The Journal
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Are you thinking about...

Culture Change?

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welcome

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Welcome to the latest edition of the NSF-DBA Journal. We hope you enjoy reading the articles, comments and observations on the industry we serve. The theme of this edition is 'Facilitating Change'.

Our objective when we work with our clients is to bring about change. We aim to leave our clients better than we found them – perhaps better aware of the rapidly changing regulations that govern our industry, better aware of their strengths and areas for improvement and, most of all, better motivated to build on those strengths and to improve in those areas where improvement is needed.

We live in changing times and the pace of change is accelerating day-by-day. Those companies which embrace change will succeed in an increasingly competitive world, whilst those which don't will be left behind. We have helped many companies to embrace change and we have watched them improve and prosper as a result.

Change can take many forms – changes in facilities, equipment, processes, procedures, people and corporate culture. Most of these changes are relatively easy to achieve – all they take is time and money! The hardest change to make is the change in culture, but it is by far the most important, as without it many of the other changes are just window dressing and, most importantly, impermanent. There is an old joke, "How many psychiatrists does it take to change a light bulb?" Answer – "First the light bulb has to want to change". The same philosophy applies to culture change. That is why we work with people at all levels (starting with senior management) to bring about lasting culture change within organizations. So far, the results have been impressive, whether we are working with small companies wishing to improve Quality Assurance and relations with regulatory agencies or multinational companies wishing to empower staff at all levels to take ownership of Quality, and those companies who have used us keep inviting us back.

As you will see from the articles, we have helped companies to achieve lasting change through consultancy (as evidenced in Ron Johnson's article) and through training and education; both through residential courses such as QLP training and via tailored in-house education programs.

We believe we can help you too. If you are interested in discovering how we can change the culture in your company for the better, please contact us. We are here to help.

Lastly, to show you that we practise what we preach, we are going through change ourselves. Over the coming year we shall be aligning the various services offered by ourselves, Becker & Associates, NSF Pharmalytica, NSF Reference Standards and NSF Dietary Supplements into a single division to better serve our clients in pharma/biotech, medical devices and nutraceuticals/dietary supplements. The formation of NSF Health Sciences will mean the eventual loss of company names such as DBA and Becker, but only the names will change; quality of service and what we stand for will never change – they are not negotiable! We will keep you informed of progress through future editions of the Journal.

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Quality Culture For The 21st Century

Is your Quality Culture Fit for Purpose?

Want to find out?

by Martin Lush

If you Google 'culture' be prepared for days of reading. Let's just say, for the sake of expediency, that ***culture is defined by the actions taken, under pressure, when nobody is looking***. Like a moral compass, your Quality Culture keeps you heading in the right direction no matter how stormy and unpredictable the weather. With Consent Decrees, Warning Letters, fines and prosecutions running into $billions, the Quality Culture of some pharma companies, including some big players, is not what it needs to be. Their compasses are clearly pointing in the wrong direction. So how is your compass? Do you have a Quality Culture capable of navigating a chaotic and unpredictable 21st century?

To find out, grab a few colleagues and complete the following tasks. They will only take a few minutes. Tackle each as if your jobs depended on them. You never know…

TASK ONE: Time for Reflection

Let's start with a 'Quality Culture Health Check'. Answer the following with a simple yes/no:

- Frustrated by your hierarchy? Yes ☐ / No ☐
- Suffocated by your bureaucracies? Yes ☐ / No ☐
- Exhausted by internal politics? Yes ☐ / No ☐
- Management not walking the talk? Yes ☐ / No ☐
- Decision making awkward and slow? Yes ☐ / No ☐
- Insufficient education budget? Yes ☐ / No ☐
- Management focused on profit alone? Yes ☐ / No ☐
- Suffering from 'death by measure'? Yes ☐ / No ☐
- Change control system slow, complex and unwieldy? Yes ☐ / No ☐
- SOPs and documents complex and impossible to follow? Yes ☐ / No ☐
- Do crisis and fire fights dictate your agenda? Yes ☐ / No ☐
- Absence of visible and approachable leadership on the shop floor? Yes ☐ / No ☐
- Suffering from initiative overload, trying to do too much? Yes ☐ / No ☐
- Staff turnover or attrition greater than 5%? Yes ☐ / No ☐
- 30-day time limit for closure of deviations? Yes ☐ / No ☐

A 'yes' to any and your culture is probably not fit for purpose. A 'yes' to many? Well, your compass (Quality Culture) is taking you in the wrong direction. You need to read on, your job may depend on it…

So, what does a good Quality Culture 'feel like'? Since NSF-DBA are lucky enough to have some of the finest consultants around, we asked 10 of our most experienced colleagues "what does it feel like when you walk into a company with a good Quality Culture?"

TASK TWO: The Honesty Test

This is what their combined 330 years' experience has taught them to expect. How do you measure up?

- A genuinely warm welcome from security and reception
- Demonstrable pride and ownership in everything at every level (the workplace, engineering workshop's documentation, the cafeteria). Everything says 'we care'
- An environment where people REALLY matter – contractors and agency staff as well as full-timers
- Minimal levels of hierarchy and bureaucracy
- A clean and well maintained plant. Not necessarily state of the art… just well looked after. From the toilets to the Class 100
- Leaders who are modest, visible, approachable, passionate, and informed. Leaders who care about what they do beyond the profit and loss account
- A culture that is open, transparent and focused on excellent face-to-face communications
- Rigorous discipline. After all, when you have disciplined people, you don't need hierarchy, bureaucracy or excessive controls
- Excellence in the basics of GMP
- Patient-centric thinking at every level with excellence in risk-based decision making
- A very strong health and safety culture and ethos. GMP and health and safety are different sides of the same compliance coin. Both depend on positive behaviors and habits
- Low rates of turnover, typically less than 5%. People feel valued, engaged. They want to stay
- Confidence in junior staff and operators, the true custodians of quality. Clear accountability and ownership
- Total integration of QA on the shop floor. QA staff who understand the process and operators who understand the Pharmaceutical Quality System (PQS)
- Total congruency in objectives, actions, measures and rewards. No contradictions that confuse and drive the wrong behavior. 'Quality is non-negotiable'
- An obsession with right first time and a passion for simplicity. An intolerance of waste and complexity
- Mistakes are genuinely seen as good opportunities for learning, personal development and improving profit
- Suppliers and third parties are considered 'one of the family'. An extension of the production line. Treated with respect and valued, not taken for granted

Best-In-Class Practices

Over the last 27 years NSF-DBA has worked in partnership with many clients to make their Quality Culture fit for the future, not the past. A 21st century Quality Culture doesn't just evolve or happen by accident. It is a product of disciplined focused effort from the

top down. As one of our clients put it: "it's 98% perspiration, 2% inspiration". The gurus reckon 4-5 years of disciplined, painstakingly focused effort is needed. Minimum. Although there is no such thing as a quick fix, we can help make your journey as painless as possible. During our many years of experience we have identified how the best-in-class created a Quality Culture fit for the 21st century.

