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WHITE PAPER

The Real Cost of Poor Data Integrity in Pharmaceutical Manufacturing

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HIGHLIGHTS

1. The cost of reactive regulatory compliance is daunting, and erodes credibility with customers, employees, reduces time to market and limits future strategic options.
2. The risks of non-compliance increase with the number of NDAs/ANDAs and facilities, as increased scrutiny comes with scale, and regulatory authorities are willing to send warnings to multiple sites based on the review of one site.
3. A pharmaceutical manufacturer's #1 lever to pull to reduce risk of regulatory action is in improving Data Integrity. Doing so may provide a sustainable advantage in a highly competitive market.

OVERVIEW: 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 for 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").

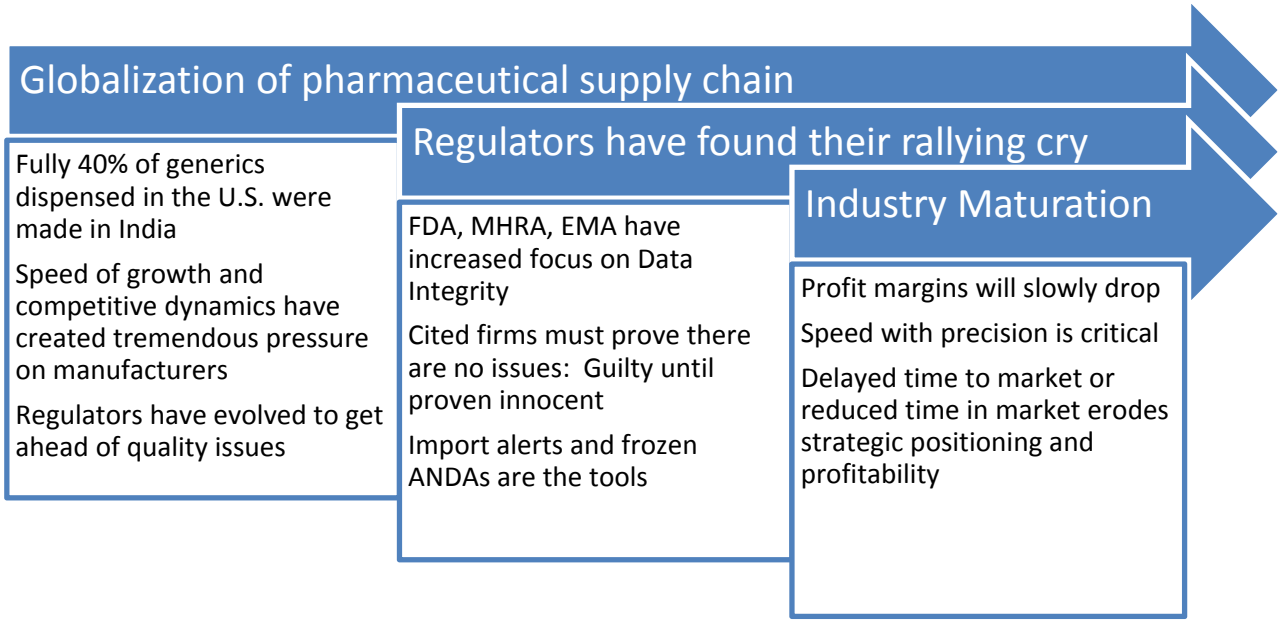


Figure 1: Key Generic Drug Trends[1]

Figure 1 summarizes the major trends that have led to the rise in importance of DI in the eyes of the FDA, MHRA, and EMA. It is important to understand that DI scrutiny is applied across the product lifecycle, 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 will only continue to increase.

The Pain of Not Doing it Right

Let's be honest. Getting data integrity right is a pain. It requires a concentrated, continuous effort to develop and maintain the policies, culture, and discipline required to avoid regulatory issues. However, it is a far, far greater pain to NOT do it right. 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 affords a company a sustainable strategic advantage.

> ***Data Integrity: What is It?***
> The degree to which a collection of data is complete, consistent and accurate.
> *U.K. Medicines and Healthcare Products Regulatory Agency (MHRA)*

The Regulatory Basics

The basics of the new DI regulatory environment are laid out in the graphic below.

