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Creating a Global IT Infrastructure for Clinical Trials

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Table of Contents

Figures

1 Executive Summary

Clinical trial development and execution is being revolutionized. The United States, European Union and Japan have recently released standards for single "folder" submission of new drug approvals to any participating country governed by the standards of the International Conference on Harmonisation or ICH.

A single submission offers both great potential and risk for the global pharmaceutical manufacturer, biotechnology company moving towards commercialization, or research organization. Although a global submission process for approval has been developed, host countries can still enact their own clinical trial security, access and control legislation and policies.

This paper will articulate the security, access and control requirements that will support global clinical trials in multiple ICH-compliant host countries. It will also define the technology required to transform the global clinical trials process from a multi-site single country trial, to a global intra-company enterprise research and development activity.

Finally, this paper will also recommend a "model" architecture to support the availability, security, data protection, data mobility, data repurposing, and data sharing required for global clinical trials for multi-national pharmaceutical companies that can satisfy both the requirements of host countries and ICH submission standards.

2 Internationalization of Clinical Trials

2.1 Impacts of the International Conference on Harmonisation

In the United States, companies spend on average $240 million on clinical trials as a drug passes through the Food and Drug Administration (FDA) for final approval. Pharmaceutical companies have billions of dollars at risk if they cannot correctly match a pharmaceutical product to a target patient population as quickly as possible. Lost earnings and revenue by pharmaceutical companies can also occur when a very small segment of a target patient population experiences side effects from an otherwise effective pharmaceutical. Warner-Lambert, for instance, temporarily pulled Rezulin from the UK market and suspended its regulatory filing in Europe to investigate why the drug proved toxic to the livers of one diabetic patient in 60,000.

To address the global needs for international speed-to-market and safety, the International Conference on Harmonisation[1] (ICH) was formed in 1990. To date, 37 guidelines covering Efficacy, Quality and Safety have been produced and accepted by the ICH Steering Committee since 1997. The United States, European Union and Japan have established these guidelines as standards for new drug submission and data collection. These guidelines will revolutionize the submission procedure for regulatory staff for much of the world. Most importantly, in November 2000, the Common Technical Document (CTD) guideline was approved. It will afford significant time and resource savings as complex multiple submissions will be replaced by a unified documentation set to be submitted in the three regions, facilitating simultaneous submission, approval and launch of new drugs.

2.1.1 Generating the Required ROI for a Single Submission

The objective of such harmonization, as stated by ICH, is "a more efficient use of human, animal and material resources, and the elimination of unnecessary and unreasonable delay in the global development and availability

[1] The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1990

of new medicines while maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health.[2]"

The global pharmaceutical industry has many compelling reasons to support ICH and its continued efforts to further harmonize the technical requirements for the registration of innovative drugs. The primary reasons are: [2]

- Reduced development time and resources, including an end to duplicate clinical trials due to ethnicity differences. The ICH guideline covering ethnic factors approved in 1998 allows foreign country data to be used by any participating nation.
- Easier simultaneous launch of a new drug in many countries (including the three ICH regions).
- ICH guidelines—as a recognized international standard—will facilitate intra-company globalization.

The key to ICH success is the development of standards for the Common Technical Document or single "dossier" on the drug under development. The value of this solution to the life sciences industry must not be underestimated. Pharmaceutical companies currently invest many thousands of hours taking the data required for a submission and preparing a dossier to meet the specific requirements of regulatory agencies in the ICH regions. The time and resource savings and resultant efficiency in dossier preparation that will be achieved by a single format for all the technical data is projected to be extraordinary. A single dossier should also facilitate review by regulatory authorities and lead to faster review times, with the overall result of a faster time-to-market in the three ICH regions.

To build the necessary infrastructure for the ICH compliant pharmaceutical manufacturer, a comprehensive global perspective is required. Data gathering and management along with basic research and clinical trials must be converted to enterprise-wide activities within the pharmaceutical manufacturer. The information technology requirement that best meets the needs of global ICH research and development is a world-wide enterprise integration of clinical, administrative and financial information for multi-national clinical trials, which will create a complete picture of each patient and record the performance of a pharmaceutical in each country and region.