How the Best Beat the Rest

The following is a summary of how the best achieved success. **You can find out more at our seminar on 'Quality Culture for the 21st Century' (see page 13).** For now just ask yourself how you compare with the behaviors and practices of market leaders:

1. Leadership: Those leading the way:

- Really 'get it'. They see the PQS as a business management system that extends across the product lifecycle, the entire business. It's considered a profit not a cost centre. The PQS is the engine that drives efficiency and improves quality as well as profit
- Firmly believe that if you do the right things profits will follow. Bad things happen to those who focus on profit alone
- Have a strong, visible CEO who demonstrably supports the PQS with the total commitment of their site leadership. Walking the talk is more important than emails
- Management is honest about where they are and where they need to be. Not, 'we've passed the last inspection…we're OK'. More, 'we were very lucky, now let's fix it'
- They have a broad understanding of the product lifecycle, not just the $ numbers
- Leaders who have a 'Value of Quality Story' they share at every opportunity. One that is personal, meaningful
  - 'Patients depend on us'
  - 'Take pride in making a difference'
  - 'Consequences of getting it wrong'
- They take a mature and intelligent approach to risk-based decision making
- They avoid the 'pendulum swing' when faced with a crisis. From doing too little to doing too much. They stay on course
- Accept full accountability. The buck stops here
- Standardize and then 'localize'. Set standards that provide a rules framework and then encourage local ownership by allowing local interpretation.

"Avoid bureaucracy and hierarchy by creating a culture of discipline, accountability without fear and ownership. Create a culture around freedom within a framework, rather than rules issued by central office that are inappropriate for most. Fill the culture with self-disciplined people. Disciplined people, disciplined thought, disciplined action"

– George Rathman, cofounder of Amgen

- Demonstrate (role model) the leadership behaviors they expect from others
- They invest in developing very strong local supervision
- Ensure there is a direct link between quality performance, incentives and rewards
- Success is celebrated and achievements rewarded, large and small

2. Company culture

- Open and blame-free. Problems are surfaced and sorted quickly, not hidden
- There is a 'see it, say it, solve it' mentality
- Attitude that quality extends across the product lifecycle. They design quality in from the start for their products, processes, systems and documents
- Transparency not secrecy
- 'Greater good beyond pure profit', not profit at all costs
- Excellent communication of the quality agenda supported by **positive** feedback on performance:
  - Face-to-face briefings for the entire workforce
- Team approach to deviation investigations and continuous improvement
- Congruency. Behaviors, actions, measures and rewards all driving the right behavior
- A culture of continuous improvement, not continuous fire fighting

3. Do the basics to PhD level with a focus and passion for simplicity

- User involvement in the creation of user-friendly documents. SOPs with more pictures and schematics than words
- Batch records that are thin and functional with fewer check signatures
- Change control systems that are simple and fast
- A focus on simplifying the lives of the users, not the system administrators
- The KISS principle reigns supreme. Keep It Simple Stupid!

4. Organization and people

- The best-in-class recruit people with the right values, attitudes and beliefs. 'You can train in the skills, it's difficult to change mindset'
- On-boarding and orientation processes and training that gets across the vital importance of what they do
- Cross-functional career development. Manufacturing spend time in QA and vice versa
- QA representation on the executive board. After all quality is business critical
- Cross-functional teams and meetings. Manufacturing, QA, QC, Engineering, Technical Support, Registration, Commercial etc. One team, with one purpose. No silos or turf wars are tolerated
- Excellent internal customer/supplier relationships. People understand what others do
- Risk-aware across all activities. Everyone understands the consequence of 'getting it wrong'. Accountability for product quality, without fear
- Engagement of the entire workforce in quality improvement
- Extensive process expertise and knowledge

If you would like to discuss any of these services please c

5. Company mantra 'we can always do better'. A hunger for continuous improvement across all business activities

- Mistakes are seen as learning opportunities, not an inconvenience
- Systems in place for sharing knowledge and 'lessons learned', the successes and the failures
- Acceptance of new ways of working, not 'we've always done it this way'

6. Risk management: intelligent, mature, integrated

- Mature approach based on process and product expertise not blind, risk-averse compliance. Best-in-class focus on the real risks rather than those imagined
- A standardized and fully integrated risk management process. Not an afterthought
- Risk management is central to every business decision. From equipment calibration to due diligence
- Decisions based on science

7. Excellent change management: to focus resource, stay in control, and say NO!

- Change control is seen as core business competency, not a compliance activity
- Used to focus resource on the 20% of initiatives that contribute 80% benefit to quality and business performance
- Ensures a 'measured' rate of change. Not a chaotic stampede

8. Surveillance and escalation systems. Sensitive, robust, fast

- Governance structures in place to oversee performance and enforce standards
- Systems in place that allow data to be collected, interpreted and acted upon quickly. Hours not days, weeks not months to ensure action is taken before it's too late – data relating to:
  - Audits and self-inspections
  - Deviation and CAPA
  - Customer complaints
  - Product quality reviews
  - Batch rejects
  - Reworks and reprocessing

9. Systems and measures that reinforce and habituate the desired behaviors

- Performance measures that drive the right behavior
- Structures, processes and systems that reinforce desired behavior, not destroy it
- Audits that offer solutions, not just criticism
- People encouraged to raise deviations, not punished
- SOPs that encourage compliance rather than making it impossible

10. Education and development: good quality people = good quality products

- Strategic investment and planning in education
- Education budget protected no matter what
- Focus on education, not training. Coaching, mentoring, not telling
- Internal 'Quality Leadership'
- Education for key decision makers
- Executive GMP education for senior executives
- Executive briefings. Staying up-to-date and ahead of the game

Key Points

- A company's Quality Culture is like its compass. It serves to guide it safely through an unpredictable world to a successful future, no matter how bad the weather
- Those suffering regulatory censure have Quality Cultures that are no longer fit for purpose. Their compass has taken them in the wrong direction
- Changing your Quality Culture takes strong leadership, company-wide engagement and disciplined execution
- The commercial and regulatory weather conditions are changing fast. Changing culture takes time and this precious commodity is fast running out. For the sake of all your stakeholders, don't get left behind!
- The good news is that others have done it. If you want to know more about their problems and pitfalls as well as their successes come along to our 'Quality Culture for the 21st Century' seminar. We will help you learn from the best
- Having the right Quality Culture will ensure that the Quality of your product remains non-negotiable, no matter what