[1] Wall Street Journal Corporate Intelligence, May 14, 2014; Acronyms: FDA (U.S. Federal Drug Administration), MHRA (UK Medicines and Healthcare Regulatory Agency), EMA (European Medicines Agency), NDA (FDA New Drug Application), ANDA (FDA Abbreviated New Drug Application)

Who Does it Apply To?

In today's regulatory environment, GMP and DI is expected from the entire pharmaceutical supply chain. This includes companies responsible for clinical trials, research, manufacturing, and distribution. For the US FDA, **'import alerts'** and delaying **review of new NDAs and ANDAs** are the tools of choice to enforce compliance.

Is there a Key Focus Area?

Regulators in the US, Europe, and the UK recognize the growth in complexity and scale of the drug industry, and are increasing global inspections as well as **the foci of those inspections** to get ahead of product recalls. **Any lab data used for regulatory approval is 'ground zero'** for regulatory inspection. More specifically, the FDA and MHRA have announced they will scrutinize DI.

Guilty Until Proven Innocent

The FDA's policy is to not waste resources reviewing applications where there is a question of reliability. If the FDA feels an applicant's processes, adherence to processes, or reputation is not pristine, the FDA will require additional support to prove lack of 'guilt'. **Many recalls are now based on "lack of assurance" of GMP, as opposed to the finding or likelihood of defects.**

Aggressive Data Forensics

Aggressive data experts hunt for common DI deficiencies, including lack of 1) GMP knowledge, 2) understanding regulatory expectations, 3) management interest in compliance reporting, 4) escalation of problems, 5) continuous improvement techniques, 6) mature QA oversight, **7) strong electronic record controls.**

Regulatory deficiencies come in the form of a 483, followed by a Warning Letter (FDA). In the first 10 months of 2015, 16 warning letters were sent out by the FDA, of which 12 were DI specific, up from 10 in 2014 and 6 in 2013.

8 Warning Letters to API Manufacturers

100% cited DI issues

8 Warning Letters to Dosage Form Manufacturers

50% cited DI issues

Global Warning Letters (It's not Just India)

2013: 100% to India
2014: 70% to India
2015: 56% to India

483s and Warning Letters do not explicitly state that an import alert or ban on review of new ANDAs is in effect, but that is generally what happens in practice, causing considerable delays in time to market.

Fastest time to resolution: 6 months

Average typical time to resolution: 12 months

Frequently takes 2 years

Warning Letters could take even longer

Figure 2: Lachman Consultants estimates of timelines to resolve DI issues in FDA Form 483

The FDA is not alone in its heightened focus on data integrity. The U.K.*'s MHRA* report on inspections in 2013 highlighted an increase in data integrity 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, DI issues have been the key reason for a growth of critical deficiencies since 2013.

Across the Channel in Europe, the EMA conducted 50% more GMP inspections in first half of 2015 than same period in 2014. Their inspectors have also revised their approach to inspecting data integrity, becoming more aggressive.

REGULATORY DEFICIENCY IMPACT ON PROFITABILITY

With the rapid growth of the generics market, 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 impact project Internal Rate of Return (IRR) along with the company's return on capital employed (ROCE) and cost of capital.

> ***Case Study: Lipitor and Atorvastatin***
> *In Q4 2011, generic atorvastatin entered the market to compete with Lipitor. With an estimated cost per unit of $7.75, gross profits of generic atorvastatin were $1.9 billion during the 6-month exclusivity. Keeping the cost per unit constant, gross profits were $1.8 billion over the next 3.5 years.*

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 US 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 2010-2015[4].

Compounding these effects is a likely reduction in the growth of generics' U.S. market share. Figure 3 illustrates the asymptotic growth from 60% just 10 years ago to 87.5% in 2014.[5] While the overall U.S. drug market is

