Long-term QA trends in pharma

The quality assurance (QA) environment is changing dramatically and forcing pharmaceutical companies to face new challenges. In light of this, JSC AG (Germany) and Norbert Skubch conducted a study of professionals from some of the world's top pharmaceutical companies to identify key QA concerns. This article highlights some of those concerns and provides recommendations for the future.

Norbert Skubch[1] & Thomas Zimmer[2]
[1] JSC Management und Technologieberatung AG
[2] Boehringer Ingelheim GmbH

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The study on quality assurance (QA) stems from a related project we conducted for a client in 2008/2009 on QA organization in pharmaceutical companies, which raised questions regarding QA. The study, conducted earlier this year, aimed to understand pharmaceutical employees' thoughts relating to QA and to highlight some of their key concerns with respect to implementing QA processes and techniques. We intend to conduct the study again at a later date to obtain further information on upcoming trends.

We surveyed one or two persons (mainly heads of corporate QA) from 14 pharmaceutical companies (10 of which are in the top 20 worldwide pharmaceutical companies) — representing more than $300 billion net sales in 2008. Once we understood some of the key issues relating to QA implementation amongst our survey respondents, we were able to provide some recommendations that would allow pharmaceutical companies to adhere to good QA practice.

Key concerns

Four key areas of concern relating to the implementation of QA techniques in the pharmaceutical industry were highlighted at the study's conclusion:

- Respondents were not convinced that a high standard of quality could be guaranteed in a production network comprising own plants, contract manufacturers and suppliers.
- With the increasing importance of integrated risk-based concepts in quality management (e.g., risk-based auditing integrating most GxP topics, stricter use of preventive risk management tools

and introducing comprehensive risk-based key performance indicators (KPI) reporting), regulations harmonization and the rising pressure to reduce costs, respondents were uncertain how each of these concepts could be enforced whilst still maintaining high standards of quality.

- Respondents emphasized the need for a unified approach to QA throughout the industry — allowing manufacturers to make a seamless transition from classical processes to a modern control strategy — in particular as the Quality by (QbD) Design concept becomes more widespread.
- Driven by ICH Q10,[1] which demonstrates industry and regulatory authorities' support of an effective pharmaceutical quality system, the idea of continuous improvement and of pharmaceutical product lifecycle management globally is gaining importance. Respondents highlighted that this drive towards excellence will require a shift in communication methods across corporations. The exchange of expertise and knowledge of new processes will also be essential. Thus, it is believed that the shift towards quality and excellence will require more of employees; however, the overall notion is that this will eventually lead to more stable and cost-effective processes, rather than a more costly enterprise in the long run.

Key recommendations

In summary, based on the results of the study and, in particular, the four key areas highlighted above, we recommend five key actions that should be taken by management to ease the transition to QA excellence:

- Adjust the corporate-wide QA organization on all tiers to be well prepared for virtual networks and to encourage better cross-functional integration.
- Develop and install business processes that are necessary for a comprehensive third-party quality management with regard to outsourced and in-sourced products, APIs, packaging materials and excipients.
- Foster integrated risk-based concepts, QbD concepts and continuous improvement ideas in the entire QA organization.
- Design and implement a robust enhanced QA related IT system architecture (eQA) that is cost-efficient and flexible enough to fulfil future requirements.
- Communicate to management that the outlined actions will lead to more transparent, robust and controlled processes contributing to a cost-efficient production.

To adhere to these recommendations, the QA units at corporate level (CQA) will have to play a leading role; each recommendation has strategic importance and will have a corporate-wide impact.

Key tasks for company QA units

The study group identified four important tasks that CQA units should undertake to ease QA implementation across a company (**Figure 1**):

- Develop strategy, policy and corporate-wide quality and compliance standards.
- Design quality systems, cross-functional business processes, IT systems and underlying architecture.
- Audit and/or monitor implementation progress and proper application.
- Report performance level and major deviations to senior management.

Effective communication platforms are crucial

The role of a CQA manager is akin to a strategic architect who develops the basic quality and compliance standards, and monitors their successful implementation. As QA compliance continues to gain importance, so too will the need for a communication platform that enables the effective exchange of know-how and continuous improvement concepts.