"Quality is not an act. It is a habit." **– Aristotle**

ontact Neil Wilkinson, Senior Partner at njw@nsf-dba.com

Organizational Culture…
The Achilles' Heel

by Ron Johnson – *NSF Becker Consulting*

Much of Becker Consulting's work involves assisting companies remedy flawed quality systems. This is usually done as a result of threatened or actual enforcement action by the Food and Drug Administration. In these circumstances, companies are desperate and willing to do 'whatever it takes' without a full understanding of what that means. While expansive in concept, 'whatever it takes', for many, means simply marshaling internal and external resources to design and document a new quality management system. While this is not an insignificant commitment, it unfortunately fails to consider the cause of the crisis, ie how did this happen? In our experience, the answer to this question is, universally, organizational culture. Failing to address this root cause in the remediation initiative foretells an unsuccessful outcome. Lack of success, in spite of a major commitment by the company, albeit a fatally flawed one, leads to frustration for management and employees…and the company's consultants. Worse, such a failure may lead to even more aggressive and draconian enforcement action.

Principles, values and beliefs shape the culture of a society just as they do in an organization. The culture of an organization drives employee behaviors. The best designed, most sophisticated quality systems can be subverted by employee behaviors driven by an organizational culture that is not aligned with quality doctrine. In some cases, undesirable behaviors are, unknowingly, incented by the organization's own policies and programs. FDA files are replete with companies that have invested millions of dollars attempting to comply with FDA quality system requirements, only to fail and succumb to FDA enforcement action. FDA attributes what it calls "corporate culture" as the root cause of most company compliance problems.

We, at Becker, possess the skills and methodology needed to help a company design and document a world class quality system. We also learned very early that this methodology must address the imperative of cultural alignment, lest our efforts and those of the company are for naught. Frankly, this is the most difficult part of a remediation project. Individuals are drawn to the healthcare industry by altruistic desires to help people. Consequently, healthcare companies are bewildered at the suggestion that their cultures may not support quality principles. Some are actually affronted by the notion. After all what healthcare company doesn't want to produce high quality products? It is no wonder that a company would challenge a consultant's suggestion that attention to the corporate culture is necessary.

During the remediation project, our consultants are on site working with the company to create a new system. During this time, we can be effective in counteracting the negative impacts of organizational culture. Once the system has been established and operated for a short period of time, we depart leaving full execution to the company. Recognizing that an antagonistic corporate culture can have its greatest negative impact at this point, our overall approach is designed to address cultural issues early in the process. This enables the company to execute in a quality-supportive environment assuring them of ultimate success.

We encourage a self-assessment by company management of its policies and practices that influence employee behaviors. Organizational values and principles are established by the top of the organization. While most companies have stated values supportive of quality objectives – the easy part – it is management's compliance with them that is determinative in influencing employee behaviors.

- Does management override the Quality Assurance Unit's decision to withhold product release?
- Does management cut funding of the quality function before, or to a greater extent than, others?
- Does management recognize and reward quality achievements as it does financial ones?
- Does management effectively balance its capitalistic imperatives and its commitment to quality?

Management's behavior speaks volumes in communicating the company's 'real' values and, in turn, creates the company's culture. An integral element of our methodology addresses management's responsibility to 'walk the talk' and model the company's quality values. Among other things, we encourage each member of senior-most management to have at least one performance element related to quality. Our goal is that each member of the company's executive management team has as intimate a knowledge of the state of the company's quality system as it does its financial condition.

A company's rewards, recognition and bonus programs are designed to promote employee behaviors in support of its company values. Execution of these programs quickly enlightens employees that the company's real values are important and they react in kind. However, it is not uncommon to find that these programs sometimes encourage wrong behaviors – those that do not support stated company values. For example, we have seen bonus plans that have rewarded employees for meeting regulatory market clearance and product launch milestones. When these milestones are met, everyone celebrates and employees are duly rewarded. Yet, there is no accountability when the new product has to be recalled six months later because of design and/or manufacturing defects. This misalignment communicates the company's priorities, ie obtaining market clearance is more important than assuring product quality. Other personnel practices such as salary adjustments, promotion, informal recognitions, etc can similarly incent inappropriate behaviors.

A company's ability to effectively develop and successfully implement an effective quality management system is reliant on a supportive organizational culture. Those who do not incorporate a cultural evaluation when re-engineering quality systems risk failure. Creating competent systems on paper is pretty straightforward. Employee behaviors during execution can trump the best designed system.

Roche Quality Certification Program (QCP) – Helping Embed a Quality Culture in a Global Organization

Looking back at the Pharma world over 2012 has shown that as an industry we still have many challenges ahead and improvements to make. Public health issues and regulatory enforcement actions still continue to make the headlines and show problems with quality management approaches and supply chains, all too often potentially putting patients at risk.

Why is this still the case in a mature industry sector, and what can we do to improve the situation?

Key factors now increasingly discussed at industry/regulatory events include the need to establish a 'quality culture' throughout an organization, and to ensure that key staff throughout the operations, not just in the quality organization, have the appropriate skills, knowledge and experience to make the right decisions – for the patient, for the business and for the regulators.

The Roche QCP, as reported in previous journals, continues to play a major part in helping Roche drive forward a culture of quality and continual improvement, aided by a growing network of QCP graduates across their global network.

2012 saw the successful completion of the fourth QCP based in the US, and the initial run of a parallel European-based QCP from Basel, Switzerland. QCP participation included attendees from the US, EU, Mexico, Brazil, Singapore, China and Japan.

Both Roche and NSF-DBA are proud of this program and the benefits it is providing to both the organization and the participants. John Pinion, as Roche Senior Vice President for Global Quality & Compliance, continues to champion QCP with a strong personal vision, shared by many, that this is not a quick fix to a problem, but a proactive long-term commitment to the future of a strong quality culture in Roche.