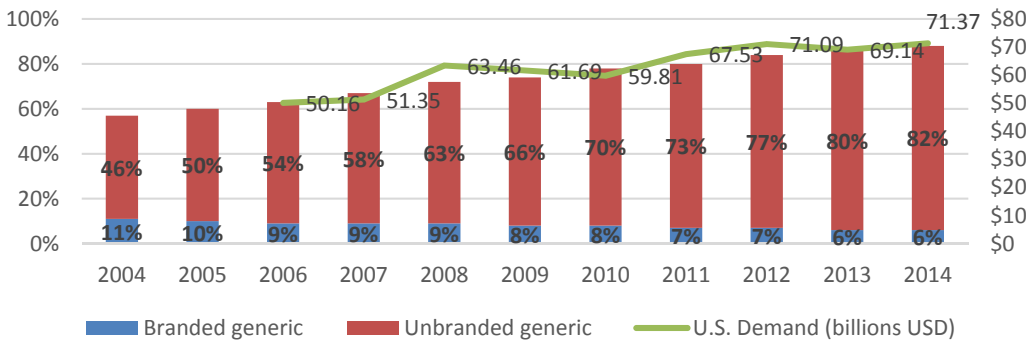


Figure 3: Generics as percentage of total U.S. retail prescriptions

[2] GMP Inspection Deficiencies 2013, published report by the MHRA

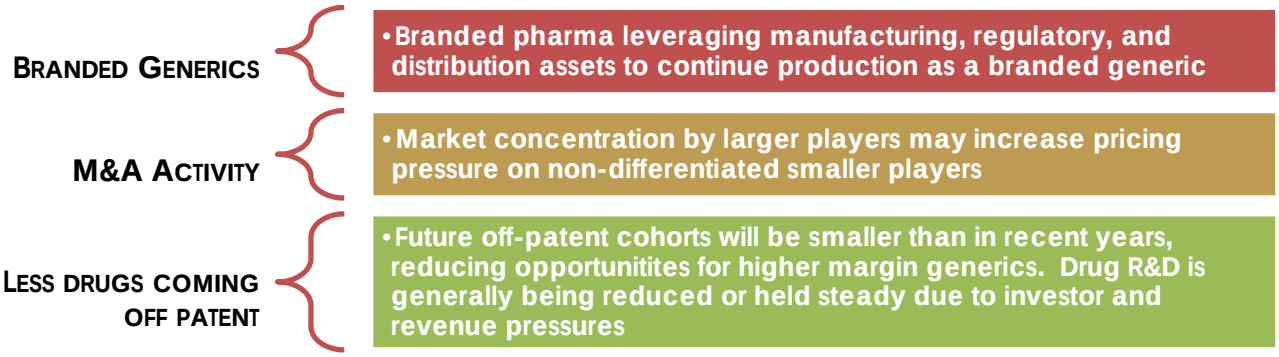
[3] Generic company gross margin of ~25% used, calculated against post-exclusivity price of $31/dose; Atorvastatin price per unit averaged $239 during exclusivity; Atorvastatin sales and per unit price from publicly compiled data

[4] IBISWorld Industry Report 32541b: Generic Pharmaceutical Manufacturing in the US, published Sep 2015

[5] Ibid, IMS Health, National Prescriptions Audit 2015

expected to grow at 4% annually through 2020[6], general industry consensus suggests growth will be driven by biosimilars.

Other factors impacting margins include the following.



Cost of Market Removal

Receiving a Warning Letter or other notice of regulatory deficiency will have long-standing 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 – **but 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, or 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 1. Along with regulatory highlights, the impact of regulatory action on revenues, expense, and opportunity costs are calculated.

Table 1: Market Removal Case Studies

Regulatory Details	Lost Revenue & Hard Costs[7]	Opportunity & Other Costs
Major global manufacturer received 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 two years later. **Total Cost: $64 million**	**Revenue:** Facility projections 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 WL for India facility in late 2015. Previously FDA approved innovator drug rescinded, generic production forced to move. Site re-inspection not likely until Q2 2017.	**Revenue:** Projected loss of **$50 million**[8] a year from drug delay for at least the length of the import alert period (estimated at 18 months). Production at facility being shifted elsewhere.	**Opportunity:** With a historical ROCE of 21.6% and net margin of 33%, the opportunity cost of reduced profits and increased expenses estimated to be **$13.5 million.**

[6] IBISWorld Industry Report 32541b: Generic Pharmaceutical Manufacturing in the US, published Sep 2015

[7] Financial Details from company Annual Reports for the periods in question.

[8] In some cases, securities analyst research was reviewed where figures were unavailable. Securities firm names withheld to protect company confidentiality.

