This article investigates the software-supplier auditing practices in the pharmaceutical manufacturing environment by reviewing 17 quality audit reports performed between 1992 and 2003 by a major international pharmaceutical company. From this analysis three novel time frames of audit maturity (eras) are defined on the basis of government regulation enforcement patterns, supplier quality practices, and the pharmaceutical customer’s evolving expectations of quality and auditing practices. Increased government scrutiny resulted in the pharmaceutical company making increasingly greater demands on its suppliers to establish and comply with quality management practices as a contractual obligation. The new maturity eras are described and proposed as a new dimension for audit maturity in the pharmaceutical industry.

Key words: audit, FDA, GAMP, pharmaceutical manufacturing, software quality, validation

INTRODUCTION

Software applied in the manufacture and quality control of pharmaceuticals or the documentation of these activities is judged against quality expectations set by government agencies such as the U.S. Food and Drug Administration (FDA), where the intent is to prevent the distribution of potentially hazardous drugs that were adulterated or mischaracterized by incidents that can be traced to faulty software.

While the FDA has regulated computer systems since the 1980s, only over the last decade have software-utilizing systems become widely integrated in the procedures and processes of pharmaceutical development and manufacturing:

- Programmable logic controllers control and monitor equipment in manufacturing facilities.
- Analytical instruments, as part of the quality control process overseeing raw materials through to characterization of the final drug product, may be computer controlled.
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FIGURE 1 Pharmaceutical manufacturing fault tree—chain of events working upward through each stage of the manufacturing process that led to occurrence of a mishap, namely the delivery of a hazardous drug

- Raw data from manufacturing activities and analytical characterization may be collected directly to, or hand entered and stored in, databases.
- Electronic records such as standard operating procedures, batch reports, and government regulatory agency submissions are prepared and controlled in document management systems.
- Archiving systems store these electronic records for future use.

In an effort to control the quality of software used in pharmaceutical manufacturing, the FDA published a guidance document, commonly known as the “Bluebook,” for field investigators to use in inspections (FDA 1983). Then in 1986 the issue of software quality in medical devices came into the spotlight when a number of deaths and serious injuries resulting from the computerized Therac-25 radiation therapy device were linked to faulty software (Leveson and Turner 1993). While medical device regulation falls outside the directorate that has oversight of pharmaceuticals, the Therac-25 incident became a focal point throughout the FDA for implementing computer system controls. A simple fault-tree analysis (Leveson 1986) demonstrates the rationale for such attention with respect to pharmaceutical manufacture, as shown in Figure 1.

The FDA responded with a set of regulations known as the current Good Manufacturing Practices (cGMP), which call for the validation of systems, where validation is defined as “confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses, and that particular requirements implemented through software can be consistently fulfilled” (CDRH 2002). Achieving a validated system is then a combination of activities including but not limited to (Wyn 1996):
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- Properly written and authorized specifications
- Documented review and approval processes
- The ability to provide evidence of change control and configuration management
- Documentation of test plans and results
- Establishment of practices to ensure control and appropriate maintenance of an operational system

The burden of achieving compliance with these government regulations is the responsibility of the pharmaceutical manufacturer, not the software producer. While much in the way of quality assurance can be accomplished through customer performed black-box testing, such testing alone is not considered by the FDA as adequate proof that the system performs as intended (CDRH 2002). Accordingly, the additional step of conducting audits of the software supplier’s quality management system (QMS) and development practices is recommended and has become commonplace as a precondition of system purchase. The FDA has not come forward with a definitive standard for software quality, however, and studies indicate that existing software process standards do not fully satisfy the government agency’s expectations (Bovee, Paul, and Nelson 2001). Additionally, there is limited evidence proving that these regulations actually contribute to system quality or, for that matter, what quality aspects are affected. When questioned about the need for regulatory compliance, however, the FDA noted that while no injuries or deaths had occurred, there were numerous incidents that led to product recalls that would have been avoided with full compliance (FDA 2002a).

The FDA announcement in 2002 of transitioning to a risk-based approach to regulating drug manufacturing (FDA 2002b) has prompted new interpretations of existing laws that, while narrowing the scope of affected computer systems to those with a greater potential of affecting product quality, safety, and record integrity, still reaffirm the value of a Good Automated Manufacturing Practice 4 (GAMP) approach to computer system validation that has, at its center, supplier audits (FDA 2003a). One recent FDA guidance document even makes use of the old software engineering mantra: “Quality cannot be tested into products; it should be built in or should be by design” (FDA 2003b). It remains to be seen if audits will become even more rigorous over time or if they will only be performed for software products destined for a quality critical role.