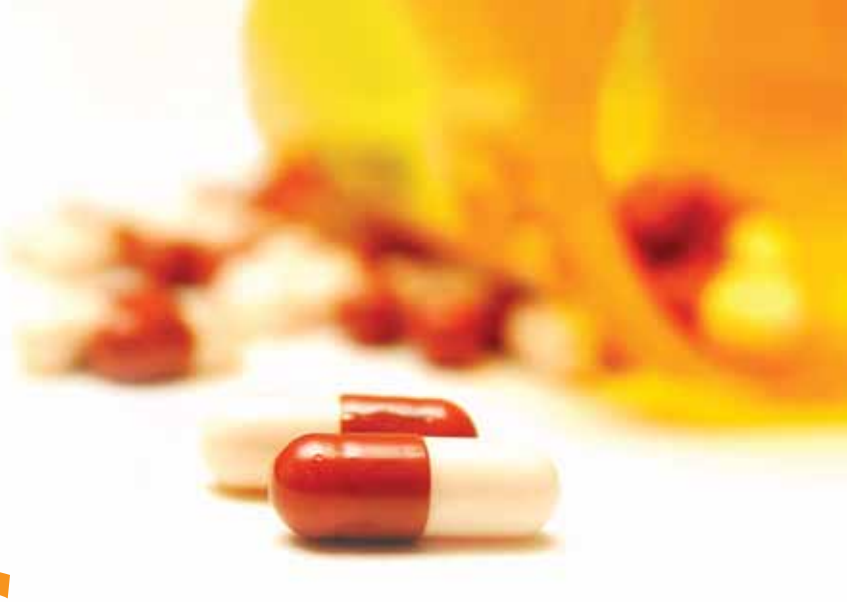
The following comments came from the participants of the first Basel QCP class in 2012, who are pictured below with John Pinion *(front row, second from left)*.

"The program provided an excellent end to end overview and enhanced the understanding as well as critical thinking and discussions"

"One of the best trainings ever participated in!"

"The mixture of NSF-DBA lectures by experienced tutors and Roche SME presentations showing the company's approach was an excellent combination to ensure the most efficient training possible"

Contact Neil Wilkinson at njw@nsf-dba.com if you wish to learn more about the types of in-house Quality Programs we are delivering for our key clients



Industry News

Don't Overlook Pharmaceutical Supply Chain Quality Provisions in the Food and Drug Administration Safety and Innovation Act (FDASIA)

by Janeen Skutnik, NSF-DBA, part of NSF Health Sciences

The Food and Drug Administration Safety and Innovation Act (FDASIA) is a remarkably broad law with far-reaching implications for the pharmaceutical industry. Until now, most pharmaceutical manufacturers and the media have focused on the law's high-profile provisions related to user fees for the makers of pharmaceuticals, generic drugs, biosimilars and even medical devices, but several provisions of the law focus on ensuring safety and quality in the increasingly global pharmaceutical supply chain. It's easy to see why many in the industry have overlooked this aspect of the law; the July 9, 2012 news release announcing signage of the new law devoted less than a sentence to the supply chain safety provisions. However, after the 2008 Heparin contamination incident and the questions it raised about pharmaceutical safety, it's no surprise global supply chain safety provisions found their way into the pages of the FDASIA.

Supply Chain Safety Provisions in FDASIA

The supply chain safety provisions can be found in Title VII of the law and address a wide range of topics including registration of domestic and foreign manufacturers and suppliers; identification of excipient information in product listings; a new model for risk-based inspections; new requirements for record keeping; recognition of foreign government inspections and the registration of commercial importers. While all of these provisions are ultimately aimed at enhancing safety of the global supply chain, some may seem more like administrative tasks than frontline quality and safety efforts. But beware – failure to comply with any part of the law will result in your product being declared "adulterated and misbranded". In our fast-moving age of social media and 24-hour news coverage, news of this designation can do costly damage to your product's reputation while also resulting in delays and recalls.

So pharmaceutical manufacturers and ingredient suppliers alike have a vested interest in understanding Title VII of FDASIA. Let's take a look at the highlights of the new law – keeping in mind this is just the starting point for understanding what's now required of pharmaceutical manufacturers and their ingredient suppliers.

Pharmaceutical Manufacturers Must Establish and Manage the Safety of their Raw Materials

Most manufacturers are used to adhering to cGMPs for their finished products, but FDASIA now requires manufacturers to verify and document that the raw materials used in finished products are also meeting the appropriate cGMPs. In the past, many manufacturers relied on ingredient testing or questionnaires sent to suppliers to assure cGMPs. This is no longer sufficient. To comply with the law, manufacturers will need to audit their ingredient suppliers themselves or use a third-party auditor to verify the quality and safety of raw materials. Importantly, this applies to suppliers of excipients as well as APIs. This presents a special challenge since most excipients are manufactured in bulk and sold to many industries, not just the pharmaceutical industry. And typically the pharmaceutical industry isn't the largest buyer of these excipients. For example, only 0.02 percent of cellulose is used in pharmaceutical products. The pharmaceutical industry will need

to work closely with its excipient manufacturers to ensure they are manufacturing ingredients with the appropriate cGMPs in mind.

Simply put – manufacturers need to know where their raw materials are coming from and how they are made. In the past, this was a much easier proposition. In the 1970s and '80s, manufacturers often bought raw materials from a supplier down the road. With today's globalization in the industry, most raw materials are now coming from countries that may not share the same GMP standards as the United States and Europe.

Prepare for Risk-Based Inspections

Instead of bi-annual inspections of pharmaceutical manufacturing facilities, the new law calls for risk-based inspections based on a facility's compliance history, its history of and nature of recalls, and inherent risks in the finished products. This new inspection paradigm will help the FDA focus its resources where they are needed most, but manufacturers with good quality records should be careful they don't lose their focus on the cGMPs. It's important to remain focused on quality manufacturing every day, not just in preparation for an inspection.

Registration of Foreign and Domestic Drug Manufacturers and Suppliers

In the past, manufacturers needed to provide regulators with the name and place of business of their drug manufacturing facilities and suppliers. Today, they must now provide additional information, including a unique facility identifier for each drug establishment and a point of contact email. It is still unknown how the unique facility identifier will be established, and industry anxiously awaits FDA regulations on this subject.

Transparency of Inspections

Beginning in 2013, FDASIA requires the FDA to publish annual reports outlining the number of foreign and domestic facilities that have been registered and inspected. This will also include the number of API and excipient facilities registered and inspected, which has not previously been required.

Collaboration with Other Government Agencies

Under the terms of FDASIA, the FDA now has the authority to collaborate with the regulatory agencies of other governments. The FDA can now enter into memorandums of understanding with these government agencies, which should be helpful for both patients and industry. The collaboration of FDA with other government agencies facilitates the exchange of information and, importantly to industry, should drive collaborations on inspections and help ensure inspections across the supply chain.

Requirements for FDA-Regulated Persons to Report Issues

In a slightly controversial provision of Title VII, the law requires "any FDA-regulated person" to report issues to the FDA if they believe a finished product or ingredient could be harmful to consumers. Many in the industry believe this provision is problematic as it may have unintended consequences and it is difficult to understand how it would be measured and enforced. Could this new provision have a chilling effect on individuals working in the pharmaceutical industry? Will people in the industry avoid certain jobs and positions that could be considered an FDA-regulated person? Will it be more difficult and costly to find third-party auditors willing to take on this risk? The effects of this provision remain to be seen.

