

# The Future State of Computer Validation, Part I

## Increasing the Efficiency of Computer Validation Practices

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The objective of this article is to attempt to look at the future state of computer validation principles based on the current events and trends in regulations, business practices, and technology. This crystal-ball approach will prepare the industry for the future by establishing a current-state best-practice foundation of computer validation principles as well as improving computer validation practices.

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In Part I of this article, the authors address the regulatory, business, and technological events and trends in computer validation in the past 25 years. Current industry efforts and the future of computer validation infrastructure will be discussed in Part II.

### Regulatory events and trends

FDA, by way of its Modernization Act of 1997 (1), has indicated its intention to achieve the following goals by 2002 (2):

- official submissions received and archived electronically
- electronic submissions and reviews accessed from the reviewer's desktop computer
- standardized analytical tools
- publicly releasable material available on the Internet.

The above goals point to the agency's movement toward more automated and electronic information. This movement also is shown by the number of guidelines recently published by the agency in support of this activity. For example:

- "Guidance for Industry: Pilot Program for eIND Applications for Biological Products" (3).
- "Guidance for Industry: Computerized Systems Used in Clinical Trials" (4).
- "Guideline for Industry: Structure and Content of Clinical Study Reports" (5).
- "Guidance for Industry: Regulatory Submissions in Electronic Format for NDA" (6).
- "Guidance for Preparing Data for Electronic ANDA Submissions" (7).
- "Revised Guidance for Providing Regulatory Submissions to CBER in Electronic Format" (8).

Specific to 21 *CFR* Part 11 (Electronic Records and Electronic Signatures Rule), the agency has published a Compliance Policy Guide (9). A guidance document on this ruling also is being developed, and a public docket has been established for public comment on the regulation (10).

Besides moving toward a more automated and electronic environment, the FDA Modernization Act indicated the agency's intention of pursuing a harmonization effort between countries to achieve mutual agreements in regulatory requirements (11). An example of this harmonization effort that can be related to computer validation activity is the discussion on the

integrity of data and computer software validity in section 5.8 of the International Conference on Harmonization: "Guidance on Statistical Principles for Clinical Trials" (12). An extrapolation of this harmonization effort has the potential to address computer validation as part of the future global harmonized regulatory requirement. Another agency effort is leveraging government agencies and the private sector to increase the knowledge base and the decision-making process for a more expedient review process (13). The importance of this initiative also was voiced by FDA Commissioner Jane Henney, MD, in her speech in February 2000 (14). Through the Product Quality Research Institute, cited by Dr. Henney, FDA has demonstrated its willingness to work with industry and academia to ensure that agency regulations and guidances are scientifically based. In addition to the above, the Government Paperwork Elimination Act, Public Law 105-277, Title XVII, which was signed into law on 21 October 1998, mandates all agencies (including FDA) to accept all documentation and signatures in electronic form, where practical, by October 2003 (15). The effort to improve and speed up the regulatory review process may increase the future scope and types of computer systems to be validated. The increase in the number of domains affected by computer validation could extend to the food industry, as demonstrated by FDA *Guide to Inspection of Computerized System in the Food Processing Industry* (16).

On the enforcement side, a quick search of the FDA Web site for warning letters will reveal several that are related to computer validation (17). Many observations (483s) related to computer validation that did not make it into warning letters also have been issued. Some examples of these observations discussed issues related to expectations regarding documentation of software development, remote access and software modification, software hazard analysis, and electronic chromatography files maintenance. These documents are available publicly and can be obtained through the Freedom of Information Act (18) as well as from the FDA Web site.