With hundreds of millions of dollars at risk during new drug development, meeting regulatory requirements in a timely way and speeding market launch is critical. Each day a new drug is on the market can add millions of dollars of revenue. These demands create time pressure on the entire value chain required to produce a new pharmaceutical. Data integration and coordination to produce a single dossier is required between internal research and development organizations, external firms that may have licensed the discovery, contract research organizations, regulatory bodies and target market distribution firms.

3 Enterprise Information Systems for Global Clinical Trials

3.1 The ICH Requires Complex Data Integration

Within the research and development organization(s), each researcher needs immediate access to the latest research data and analytical results. Multiple clinical trials may need coordination at multiple research centers. These requirements generate demand for complex information management tools and techniques that maximize the ability of research organizations to communicate and disseminate research results. The results must also be communicated to multiple participants to meet the demanding and complex time schedules encountered in new drug research and development.

[2] Caroline Nutley, "The Value and Benefits of ICH to Industry," International Federation of Pharmaceutical Manufacturers Associations, January, 2000

The solution to these complex requirements is a new information management architecture and delivery model for clinical trials. The architecture should:

- Enable a company-wide secure solution for developing, maintaining and executing multi-country, multi-site clinical trials
- Integrate all clinical data into a single submission dossier in ICH format including the necessary ICH content
- Integrate all data developed during research and development, approval and marketing into a comprehensive enterprise-level "data warehouse" [3]
- Facilitate sharing of key data by all researchers and research entities—not only the primary researcher and prime research organizations
- Enable pervasive access to the drug dossier through the Internet
- Store all key documents involved in the clinical trials process [4]
- Apply Good Manufacturing Process standards of audit, control and verification to all versions of software and data so that a comprehensive history of the research process emerges from the raw data [4]

A global ICH compliant clinical trial architecture should provide numerous benefits including:

- Ability to submit a trial from a single repository to any ICH participating country
- Timely access to mission critical research, approval and marketing data
- Facilitate communication among researchers and marketing personnel during all aspects of discovery, testing, market introduction and after-market verification/validation of efficacy
- Improve analytical processes that result from having integrated clinical, financial and administrative data in a single repository during clinical trials
- Provide more comprehensive and complete documentation with full audit trails
- Enable more timely regulatory filings for the country of submission

3.2 Information Delivery and Management Requirements

The information delivery and management requirements can be summarized as follows:

- A security, access and control (SAC) architecture to protect the integrity of an international application such as clinical trials
- Pervasive and comprehensive reporting, *ad hoc* query and analysis tools creating a web-enabled Internet-based EMC E-Infostructure®
- High availability database management systems to maintain availability and integrity of the data warehouse
- Continuous availability of the clinical repository to each enterprise and party associated with the drug discovery and development process

The integrated clinical trials systems environment will combine massive computational power with comprehensive analytical and reporting tools—all built upon a foundation of real-time, non-stop databases within the central R&D clinical repository supporting the ICH compliant trials.

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[3] See "Preparing Your Life Sciences Organization for Bioinformatics", Perseid Software Limited, August, 2001, www.perseidsoftware.com

[4] See "Building Mission Critical Document Management Solutions for Global Pharmaceutical Companies", Perseid Software Limited, May, 2001, www.perseidsoftware.com

Pervasive and continuous enterprise access is a critical requirement for the model information management and delivery architecture. The information delivery and reporting processes must present a uniform and easy-to-use application "user interface" to the enterprise data warehouse. "Metadata" or information about the contents of the drug dossier must be continuously available and updated regularly so each dossier user is aware of the contents and state of data. Enterprise storage management systems must connect to all computing platforms within the central research and development facility so that all data is available continuously with a high degree of security, integrity and reliability.