Standards for Admission of Imported Drugs and Registration of Commercial Importers

Another important aspect of Title VII is the new requirement for the FDA to establish standards for admission of imported drugs and criteria for registration of commercial importers. The FDA has until July 2013 to publish guidance on this provision of the law. Once good importer practices have been established, facilities can be found to be out of compliance with the law and their products declared "adulterated and misbranded".

Next Steps

All this may seem like a lot to digest, so we suggest you start with a few simple steps:

- Get to know your suppliers and let them know what you expect from them
- Look at your smaller suppliers as well as the top 10 percent. Chances are you already know your top suppliers quite well, but what about that company that provides you with a single barrel of an ingredient a year? How well do you know that company and its manufacturing practices? This is often where problems arise
- Open a dialog with your suppliers about the new rules and make sure they know what is required. If many US manufacturers of finished products aren't familiar with all the requirements, it's a safe bet many ingredient suppliers around the world are unclear as well
- Review Title VII of FDASIA closely and seek help from a qualified pharmaceutical consultancy like NSF-DBA if you need help interpreting or implementing the changes

In almost every industry, there's a tendency to be skeptical of new rules and regulations, but overall we believe FDASIA is an excellent piece of legislation that will help the pharmaceutical industry provide safer and more effective drugs to consumers. But the law is not perfect – while we understand and agree with the penalties and repercussions of failure to comply with the elements of FDASIA, it would have been beneficial to incorporate incentives for compliance. However, in light of the FDA's and the US Congress' unprecedented willingness to involve the pharmaceutical industry, third-party auditors and the scientific community in crafting the legislation, we're hopeful they will continue to listen to industry during implementation of FDASIA, and other initiatives like ICH Q10, and apply a risk-based approach that rewards companies who demonstrate quality excellence, Q10-like Pharmaceutical Quality Systems, effective supply chain controls and an effective quality culture. FDASIA has been – and we hope will continue to be – a model of how the federal government, industry and the scientific community can work together to enhance safety for prescription and OTC drugs.

Janeen Skutnik is a Partner at NSF-DBA, part of NSF Health Sciences, a division of NSF International. NSF-DBA has more than 27 years of experience in consulting, training and auditing services for the pharmaceutical industry. She can be reached at **jskutnik@nsf-dba.com**

EU News from our European Offices

Implementation of the Falsified Medicines Directive (FMD)

The FMD, Directive 2011/62/EU, requires that from July 2, 2013 all APIs imported into the EU have to be certified as meeting EU GMP by a Competent Authority of the exporting country unless they have been assessed by the European Commission as having acceptable regulatory controls in place and have been listed as an acceptable country.

As of the end of January 2013 the only country which the Commission had approved, and will not require their APIs to be certified, was Switzerland. Six other countries have applied to go onto the list of acceptable countries and are in the process of being assessed: Australia, Brazil, Israel, Japan, Singapore and the United States of America.

The Commission has published an 'Implementing Decision', dated January 24, 2013, on the assessment of a third country's regulatory framework applicable to APIs. This provides confirmation of the criteria to be assessed when a country applies to go onto the Commission's list of acceptable countries. The criteria are:

- The GMP standard being applied is equivalent to that given in Part 2 of the EU GMP Guide; ie ICH Q7
- The inspection resources, the qualification and training of inspectors, inspection procedures, inspection strategies and mechanisms to address conflicts of interest, inspection performance standards, enforcement powers, alert and crisis mechanisms, and analytical capacity taking into account the applicable EU GMP guidelines
- The third country's arrangements in order to ensure regular and rapid provision of information by the third country to the EU in relation to non-compliant producers of active substances

On January 28, 2013 the Commission published version 3 of their Q&A regarding the importation of APIs from outside the EU and version 2 of the certification template. The changes are only minor, with just three changes to the Q&A and the addition of the inspection authority (if different from the issuing authority) to the template.

In mid-January 2013 India announced that the Central Drugs Standard Control Organization (CDSCO), through the Drugs Controller General of India (DCGI), had been appointed as the competent authority to issue the certificates for API exports to Europe. The Indian API industry has expressed reservations over the speed with which the DCGI can sanction the certificates and some officials have also raised concerns over the accountability of the competent authority in case EU regulators find fault with any of the consignments.

European Commission issues three draft documents for comment:

1. Guideline on GDP for APIs for Human Use

At just seven pages this draft is, mercifully, much shorter than the 30 page draft EU GDP for Finished Products that was issued in July 2011 (and which has still not been finalized).

Neil Wilkinson will be delivering a Pharmaceutical Legislation Update course in the NSI

EU GMP Guide Part 1

Draft Revision of Chapter 3 (Premises and Equipment)

On January 17, the Commission published a draft revision of Chapters 3 and 5 to address the management of the risks of cross-contamination in shared manufacturing facilities. This issue had been the subject of debate within the EU inspectorates for the past 10 years. The new approach that is contained in these drafts is risk-based and includes a toxicological evaluation of the potential risks. This represents a major shift in the currently accepted way of calculating cleaning validation acceptance limits and whether or not dedicated facilities are required.

The draft Chapter requires that Quality Risk Management principles should be used to assess and control cross-contamination risks. Risk assessments should include, amongst other parameters, a toxicological evaluation of the products being manufactured and refer to the Guideline on setting health-based exposure limits (see later).

Draft Revision of Chapter 5 (Production)

In November 2010 the Commission published a draft revision to Chapter 5 of the EU GMP Guide. A further draft of Chapter 5 was issued for comment on January 17, 2013. This new draft contains changes to sections 17 to 20 to improve the guidance on prevention of cross-contamination and to refer to toxicological assessment guidance. Changes were also introduced in sections 26 to 28 on the qualification of suppliers in order to reflect the legal obligation of manufacturing authorization holders to ensure that active substances are produced in accordance with GMP. The changes include supply chain traceability. Section (33) is inserted to clarify and harmonize expectations of manufacturers regarding the testing of starting materials, while section (68) introduces guidance on notification of restrictions in supply.

Guideline on setting health-based exposure limits

The 'Guideline on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities' that is referred to in the proposed revisions to both Chapters 3 and 5 was published as a draft for comment on January 8, 2013.

This guideline attempts to provide a more scientific approach to the setting of acceptance limits. For the past 25 years the generally accepted method for setting the acceptable level of carryover has been the lower of either no greater than 1/1000th of the lowest clinical dose of the contaminating substance in the maximum daily dosage of the next product or a maximum contamination of 10 ppm of the previous active substance in the next product manufactured. These limits do not take account of the available pharmacological and toxicological data and may be too restrictive or not restrictive enough.

