharmaceutical manufacturers across the globe, it is unclear how many operate in a way that ensures compliance with current and future regulatory agency DI expectations. Our experience tells us that the number is painfully low. Regardless, what does this mean for YOUR organization?

The decision on how to approach regulatory compliance is a strategic one, and varies based on the size and state of your company. It's risk–reward.

Table A: Market removal case studies

Regulatory details	Lost revenue and hard costs[5]	Opportunity and other costs
Major global manufacturer received a WL in early 2012 for a US plant, highlighting GMP and testing issues. This led to reduced output and the eventual closure of the facility for 9 months. The WL was closed out 2 years later. **Total cost: $64 million**	**Revenue:** Facility projections were reduced by **$20 million** for the remainder of FY 2012. Production shifted elsewhere, mitigating lost revenues post-2012. **Costs: $35 million** in remediation.	**Opportunity:** With a historical ROCE of 20%, opportunity cost of reduced profits estimated to be **$9 million**. The impact on delayed ANDAs is unpublished.
Large India-based manufacturer received a WL for a facility in late 2015. A previously FDA-approved innovator drug was rescinded, and generic production was forced to move. Site re-inspection is not likely until Q2 2017. **Total cost: $113–$133 million**	**Revenue:** Projected loss of **$50 million**[6] a year from a drug delay for at least the length of the import alert period (estimated at 18 months). Production at the facility is being shifted elsewhere. **Costs:** The amount of remediation and write-downs is expected in the 2016 annual report. Estimated to be **$25–$45 million**.	**Opportunity:** With a historical ROCE of 21.6% and net margin of 33%, the opportunity cost of reduced profits and increased expenses is estimated to be **$13.5 million**. The impact on delayed NDAs and ANDAs is unpublished.
Global manufacturer received a WL and import ban for two facilities in Jan 2015 and Mar 2015. Currently in remediation. **Total cost: $148–$178 million**	**Revenue:** Exports dropped $48 million from the previous year, after growing 39% over the previous 4 years. EBIT dropped $41 million. **Costs:** The amount of remediation and write-downs is expected in the 2016 annual report. Estimated to be **$40–$70 million**.	**Opportunity:** With a historical ROCE of 20%, the opportunity cost of reduced profits and increased expenses is estimated to be **$26 million**. 41 ANDAs and 38 DMFs are in jeopardy of experiencing delays.
Large India-based manufacturer received an FDA import alert in early 2013, followed by an MHRA recall of multiple products. Received a second facility import alert in late 2013, which was expanded to include all company APIs. All US products were recalled in early 2015. The MHRA closed out in late 2015, with the FDA closeout expected in Q2 2016. **Total cost: $911 million**	**Revenue:** US revenues dropped from 50% to 24% of totals from 2013 to 2015. A total revenue loss of $760 million is expected. **Costs:** Write-off of **$18 million** plus unknown remediation expenses. Further amounts expected in 2016 according to the annual report. Estimated to be over **$100 million**.	**Opportunity:** With a historical ROCE of 18.6%, the opportunity cost of reduced profits and increased expenses is estimated to be **$51 million**. **Other:** 7.2 million units were recalled, a loss of **$2.3 billion** in market cap.

Given the strategic complexities and challenges that generics will increasingly face, however, DI can be a sustainable competitive advantage in balancing speed with precision.

We have found those companies that have accepted that quality is an investment rather than an accounting cost center also realize that DI done right can create a sustainable competitive advantage. Investing in a system of accurate, effective, and sustainable compliance will protect profitability and shareholder equity in the long run, as well as serve to maintain brand goodwill among customers.

This requires a mindset shift away from being a victim of the winds of regulatory demands to proactively seeking the source of quality deficiencies. Many regulatory agency inspection-deficiency letters specifically highlight the lack of preventive actions as a reason for regulatory action.

With this in mind, we offer a few strategic tips to ensure that your company thrives in this regulatory environment and critical time in the pharmaceutical industry:

1. Develop improved R&D capabilities to fight pricing pressures on nondifferentiated offerings.
2. Develop a diversified manufacturing strategy of multiple products in multiple locations.
3. Speed time to market and maximize time in market by investing in the area of greatest focus and consequence during regulatory inspection: DI.

Best practice recommendations:

1. Be proactive and work with experts.
   - Work proactively with an outside specialist (fresh set of eyes!) to educate your firm and leadership on their responsibilities and the need for absolute personal accountability in ensuring the integrity of practices, data, records, and documentation.
2. Staff appropriately for the new challenges and increased expectations.
   - Ensure that your firm has sufficient quality and supervisory personnel with knowledge of DI systems, control, and oversight requirements.
3. Make DI standards clear.
   - Create and enforce company-wide standards for DI, the behaviors required to follow such standards, and provide expert training to effect, sustain, and monitor compliance with these standards for effectiveness.
4. Keep testing and monitoring for compliance.
   - Continuously and rigorously audit actual performance against integrity standards for the systems, procedures, controls, and documentation practices that ensure the reliability of data, records, and their documentation.

Support and Next Steps

To better understand the risks at your firm, it is recommended that knowledgeable and experienced, internal or external, resources be strategically and continuously employed in four primary areas to ensure the integrity of your firm's data.

Audit: Recommended prior to anticipated regulatory agency inspections and as a regular part of the internal efforts to ensure DI. Resources must understand the control and use of data systems and be able to review such systems electronically.

Training: Ensure, through continuous training and employ effectiveness measures that laboratory, production and quality staff can understand and apply, current and evolving DI principles.

Systems enhancement: Enhance procedures and policies as knowledge is gained and new regulatory requirements and expectations are communicated. Address internal and external inspectional observations.

Sustainability and controls: Ensure the adequacy of staffing, conduct internal and external audits, gather and analyze appropriate metrics, and commit to ongoing continuous improvement. ■

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About the Author

James Davidson, PhD, is the Vice President of the Science and Technology practice at Lachman Consultants. He is currently responsible for all aspects of Lachman's work in the areas of laboratory compliance, including data integrity, as well as API, dosage form and analytical development and QbD. He held positions of increasing levels of responsibility during his 20 years in the pharmaceutical industry at a major global pharmaceutical company, prior to his career in pharmaceutical consulting. Dr. Davidson has been responsible for all aspects of technical, chemical, analytical, and pharmaceutical development, from early development through commercial development and technology transfer of processes and analytical methods to commercial manufacturing. He holds an AB degree in chemistry from Hope College and a PhD degree in organic chemistry from the Georgia Institute of Technology.