INDUSTRY AUDITING PRACTICES

The practice and burden of supplier auditing is not new to the pharmaceutical manufacturing industry. The industry, for a long time, audited the quality systems of raw material suppliers as a precondition of purchase so that the auditing of software suppliers is really an extension of their previous quality policies. That is not to say that the practice has come easy. The industry has often struggled with interpretation of regulations, and the efforts to comply with FDA scrutiny of computer systems are no exception.

In response, a number of industry groups have established initiatives or published guidance and opinion papers for use by both pharmaceutical manufacturers and suppliers of automated systems. Directly or indirectly, these papers also inform the government regulatory agencies of the industry’s state of mind, and of difficulties encountered in achieving compliance. Examples from four groups—GAMP Forum, Parenteral Drug Association (PDA), Pharmaceutical Research and Manufacturers of America (PhRMA), and the National Physical Laboratory (NPL)—will be provided, although GAMP currently appears to be dominant and, consequently, will receive more attention. A common theme of these efforts is to facilitate cooperation by all parties, private and public, in meeting the regulations. This guidance can lead to higher confidence and lower validation costs for the customer such that a supplier can gain an advantage over competitors who fail to do so. Indeed, many suppliers now prominently display ISO 9001 certifications, highlights of their quality control system, and procedures for requesting an audit in marketing literature.

A secondary benefit of the guidance papers is that they can become de facto standards for performing and grading audits. Since the guidance is widely distributed, suppliers are able to predict the customer’s expectations and can act accordingly in striving to meet them. Because of this the supplier is less likely to be surprised by inconsistency in various customers’ expectations for quality management. Thus, audits will become a routine part of doing business and be
less traumatic for all parties. By being performed against a standard, audit reports can be more consistent and reusable for a large customer, and can be shared across research and development (R&D) and commercial manufacturing sites.

As an interesting corollary, while the auditing of software construction is a new phenomenon for the pharmaceutical industry, it is an area that has long been considered, researched, and practiced in the greater software engineering industry. Efforts such as TickIT, the Software Engineering Institute’s Capability Maturity Model (CMM), and CMMI are well known and deployed. Indeed, in many government-awarded contracts the CMM maturity level of the competing suppliers is a discriminant used to determine the contract winner, or even a requirement of all competing suppliers. Considering the maturity of these process meta-models and standards one could reasonably expect that the pharmaceutical industry would adopt, or at least adapt, these models for their own purposes. It appears, however, that this is not the case, and no definitive reason for this position can be determined. Perhaps CMM-based standards are seen to be more defense-contractor centric, or perhaps the pharmaceutical industry thinks a custom-defined process is more appropriate, but these are merely speculations. In light of this the authors will consider the dominant guidance schemes preferred by the pharmaceutical industry.

**GAMP Guide for Validation of Automated Systems**

First published in 1994, the GAMP guidance seeks to improve the understanding and interpretation of automated system regulations by pharma, system suppliers, and regulators. GAMP has become an industry standard for computer system validation and is cited as a reference within an FDA guidance document (CDRH 2002). GAMP 4 is the latest version of the guide, available through the International Society of Pharmaceutical Engineering (ISPE 2001). In addition to assisting companies in validating computer systems, the guide also offers assistance to suppliers in producing the documentation that would be reviewed in an audit supporting validation (see Figure 2).

GAMP 4 also offers guidance for the performance of supplier audits. Reasons identified for performing audits include review of an organization and its QMS, product or service delivery from a supplier, adequacy of the QMS for delivering quality requirements, and checking for evidence of QMS compliance during the development of a system or delivery of a service. Four stages are identified in the GAMP 4 audit process:

1. A preliminary assessment, often in the form of a prepared questionnaire, is an inexpensive way to perform an initial evaluation.
2. A detailed audit is performed as a prerequisite to completing a purchase.
3. Follow-up audits revisit detailed audit findings looking for evidence that corrective actions have been performed.
4. Ensuring that a supplier is continuing to adhere to agreed-upon quality standards can require surveillance to be performed on a regular basis. A checklist of items to address in an audit is shown in Figure 3.

