21 CFR Part 11 Audit

of

UNICORN 5.0
Amersham Biosciences

December 11-12 2003

Dr. Sandy Weinberg

21 CFR Part 11 Audit
Unicorn 5.0
Amersham Biosciences

On December 11-12, 2003 I visited the development facility of Amersham Biosciense in Upsalla, Sweden, in follow up to previous Unicorn audits, focusing on the newly released Version 5.0. At the on site visit I conducted an 21 CFR Part 11 audit. This audit considered relevant provisions of the following US FDA regulations as interpreted through guidance from the US FDA through 1 December 2003, through current GAMP4 guidelines, and emergent industry standard practices:

21 CFR Part 11 – Electronic Records, Electronic Signatures;
21 CFR Part 50 – Protection of Human Subjects (also knows as Good Clinical Practice,GCP);
21 CFR Part 58 – Good Laboratory Practice for Nonclinical Laboratory Studies (GLP);
21 CFR Part 210 – Current Good Manufacturing Practice in Manufacturing, Processing, Packing or Holding of Drugs (cGMP);
21 CFR Part 211 – Current Good Manufacturing Practice For Finished Pharmaceuticals (cGMP);
21 CFR Part 820 – Quality System Regulation.

This audit also considered relevant provisions of the following US EPA regulations:

EPA Directive 2185 – Good Automated Laboratory Practices;
Cross Media Electronic Reporting Rule (CROMERR).

Based upon my review of documents (attached), my observations and discussions of practices, and my observation of the operation and support environments, I am prepared to testify that the Unicorn Version 5.0 complies with the letter and intent of 21 CFR Part 11 and all other relevant regulations and guidelines.

The personnel and management are clearly committed to maintaining a compliant development process and line of products, and show the highest level of concern for quality.

Dr. Sandy Weinberg
23 December 2003

AMERSHAM PERSONNEL
Participating in the Audit:

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CHECKLIST: VALIDATION and 21 CFR Part 11

Electronic Records – Electronic Signatures

[all blocks checked as compliant]

System is used in support of drug related research, laboratory analysis, clinical research, manufacturing, production, and/or tracking

Record and/or signature system has been subjected to an appropriate and through system validation audit

Audit conducted within 24 months

Audit conducted by independent or outside expert

Audit included review of:
- Testing documentation
- Development documentation
- SOP documentation

  Change control
  Archive
  Disaster recovery
  Use
  Training
  Audit trail review
- Archive

Audit included inspection of operating environment

System Validation documentation has been collected, including evidence of requirements and design approvals, testing, and implementation

  Validation Protocol
  Validation team credentials
  Development documentation
- Requirements/design document
- Trace Matrix

  Standard Operating Procedures
- Use
- Training
- Change Control
- Archive

- Disaster Recovery
- Audit trail review

Testing

- Boarder cases
- Norm cases
- Code review

System inventory

- Hardware
- Software

Records are retained for appropriate length of time (generally ten years or two generations over treatment duration) in machine-readable form

Records are retained for appropriate length of time (generally ten years or two generations over treatment duration) in human readable form

Records are retained in heatproof, fireproof, flood protected environment; are appropriately labeled; and can be restored in reasonable (generally 72 hours) time

Procedures are in place to restrict access to data and records to appropriately authorized persons

Operations checks of system have been designed in to assure appropriate functioning of hardware and software

Audit Trails (preferable electronic and protected; alternately manual and carefully monitored) have been built into the system to detect and identify data changed, including tracking of time and date of change, change agent; and reason for authorized change

Electronic signatures are utilized only in systems with dual level unique identifier authorizations

Password/password
Password/key
Password/biological
Other:

Electronic signatures are utilized only in systems with internal procedures to assure that approved documents have not been modified (without authorization) from specified date and time

Time system

- Zulu time
- GMT time
- Location-affixed time
- Single time zone

Date system

- International (dd/mm/yy)
- US (mm/dd/yy)

A methodology has been implemented to assure the validity of input data. Such methodologies might include dual confirmation of input; the use of check digits; internal norm confirmations; or other techniques.