The central databases within the clinical trials repository will contain tiers of information — from low-level raw transactions and biological "objects," such as molecules— to complex disease management summaries by patient populations. Figure 1 describes the tiers of information that can be expected to exist in central databases supporting the ICH compliant clinical trial.

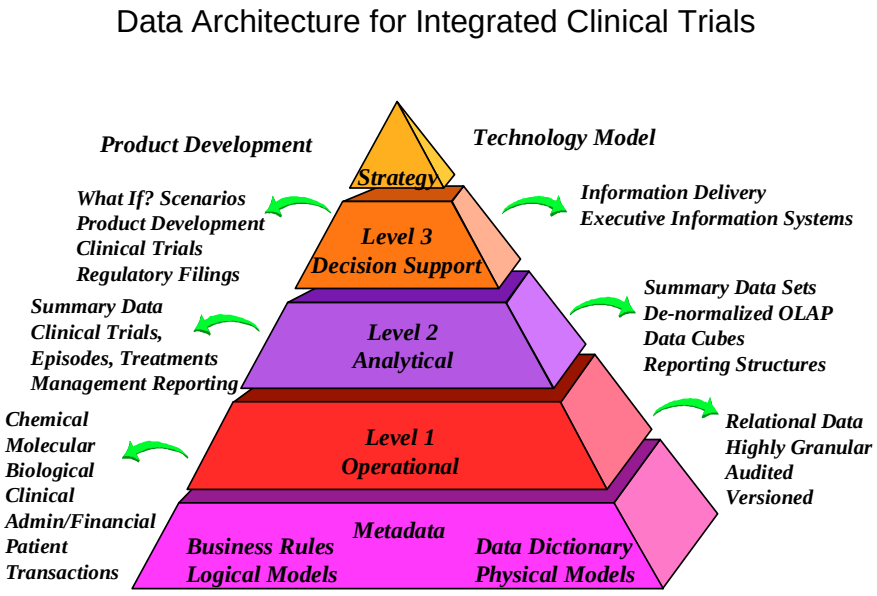

Figure 1 Data Architecture for ICH Compliant Clinical Trials

3.3 Security, Access and Control Requirements

No functionality for the global clinical trial application is more critical than the security, access and control (SAC) functionality. Healthcare SAC standards in the U.S. are defined by the interaction of state laws with the Health Insurance Portability and Accountability Act (HIPAA). [5] The Act implies that computerized healthcare information systems must have certain features and functions that address the proposed requirements of HIPAA. This section describes how the SAC requirements of an international clinical trial application can address the HIPAA privacy rules, which took effect in April 2001. [5] Note that state law in the U.S. or European Union law may preempt HIPAA. Thus, the Act does not entirely nationalize and federalize security, access, and privacy rules. The Act sets minimum standards for all healthcare organizations.

[5] As described in the Federal Register/Vol. 63, No. 155/Wednesday, August 12, 1998/Proposed Rules, pages 43269 to 43271.

The following sections define the basic security, access and control requirements of a global ICH clinical trial application. By their very nature, these requirements are enterprise-wide. They imply requirements that must be satisfied by the pharmaceutical manufacturer at the enterprise-level, that is, above the level of each individual clinical trial application. For example, a single global authentication system for each user should be employed by the pharmaceutical manufacturer for all clinical trial applications that access a central dossier.

3.4 Security, Access and Control Functionality

The functions required by clinical trials applications to ensure integrity, security, reliability of the application and its respective data are listed below. These functions in unison create a secure application supporting privacy and security policies that can be applied to an individual or a single transaction.

Because of the extraordinary legal and regulatory exposure of the global pharmaceutical manufacturer to both U.S. and European Union SAC regulations, no component of the global clinical trials application is more important than the security model:

Personal Security — Protection of a researcher's or user's data or work in progress from unauthorized access. The ability to audit access to such data.

Authentication — Knowledge of the user through unique identification of the user using multiple attributes, e.g., ID, password, role, etc.

Role-based Activity — Knowledge of current role of authenticated user. Application of the user's role to determine which data and transactions may be executed.