The team performing a detailed audit should include at least one person with formal qualifications and prior experience in auditing of regulated systems and one person with an understanding of the underlying technology. It is common to fill these slots with third parties if an experienced person is not available in-house, and doing so can address the possibility of biases for or against the supplier, but GAMP warns against conflict of interest and confidentiality issues that can occur when using a consultant.

**FIGURE 2  GAMP 4 Section 7.8: Development and Review of Software (ISPE 2001)**

"Suppliers should establish suitable techniques to ensure that developed or configured software meets predefined requirements. They should implement a quality management system to monitor and improve software development and configuration."

"Users should review the supplier’s capability, taking account of issues such as:

- Methods and tools
- Policies and procedures
- Programming rules and conventions
- Review methods
- Testing and verification
- Security and confidentiality"

"Application source code should undergo formal review during its development. The user should ensure that formal reviews are conducted and documented, and that corrective actions are tracked to satisfactory completion."

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FIGURE 3  GAMP 4 checklist for supplier audits

<table>
<thead>
<tr>
<th>Section</th>
<th>Partial list of suggested audit subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Company overview</td>
<td>Product history and development plans</td>
</tr>
<tr>
<td>Organization and quality management</td>
<td>Methods of assuring quality, QMS practices, metrics collected, staff qualifications, use of subcontractors, awareness of regulatory requirements</td>
</tr>
<tr>
<td>Planning and product/project management</td>
<td>Project management tools, practices, and conformance to SDLC used</td>
</tr>
<tr>
<td>Specifications</td>
<td>Requirements specifications, traceability, reviews and approvals, accuracy and conformance to process, use of CASE tools</td>
</tr>
<tr>
<td>Implementation</td>
<td>Programming language standards, version control, builds, tools, code reviews</td>
</tr>
<tr>
<td>Testing</td>
<td>Strategy, specifications, scripts, procedures, completeness, remediation, independence of testers, accuracy and conformance to process, traceability to specifications</td>
</tr>
<tr>
<td>Completion and release</td>
<td>Documentation of release, archiving of tools and documentation, source code in ESCROW, accuracy and conformance to process</td>
</tr>
<tr>
<td>Support/maintenance</td>
<td>Explanation of services, fault reporting and resolution, accuracy and conformance to process</td>
</tr>
<tr>
<td>Supporting processes and activities</td>
<td>Documentation management, software configuration management, change control, security, accuracy and conformance to process</td>
</tr>
</tbody>
</table>

PDA

An industry group, the PDA, has developed, through a team of pharmaceutical companies, suppliers, auditors, and FDA representatives, a standard approach to assessing the structural integrity of purchased software (PDA 1999). The six-step process is intended to promote consistency in auditing and creation of a deliverable that can be shared within the industry. Each step in the process is assigned activities to be performed by customers, auditors, and suppliers. The steps in the process are (PDA 1999):

1. Initiation—involves definition of audit scope and aims and constitution of the audit team
2. Preparations and pre-work
3. Audit
4. Observations and reporting
5. Decision—analysis of the audit results and reports by the client
6. Follow-up and close out

The PDA maintains a repository of supplier audits, the Audit Repository Center (http://www.arc.com), performed by certified auditors that are available for share on a subscription basis. Currently 28 reports are available for a diverse range of suppliers and products such as laboratory data management systems and SAP AG products applied to pharmaceutical manufacturing applications. GAMP 4 recommends, however, that users of shared audit reports confirm that the audit scope remains valid, the qualifications of auditor(s) are adequate, the audit process and deliverable formats are acceptable, and liability and confidentiality issues are addressed.

PhRMA

The Pharmaceutical Research and Manufacturers of America (PhRMA), a lobbying group representing pharmaceutical and biotechnology companies, frequently submits written comments to the FDA regarding proposed regulations. In one example, PhRMA points out drug industry movement away from custom software development toward the purchase of commercial-off-the-shelf (COTS) software, with the consequences being reduced abilities to influence product design and perform certain types of testing (PhRMA 2002). Specifically, limited access to design specifications will restrict the customer’s ability to trace requirements through the system development life cycle. Given the complexity of current software, the value of code inspections as a measure of product quality is questioned as well as the willingness of suppliers to disclose known limitations. Also questioned is the drug industry’s ability to influence suppliers of broad-based software products such as spreadsheets to produce the documentation required to support validation.