The approach outlined is based on the calculation of health-based exposure limits and is very similar to that given in the ISPE 'Baseline Guide' on the subject of 'Risk-Based Manufacture of Pharmaceutical Products (RISK-MaPP)' that was published in September 2010.

Revision of Chapter 6 (Quality Control)

A draft revision of Chapter 6 was published on January 17, 2013. This revision adds more emphasis to the need to investigate Out Of Specification (OOS) and anomalous results and Out Of Trend (OOT) results. The need for a procedure for OOS/OOT results is added to the documentation section and the requirement that "Any out of trend or out of specification data should be addressed and subject to investigation" is added.

The principal changes introduced by this revision are around requirements for test method validation and transfer. The need to verify test methods that were not originally validated by the laboratory using them (eg pharmacopoeial methods) has been added, as has the requirement for reference standards to be certified, qualified and verified as suitable for the intended use. A whole new section on 'technical transfer of testing methods' has been added.

2. Guideline on the formal Risk Assessment to determine the appropriate GMP for Excipients (as required by the Falsified Medicines Directive, 2011/62/EU)

This draft guidance consists of three main sections:

Section 2: 'Determination of appropriate GMP based on type of excipient' provides guidance on how to assess and rank the risk presented by the excipient.

Section 3: 'Determination of Excipient Manufacturer's Risk Profile' covers identification of appropriate GMP and assessment, ranking and control of the risk profile of the excipient manufacturer.

Section 4: 'Confirmation of Application of Appropriate GMP' presents guidance on how to manage the risks of use of the excipient on an ongoing basis.

3. Template for QP's Declaration of GMP Compliance for IMPs manufactured in non-EU countries

This is a simple two-page template. The declaration can be made on the basis of either a personal audit by the QP or an audit conducted by a third party (which includes audits by other QPs employed by the same company). If the manufacturing site has not been audited a justification as to how the QP knows that the site meets EU GMP has to be provided.

F-DBA Boston Office on November 19. Come along and get all the latest industry news

Forthcoming Pharmaceutical Courses

What's planned for April – June 2013

Quality Management Systems

Boston Marriott Cambridge, Cambridge, MA

April 10 – 12

We all know that the quality of your products depends on the quality of your people and the effectiveness of your quality system. In fact, as quality professionals, you can't release product and stay in business unless your QMS is 'in control'. This is easier said than done. Supply chains are more complex than ever before and you are being asked to do more with less, and faster!

This course will provide you with answers to the really tough questions you have to deal with day-to-day, such as:

- How to design a quality system that is fast, flexible, simple and compliant
- How to ensure that your system remains fully compliant no matter how tough the business environment
- How to accurately measure and continuously improve your quality system

Course Fee: $2950.00 (First booking)
$2360.00 (Early bird/additional bookings from same site)

Workshop: Laboratory GMP Requirements and Investigating Out of Specification Results

NSF-DBA Boston Office, Boston, MA

May 16

Laboratory GMP Requirements
Morning Session 08:30 – 12:00

This short course will provide an overview of GMP expectations of the pharmaceutical laboratory and common areas of weakness cited by regulators – data management, sample management and best practices. Differences between laboratories supporting clinical operations versus commercial operations are highlighted. Your tutor will share his experience of global laboratory management and Process Analytical Technology applications.

Investigating Out of Specification Results
Afternoon Session 13:00 – 16:30

The management of Out of Specification (OOS) results is a critical aspect of laboratory operations. Frequently, OOS procedures are difficult to follow, leading to skipped steps and data gaps. This course will review best practices and system weaknesses frequently encountered. The history and background of current OOS guidelines will be covered by your tutor. Attendees will realize that to meet the requirements of the Equilibration Time and Bowie and Dick test, the cycle must be highly efficient. The efficient cycle has the knock-on effect of being relatively short, ie 1.5 hours as against 4+ hours and therefore the impact of this approach is highly significant in an operational sense as well as from a quality perspective.

Course Fee: Half Day: $300.00
Full Day: $500.00

Investigational Medicinal Products

Boston Marriott Cambridge, Cambridge, MA

June 11 – 13

The manufacture and supply of IMPs presents some unique challenges and there are some significant differences around how GMPs are interpreted through the phases of clinical manufacture. This course provides a clear understanding of the current regulatory and GMP/GCP expectations and industry practices.

Course Fee: $2950.00 (First booking)
$2360.00 (Early bird/additional bookings from same site)

Understanding HVAC and Key Utilities for Biopharma Facilities

NSF-DBA Office, Boston MA

June 14

This full-day workshop will be invaluable to those who need to understand these key utilities in the biopharma environment from the point of view of what questions to ask when qualifying, auditing or investigating plant utility systems. What to look for to avoid problems during start up and ongoing operations.

Each half-day will focus on topics that are crucial to maintaining high standards of quality and maintenance in a cleanroom environment. Attendance is recommended for all biopharmaceutical supervisors, technicians and engineering support.

Course Fee: $500.00

Effective Pharmaceutical Audits and Self-Inspections

(PQMS Auditor/Lead Auditor)

Boston Marriott Cambridge, Cambridge, MA

June 24 – 28

Faced with industry and regulatory pressure, NSF-DBA was actively encouraged to successfully redesign an existing, popular course and reintroduce it as the first International Pharmaceutical Quality Management Systems Auditor/Lead Auditor Qualification. This course has been specifically designed to provide delegates with education, understanding and development to meet today's pharmaceutical pressures, including the auditor skills and toolbox of auditing techniques needed by the successful pharmaceutical lead auditor. Given the course focus, content and delivery of EudraLex Volume 4 Chapters 1 to 9, ICH Q10 as the combined QMS, the team at NSF-DBA sees this as the first truly certified GMP auditor training course available globally today.

Course Fee: $3200.00 (First booking)
$2560.00 (Early bird/additional bookings from same site)

Our workshops are designed to give you practical examples of key pharmaceutical areas. These will be ideal for those people looking for ways to operate more compliantly and effectively.

Book online at www.nsf-dba.com

Get in touch now to book your place on any of these courses

Call us on: +1 857-277-0060 or email: USinfo@nsf-dba.com

Course details and prices are correct at the time of printing and are published in good faith. NSF-DBA reserves the right to make any changes which may become necessary.

QUALITY CULTURE FOR THE 21st CENTURY

Some thoughts from Neil Wilkinson

Over the past few years many pharmaceutical firms have begun to implement modern Q10 style Quality Management Systems that go well beyond just meeting basic cGMPs and seek to drive improvement and operational excellence.

Within many firms it has also become apparent that without a strong Quality Culture none of these good intentions will stick. Establishing and measuring a 'Quality Culture' is not easy, not a quick fix, not a project…it requires strong leadership to champion and maintain.