Context-based Activity — Knowledge of current role of an authenticated user and context of his/her actions. Use of role and context to determine which data and transactions may be accessed or executed.

Security Policies—Ability of the system to establish security policies that apply to groups of users and organizations, transactions, SAC attributes, roles, data, computing objects and transactions.

Authorization—Ability to obtain access, log, audit and disclose protected healthcare data as defined by HIPAA.

Preemption—Ability of the clinical trials application to match local (state or country) legal requirements for security, access and control functions as uniquely defined by a state which preempt HIPAA minimum standards.

Ownership—Knowledge of who "owns" data, work in progress (transaction states) and transaction functions. The ability to ascribe legal or functional ownership to data and transaction activity and their results.

Integrity—Persistent protection of data from unauthorized access, modification or SAC threats, e.g., virus attacks.

Auditable Activity—Ability to show the history of modifications to data and transactions executed against data.

Security of Data—Ability to protect contents of the database from disclosure.

Message Integrity—Ability of system to protect from disclosure messages in transit among processing systems or clinical trials applications.

4 Web-Enabled Global Clinical Trials Speed Time to Market

Pharmaceutical companies require massive scalability as they move to an integrated database of clinical, administrative, financial and bio-information required to support global ICH clinical dossiers. Pfizer, for example, expects its network traffic alone to increase by a factor of 10 within the next few years.[6] What may have worked in the single research laboratory will no longer work in the new global ICH environment for clinical trials.

The goal for a global clinical trials application is integrated information and enterprise-wide data management, independent of country of submission. Solutions that worked for a multi-site single country trial must now scale to support terabytes of integrated bio-information for each dossier. Data must be aggregated by patient population, trial, site, country, drug and be continuously available for use in research, development and marketing. The opportunity for discovery of novel unintended uses for a pharmaceutical will require that all data be kept on-line and be immediately available after submission to a host country's regulatory authority.

Figure 2 illustrates a recommended global security model that supports international, integrated ICH compliant clinical trials application incorporating the pervasive access required from the Internet.

The SAC model architecture assumes the following classes of data and functions are available:

- Security policies for each user and authorized transaction
- Privacy characteristics for data by user and user role for each transaction
- Internet LDAP attributes for global access to user and application attributes
- Audit trails on each modification to each SAC attribute
- Continuous audited history of each user attribute
- Single, global sign-on and authentication
- Integration with SAC features of the database management system
- Secure, pervasive access to the Internet with full-audit of each access
- Continuous availability of the SAC subsystem and clinical trials application

[6] Network Management Systems 2001, Developing the Network Management Systems for Next-Generation Networks, June 12-14, 2001, Swiss Hotel Washington-Watergate, Washington D.C.