NPL

While not specifically targeting regulated systems, the United Kingdom’s National Physical Laboratory (NPL) has published a guide for judging the quality of scientific instrument software where the role and some techniques of audits are discussed (Wichmann 1997). In this document Wichmann defines four software...
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integrity levels that may be useful. ISO 9001 certification is considered to be a basic standard of quality management and is mapped to the least stringent of the four levels, which is characterized by a very simple level of data processing complexity. Level 2 requires software inspection, mathematically based specifications, and testing. At level 3, the level the authors believe best approximates to the FDA expectations for pharmaceutical manufacturing software requires regression testing, black-box testing, and independent auditing. The highest level then requires white-box testing of code, formal specifications, and static code analysis.

AUDIT ANALYSIS

Seventeen supplier audit reports dating from 1992 to 2003 were reviewed. All reports originated from one pharmaceutical company with worldwide R&D and manufacturing presences. This pharmaceutical company, to be herinafter referred to as Big Pharmaceutical Company (BPC), has undergone numerous mergers and acquisitions in this time frame and, as a consequence, the audit reports may reflect practices characteristic of a legacy company. Audits were usually performed as a precondition of exercising a purchase contract where the focus was on the perceived ability to validate the software. As BPC expectations increased so too did the number of audits performed on perspective suppliers as part of the system selection decision criteria.

The 17 reports reflect summarized results of audits performed on five software suppliers. One supplier was contracted to build a novel custom-made system and for this supplier audits were performed by BPC for monitoring performance prior to and during the build. The remaining supplier’s primary business is the production of COTS systems that are used for laboratory instrument control and analysis/management of the resulting data. From this series of reviews a novel classification of the evolution of auditing practices and quality expectations has been derived.

One striking change over time noticed in this series of audit reports is how the BPC’s audit process evolved from an ad hoc and almost informal inspection into a well-defined process with a defined purpose that targeted specific areas for inspection, along with predefined expectations of the level of adherence to be achieved by the suppliers. Inspections that were initially done by a single BPC representative evolved into a team of four auditors, each with a specific role, responsibility, and accountability, and occasionally included independent consultants. This dramatic operational change is likely due to the adoption of GAMP as guidance.

It is important to mention that most of the suppliers do not solely supply the pharmaceutical industry, and, in fact, the majority of systems they sell will not be subject to FDA regulations as used, only those few systems sold to the pharmaceutical companies. Furthermore, even within a pharmaceutical environment a significant percentage of software systems are used in research and development activities not subject to government regulations. The willingness of suppliers to accept the auditing is then a willingness of the supplier to modify and adapt to laws and customer expectations of quality for sales that will contribute what could be a small percentage of their company profits.

Quality Eras

All of the 17 audit reports were reviewed as a whole. From this inspection three distinct periods (eras) of quality practices and expectations were identified (immature, adolescent, mature). The analysis (shown in Figure 4) maps the quality assurance practices of suppliers to BPC auditing practices and expectations for quality based upon the study of the audit reports. All information is set in a time frame of observed FDA enforcement practices.

Immature (predating 1996)

While only two audit reports predating 1996 were obtained (both for the same supplier) it was possible to set this time frame apart. During this period the supplier, recognizing the need for and advantages of, a rigorous QMS, initiated a quality program where company practices were dramatically revised and which in time resulted in ISO 9001 certification. BPC auditing practices were inconsistent and at times seemingly ad hoc with little evidence of clear objectives for what practices would be subject to appraisal or supplier compliance to the quality practices. The confirmed existence of a supplier QMS was viewed as sufficient and ISO 9001 certification as laudable. Few demands were made of the supplier; instead, recommendations were provided with no timelines given for
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FIGURE 4 Quality eras

<table>
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<tbody>
<tr>
<td>BPC auditing practices</td>
<td>Ad-hoc observations evolve into company defined auditing procedures. Suggestions given for supplier improvement.</td>
<td>Best practices evolve into industry standard (GAMP 3). Specific examples of noncompliance cited and graded for severity. Corrective measures suggested and supplier response tracked.</td>
</tr>
<tr>
<td>BPC expectations</td>
<td>Supplier OMS finalized and enacted. Documentation of testing activities.</td>
<td>Evidence of OMS compliance. ISO 9001 certification desirable.</td>
</tr>
<tr>
<td>FDA expectations</td>
<td>Regulations issued for more than 10 years but seldom enforced during inspections of drug manufacturers.</td>
<td>Increase seen in warning letters issued for invalidated computer systems. 21 CFR Part 11 enacted.</td>
</tr>
</tbody>
</table>

The performance of remediation activities. FDA regulations governing computer systems within pharmaceutical manufacturing had been enacted for about 10 years, but enforcement continued to be sporadic (a BPC legacy company had received citations during one of these inspections for nonvalidated computer systems).