It is about behaviors and values – Quality Culture becomes 'the way we do things around here' without having to think about it.

Sadly we are seeing more and more examples in the pharmaceutical sector of profit and greed driving behaviors, often led by those in the most senior positions. Whilst the worst examples make the headlines, and unfortunately will result in more regulation and enforcement for those who try to be ethical, as well as the 'bad actors', there are many firms out there who, without the embedded 'Quality Culture', still struggle to make the right decisions. Maybe they will be next in the headlines?

A true 'Quality Culture' will ensure the right decisions are made – for the patient, and ultimately for the business and its reputation.

NSF-DBA is a strong believer that where firms embed a true 'Quality Culture', and not just pay lip service to using the right words, they will both deliver better products for their customers/patients and also become better performing businesses and places to work.

We try to work with our clients to help them on their journey via training/education, consulting and auditing – there is no magic wand or standard solution! Establishing and maintaining a Quality Culture fit for the 21st century takes strong leadership, disciplined execution and a lot of support, particularly as today's world of financial pressure, mergers and acquisitions often leads to acutely short-term thinking. We work in partnership with our clients to create and maintain a culture that satisfies all stakeholders. Anyone who tells you culture change is quick, smooth and painless isn't telling the truth. It takes years and rarely goes according to plan. When stuff happens we stick with you. With over 27 years of global experience in culture change we know what works and what doesn't.

Customized Quality Leadership Education Programs

Culture change without education is impossible. Not training, but customized educational programs that change the way people think and act. NSF-DBA's unique style of education is designed to change behaviors, not just provide information.

Best-In-Class Practices: Don't Reinvent the Wheel

Culture change is tough but achievable. NSF-DBA has worked with many organizations that got it right. We can help you learn from their successes (and their mistakes) so you don't waste time reinventing the wheel. The best-in-class practices summarized in the earlier article are just the tip of the iceberg!

Consultancy Support

We are fortunate to have some of the most experienced consultants available. With a minimum of 25 years' hands-on industry experience they can gauge your culture within hours by what they observe and the people they meet. Having been in your shoes they also understand what works in the real world.

Regulatory and Industry Updates

To know if your compass is pointing in the right direction you need to understand the weather you have to navigate. In short, the industry and regulatory challenges on the horizon. We keep our clients informed about what's coming and, importantly, what course to steer.

Executive Briefings

Culture change without informed leadership simply doesn't happen. These briefings are designed to be short, sharp and to the point. After all we recognize you are busy people. We provide an easily digestible assessment of the global regulatory challenges and the best-in-class practices for leading culture change. Leading culture change is lonely and nerve-wracking. These briefings provide a safe haven to examine concerns, generate solutions and provide support.

If you wish to know more about our views and services in this area contact **Austin Caudle** on **acaudle@nsf.org**

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OUR PEOPLE

We welcome three new associates to NSF-DBA. Their broad expertise and substantial industry experience will clearly be of benefit to our clients in a consulting, auditing or training capacity. We hope you get to meet them in the near future.

Ms Helena Champion

Consultant

BSc, MSc, MBA

Helena has over 25 years' US and international experience in biotech, biologics, small molecule drug substance, drug product development and manufacture, gained from many years in product development and quality assurance, most recently as Quality Assurance Director at Wyeth Biotech External Supply/Pfizer.

Helena has a broad experience in the manufacture and control of aseptically prepared sterile pharmaceuticals, including pre-filled syringes and lyophilized products, various oral dosage forms and drug device combinations, including inhaled drugs.

Dr Janice Wilson

Consultant

BS PhD Chemistry

Janice has more than 20 years in quality and compliance developing and implementing global solutions that meet the regulatory compliance requirements of the FDA, MHRA, EMA, WHO, PEI, ISO and the MOH of several European Union and non-EU countries.

She has experience with all aspects of QA, QC and compliance monitoring that supports phase I - III clinical trial materials as well as drug product for both biological and non-biological entities. Along with her extensive GCP and GMP experience, Dr. Wilson also has experience with GLP and ISO and fully understands the critical interfaces among the codes/regulations.

Dr Shih-Hsie Pan

Consultant

PhD, MSc, BSc Chemical Engineering

Shih-Hsie has over 30 years' experience in the industry and held senior management positions at Merck, Genentech and Bristol-Myers Squibb in global manufacturing sciences and technology, biologics process development, biopharmaceutical process engineering and chemical technology operations.

Shih-Hsie's primary areas of expertise are with process development and commercialization for biologics (monoclonal antibody, antibody conjugate, vaccines) and synthetic pharmaceuticals. He is also experienced with QbD applications, validation, CMC registration and global manufacturing network process lifecycle management.

In December of 2012, Kate Principe, the Lead Office Administrator for the NSF-DBA Boston office was honored with the prestigious Employee of the Year Award from our parent company NSF International. As our clients, many of you will know Kate from the key role she plays interfacing with you to ensure key items such as logistics and materials for our courses and audits are on time and of high quality. This April, Kate will have been with NSF-DBA for 2 years during which she has consistently demonstrated a strong work ethic and dedication to producing the highest quality of work in all aspects of her role as Lead Admin. Her dedication and consistency to providing service of high standards, particularly during periods of high activity, is notable and reinforces NSF-DBA's dedication to quality. In addition to Kate's undying dedication to her work, she exudes a positive and 'fun' attitude in the office and has been an instrumental part of keeping the team in good spirits during demanding and hectic times. We would like to congratulate Kate on her achievement and thank her for her devotion to the support and growth of NSF-DBA!

PROPOSAL FOR A QUALIFIED PERSON IN THE NEW EUROPEAN REGULATION FOR MEDICAL DEVICES

By John Worroll

This Article describes the requirement for a 'Qualified Person' (QP) contained in the EU Commission Proposal for a new Regulation to cover medical devices and active implantable medical devices.

The Proposal is the result of long discussions between the Commission and stakeholders in the 27 Member States and aims to address the perceived weaknesses of the current Directives 93/42/EEC and 90/385/EEC.

The Proposal says that the QP should be responsible for regulatory compliance within a manufacturer's organization and points out that a similar requirement exists within the EU legislation for medicinal products.

Some Member States (eg Germany) have a similar requirement in their local laws for medical devices.

REQUIREMENTS FOR A QP

Article 13.1 of the Proposal says that:

"Manufacturers shall have available within their organization at least one qualified person who possesses expert knowledge in the field of medical devices."

It goes on to say that the expertise of the QP shall be demonstrated in one of two ways:

Either: "a diploma, certificate or other evidence of formal qualification awarded on completion of a university degree or of an equivalent course of study, in natural sciences, medicine, pharmacy, engineering or another relevant discipline, and at least two years of professional experience in regulatory affairs or in quality management systems relating to medical devices."

