



WARNING LETTERS GALORE: CAUSES AND PREVENTION

WHAT CAN WE LEARN FROM THE MISTAKES OF OTHERS?

With Warning Letters and other regulatory action hitting an all time high let's take time to reflect and ask "What can we learn from the mistakes of others?"

In preparation for this article I canvassed the opinion of some learned friends and colleagues within NSF and, importantly, some senior managers still at the industry coal face. This illustrious group have over 260 years' combined pharma experience, and the scars to prove it. Some have been on the end of Warning Letters and other severe regulatory action, all keen to share their experience. As one of them put it "The moment that letter arrives nothing gets quicker, easier or cheaper. Nothing".

Although the 10 'Causal Factors' is not an exhaustive list, your probability of severe regulatory action will be greatly reduced if you give serious consideration to the 'Learning Points'.

So, with their collective minds focused on causes and prevention, this is what they had to say!

CAUSAL FACTOR: MERGERS, MURDERS AND TAKEOVERS

Glance down the list of companies in strife and you see a few familiar household names. Most have one thing in common.

Over the last 2-3 years they either 'merged' or were taken over by someone else. Many of you reading this will know how this feels and what follows. The uncertainty, fear, confusion, complexity and chaos as sites are closed, departments streamlined and systems 'merged'. With everyone's attention focused elsewhere it's easy to take your eye off the quality and compliance ball. Attention focuses on the next mortgage payment rather than process improvement.

Change of this magnitude is not only disruptive but incredibly expensive and the accountants want to balance the books sooner rather than later. After all,

share price has to be protected and investors placated. Someone has to pay. This payment usually comes in the form of fairly immediate cut backs, streamlining and efficiency improvements that all tend to boil down to one thing. Do more with less.

Learning Points

Change of this magnitude is always complex, stressful and risky. Although we can't really do this subject justice in one small article our industry stalwarts advise:

- > Total transparency throughout the entire process. Lack of communication leads to a vacuum which is then filled with rumors and gossip, adding to the uncertainty. Above all tell the truth, the whole truth and tell it quickly
- > Pace yourself! The post mortems that follow every failed merger (a worryingly high percentage) always say the same... "They tried to do too much too soon" or, paradoxically, "they took too long". The key it seems is fast decision making to keep the momentum going.



AZ's CEO, Brennan said "Making decisions quickly and moving on is very, very important. If you drag it out everybody's tortured. We did 75% right but 100% fast" (ref: The Gold Sheet Vol 4 No 10)

- > Have a change management system that is fast and effective! During this process the volume and magnitude of change is immense. Absence of an effective change management process leads to chaos, disunity, massive risk and ultimate failure. Fast and effective change management, on the other hand, maintains order and intelligently manages both risk and valuable resource
- > Educate 'change leaders 'at every level. People are more likely to accept new ways of working if they have confidence in those leading them to the Promised Land. Change leaders maintain order out of chaos and respect and work with resistance, not fight it. Although change leadership is a skill that can be taught it rarely is. This is particularly important when you are attempting to merge cultures, not just companies. One of the biggest failures in merging quality systems comes down to cultural 'misunderstanding'
- > Accurate and reliable measures of quality performance. Maslow's pyramid of 'hierarchical needs' reigns supreme during any major change. With people's attention focused elsewhere mistakes happen. Levels of reworks, reprocessing, deviations, customer complaints, planned change, write-offs, out of trends, missed order due dates and other measures of performance need to be carefully monitored and action taken. How many fires are breaking out? What are the common causes? What must we do?
- > Escalation. During the transition from the old to the new organization things can go badly wrong. When a potentially severe incident happens anywhere in the supply chain this must be escalated, 'pushed upstairs', within hours. When these get buried in the organizational chaos surrounding many mergers senior management typically find out too late

WARNING LETTER HEALTH CHECK

Any of These Symptoms Sound Familiar?

	Yes	No
Recently merged or experienced massive organisational change?		
Do you lack 'Quality Oversight' of your entire supply chain?		
Your KPIs fail to drive quality improvement?		
Do you FULLY understand your processes?		
Are you suffering from over complexity?		
Are 'experts' leaving your organisation?		
Do your managers spend more time in their office than 'on the line'?		
Do your operators 'press buttons' without understanding why?		
Do you excel at firefighting?		
Have your Quality Systems ever been criticised by an Auditor?		

If you have said YES read this article and learn from the mistakes of others. Your health may be 'at risk'!