Adolescent era (1996–2000)

This period was characterized by a noticeable increase in FDA enforcement activities for computer systems used in pharmaceutical manufacturing, and the issuing of new regulations (21 CFR Part 11) that designate conditions needed to be met for the substitution of electronic records for paper-based records (FDA 2000). It was determined that six of the audit reports fall within this period. Here, supplier quality practices continued to evolve with implementation of total quality management (TQM) initiatives. The BPC’s previously ad-hoc auditing practices transformed into a reproducible process based on the GAMP 3 industry standard. Specific areas of the suppliers’ quality and development practices subject to inspection were identified in advance. Evidence of compliance was demanded and findings were now graded for severity with corrective actions specified. Inconsistencies in the report scope and execution between legacy companies complicate direct comparison, but using the definitions given in Figure 5 it is possible to summarize the audit findings (see Figure 6). Where one supplier practice may have received multiple findings, in a single audit only the highest severity is given.


Based on inspection of nine audit reports, this period was defined by continued FDA vigilance in enforcement of regulations for system validation, as well as the issuing of the first warning letters for noncompliance with 21 CFR Part 11. The supplier’s quality practices generally matured with most having achieved certification for the ISO 9001:2000 standard that adds measurements of processes, products, and quality objectives. BPC’s auditing practice likewise grew with...
the adoption of a process based on the next generation GAMP 4 industry standard. Expectations for supplier performance in each area were clearly defined. Audit findings were now much more detailed with a template used to document each observation with supporting information and associate corrective actions to be taken. Follow-up audits were more frequently performed, usually at shorter intervals than the original report, in order to collect and assess evidence of supplier corrective actions. Duration of the on-site audit inspection was largely unchanged, generally remaining at two days at the suppliers main site of software development, though it was noticed in two mature era reports that the auditing team visited all sites where components of larger systems were developed even though international travel was required.

Findings from the various reports are presented in Figure 7. Because of the standardized report format the results are more easily condensed than in previous time periods, although there remains some deviation from the GAMP 4 checklist seen in Figure 3. Figure 6 definitions remain valid for Figure 7.

It is evident in comparing Figures 6 and 7 that the level and detail of scrutiny has evolved significantly between the identified adolescent and mature eras. In the adolescent era the audits focused only on software development life-cycle phase issues, whereas in the mature era supporting processes, policies, and activities have been examined including the company itself and FDA regulatory compliance aspects. Additionally, one can see that the number and severity of findings have increased in the mature era, particularly with regard to major findings. The authors take this as indicative, or at least suggestive, of a maturation of the auditing practices rather than a falloff in supplier quality performance.

**CASE STUDY**

A software house with no prior experience in building software subject to FDA regulations was contracted to develop a novel custom-made system. During the selection process the supplier exhibited evidence of good software development practices. An incremental project life cycle was applied and UML used (use cases) in defining requirements. Prior to signing the contract, BPC performed an informal review of the supplier’s QMS and found it lacking. In response, BPC supplied an independent quality expert to introduce the supplier to quality expectations.
Once the project moved into active development, a formal audit by BPC identified uncorrected problems with the supplier’s QMS. Corrective actions were promised. A follow-up audit six months later, now well into coding, found that some corrective actions had not been implemented, and new findings were documented, with some considered to be critical (configuration management). Additionally, design documentation was incomplete, a new development methodology had been implemented midway through the coding phase, staff turnover resulted in inadequate training of new developers in BPC expectations, and established programming standards were not followed. The supplier stated that previously identified corrective actions were not completed, in part, because of schedule constraints.