Or: "five years of professional experience in regulatory affairs or in quality management systems relating to medical devices."

Another point to note is that the Proposal is quite explicit about the QP being "within the manufacturer's organization" which appears to preclude the use of an external consultant. On the other hand, most manufacturers who are complying with the medical devices directives will already have, de facto, such a person within their organization.

There are two minor derogations for manufacturers of custom made devices. Firstly, the experience requirement is reduced to two years regardless of academic qualification. Secondly, there is no need for custom manufacturers who are 'micro-enterprises' as defined by Regulation 2003/361/EC to have a QP.

ROLE AND FUNCTION OF A QP

The Proposal states that the QP is responsible for ensuring:

(a) that the conformity of the devices is appropriately assessed before a batch is released

(b) that the technical documentation and the declaration of conformity are drawn up and kept up-to-date

(c) that the reporting obligations in accordance with Articles 61 to 66 are fulfilled

(d) in the case of investigational devices, that the statement referred to in point 4.1 of Chapter II of Annex XIV is issued.

There is an analogy with the ISO 9001 and ISO 13485 requirement for a 'Management Representative':

"Top management shall appoint a member of management who, irrespective of other responsibilities, shall have responsibility and authority that includes… ensuring that processes needed for the quality management system are established, implemented and maintained."

In the case of the proposed Regulation, the function is to ensure and maintain regulatory compliance and in the case of the QMS standards, the function is to ensure and maintain the QMS.

Finally, the proposed Regulation states that:

"The qualified person shall suffer no disadvantage within the manufacturer's organization in relation to the proper fulfilment of his duties."

This appears to mirror the QMS phrase 'irrespective of other responsibilities' in giving QPs freedom to discharge their responsibilities without fear or favor.

QUALIFICATIONS AND ANALOGY WITH THE PHARMACEUTICAL EQUIVALENT

It can be seen from the foregoing that, although the role and responsibility of the QP is similar in principle between the pharma and medical device worlds, the differences in detail are significant:

- The educational requirements are different in that the medical device QP can rely on professional experience alone
- Batch release is a major factor in the pharma world, but it plays a much smaller role in the medical device world. In practice the requirement for the QP to ensure that the "conformity of the devices is appropriately assessed before a batch is released" is probably more to do with ensuring that the conformity assessment has been properly carried out and that there is a quality system in place for product release rather than with physically releasing each batch

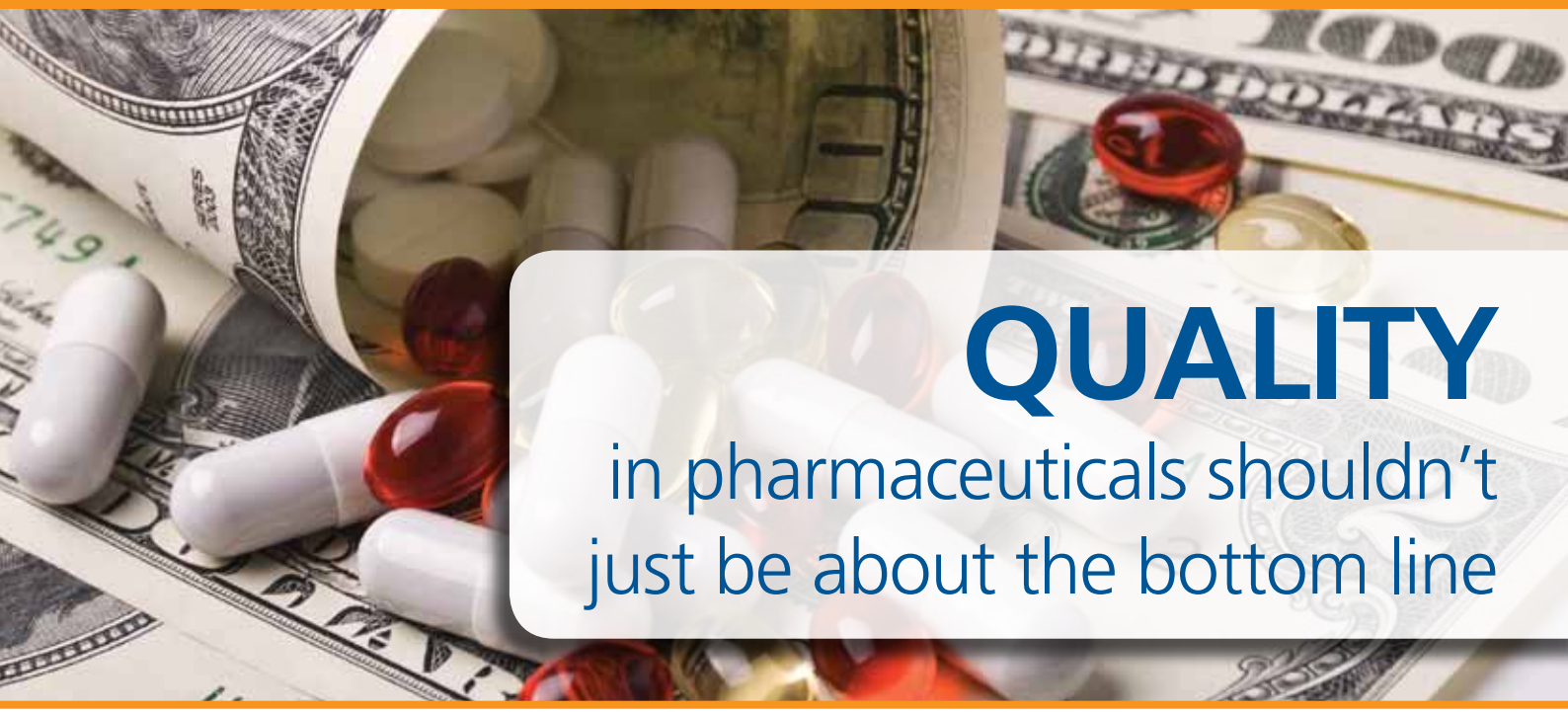
Because of these differences, it has been argued that the term 'QP' should be changed for medical devices to avoid confusion with and 'mission creep' towards the pharmaceutical term.

On the other hand, any medical device manufacturer wishing to comply with the Harmonized Standard for a quality management system, EN ISO 13485, will take note of the Human Resources requirement in para 6.2 that:

"Personnel performing work affecting product quality shall be competent on the basis of appropriate education, training, skills and experience."

Manufacturers may therefore wish to implement a training program to ensure their QPs have a good theoretical and practical knowledge of the regulations, covering the whole area rather than just relying on what they have picked up 'on the job'.

The Health Sciences, Training, Consulting and Auditing Experts



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