PERSEID
SOFTWARE LTD

Building Mission Critical Document Management Solutions for Global Pharmaceutical Companies

Perseid Software Limited
Needham, Massachusetts

May, 2001

Table of Contents

Figures

1 Executive Summary

This paper defines the requirements for a pharmaceutical manufacturer's global quality system that must manage millions of documents. It examines the requirements for constructing a scaleable, continuously available, enterprise document management system and defines a "model" information systems architecture for a global good manufacturing process system.

Currently, the required quality standards are mandated by actual and *de facto* international standards, such as the ISO 9001 and U.S. government's "Quality Standard for Good Manufacturing Processes."

Quality systems are typically implemented by global manufacturers as a body of intellectual property—process standards and associated documentation that make up the definitions of a quality system for a pharmaceutical company or distributor.

The availability, integrity, consistency, reliability and validity of a pharmaceutical company's quality system is subject to audit and enforcement by governments and agencies, such as the U.S. Food and Drug Administration (FDA) at any time. A pharmaceutical manufacturer may be fined by public notice for failure to maintain a quality system with complete integrity.

The recommended model information system provides a high return-on-investment for a global pharmaceutical manufacturer. This is because it is based on a primary centralized enterprise solution that reduces the number of physical documents required and provides pervasive and immediate access to all good manufacturing processes and their associated documents.

A global good manufacturing process document management system is presented that represents a computing solution that is scaleable, reliable and it supports a global enterprise requiring the highest standards of information systems integrity available at this time.

1.1 "Good Manufacturing Practices" Defined

The Current Good Manufacturing Practice ("CGMP" or simply "GMP") requirements set forth in the Quality System ("QS") regulation are promulgated under U.S. Title 21 Code of Federal Regulations (21 CFR Part §11) and enforced under the Food, Drug and Cosmetic (FD&C) Act of the U.S. government. The Food and Drug Administration (FDA) monitors problem data and inspects the operations and records of pharmaceutical manufacturers to determine compliance with the GMP requirements in the QS regulation. They require that domestic or foreign manufacturers have a quality system for the design, manufacture, packaging, labeling, storage, and delivery of finished medical pharmaceutical products intended for commercial distribution in the United States.

The regulation requires that various specifications and controls be established for pharmaceutical products; pharmaceutical products be designed under a quality system to meet these specifications; pharmaceutical products be manufactured under a quality system;

finished pharmaceutical products meet these specifications; quality data be analyzed to identify and correct quality problems; and complaints be processed. Thus, the Quality System, also known as the GMP regulation, helps assure that medical pharmaceutical products are safe and effective for their intended use.

The new Quality System regulations make standards for American medical pharmaceutical products consistent with quality system requirements worldwide, thereby meeting an important goal of global harmonization. The new standards closely follow the international standard, ISO 9001, and fulfill a mandate of the Safe Medical Pharmaceutical Products Act of 1990 to harmonize these requirements.

1.2 Good Manufacturing Practices are a Global Enterprise Management Issue

As a result of the harmonization of U.S. and international pharmaceutical regulations, QS/CGMP (simply "GMP") has an international scope and reach. The U.S. FDA may audit any manufacturing plant, anywhere in the world, that manufactures pharmaceutical products for distribution in the United States. For senior management of pharmaceutical companies, the Information Technology ("IT") considerations are significant:

- The extent of the documentation required to support international GMP corporate standards is substantial, typically in the millions of documents.
- GMP implies that current quality standards documentation is available with full audit trails at all times at each required location.
- Ease-of-use and pervasive access to GMP documentation must be emphasized.
- Process and organizational behavior must facilitate GMP.

1.2.1 Return on Investment for GMP

The return on investment for information technology to support GMP can be substantial. Well-documented GMP improves manufacturing efficiencies, production volumes, speed-to-market, and reduces or eliminates regulatory compliance actions. It may also positively influence consumer behavior with the advent of direct consumer marketing.