Based on the audit findings BPC determined that the system could not be validated. A business decision was made to continue with the project but only following the placement of a quality consultant responsible to BPC at the software developer’s site. Following total renovation of the supplier’s QMS, using ISO 9001 as guidance, and a two-year delay, the system was successfully validated: 96 percent of the requirements were verified, with most of the remainder determined to be untestable. As can be seen in Figure 8, 230 exceptions were observed during the execution of all protocols. This number includes more than 20 system fatal errors and 57 operational exceptions. Two hundred and twenty-seven were closed on completion of validation activities. The three open exceptions were determined not to have an immediate impact on system use. A follow-up audit performed just prior to initiating validation activities identified only minor deviations. Unfortunately, the granularity of details available did not allow for determining whether the defects, if remained undetected, would contribute to a potential drug mishap.

This case study supports the position that good software design alone cannot be substituted for testing, which validates the FDA’s stance calling for pharmaceutical manufacturers black-box testing as an obligatory yet complementary activity to monitoring the supplier’s quality practices. However, this is not to say that ISO certification and the auditing of those practices are without value. The high degree of customer oversight following the failed audit likely resulted in fewer defects surviving through to system delivery.

**CONCLUSIONS**

If one of the cornerstones of software engineering that has quality management systems and practices acting as facilitators of higher quality is correct, then this review of audit reports and case studies provides evidence of the influence supplier audits can have in improving software quality. By demanding adoption and adherence to a QMS and other methods of process improvement such as those defined by a combination of ISO 9001 and GAMP standards, it can be argued that the pharmaceutical manufacturer receives a product capable of satisfying FDA expectations and the general public can be assured that the medications it receives are not adulterated or otherwise dangerous as a consequence of faulty software. As seen in the quality era, the correlation between the increased expectations of BPC and those of the FDA suggest that, while the pharmaceutical industry acts reactively rather than proactively to government demands, this reaction is conducted with the intent of compliance with the letter of the law, not avoidance.

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**FIGURE 8** Customer detected faults

<table>
<thead>
<tr>
<th>Definitions of exception levels</th>
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<tbody>
<tr>
<td>High: Requires computer restart.</td>
</tr>
<tr>
<td>Medium: Software remains functional, requires workaround.</td>
</tr>
<tr>
<td>No impact: User interface design or presentation.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>High</th>
<th>Medium</th>
<th>No impact</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design qualification</td>
<td>2</td>
<td>10</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>Installation qualification</td>
<td>14</td>
<td>39</td>
<td>21</td>
<td>74</td>
</tr>
<tr>
<td>Operation qualification</td>
<td>• 21 bugs found in first pass resulted in 45 exceptions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 10 bugs found in testing of updated build resulted in 12 exceptions, all viewed as minor and not requiring immediate remediation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance qualification</td>
<td>6</td>
<td>41</td>
<td>30</td>
<td>77</td>
</tr>
<tr>
<td>Totals</td>
<td>36</td>
<td>121</td>
<td>60</td>
<td>230</td>
</tr>
</tbody>
</table>

Thirty-six exceptions were not designated for corrective action prior to the first release. Twenty-two relate to screen displays, 11 to usability issues considered as minor, and 3 to documentation. Workarounds were identified for 28 of these exceptions. None of the unaddressed exceptions are thought to have an impact on intended operation.
While the review of 17 audit reports is not a statistically valid study, several observations and deductions can be made. The distribution of critical, major, and minor audit findings over the mature era (2, 19, 26) (see Figure 7) compared with the adolescent era (1, 9, 25) (Figure 5) suggest that BPC became more sensitive to detection of deviations that might result in an FDA citation. As there are relatively few critical findings, this might indicate a desire to retain a good working relationship with the supplier to better address remediation, something that could be difficult with the more derogatory finding. There also appears to be a shift over time in the type of supplier practice being cited. Adolescent era critical and major findings tend to relate to issues of core quality practices, such as configuration management and the QMS, while in the mature time frame there are more comments on issues of finer granularity such as specifications, testing, and programming practices. This suggests that suppliers have made significant progress in implementing and maintaining quality programs, though occasional slips in compliance can occur, which argues for the need of continued surveillance through follow-up audits prior to purchase of major upgrades or revisions.

It is possible to see a tail-wagging-the-dog situation developing here. As drug manufacturers represented only a minor percentage of all monitored suppliers’ overall business, it is probable that other industries using the same software products benefited through the higher quality demanded by BPC. One interesting question not addressed at this time is to what extent these other customers have subsidized the costs assumed by the supplier in achieving the pharmaceutical industry (and FDA) quality expectations.