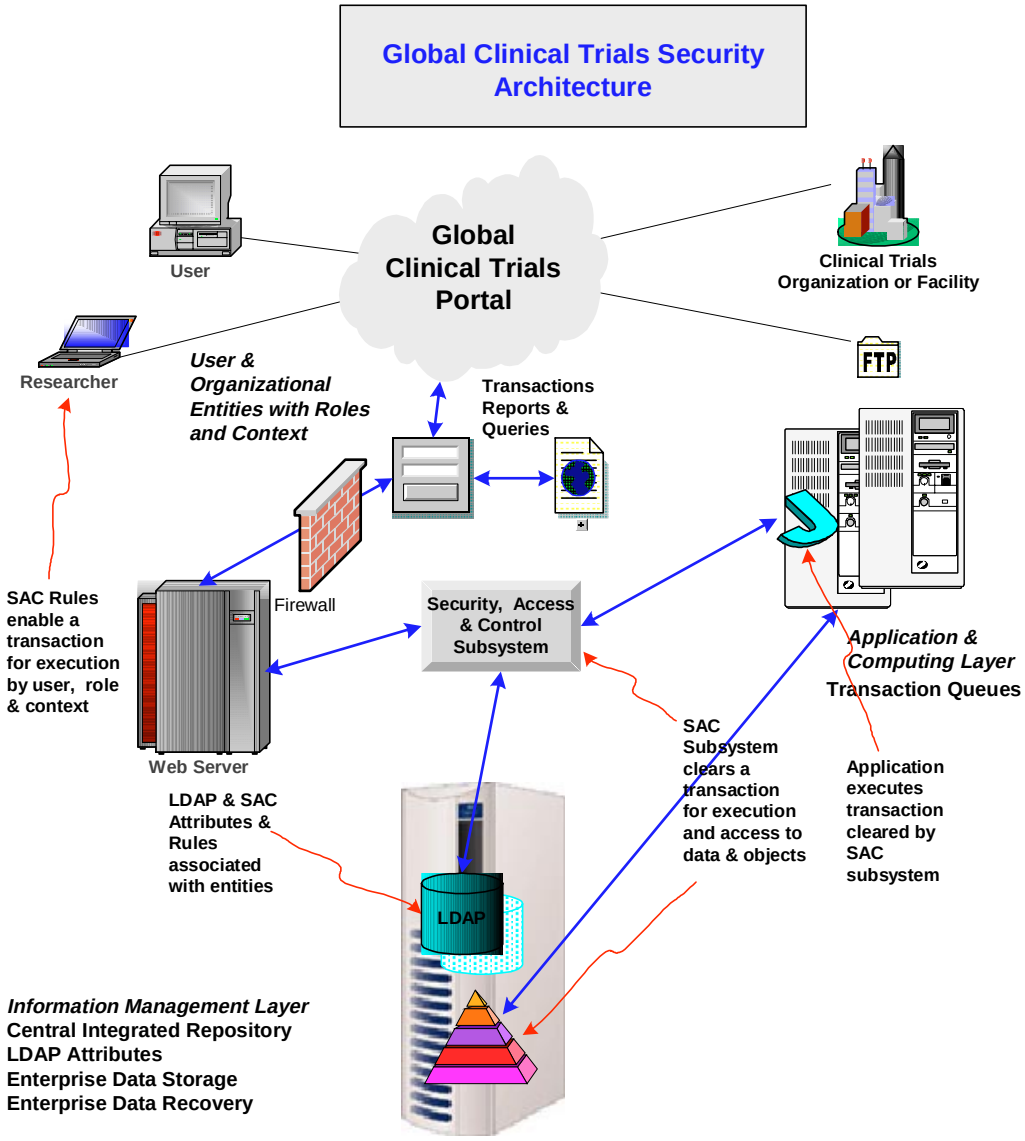

Figure 2 Global Clinical Trials Security Architecture

5 Enterprise Architecture for Global ICH Clinical Trials

The information technology required to support global ICH-compliant clinical trials is diverse, with complex operational requirements. These requirements can be summarized as follows:

- Availability—Continuous access to the enterprise clinical repository and websites
- Security—Appropriate controls for access by user, policy, role and certificate
- Data protection—Complete audit trails on data with appropriate security privacy rules by user
- Data mobility—Data must move among researcher, research organization, site, agency, when it is needed and in the form required

- ❖ Data repurposing—Data and information have multiple purposes/roles and the ICH central clinical repository must satisfy all required purposes.
- ❖ Data sharing—Access to all information by all researchers and organizations, regulatory agencies, clinical trial sites, not just primary reviewer and his/her team

5.1 Building the Infrastructure for the ICH Compliant Clinical Trial

Today a single technology supplier cannot meet *all* the complex security, operational, reliability, availability and flexibility requirements anticipated for information management demands of the global ICH compliant clinical trial. The most successful solutions will be those that invest in "best of breed" components — from enterprise servers, enterprise storage systems, database management systems and clinical trials applications — that give the enterprise a unique solution that matches ICH global requirements.

The complexity involves moving from the current generation of information technology to support a single clinical trial to the "next generation" in clinical trials that requires enabling information and data management solutions for ICH compliant clinical trials globally.