For senior executives of pharmaceutical companies, GMP provides a competitive advantage based on manufacturing excellence and provides assurance that manufacturing processes are world-class. GMP also provides concrete evidence that the enterprise is a high performance organization, thus enhancing the brand image of the company. Difficulties in coordinating compliance-critical documents between new product development and production plants can often result in months of delay. Every day a launch of a new pharmaceutical product is delayed can cost, on average, $1 million. In a typical medium-sized manufacturing plant, the operational costs for GMP can range from 10-15% of the total plant's operational costs or about US$10M. Using a price/earnings ratio of 25, this savings could generate an additional $125 million in market capitalization.

For the operating financial management of pharmaceutical companies, GMP may be considered merely a cost of doing business. But given the free access of the general public to regulatory process review and importance of the brand name in the pharmaceutical industry, GMP may be viewed as the foundation for a competitive advantage for a pharmaceutical manufacturer or marketing firm. As an example, direct advertising of pharmaceutical products to the general public can alter the relationship of the consumer to the pharmaceutical company. No longer simply marketing to physicians, the pharmaceutical company that is marketing directly to the consumer faces scrutiny by the general public. Inevitably, this will result in an even stronger emphasis on brand name recognition, quality of manufacturing and scrutiny by the consumer. Direct marketing closes the final loop with the consumer, so GMP is now ultimately tied directly to the retail brand name and image in the consumer's mind.

1.3 Reducing Risk with an Enterprise Information System for GMP

With global regulatory standards of GMP in existence, the global pharmaceutical company faces a classic information systems problem: how to manage global GMP processes, documentation and standards, while maintaining the ability to locally and regionally respond to management needs of plant managers and other regional managers.

Fortunately, with the emergence of the Internet as a platform for low-cost telecommunications and the development of enterprise-scale computing technology, tools are in place to design and build global information systems that respond to local and regional needs.

1.3.1 Scalability to Manage Millions of Documents

Document management has become a significant part of GMP and the solution to managing the millions of documents required to support local, regional, and global GMP. FDA audits can examine individual systems, procedures and processes. They can also examine the entire audit trail of modifications to documents and processes over time. The effects on a pharmaceutical companies inventory of intellectual capital is enormous. Even the smallest pharmaceutical company typically manages millions of documents. Each document must be managed through its own life-cycle, that is, stored, logged and each modification audited in the GMP document management system.

Requirements of global manufacturing systems driven by GMP include:

- A central database of all GMPs to identify and protect the core intellectual property of the enterprise
- Pervasive, global access to a reliable non-stop 24x7 information system

- Information sharing including ease-of-use and access to each GMP and within each GMP, each document
- The complete history and audit trail of each current good manufacturing process and document.

1.4 Information Sharing Contributes to GMP Application Success

Information sharing including ease-of-use and ease-of-access to GMPs are the keys to success for a GMP application.

Ease-of-use translates in a GMP application into the ability to quickly and easily access each GMP from any site, at any time, anywhere in the world. Since good manufacturing processes are sequences of process and documents, management of document changes in a GMP are critical. Many FDA fines are due simply to the failure of a pharmaceutical company to maintain proper documentation on a GMP, including outdated documentation or having no documentation on a process. Having access to the audit trail of modifications to the GMP and each document in a central, enterprise GMP document management system simplifies the task of maintaining, auditing and distributing global GMPs, since only one copy of a document or revision to a GMP would be required.

GMP applications must be available for use immediately, at all times, everywhere. Simply the act of making every GMP available to each employee, easily and quickly, will improve manufacturing efficiency and the depth of knowledge within the enterprise.

Given the global necessity that GMPs be made available to all employees, independent of locale, language, and organization at all times; GMP is essentially an enterprise application. Thus, it is unlikely that legacy information systems can serve the needs of a modern GMP application. Ease-of-use and ease-of-access are synonymous with the Internet, web-enabled, browser-based applications. Downloading and installing software, configuring and maintaining GMP applications in a traditional manner is inconsistent with the basic goals and objectives of a global enterprise GMP system. High ROI GMP applications are going to be those that minimize the total cost of ownership of the applications, including a focus on:

- High reliability and integrity of the information system for GMP
- Centralization of database management
- Pervasive, immediate global access
- Ease-of-use for a diverse population of users
- Web-enabled presentation management
- "Thin-client" solutions requiring only an Internet browser[1]
- Minimizing number of complex workstations requiring deployment and maintenance

[1] Rather than a complete installation of the software on each workstation or portable computer.