This rising importance of communication platforms is a common sense approach, given that successful implementation is only sustainable when all QA employees fully understand and identify with the quality strategy and resulting concepts. Furthermore, a networked, team-oriented organization should be more efficient and innovative, and more inclined to avoid traditional, hierarchical company structure. Corporate-wide communication platforms offer one key method of knowledge management; most of the corporations that participated in the survey expect a higher need in the future — particularly with respect to adequate IT support that helps avoid human error or inconsistencies in daily practice.

Supervision of quality is not good enough

The way in which management supervises QA implementation will

Figure 1: Mandatory and optional task of CQA — general classification.

Define	Develop strategy, policy and standards — focusing on "what", "how" to be specified on operational level	Mandatory
	Specify tools, systems and underlying architecture	Optional
Control	Monitor (audit) implementation progress and proper application in the daily business	Mandatory
	Report performance level and major deviations to the Executive Board	Mandatory
Support	Provide communication platform to enable know-how exchange and continuous improvement	Optional
	Facilitate correct use via consulting, counseling or training of affected staff	Optional

soon be subject to GMP inspections, following on from the results of a confidential agency audit that confirmed a distinct lack of quality monitoring at management level in pharmaceutical corporations. This, therefore, raises question marks regarding whether the management and supervision of QA is sufficient or whether the quality culture of a corporation is the right one. Most survey respondents confirmed that their company needed to place a greater emphasis on improving managerial supervision and quality monitoring — especially in light of the latest regulations set out in ICH Q10 and Q8 (revision 2).[1,2] The areas in which management lacked effective quality supervision processes varied amongst survey respondents, but the supervision of several key processes was highlighted as being largely neglected by management: functional performance, compliance, quality performance of products, quality culture and guidance.

Audits are the most effective tools for monitoring and tracking quality and performance within a manufacturing facility, but only half of the companies surveyed admitted to having harmonized audits between all GxP practices. Most of the participating corporations felt there was a distinct need for better integration of GxP practice across all levels of the corporation, particularly in the future. However, the lack of knowledge of auditors for the various GxP areas was perceived as an obstacle to harmonizing the methodology and the audit process itself.

Risk-based auditing techniques are judged as a must for the efficient use of resources in the future. The main requirements of a risk-based approach include good technology, and a good level of experience and knowledge amongst both third-party sites and in-house employees. Consequently, it is of paramount importance that CQA managers pay particular attention to third-party sites to ensure that in-house and external QA processes can be harmonized. To overcome any possible resource bottlenecks in implementing thorough risk-based auditing, it may be important to use shared audits, mutual recognition agreements, outsourcing of audit activities or use of certified third-party auditors.

Furthermore, the quality check for in-licensed or in-contracted products, regardless of where they are manufactured, was considered by half of the corporations surveyed as a vital task for CQA.

Validation variations

Product validation remains topical in light of the dynamic lifecycle approach of ICH Q10's new quality system and the adapted validation guideline of the FDA.[3] Many GMP audits conducted by the FDA and the EMEA have discovered that original validations have never been updated, trending is not carried out and that product quality reviews fail to consider the lifecycle management of a pharmaceutical product.

Product validation is mainly based on annual product reviews (APR) in the US and/or product quality reviews (PQR) in the EU. Other instruments such as out of specification (OOS) reports or product design studies are used less frequently. Product quality design studies go beyond APR and PQR; they follow the philosophy of 'continuous improvement' and the idea of 'integrated quality risk management'; both do not differentiate between new and old products; both try to make products fit for the future. They can also highlight potential formulation problems relating to excipients and intermediates, and identify unknown impurities. Because of the limited use of OOS and product design studies, however, questions regarding the validation of legacy products remain. According to survey respondents, there is neither 'grandfathering' of products nor 'grace periods' to bring them to an adequate quality or compliance level. In fact, only 60% of interviewed companies report that product validations are updated regularly and only one-third consider this an issue with growing importance in the future.

Contrary to popular belief, we have found that the use of risk-based tools is widespread; the most dominant method is the failure-mode-and-effects analysis (FMEA), followed by hazard analysis and critical control points (HACCP), and the cause-and-effects diagrams (Ishikawa), according to the results of our study. All companies should employ a stricter and more intensive use of tools for preventive risk management; however, our study concluded that efficiently integrated quality risk management concepts, as set out in ICH Q9,[4] have not yet been widely implemented.

A quality control and validation strategy that is both in accordance

Figure 2: Unknown impurities: valuation and countermeasures — selected quotes.