5.2 Information Technology for the ICH Compliant Clinical Trials

The goal of the information technology solution for ICH compliant clinical trials is pervasive and reliable access to the dossier, whenever and wherever it is needed. This means a global telecommunications infrastructure, high reliability databases and pervasive access to real-time clinical and ICH dossier data.

The foundation of the recommended model architecture is based on EMC "E-Infostructure" composed of physical, connectivity and functional layers of hardware and software. The physical layer includes Symmetrix™ and CLARiiON™ enterprise storage management hardware that provide the basic foundation for performance, capacity, availability and other physical requirements of the central repository and database 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 enterprise application and data management platforms. These systems could include IBM operating systems, Unix operating systems, including Linux and those from Compaq, Sun, HP, and Microsoft operating systems.

5.3 Model Enterprise-Wide Clinical Trials Application

Building on the previously described SAC model architecture, the application model architecture is based on a five-tier information technology architecture. Each tier can be replicated to enhance reliability and availability of the operational systems. The tiers of the proposed model architecture support:

- **Presentation** — Multiple devices with multiple modes of information delivery. Each device should be receive the mode(s) of information delivery suited to the device's characteristics. For example, a PDA would receive formatted XML to map the display contents to screen size of the PDA.
- **Network** — Wide-area and local-area redundant access to the computational and data management layers below and presentation layers above. Wireless presentation access is included as a presumed capability of the network layer.
- **Computational** — Computational, analytical, application-oriented servers providing the services needed for the model architecture on a "best-of-breed" basis. Highly scalable central processors with high-availability operating systems, e.g., IBM Z/OS and AIX HACMP. Inexpensive processors for secondary applications, e.g., Intel-based processors for Windows 2000 applications.
- **Database Management**—Oracle Parallel Server or IBM DB2 to support databases for the central repository
- **Enterprise Storage Management** — The storage management layer composed of the Enterprise Storage Network ("ESN") and the Database Management System(s). EMC Symmetrix™ and enterprise storage management software to integrate all operating systems and database storage into a

uniform central repository. EMC Connectrix storage management to handle multiple connections to the servers. EMC TimeFinder™ software to provide each researcher with local copy of certain data to analyze, thereby increasing researcher productivity. TimeFinder can be used to refresh data warehouses with timely information without disrupting production systems. The remote mirroring capabilities of EMC's SRDF™ software can protect clinical trial and other critical data to avoid costly interruptions in speed to market.

- EMC TimeFinder for non-disruptive backup and data warehouse loading
- EMC SRDF for disaster recovery and information mobility
- Continuous availability of reporting, decision support and web access
- Continuous availability of databases