- Computer-based training and support/multi-language support.

1.5 A Centralized Enterprise Architecture Leads to Better Decision Making

Our model GMP architecture employs state-of-the-art technology to (1) meet the global GMP requirements defined above, (2) lower the total cost of ownership and (3) ensure integrity of the core GMP database in a non-stop, high availability operational environment.

Components of our recommended model architecture include:

- An Enterprise-scale computing platform and storage system to ensure availability of the central document management systems database
- A web-enabled "infostructure" based on 24x7 portals to access easily and quickly each GMP document
- A high-availability and high-reliability central database management system to store millions of documents with integrity
- Use of the Internet to make pervasive access to all GMPs immediately available to each employee throughout the world
- Reporting applications to allow managers of GMPs to monitor the state of each GMP thread of documentation at all times
- A secure access and control system to ensure the integrity of the chain of control over each GMP
- Reporting applications to allow managers of GMPs to the monitor the state of each GMP thread of documentation at all times.

1.6 Building the Infrastructure for Custom Document Management

State-of-the-art operating systems such as IBM z/OS™, IBM OS/390™, IBM AIX™, Sun Solaris™, Microsoft Windows 2000/Data Center™ and enterprise storage management systems mitigate the technological risk associated with managing an enterprise GMP document management solution.

Non-stop enterprise storage management solutions provide the foundation for continuous availability of the GMP solution. IBM, Compaq and EMC provide alternatives for continuous business operation.

IBM provides connectivity of storage systems and the operating system for its individual operating systems: z/OS, IBM MVS, AS/400™ and IBM AIX (Unix). Secondary support for Microsoft NT™ and Windows 2000™ is also available from IBM.

Compaq provides storage solutions focused primarily on Microsoft Windows NT, 2000 and 2000/Data Center. In Compaq's case, the storage management solutions are more appropriate for departmental or distributed local solutions. For large-scale, enterprise-grade

or central corporate solutions, only EMC provides a comprehensive and fully integrated solution for global enterprises.

EMC's "E-Infostructure" has been in development for more than 10 years with an investment of more than $1 billion. It is composed of physical, connectivity and functional layers of hardware and software. The physical layer includes Symmetrix™ and CLARiiON™ enterprise storage management hardware which provides the basic foundation for performance, capacity, availability and other physical requirements of central document management systems. The Enterprise Storage Network ("ESN") is the connectivity layer and through two information connections—Connectrix™ and Celerra™—it provides a means of using *all* primary and secondary operating systems to connect into the central or regional GMP document management platforms. These include each of the IBM operating systems, every major Unix operating system, including Linux and those from Sun, HP, and IBM; and each Microsoft operating system.

At the functional layer, there are a wide range of EMC products that provide protection, sharing and common management throughout the infrastructure. Most importantly, EMC system software supporting E-Infostructure ensures continuous business operation of operating systems *and* the database manager. Since most application failures occur as a result of a corrupted database, the unique ability of EMC software and hardware to synchronize, checkpoint and immediately recover a database are key functional requirements of a successful global GMP document management system. Of particular import is the ability to continuously backup, without stopping the database, enterprise database managers such as Oracle. EMC and Oracle have partnered to develop a continuously available version of Oracle Open Parallel Server ("OPS"). By combining Oracle OPS and EMC solutions, a continuously available database can be developed for GMP document management.

1.6.1 Business Continuance Solutions for Document Management

Given the mission critical nature of GMP systems, ensuring business continuance/high reliability is a prerequisite for a successful GMP document management system. We define high reliability as the ability of the GMP document management system to be available for use with an extreme degree of confidence, usually at least 99.9999% of the time. For a high performance GMP application, this level of reliability would translate into approximately one hour of "downtime" per year.