In addition to communicating its expectations for validation of computer systems and software through warning letters as previously mentioned, FDA has published a number of guidance documents, and additional references are currently under development. Some of the pertinent ones are:

- The guidance document "Off-the-Shelf Software Use in Medical Devices" (19), issued 9 September 1999, contains the latest ideas about software risk management. In a related cooperative project with the Association for the Advancement of Medical Instrumentation (AAMI), a software engineering standard for medical device software is under development. The draft standard requires compliance with ISO/IEC 14971 Medical Devices — Risk Management.
- The guidance document "Computerized Systems Used in Clinical Trials" (20), issued in April 1999, provides current FDA views on features of regulated computer systems, their validation, and the expectations to have when off-the-shelf software is used to achieve a regulated activity.
- The draft guidance document "General Principles of Software Validation" (21), published in June 1997, has been revised in response to industry and public comments, and the final docu-

ment currently is proceeding through review and approval within Center for Devices and Radiological Health (CDRH). Also related to this document is the AAMI project (cochaired by a CDRH software engineer) to develop a software engineering standard, i.e., the American National Standard for Medical Device Software—Software Life Cycle Processes.

It is important to recognize the influence of the software engineers in the Office of Science and Technology (CDRH) on the direction of FDA in regulating software systems. A pertinent illustration is the statement made during the satellite broadcast on design controls in December 1996 that software validation is a control of the development process, which foreshadowed statements in two January 2001 Center for Drug Evaluation and Research warning letters: "Software is validated in its controlled development and in control of ongoing maintenance of the software throughout its life cycle" (22).

FDA also has issued warning letters related to the content of marketers' Web sites because of site contents that are considered in violation of the Food, Drug, and Cosmetic Act such as those sites containing misleading or even false marketing or advertising (23). Although this is not directly related to computer validation, it demonstrates the agency's commitment to enforcing the validity of the content and data being claimed by marketers. Hence, this demonstrates the need for verifying Web site content.

In addition to the above events, FDA activities can influence the industry and, consequently, also may affect computer validation activities. For example:

- Training of FDA investigators in computer validation and 21 CFR Part 11. This training may lead to an increase in the number of computer system inspections and to more consistent FDA computer system inspections.
- In the past four years, 11 drugs have been recalled from the market (24). These recalls have the potential to cause FDA to look into patient data kept by health insurance companies as a means to a better postmarket drug monitoring program. Consequently, ensuring the integrity and confidentiality of patient data becomes a factor that must be addressed by our industry and by the insurance industry. In addition, FDA also may look into its drug approval process, which may translate into looking at the systems that generated and processed the data submitted for drug approval.

- FDA also has allowed pharmacists to re-import prescription drugs (e.g., from Canada and Mexico). This allowance may affect drug pricing in the United States, which could adversely affect the amount of resources available for computer validation.

Besides the United States, several other countries also have requirements related to computer validation, including Australia, the United Kingdom, the European Union (EU), and Japan. Both the EU good manufacturing practice (GMP) directive, Annex 11, and Australia's Therapeutic Goods Administration (TGA) GMP have requirements for computer quality assurance. As a matter of fact, the TGA GMP has required electronic audit trails since 1991.

After review of this section, one can easily conclude that there is a future trend toward increased automation and electronic information transfer and availability in our industry, which parallels other industries. Also, the increased regulatory enforce-

ment focused on computer system integrity (i.e., computer validation) is a concern at a national and international level.

### **Business events and trends**

In the past few years, several major pharmaceutical companies have merged or expanded their business presence by acquiring other companies (e.g., Aventis, Novartis, Pharmacia, Glaxo-SmithKline, and Pfizer's acquisition of Warner-Lambert/Parke-Davis). These newly expanded companies have looked at, or will need to look at, how their businesses are conducted and how synergies in the newly formed or merged companies can achieve an increase in efficiency and productivity in research, manufacturing, and sales and distribution. Hence, it is not uncommon for these companies to review all aspects of their business processes and information technology strategies and practices when looking for ways to increase efficiencies. The bigger-is-better trend and the increased need to operate the business more efficiently will have an effect on computer validation. This effect will reveal itself in the need to validate the integration of various systems, the development of new systems, the retirement of systems, and other validation activities related to those systems such as data migration and data archival activities. Furthermore, there is also the need to evaluate the computer validation practices carried over from the premerged or preformed companies and to harmonize those practices. In some cases, this has resulted in mature computer validation programs being diminished in order to compensate for their new partners having a less comprehensive program.