CAUSAL FACTOR: LACK OF QUALITY 'OVERSIGHT'

When regulators visit they have very little time to do a very important job. In theory they shouldn't find any surprises for a company genuinely 'audit ready'. After all, you have teams of people immersed in audits and self-inspections, periodic quality reviews, deviation investigations, product failure investigations and the like, with two objectives in mind. Find the problems, ideally before they mature into a quality defect, and fix them. One recently retired regulatory auditor commented "If I can find all this stuff in three days why the hell can't they?" Why indeed. With inspectors



finding more observations, not less, we can only surmise one or any combination of the following has happened:

- > The inspector's standards and expectations exceeded yours. Either because you set the wrong quality standard or they were being 'unreasonable' (more on this later). Keeping up with what's new on the regulatory front is challenging, particularly when supplying multiple markets
- > You found the problem but failed to implement the CAPAs
- > You implemented CAPAs but failed to prevent recurrence due to a poor 'root cause' investigation. You focused on the symptom, not the multiple causes
- > You failed to notify senior management through your escalation and performance measurement process... or you did and your warnings were ignored
- > With supply chain complexity increasing almost exponentially, quality oversight becomes even more challenging

Learning Points

- > Make sure you have accurate and reliable performance measures and a fast and effective escalation process. These are discussed in more detail later
- > You rely on your audit and self-inspection systems to monitor performance, identify weaknesses and fix them. For many, this internal surveillance system is clearly not working. To improve your chances of success we recommend:
 - Taking a risk-based approach. Focus your resources on areas of greatest risk
 - Focus on improving and maintaining your auditor's 'skill set'. Good auditors are remarkable people. They have excellent interpersonal skills; know where to look, and what questions to ask. They are able to assess risk pragmatically and offer solutions, not just state the obvious. Overall they add value and leave the plant

better off than they found it. If you want to know more about what makes a world class auditor come along to our course on 'Effective Pharmaceutical Audits and Self-Inspections'

- 'Certify' your auditors to set and maintain standards and ensure they are up-to-date
- > For your suppliers and third parties:
 - Firstly, build mutual trust and treat them as an extension of your site; establish good personal relationships. Make sure they understand the needs and requirements of the pharmaceutical industry
 - Use a risk-based approach to supplier auditing; those of greatest risk should be audited at least annually
 - Make sure your 'quality agreements':
 - Ensure you're notified of significant quality incidents and trends
 - Ensure you're informed of the outcome of regulatory audits

CAUSAL FACTOR: KPIS THAT DRIVE THE WRONG BEHAVIOUR

When it comes to motivation us humans are really quite simple. We're motivated by fear or reward, so the types of performance measures we adopt are vital. As the old saying goes, you get what you measure. So for companies in trouble this is typically what we see:

- > They have lots of performance measures, so many in fact that no one really pays any attention to them. Data is not turned into action
- > Mechanisms are slow and bureaucratic. By the time the data has been collected and analyzed it is too old to be relevant and used to drive continuous improvement
- > Measures are, in the main, output and accountancy based, leading to an obsession with getting product 'out the gate'. Measures on the manufacturing process and quality are largely ignored



- > Some performance measures are just plain wrong. Companies with a KPI to 'reduce deviations' by x% achieve just one thing, under reporting of incidents

One company insider laid the blame for their Warning Letter firmly at the door of 'senior management'. After all "a fish rots from the head down" he said. We don't think it's that simple. We think that most senior managers are no different to anyone else, doing the best they can with what they've got. Sure there will always be exceptions, a few rotten apples, but most make the best decisions at the time with the information they have available. Therein lies a problem. Often by design or default the data they receive is inaccurate, unreliable, accountancy based and too little too late. They think their legions are doing well, when in fact Rome is burning. They just haven't seen the smoke.



Learning Points

- > Decide what behavior you wish to encourage before you select your measure. 'Repeat deviations' is the only worthwhile measure for your deviation system. This tells you how effective your CAPAs have been!
- > Focus your measures on the manufacturing process and quality performance not output. If you improve the process and quality, output will follow. Manage your site using key metrics agreed by all functions

- > Process users must be made responsible for selecting the measures, collecting the data and using it to drive continuous improvement. From data collection to action and improvement should be days, not weeks or months

CAUSAL FACTOR: LACK OF PROCESS UNDERSTANDING

Our view is that many companies feeling regulatory heat simply don't understand their processes. When you have process drift you can't explain, high levels of rework, reprocessing and write-offs, it's difficult to convince anyone that you're 'in control'... because you're not!

Learning Points

- > Start taking Q8 seriously!
- > As a minimum everyone must have a firm grasp on what your products are used for, their key quality attributes and your process critical control points. Without this knowledge, engrained throughout your organization, you frankly don't deserve to be in business
- > Bring greater quality and compliance focus on R&D
- > Start removing process variability (ref: The Gold Sheet Vol 5 No 1 provides some excellent, pragmatic guidance)

CAUSAL FACTOR: OVER COMPLEXITY

A Warning Letter is another way of saying your quality system is no longer fit for purpose. NSF auditors often find bewildering levels of complexity. SOPs 30+ pages long, change control policies even Einstein would struggle with...the list is endless. A level of complexity that is unaffordable, increases risk and renders systems unworkable.