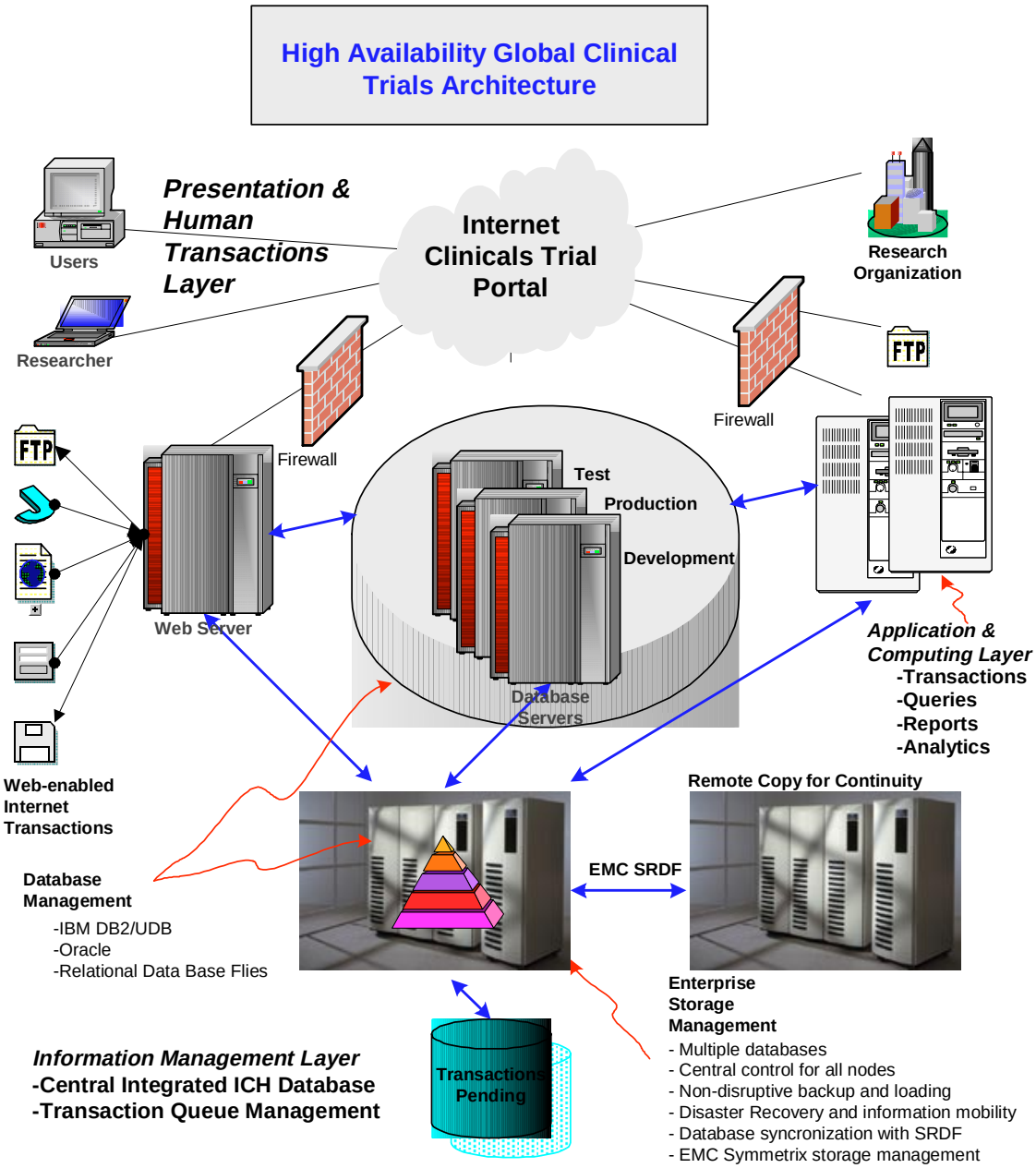

Figure 3 High-Availability Global Clinical Trials Architecture

6 Conclusion

This paper recommended a *secure* architecture for ICH-compliant clinical trials satisfying information management requirements that include attributes of availability, security, privacy, data protection, data mobility, data repurposing, and data sharing. These attributes form the foundation for a global clinical trials solution that results in a single submission clinical trials dossier for a new pharmaceutical product in ICH format. The delivery architecture ensures that information concerning the ICH dossier in development is secure, continuously available and accurate—key goals and objectives of the ICH compliant clinical trial.

From a business perspective, next generation clinical trial solutions will focus on security, access, control and data integration. Integration of multi-site, multi-country ICH clinical data and post-market data will ensure that the entire life-cycle of a pharmaceutical is available to each authorized user globally. A centralized storage network is required to store massive amounts of clinical, administrative, financial, marketing and bio-information. The central storage network must facilitate sharing, backup and recovery, and protection of the global clinical trials data.

Finally, speed-to-market for each pharmaceutical developed from an ICH compliant clinical trial is critical. Business and information technology requirements must be defined quickly and their respective solutions executed with precision if the ICH compliant clinical trials is to generate immediate and persistent return-on-investment for the aggressive manufacturer.

The International Conference on Harmonisation has created a challenge for each life sciences company to meet—a single submission resulting in near global pharmaceutical approval. Those research organizations, biotechnology companies and pharmaceutical manufacturers that meet this challenge will reap global financial benefits.

7 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 some of the largest and most progressive computer, healthcare and manufacturing companies in the world.

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