Within the business operation units (i.e., laboratories, quality controls, manufacturing, sales and distribution, etc.), the use of computer systems, instruments, and equipment is proliferating. To increase operational efficiency in the automated business units, most companies are trying to integrate those systems. For example, the integration of the laboratory information management systems (LIMS) with the manufacturing resource planning (MRP) and manufacturing execution systems (MES), etc., provides the firm with a more efficient interface between departments and can be a facilitator for staff reduction as administrative tasks are assumed by more effective systems. Hence, these integration activities also will increase the need for computer validation, especially in situations where human judgment is removed from the processes.

In the research arena, computers have played a major role in advancing genome science and completing the mission for finding the sequence of human genes — advances that have led the industry to new gene-therapy products and have the unlimited potential to guide the industry to other new products. Computers also will play a major role in the future research of these potential gene-therapy products. Computers first will be used in bioinformatics to predict the type of protein that is encoded by the newly sequenced DNA genes. After the type of protein is predicted, computers then will be used in proteomics to find the potential active interaction site for the proteins. Besides the major pharmaceutical and biotechnology companies, several companies have been formed to work in genomics. Jason Reed, PhD, vice-president of Gruss and Son Co. (New York, NY), predicted this business will grow to \$2 billion in five years (25). On

the Internet, the basic local alignment search tool (BLAST, 26) and Entrez (a software tool to perform meta search and retrieval, 27) are just a couple of examples of computer programs being used in genome science.

The use of computers in other areas of research also has expanded. For example, many sophisticated analytical techniques (e.g., X-ray crystallography and high-field multidimensional nuclear magnetic resonance studies) are performed early in the drug development process as part of structure elucidation and eventually become part of regulatory submissions. Other examples include the use of electrophotography methodology for developing a novel drug-delivery method (28) and the use of a Web-based application for reviewing clinical data and as a remote clinical data capture tool (29). All of these examples are indications of the increased usage of computer systems, which translates into increased computer validation activities.

### **Technological events and trends**

The advances of Internet- and information-browsing technology without a doubt have played a major role in how information is being distributed and accessed, which leads the movement of applications to this Web-browsing technology. These so-called e-applications will take advantage of the Internet's global data distribution capability. Key points to consider when validating e-applications are the increased security risk and data integrity factor as well as data privacy. The Public Key Infrastructure (PKI) and Pretty Good Privacy (PGP) combination is one of the current mechanisms and methods available to address data integrity and security issues. An example of this trend is the availability of browsing technology as part of the e-manufacturing implementation (30). Similar to the concept of MES, e-manufacturing is the total integration of the enterprise — from the plant floor all the way through to the customer — by using Web-based technologies. The result is a system that is focused on solving business problems with an aggregate of software, hardware, and systems. In the future, computer system validation must be adaptable enough to address these aggregates based on aspects unique to each technical solution.

The electronic data interchange effort has been around for a few years, and standards are available. However, for business to business (B2B) e-applications, no standard exists for data interfaces and the presentation of data for the interchanges. To address the lack of standard, an e-business extended markup language (ebXML) effort has been sponsored by the United Nations Centre for Trade Facilitation and Electronic Business and the Organization for the Advancement of Structural Information Standard to develop an XML-based infrastructure for B2B commerce that was scheduled to be completed in May 2001 (31). Validation practitioners must keep up with not only the technological advances of application software but also the advancement of security-related tools such as PKI and PGP and new e-applications, including the ebXML technological effort.

Besides advances in software applications, there are technological advances in the hardware arena. Electronic ink is one example (32). Lucent Technologies (Murray Hill, NJ) has demonstrated the world's first flexible electronic ink display with plastic transistors (33). There also are advances in the availability of vari-

ous types of data storage mechanisms (e.g., compact flash and rewriteable CD-ROMs) as well as the availability of various computing platforms and devices that are smaller and faster (e.g., smaller notebook computers and personal digital assistants). Computer validation staffs will feel the effect of these advances in the form of a need for an enhanced or enlarged skill set that allows them to handle the expanded range of technologies.