An architecture for GMP document management with high reliability will be based on the following set of alternatives:

1. Central architecture using enterprise-scale computing equipment, applications and data base management systems
2. Regional architecture using enterprise-scale computing equipment
3. A Decentralized architecture using plant-level information systems

Each architecture has a distinct advantage and associated risk:

The decentralized model allows greatest control over local GMP practices and documentation for a particular plant. However, this approach increases the risk that multiple versions of similar or the same GMP document, with differing versions, may exist across the enterprise. It also dramatically increases the number of stored documents and increases maintenance costs.

The regional model allows centralization by region, country or line of business and allows greater control over document variations that may develop, over time, and from plant-to-plant. Although it may facilitate regional control, this approach also risks developing multiple versions of the same GMP with a lack of consistency.

The centralized architecture ensures ease-of-integration since one copy of each document is centralized and made available globally through Internet-based presentation software. Ease of audit trail maintenance is also facilitated, since there is no need to synchronize multiple copies of the document across multiple instances of the document management system. Also, the centralized enterprise-scale solution allows for the application of scaleable, high-reliability, high-availability hardware, operating system and database management software with the greatest economies of scale.

With the technological risk well defined, planning and execution become the focus of pharmaceutical manufacturer:

- Team Building—Gaining a corporate "champion" to lead the effort within the ranks of senior management and building global /regional consensus on execution
- Requirements Analysis—Defining the customers, goals and objectives and return-on-investment of a GMP application
- Engineering—Selecting the right implementation and engineering partners, technology and implementation plan
- Execution—Delivering solutions that work on time, on budget
- Return-on-investment—Defining success and measuring its progress.

1.6.2 Diagram of a High Reliability Document Management System

A high reliability GMP application requires protection of the database, the operating system, the GMP application and the telecommunications network integrity. In the example model architecture, an emphasis is placed on maintaining the integrity of the database and surviving telecommunications failures.

Database integrity is key to the survival of the GMP application. There are few integrated solutions for database integrity that meet the stated objective of 99.9999% uptime. In the model architecture, the recommended enterprise-computing platform is based on Oracle Parallel Server operating with a Unix or Microsoft Windows 2000 operating systems using EMC Symmetrix hardware and business continuance software. Since the mean-time-to-

recovery ("MTTR") of the enterprise database servers is the key to a high-availability GMP application, the emphasis must be placed on protecting the enterprise GMP database. Database rollback and recovery is a time-consuming process, in a high-availability application like GMP, downtime of the database is not acceptable. Thus, an emphasis on continuous availability of the enterprise storage system is paramount.

Separating the enterprise storage management solution from the basic computer platform allows a high degree of flexibility and can result in a major return-on-investment. IBM, Sun, Compaq®, HP and Unisys® computer platforms using Oracle can be configured to meet the continuous growth demands of enterprise GMP systems by careful expansion of the computer platforms. The pharmaceutical company need purchase only the computer platform required at each stage of development with knowledge that the information storage solution is intact and continuously available. One of the unique features of EMC's E-Infostructure solution is the ability to deploy mixed computing platforms without changing the database or the enterprise storage infrastructure.

Figure 1 presents a model architecture for an enterprise GMP application. Its characteristics are:

- An employee utilizing a browser to access the GMP applications (Level 1)
- Optional regional or plant-specific GMP servers (Level 2)
- A non-stop central computing platform with redundant enterprise servers (Level 3)
- Redundant GMP applications and databases (Level 3)
- Highly redundant telecommunications to ensure high-reliability/availability of the GMP application and database

In the model architecture, an employee accesses, through a browser, either a regional (Level 2) or enterprise GMP application. Access to an enterprise GMP document management system would occur at Level 3. High availability is provided by the use of redundant servers with fail-over protection at each level. Each server is sharing a central storage management system at Level 3 such as EMC's Symmetrix solution using Symmetrix Remote Data Facility™ (SRDF) to protect and backup the database, without interruption to the GMP application. EMC's SRDF is used to maintain global availability of the central database and production GMP application. EMC's SRDF is an operating system-independent software solution that allows GMP applications based on Oracle to maintain real-time or near-real-time physically separate mirrors of selected disk volumes, all without requiring host or server resources.