Total Cost: $113-133 million	**Costs:** Amount of remediation and write-downs expected in 2016 annual report. Estimated to be **$25-$45 million**.	The impact on delayed NDAs and ANDAs is unpublished.
Global manufacturer received WL and import ban for 2 facilities on Jan 2015 and Mar 2015. Currently in remediation. **Total Cost: $148-178 million**	**Revenue:** Exports dropped $48 million from previous year, after growing 39% over previous 4 years. EBIT dropped $41 million. **Costs:** Amount of remediation and write-downs expected in 2016 annual report. Estimated to be **$40-70 million**.	**Opportunity:** With a historical ROCE of 20% the opportunity cost of reduced profits and increased expense estimated to be **$26 million.** 41 ANDAs and 38 DMFs are in jeopardy of delays.
Large India-based manufacturer received FDA Import alert in early 2013, followed by MHRA recall of multiple products. 2nd facility import alert in late 2013, expanded to all company APIs. All US products recalled early 2015. MHRA closed out late 2015, with FDA close out expected Q2 2016. **Total Cost: $911 million**	**Revenue:** US Revenues dropped from 50% to 24% of totals from 2013-15. Total revenue loss of $760 million expected. **Costs:** Write-off of **$18 million** plus unknown remediation expenses. Further amounts expected in 2016 according to annual report. Estimated to be over **$100 million.**	**Opportunity:** With a historical ROCE of 18.6% the opportunity cost of reduced profits and increased expense estimated to be **$51 million.** **Other:** 7.2 million units recalled, loss of $2.3 billion in market cap

A Note on Opportunity Costs

This analysis limits the estimated opportunity cost by only taking into account a company's Return on Capital Employed (ROCE). ROCE, calculated as profits divided by total capital invested in a company, provides a simple estimate of what the company would have earned if lost costs and revenues were invested somewhere else. The full impact on opportunity costs of lower profits, market delays and resource re-allocation depend upon the individual strategies and market opportunities of the company in question. This in-depth opportunity cost assessment is beyond the scope of this white paper.

Cost of Delayed Market Entry

Analyses of historic performance data show the bulk of generic profits are generated in the six 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 pre-generic high. This erosion grows with the number of market entrants for that drug.

Value of 180 Day Exclusivity
30% of the branded drug price

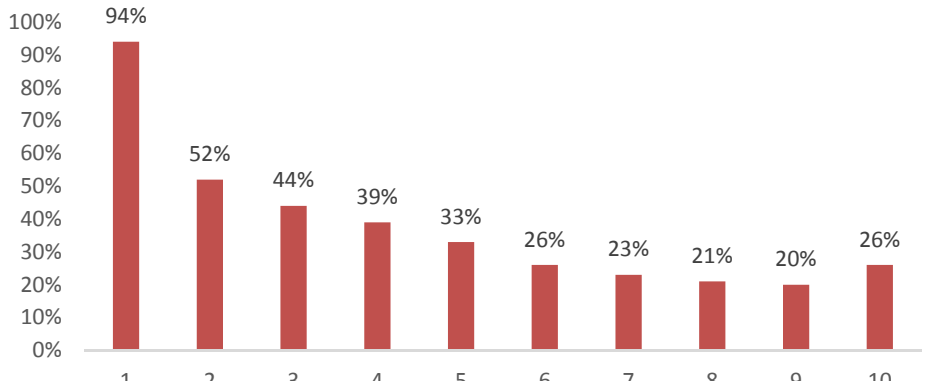


Figure 4: Generic Price per Dose by Number of Manufacturers in Market

The average number of manufacturers during the period of exclusivity has historically been less than 2. Post-exclusivity, for drugs with over $100 million in combined annual sales amongst all manufacturers, there are at least 7 manufacturers, on average. Where the drug market size is

around $40 million annually, there are just under 5 manufacturers, on average[9]. The impact this has on pricing is significant (Figure 4)[10].

To illustrate this in the context of avoiding regulatory delay, consider a generic 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 differences 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.