— One of the biggest gaps in the pharmaceutical industries
— Ongoing challenge but …
— … no guarantees against criminal activities
— A weakness in our current system
— 100% assurance is not possible

+ QMS must be sufficiently robust to provide a high degree of assurance
+ Rigid supplier qualification/management
+ In-depth knowledge on/intensive relationship with supplier
+ Monitoring of performance history, process know-how, review of test methods, robustness of specifications, material traceability
+ Testing to full specification on recent using filed methods
+ Testing each container of API product
+ Use of (CEP) when possible, application of EP monographs as well as ICH Q3 A–C
+ Monitoring of impurities/their appearance

with ICH standards and meets FDA guidelines is an important target for most of the companies surveyed. The challenge is to find the balance between 'time-to-market' to guarantee patients fast access to new drugs and the lack of experience in production methods, which may lead to deviations from registered quality specifications. A good quality strategy should ensure product safety and efficacy for the patient, whilst also ensuring quality and compliance by implementing a flexible management approach to QA for commercial production. The pharmaceutical industry is still on a learning curve in this regard, and engaging the involvement of cross-functional teams to develop an enhanced risk-based control strategy is ongoing.

Product and supply chain integrity

Product integrity is a key element in supply chain protection. The survey results revealed that the main tools used by pharmaceutical companies to protect product integrity include overt and covert physical security features embedded into labels, barcodes and tamper-proof packaging. There is no dominating safety or quality standard governing supply chain protection as yet; however, combining these security elements could be an option for the mid- to long-term future.

As the legal aspects of product security and protection have yet to be defined, testing is ongoing and technical standards are still in discussion, the industry is hesitant about investment in any one method of security on a large scale. Questions remain over the ease of integration into the supply chain and cost of investment for all available solutions. In spite of this uncertainty, however, all pharmaceutical companies surveyed confirmed that the issue of product integrity and supply chain protection is well and truly on their radar — and is being dealt with.

Supply chain integrity has four core elements: supplier certification scheme, auditing — of suppliers and for the entire supply chain — track and trace (RFID) and special distribution methods. Most corporations still rely exclusively on supplier audits. Currently, there is no single solution, but a combination of several approaches will probably apply in the future. New technologies in this area are, however, emerging; track and trace technology is showing increasing importance and it appears that it will supplement the 'traditional' concepts. The effectiveness of product serial numbers and tamper evidence has been demonstrated in several other markets and will gain wider acceptance in the pharmaceutical market, whilst pilot projects for coding/track and trace technologies have been initiated.

Global technical standards for all these new approaches are required to enable their successful penetration and to act as a guide for the industry; for example, standards to guarantee interoperability of global security codes with existing local code systems established for reimbursement or other purposes, would be beneficial.

Managing suppliers and third parties

The sourcing of pharmaceutical materials represents one major quality risk that is currently not fully addressed; only a minority of the corporations surveyed have fully implemented quality control processes for all third-party sourced products. Sourced materials believed to require the strictest level of quality control are APIs, followed by intermediates and excipients. According to survey respondents, packaging material requires the weakest level of quality control amongst all third-party sourced materials.

Most of the companies surveyed felt that the importance of sourcing pharma materials will significantly increase in the future. This rising use of sourced materials will naturally lead to a rise in interest in quality control methods. In line with this, a recent draft US importer guidance calling for tighter measures to control the risks of sourced materials is urging pharmaceutical companies to invest more in this area.[3] Recent high-profile cases, where lack of quality standards have had devastating effects; including the fatalities associated with tainted heparin and infant deaths associated with milk contaminated with melamine, have also caused the industry to pay more attention. **Figure 2** outlines some verbatim comments made by survey respondents regarding the detection of impurities.

The key message in the US guideline is "know your supplier". As such, conceptual work for creating an integrated and strategic risk management is needed; business processes, audit schemes and certification schemes must be installed.