The EMC storage management system provides a continuously available backup copy of the GMP databases.

Protection of the GMP application from failure is provided by a combination of application and system services. Operating systems such as z/OS, MVS, and AIX/HACMP™ from IBM, Sun Solaris from Sun Computers and Windows 2000/Data Center provide for integrity

of the GMP application. Failure recovery and roll-over of the application code can be detected by the operating system and the computers themselves.

Special protection, however, must be provided to the database management system, Oracle OPS, in our example, to ensure the ability to immediately recover from an application failure. Software applications, including latent bugs in the GMP application itself, can corrupt the GMP document database. This corruption may be detected by the application or Oracle and require a rollback and restart of the DBMS. Storage management hardware and software from EMC, for example, provide protection from DBMS restart and recovery delays by maintaining a synchronized DBMS "hot" copy of the production GMP database. EMC's TimeFinder™ Software and the EMC Foundation Suite™ and Database Edition for Oracle™ are examples of enterprise class system software for protecting the integrity of enterprise GMP applications.

The online operating system-independent, mirrored data storage solution duplicates central GMP site data on one or more physically separate target Symmetrix systems. Systems can be across the room, across the globe or anywhere in between. SRDF replicates data over virtual private networks using Internet Protocol (IP), ATM, T1 and T3. SRDF provides the GMP application with a complete business continuance capability in the event of a data center disaster and during planned events such as daily backups, database loads and refreshes, application testing, scheduled maintenance and data center migrations or consolidations. EMC SRDF is the only solution providing this facility simultaneously to mainframe, UNIX, Microsoft Windows NT/2000 and IBM systems.