Advances in the infrastructure arena include a wider data bandwidth that increases the amount of data that can be transmitted and made available, an increase in public accessibility to the Internet, and an increase in the number of users accessing the Internet. The effect of the increasing number of users (and presumably the number of hackers) and the increasing amount of data being transported is increased security risk, therefore a potential increased data integrity risk.

### **Current industry effort**

Several professional organizations currently are working on guidelines and standards that will affect the future of computer validation principles and practices.

The Good Automated Manufacturing Practice (GAMP) Forum together with ISPE have recently established GAMP Americas (34). This newly formed GAMP structure is currently working on a new version of the GAMP guide (version 4) that will be available by the end of this year. GAMP special interest groups (SIGs) also are drafting papers on network qualifica-

tion, infrastructure qualification, and 21 *CFR* Part 11 compliance. GAMP Americas has formed several SIGs such as e-applications, MES, clinical systems, medical device, laboratory systems, joint equipment transition team forum (process equipment), and suppliers' forum. Additional information about GAMP and the associated SIGs is available on their Web sites.

The Parenteral Drug Association (PDA) has produced work products related to computer validation such as a harmonized glossary for computer validation, "Technical Report #31: Validation of Laboratory Data Acquisition Systems," and "Technical Report #32: Auditing Computer Product Suppliers" (35). PDA and its Computer System Interest Group steering committee are currently supporting task groups working on good electronic records management and the revision of "Technical Report #18: Validation of Computer Systems."

The Consumer Healthcare Product Association leads the Industry Coalition on 21 *CFR* Part 11, which is a coalition of 10 national trade associations representing industries regulated by FDA, and is working with the agency in preparation of FDA guidance on the implementation of 21 *CFR* Part 11.

The Pharmaceutical Inspection Convention (PIC) has developed a draft guidance titled "Best Practices for Computerized Systems in Regulated 'GxP' (GMP, GCP, or GLP) Environments." In support of this effort, international regulatory agencies have collaborated to produce this harmonized guidance for the validation, control, and use of computer systems

in GxP-regulated applications in the pharmaceutical industry. It is intended for both external reference by the pharmaceutical industry and its suppliers and also for internal use by regulatory inspectors and investigators (36).

Other professional organizations related to the computer industry also are working on standards that may affect the way regulated business is conducted as well as the method and extent of computer validation practices. For example, the Information Society Standardization System has the mission of providing market players with a comprehensive and integrated range of standardization-oriented services and products to contribute to the success of the Information Society in Europe (37). The International Biometric Industry Association provides information and a list of biometric companies (38). AAMI is currently developing a software engineering standard applicable to medical device software life-cycle processes. The title of this draft document is "Medical Device Software — Software Life Cycle Processes." Of course, many other organizations are developing standards but are too numerous to reference in this article.

### Summary of the trends

The following points summarize the trends from the regulatory, business, technological advances, and industry sections of this article:

- Regulatory. Moving toward the e-format and increasing focus

on computer systems, including the data integrity and security of those systems.

- Business. The need for cost-effective and efficient good fast production without compromising the quality and regulatory compliance factors through business globalization, integration of systems, and use of new information technologies.
- Technology. The need to increase the system's scalability, compatibility, availability, modifiability, performance, and interoperability factor to meet business needs.
- Industry. Provide standards and guidelines for assisting the business needs of meeting regulatory compliance in the use of current technologies.

Therefore, there is a clear sign that the future need for computer validation will increase as the business needs for more systems, faster transactions, and information availability become more prominent. The trends noted above, coupled with more sophisticated compliance demands from regulatory agencies, are driving the industry toward an ever-increasing dependence upon electronic business solutions. This in turn will amplify the need for effective and efficient computer validation processes. Approaches to developing or improving these processes are suggested in the remainder of this article. future infrastructure (please note that these concepts are simply food for thought).

Part II of this article, including references, will be published in *Pharm Tech's* IT supplement in September 2001. **PT**