[9] FTC Working Paper #317, April 2013, "The Effect of Generic Drug Competition on Generic Prices During the Hatch-Waxman 180 Day Exclusivity Period"

[10] ibid

When looking at opportunity costs associated with a market delay, these can also be significant. Figure 5 summarizes that analysis.[11]

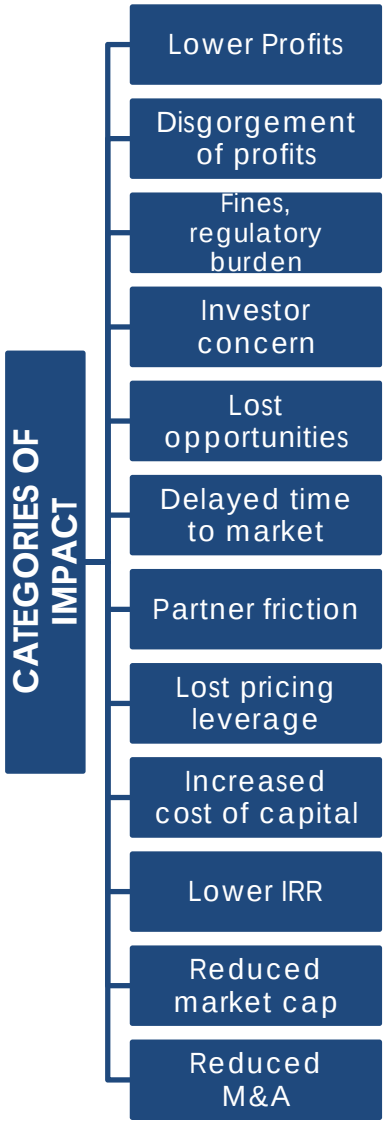
$50,000: The average monthly opportunity cost of an ANDA delay
This does not take into account expected profits on the drug once it goes to market, as that can vary considerably based on 180-day exclusivity, size of market, and company profitability.

Figure 5: Average Opportunity Cost of ANDA Delay

DIMINISHED STRATEGIC OPTIONS

Those that 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 on which projects to focus on. The media attention causes embarrassment, which can impact employees, clients, and partners. Those same partners may renegotiate 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 in a poor cash position already, 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 delivering 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.



[11] Cost of generic drug development is $1-$5 million, with the median cost around $3 million. Sources include "Gaining Market Share in the Generic Drug Industry Through Acquisitions and Partnerships", Thomson Reuters 2011. A review of public company records shows a reasonable ROCE in pharma is 20%.

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 data integrity 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. However, given the strategic complexities and challenges that generics will increasingly face, data integrity can be a **sustainable competitive advantage** in balancing speed with precision.

We have found that those companies which have accepted that **quality is an investment**, rather than an accounting cost center, are those that should expect to stay competitive in a tough marketplace. 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 amongst customers.

> ***Quality is an investment, and data integrity done right can create a sustainable competitive advantage.***

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 deficiency letters specifically highlight the lack of preventative actions as a reason for regulatory action.

With this in mind, we offer a few strategic tips to ensure your company thrives in this new era for generics.

1. Develop improved R&D capabilities to fight pricing pressures on non-differentiated 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 areas of greatest exposure for regulatory inspection - Data Integrity.

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BEST PRACTICE RECOMMENDATIONS

If you are improving your data integrity practices, or are considering it, here are a few best practices to follow based on our experience.

Be proactive, and work with an expert.	Add appropriate personnel.	Make standards clear.	Keep testing it.
•Proactively work with outside specialists to educate company and site leadership, along with all site personnel, on their responsibilities and the need for absolute personal accountability in ensuring integrity of practices, data, records, and documentation.	• Make sure you have sufficient knowlegible GMP/QA and supervisory personnel. One manager overseeing 200 scientists just won't do.	•Create and enforce company-wide standards for data integrity and the ethical behavior required to follow such standards, and provide expert training to effect these standards.	•Continuously and rigorously audit actual performance against integrity standards for the systems, procedures, controls, and documentation practices that assure the reliability of data, records, and their documentation.

WE CAN HELP

To better understand your risks and to improve time to market, contact us. We will explore how your company can gain or retain a sustainable competitive advantage through enhanced data integrity.

The four primary areas where we have found clients need the most help include

AUDIT

Preparation for inspection or as a proactive quality step

TRAINING

Ensuring lab, data, and auditing personnel can apply DI principles

ENHANCEMENT

Upgrade procedures and policies, address inspection observations or regulatory deficiencies identified in audits

SUSTAINABILITY & CONTROLS

Ensuring adequacy of staffing, internal and external audits, metrics and continuous improvement

To start the conversation, sign up for a webinar at www.lachmanconsultants.com, or contact Jim Davidson, Vice

President at 516-222-6222 or J.Davidson@LachmanConsultants.com.