GMP Model Example
"Ideal Architecture" Drawing

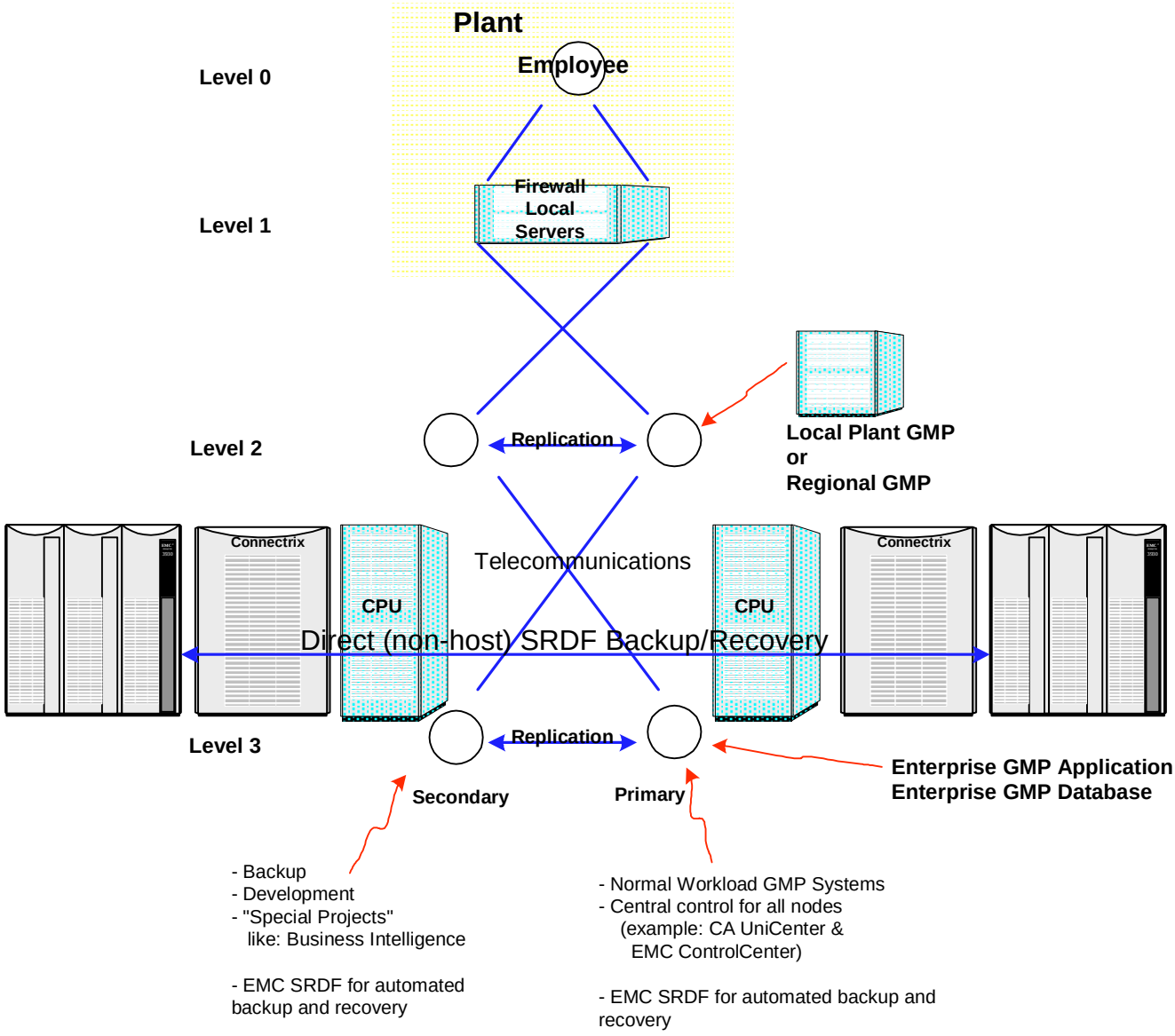

Figure 1 A High-Availability Enterprise GMP Example

2 Conclusion

Organizations are perfectly designed to achieve the results they achieve.[2] Good Manufacturing Practices are government mandated processes that ensure that pharmaceutical companies achieve good results and increase their operational control over their world-wide enterprises. Information systems leverage the documented good manufacturing processes of pharmaceutical enterprises. They provide the means to ensure that consistent operational processes and document management are continuously available 7x24xforever.

The key operational result of GMP is better and timelier decision-making for a global pharmaceutical enterprise. This requirement can only be met only by having a continuously available "bullet-proof" enterprise-scale information infrastructure.

Survivability, reliability and validity are the foundations for all Good Manufacturing Practices, since these requirements ensure the integrity and trustworthiness of the underlying information systems. And no organization can depend on unreliable systems and procedures.

Reliability and validity of the key GMP applications are provided by ensuring the performance and integrity of the central or distributed databases that house the GMP documents. Database integrity is the key to delivering GMP that enterprises can trust 24 hours per day, day-in and day-out.

High performance information systems are based on a combination of interrelated and dependent technology: modern telecommunications systems, computers, operating systems, storage management systems and database management systems. All must work in synchronization to ensure the performance of the GMP applications. They are made cost efficient by having scaleable solutions for the enterprise that can grow as GMP demands increase.

Senior executives of pharmaceutical companies can expect high returns on investment from GMP applications, since they influence the daily performance of individual plants and the enterprise as a whole in very concrete and measurable ways. "Metrics" can be defined to measure and analyze the performance of GMP systems and underlying organizational performance. These metrics validate the performance of the GMP processes and the productivity of each facility employing Good Manufacturing Processes.

[2] James Palmer, former Director of world-wide healthcare data systems, The Procter and Gamble Company.

3 About Perseid Software

Perseid Software is engaged in providing strategic consulting and information technology design services to healthcare and life sciences enterprises. For more than 30 years, the principals of Perseid Software have been engaged in the development of mission-critical information systems and in the analysis of healthcare, disability and pharmaceutical data.

Perseid Software is not merely a strategic consulting firm. It is an engineering management and design firm focusing on database design and implementation of very large and complex life sciences and healthcare information systems. Perseid's clients include or have included the largest and most progressive computer, healthcare and manufacturing companies in the world.

Contact:

Bernard P. Wess, Jr.
President
Perseid Software Limited
Needham, MA
(781)453-2351
bwess@perseidsoftware.com
www.perseidsoftware.com