Given the progression through immature, adolescent, and mature eras, will the industry move on to a golden age of quality? Now that pharmaceutical manufacturers and software houses have largely made the investment of developing quality practices, will there be enough momentum to maintain and, perhaps, enact enhancements? As the vigorousness of pursuing quality in the past appears to be linked to government enforcement practices, the recent FDA announcement of revamping the GMP regulations to a risk-based approach (FDA 2002b) would appear to muddy the waters.

There are other aspects of quality that have not yet been discussed in this article. While the supplier audit, validation, and maintenance activities examined in this article have focused on satisfying FDA regulations, there is little evidence that these same activities attempt to evaluate or monitor a software system from an end user’s point of view. In light of this, it may be valuable to look elsewhere for guidance. International standard ISO/IEC 9126-1:2001 (ISO 2001) identifies four characteristics for which metrics may be collected from actual usage in evaluating quality in use:

- Effectiveness: To achieve specified goals with accuracy and completeness
- Productivity: To expand appropriate amounts of resources in relation to the effectiveness achieved
- Safety: To achieve acceptable levels of risk of harm to people, business, software, property, or the environment
- Satisfaction: To satisfy users (interaction with and attitudes toward the product)

It has been shown in this study that current practices are addressing the safety goal. As much as quality inspections have influenced the properties of software, the collecting of data on effectiveness, productivity, and satisfaction could be used to influence the supplier to provide evidence, perhaps during follow-up audits, of remediation of inadequacies as a precondition to purchasing upgrades, or additional functionality modules.

REFERENCES


FDA Regulations and Auditing Practices for Software Suppliers at a Pharmaceutical Manufacturer


American Testing Board

The American Testing Board (ATB) is a group of highly experienced experts in software testing who volunteer their time to the development, maintenance, and promotion of the ISTQB Certified Tester program in the United States. They also represent U.S. interests internationally as the national board for the United States within the ISTQB. The ATB is a nonprofit organization. Exam and accreditation fees are charged to pay for the cost connected with the administration of exams, applications for accreditation, the maintenance of a physical office, exhibits at leading software testing conventions, and the employment of administrative staff.

The International Software Testing Qualifications Board (ISTQB) comprises representatives from each existing national board, such as the ATB. The ISTQB decides on the standards for certification and accreditation as an ISTQB accredited training provider. Working parties within the ISTQB are responsible for developing and maintaining the Foundation and Advanced Level syllabi and exams. As with the ATB, all members are volunteers.

The ISTQB Certified Tester program provides certification for software testers internationally. There are currently two levels of certification: The Foundation Level and the Advanced Level certificate. The Advanced Level certificate will become available in the United States by 2005. For both, international working parties develop and maintain internationally uniform curricula and exams. One of the core principles of the program is a strict separation between the administration of exams and the provision of training to those who would like to prepare for the exam in ISTQB compliant courses.

What does an ISTQB certificate tell me about the skills of a software tester? The Foundation Level exam tests for knowledge, not skill. It provides information about the certificate holder’s level of familiarity with the most common concepts of software testing and the associated terminology. It does not require work experience. The Foundation Level exam is a stepping stone toward the Advanced Level, which goes in-depth and is much more practice oriented, wherefore it also requires 18 months experience as a software tester. Foundation Level: Knowledge. Advanced Level: Skill.

How many ISTQB certified testers are there? Approximately 20,000 software testers currently hold ISTQB compliant certificates. Most of them can be found in Europe, since the program was recently introduced into Asia and the United States.

When will the ISTQB Certified Tester—Advanced Level become available in the United States? By 2005.

How did ISTQB certification start? In Europe, industry demand pushed the development of this certification program. The program has been introduced in the United States to truly internationalize it, and to satisfy industry demand for an internationally recognized certification, which has become an industry standard in many other countries already. The success of the program can certainly be ascribed to its transparent structure, volunteer and nonprofit character, and the representation of nationals interests through national boards.

BIOGRAPHIES

Timothy W. Theisen is a business analyst responsible for the implementation of business specific software for an R&D client base at a global pharmaceutical company. Before moving into IT he spent many years as a molecular biologist, first at the Department of Medical Genetics at the University of Wisconsin-Madison, and later in commercial pharmaceutical R&D laboratories working on experimental malaria vaccines, and recombinant (humanized) antibodies. Theisen holds a bachelor’s degree in medical microbiology from the University of Wisconsin-Madison and a master’s of software engineering degree from the Pennsylvania State University.

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