The CQA unit has an important role to play here and must become involved early in the process (i.e., during supplier pre-selection). They must also convince suppliers of their responsibilities and ensure there is true cohesion and understanding between both companies. Management must take responsibility for controlling sourcing risks and this requires a cross-functional approach that involves QA, purchasing, supply chain management and the manufacturers. Half of all pharmaceutical companies surveyed confirmed that this cross-functional

The author says…

- A survey of executives from 14 pharmaceutical companies (10 of the top 20 global firms) was conducted to ascertain employees' thoughts relating to quality assurance (QA) and to highlight some key concerns with regards to the implementation of QA processes and techniques.
- Four main areas of concern were highlighted: respondents did not believe high standards of quality could be guaranteed across supply chain networks; there was concern that integrated risk-based concepts could not be enforced; a unified approach to QA is lacking; the idea of continuous improvement will require a shift in communication methods across a corporation.
- The authors recommend a five-pronged approach to ease the transition to QA excellence: encourage cross-functional integration to prepare for a corporate-wide QA initiative; develop processes for comprehensive third-party quality management; foster integrated risk-based concepts; design and implement an enhanced QA related IT system architecture; improve lines of communication, and this must be driven by QA unit heads.

network of experts was in place in their corporation.

Each company should also perform a complete overview of their entire sourcing structure so that clear roles and responsibilities for the company as well as its suppliers are defined. This, unfortunately, is rarely the reality and is one cause of broken lines of communication and inefficiencies.

According to the survey results, third-party supervision is mainly performed using classical audits or in the form of classical quality agreements. Only a few of the corporations have a fully implemented quality management system for third parties in place, but at least 35% intend to develop one in the future. This quality management system is expected to be shaped by the expectations of regulatory agencies, which is likely to allocate the responsibility for quality problems or non-compliances to both parties; the marketing authorization holder, as well as the manufacturer.

Different levels of quality control, based on a risk-based approach with risk indicators related to the age of products, maturity level of technology used, level of experience, audit trail and so on, exist in approximately 60% of the companies surveyed. We believe that this concept will, however, not be used by all of the corporations in the future. If there is more consolidation across the industry and fewer third-party manufacturers, this picture is likely to change.

Detection of impurities is one of the unsolved problems in the pharmaceutical industry. The requirement is very clear: a quality system must be sufficiently robust to provide a high degree of assurance. But how is this done? Testing to registered specifications will not solve the problem, neither will CEPs (certificate of suitability to European Pharmacopoeia). Rigorous monitoring of impurities based on a strict supplier qualification/management might be a better approach.

Where do we go from here?

Well-described and efficient cross-functional business processes are the foundation of any quality system and are also the starting point for a more systematic, integrated and strategic risk management system.

The main corporate functions that need to be aligned and involved in a company's risk management system are product development, medicine, regulatory affairs and marketing. This is mainly because the focus of regulatory agencies will be increasingly system- and business process-oriented, giving CQA a leading role to play.

Excellent specifications must cover processes themselves, workflows (i.e., dynamic interlinking of processes), roles and their responsibilities regarding content and system. Most of the companies involved in this survey expect this topic to gain significant importance in the future.

Continuous improvement is an essential way to achieve excellent business processes. Continuous improvement concepts based on, for example, Six Sigma, ICH Q10 or ISO/TS 16949, need to be applied in line with the idea from quality control to quality systems in defined quality excellence.

KPI reporting is an essential element of a sophisticated quality system — the majority of companies surveyed confirmed that they obtain a set of KPIs forming a 'quality dashboard' out of their quality systems. However, the quality of the KPIs themselves can be improved — there can be too many KPIs and it can be doubtful as to whether they are suitable to drive change. Are they really risk indicating, and are they interesting for the top management? There should be both lagging and leading KPIs. With lagging indicators, an organization can learn from the past while leading indicators are future-oriented and show how effective preventative quality and compliance management is.

In spite of the fact that all companies surveyed have a KPI-based reporting structure, their reactions and processes for dealing with inspections and warning letters is not yet fully in place. Current KPIs mainly measure performance; risk-indicating KPIs for an upcoming inspection or warning letter are still missing. Assuming they are in place, these indicators would take precedence over the classical KPIs as the majority of corporations surveyed predict a significant increase in the need to develop such indicators.

Of course, experience from the past forms the basis for future learning. Nearly all surveyed corporations see the need to do some development here: quality systems must be risk-based, as this is the only way to bring cost under control and to qualify a quality system; and senior experts are needed in particular for the first step of risk management — risk identification — as it is pointed out in ICH Q9. PTE

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Norbert Skubch
is Managing Director at JSC Management und Technologieberatung AG (Germany).
nsk@jsc.de

Thomas Zimmer
is Head of Global Quality and Environmental Health & Safety at Boehringer Ingelheim GmbH.

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