Learning Points

- > One company I visited recently in India was waging a 'war on complexity'. If you haven't, start now

- > Remember simplification is 98% perspiration, 2% inspiration. It has to be actively pursued
- > Make sure your change control system stops unnecessary change and complexity
- > CAPAs identified by your deviation reporting and auditing systems should focus on simplification
- > Train your people in simple thinking! On our course 'Human Error: Causes and Prevention' we provide delegates with the tools and techniques to win the war against complexity. Make sure you do the same

CAUSAL FACTOR: PEOPLE!

We all know the quality of any medicine ultimately depends on those involved throughout its lifecycle. At NSF we never cease to be amazed by the level of commitment shown by everyone we meet. Without exception, everyone is doing the best they can with what they've got. However, with companies in the regulatory spotlight we often see:

- > Erosion of expertise. One of our clients recently experienced a bad inspection. Things didn't go according to plan partly because many of the 'old hands' had left. In fact, 20% of the

QUALITY SYSTEM BENCHMARKING

Maintaining the Compliance - Efficiency 'Balance'

- > How narrow is your quality system 'control band'?
- > Are your quality standards 'fit for purpose'?
- > How does your quality system compare with the 'best in class'?
- > Is it 'Q10 compliant'?
- > What are your system's strengths, weaknesses and threats?
- > Are you doing too much or too little?

Many quality systems have evolved over time, becoming complex, bureaucratic, and costly. Some 'quality standards' are unaffordably high, others worryingly low. Knowing how high to 'set the bar' is tough, particularly without any external comparison. Set standards too high and your costs rocket, too low and you risk severe regulatory criticism. We can help you get it right.

Based on 25 years of auditing and consultancy experience we've developed a quality system benchmarking process to help you get more from your system.

The process is simple:

- > We objectively (qualitatively/quantitatively) assess each element of your system against our 'best practices' database
- > This gap analysis will highlight strengths, weaknesses, threats and opportunities for improvement. Areas where you're doing too much, too little or where you've got it just right
- > We don't stop there. We then help you strengthen your weaknesses, remove the threats, maintain your strengths and build on your opportunities for improvement

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subject experts had left within the last 3 years taking with them 80% of the organization's knowledge and expertise. Over 1,400 years of combined process knowledge was allowed to walk out the gate. No succession planning, no knowledge transfer and, in some cases, not even a replacement!

- > Over reliance on heroic management. During one visit I spent time with a stressed and exhausted QP who, two weeks earlier, recalled a batch he had released. Never a pleasant experience. The long and the short of it was he had inherited a quality system that was frankly broken. The only reason it worked, of sorts, was because people held it together by heroic management. The long hours, disturbed weekends, disrupted holidays type of heroism. This works to a point, until someone makes a mistake

Learning Points

- > Protect your in-house expertise and maintain your know-how. Your business depends on it
- > Quality systems built on heroic management are like houses built on sand. They fall down. Focus on fixing the problem, invest in robust systems and procedures

CAUSAL FACTOR: INVISIBLE MANAGEMENT

BMW's first and second lines of management don't have offices, even cubicles come to that. Their 'office' is the assembly line where they mentor their team and maintain quality standards, not by force but by example. 80% of their time is spent on the line, adding value. Why should they need an office? Contrast this with many pharma companies struggling to maintain standards where supervisors, wrestling with their email backlog, need a GPS to find their line. For many, plants and production lines have become management 'no go' areas where disciplines and standards are often enforced by inexperienced, over worked senior operators focused purely on output

Learning Points

Years ago Tom Peters introduced the term 'Management by Walking About' (MBWA). Let's start

practicing it, MBWA works. Get managers out of meetings, away from emails and on the processing line where they actually add value. That includes QA!

CASUAL FACTOR: TRAINING IS THE NAME OF THE GAME AND LIFELONG EDUCATION IGNORED

During a recent audit I asked an autoclave operator a simple question. "Tell me, how does it work?" To cut a long story short he knew which buttons to press and in what order but not why. When asked what he would do with a 'wet load' he responded 'dry it of course'. For those not involved in sterile manufacture, a wet load is potentially non-sterile! Those who press buttons without understanding the 'why that underpins the how' are potentially very dangerous, particularly when things go wrong. Managers and supervisors with limited knowledge of their products and processes are a disaster waiting to happen. Through no fault of their own, routine decisions are based on assumption rather than scientific fact

Companies who suffer severe regulatory censure share some common characteristics when it comes to training, even though their training records, on inspection, look perfect:

- > They don't understand the difference between training and education
- > Training is seen as a cost center and the first to suffer when the going gets tough
- > Leaders and managers feel their various degrees and MBAs exempt them from learning more
- > They insist on using methods that don't work. The 'chalk and talk', 'death by PowerPoint', 'bore them rigid', approach to training
- > Most is SOP based, focusing on which button to press
- > Large numbers of repeat deviations resulting from poor root cause investigations. Worse still, investigations that conclude 'root cause – human error'
- > Misuse and abuse of risk management due to poor understanding of the process, risk management or both



Learning Points

- > Invest in education and not training. Remember, education is what survives when what has been learned has been forgotten
- > See your education budget as a profit center. Without an educated workforce you can't improve processes, solve problems, make the right decisions and make a profit. Training gets you by, whereas education secures your future. Ask anyone in the midst of a Warning Letter or worse and they will tell you:

'If you think education is expensive, try a Warning Letter'

- > Make sure everyone is expert in the product and process. One of the benefits of 'de-layering' (aka headcount reduction) is that it



encourages faster decision making by those at the coal face. At least in theory. Without in depth expertise you don't stand a chance

- > Assess the effectiveness of your education program by what actually changes. Make sure you close the 'Knowledge-Doing Gap'
- > Read our last journal and adopt training methods that work!
- > And finally, focus your education on the why, not the how. Remember:

'In times of change the educated inherit the earth; while those trained find themselves beautifully equipped for a world that no longer exists.'

CAUSAL FACTOR: FIRE FIGHTING PAR EXCELLENCE

Finally, something companies in crisis are good at – fire fighting. Equipment problems, repeat deviations, customer complaints, rampaging OOSs, processing problems and more. So many in fact, nothing gets fixed. Band-aids are applied and preventative surgery delayed until the patient is critical. The trouble with fire fighting is that it's addictive and gives the illusion of progress. One company had so many deviation reports they even employed additional 'technical writers' to keep up. Meanwhile there was insufficient resource and process knowledge to conduct proper root cause investigations. The longer fire fighting continues the bigger the final inferno.

Learning Points

- > Make sure problems come to the surface quickly. Having a 30 day limit for deviation investigation and closure is ridiculous and encourages only one thing. More fire fighting as root cause remains unresolved
- > Make sure your deviation reporting system triages incidents to allow each to be investigated proportionate to risk
- > Change your attitude to deviations and problems. These are good, not bad. Each incident provides you with the opportunity to improve the process. Penicillin, Viagra, the ubiquitous 'Post-Its' and other great discoveries, all came from 'mistakes'
- > Make sure your QA surveillance system is sensitive and fast
- > Move from reaction to prevention

CAUSAL FACTOR: SETTING THE WRONG 'QUALITY STANDARDS'

It's not unusual to have disagreements during an inspection. You operate one standard and the auditor expects something else. In our experience this potentially serious situation can be due to:

- > Failure to keep abreast of regulatory changes in the pipeline. With the volume of changes



taking place this is perfectly understandable, particularly for those supplying multiple markets

- > No mechanism for interpretation and implementation across your organization
- > Lack of accurate and reliable 'benchmarking'; not knowing how you compare with others... are your standards unaffordably high or too low? Do you have the right control band?

Learning Points

- > Anticipating future regulatory changes is vital. As Louis Pasteur once said "Change favors the prepared mind". Make sure someone is dedicated to 'regulatory intelligence' gathering. If you know what's on the way you can plan for it. Although many companies are good at collecting this information they often fail to act on it. Key questions to ask include:
 - What's coming and when?
 - Is it a regulatory requirement or simply 'guidance'?
 - What do we do now? What is expected and what is the 'gap'?
 - What's our interpretation, what standard should we adopt?
 - What impact will this have?
 - How do we implement and monitor compliance?
- > Every company must aspire to achieve a 'narrow control band', with standards that provide a high level of control, compliance and efficiency. Benchmarking what you do with the best in class is vital. You may benefit from NSF's 'Quality

System Benchmarking' process where we compare each element of your quality system with the best in class. Using very objective criteria, we then help you to narrow your band to improve your efficiency and control

- > Our 'Executive Briefings' can help keep your leadership informed of impending regulatory changes and their impact, to help future proof your organization. Knowing how busy they are, these 1:1 sessions are kept short and conducted on your premises

IN CONCLUSION

Remember, when that letter lands (or its equivalent) nothing gets quicker, easier or cheaper. Learning from the mistakes of others takes senior management commitment.

On this point, one last quote from a very well respected SVP who kindly contributed to this article:

"Senior Management have to stop talking about the cost of compliance. There is tremendous pressure on costs these days and the first place a company looks to cut is in the indirect costs. The very people, infrastructure and systems you need to stay in business in the first place. Let's start focusing on the cost of getting it wrong and investing in prevention. It's a whole lot cheaper.

If you are struggling to convince your senior team or you would like help in preventing that letter arriving, call us, we can help!

For more information, contact pharmamail@nsf.org or visit www.nsfpharmabiotech.org

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