Systems users and administrators have received appropriate regulatory and functional training

System users and administrators have ready and constant access to appropriately comprehensive, clear, applicable, timely, and management approved standard operating procedures (SOPs)

All aspects of the electronic records and electronic signature systems in place have been designed to provide a level of security and control equal to or exceeding the equivalent controls inherent to manual (paper) systems

Amersham Biosciences
UNICORN 5.0 Audit
REVIEWED DOCUMENT LIST

SRS: Software Requirements Specification, Doc Number 224852556-L632

SDD: Software Design Description, Doc Number 225777444-M423

ITD: Software Integration Test Description, Doc Number 225787929-M423

MDD: Module Design Description, Version AA, Module: Audit Trail

MTP: Module Test Plan, Version AB, Module: Audit Trail

MDD: Module Design Description, Version AB, Module: OCI Request Handler

MTP: Module Test Plan, Version AC. Module: OCI Request Handler

MDD: Module Design Description, Version AB, Module: Method Editor

MTP: Module Test Plan, Version AC, Module: Method Editor

Unicorn 5.0 vs Unicorn 4.12, Doc Number 11-0003-88, Edition AA, 2003-12

Software Change Description, Unicorn 5.0 vs 4.12 (Presentation)

Unicorn 5.0 User Manual

Unicorn 5.0 "Getting Started" Manual

Unicorn 5.0 Administration User Manual

Software QA Audit Project, Doc Number 250060571-C516, Version AD

SW-AFU Software Approval for Use Meeting Minutes, Doc Number 257948235-C516, Version AA

Project Meeting Minutes, Doc Number 257782131-C516, Version AA

Phase Review Report, Doc Number 258522148-S550, Version AA

SW Development Handbook:

- Development (D) Project Flowchart
- SW BMU Steps Flowchart
- Available Templates Flowchart
- Software Development "V Model" Flowchart
- Test Descriptions and Reports during Verification Flowchart

SW System Test Report (STR), Doc Number 253518428-F250

SW System Test Description (STD), Doc Number 256189215-F250, Edition AB

STD: SW System Test Description, Doc Number 224770616-F250, Edition AA

STD: SW System Test Description, Doc Number 256189215-F250, Edition AB

21 CFR Part 11 Compliance of Unicorn 5.0

SUBPART B – ELECTRONIC RECORDS

11.10 – Controls for closed systems

11.10(a) Procedures and controls shall include validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.

Amersham Biosciences has extensively validated its software with tests written to specifically evaluate accuracy, reliability and consistent performance.
IQ/OQ and other documents are available for customer use. The software has the ability to discern invalid or altered records. Also see sections 11.10(c), (d) and (e).
Observed, tested, and fully confirmed as compliant.
Dr. Sandy Weinberg

11.10(b) Procedures and controls shall include the ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency.
(date/time, operator identification, computer workstation identification).
Observed, tested, and fully confirmed as compliant.
Dr. Sandy Weinberg

11.10(c) Procedures and controls shall include protection of records to enable their accurate and ready retrieval throughout the records retention period.
All records are protected in secure storage locations and are readily retrievable.
Observed, tested, and fully confirmed as compliant.
Dr. Sandy Weinberg

11.10(d) Procedures and controls shall include limiting system access to authorized individuals.
Access to Unicorn 5.0 requires a user ID and password at the application level. A second password is necessary to "sign" a document
Observed, tested, and fully confirmed as compliant.
Dr. Sandy Weinberg

11.10(e) Procedures and controls shall include use of secure, computer-generated timestamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail information shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.

Observed, tested, and fully confirmed as compliant.
Dr. Sandy Weinberg

11.10(f) Procedures and controls shall include use of operational system checks to enforce permitted sequencing of steps and events, as appropriate.

Observed, tested, and fully confirmed as compliant.
Dr. Sandy Weinberg

11.10(g) Procedures and controls shall include use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.

Observed, tested, and fully confirmed as compliant.
Dr. Sandy Weinberg

11.10(h) Procedures and controls shall include use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.

Observed, tested, and fully confirmed as compliant.
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11.50 – Signature manifestations

11.50 Signed electronic records shall contain information associated with the signing that clearly indicates the following:
• The printed name of the signer;
• The date and time when the signature was executed; and
• The meaning (such as review, approval, responsibility, or authorship) associated with the signature.

These items are subject to the same controls as for electronic records and shall be included as part of any human readable form of the electronic record (such as electronic display or printout).
At the time of execution of an electronic signature, the system displays the printed name of the signer, and the date/time/zone. The meaning of the signature is displayed in the window requiring the signature (e.g., confirmation, review, or approval). The printed name of the signer, the date/time/zone, and the signature meaning are also captured in the database requiring an electronic signature. a user with the appropriate user role and privileges can execute an electronic signature.

Observed, tested, and fully confirmed as compliant.
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11.70 – Signature / record linking

11.70 Electronic signatures and handwritten signatures executed to electronic records shall be linked to their respective electronic records to ensure that the signatures cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means.

Observed, tested, and fully confirmed as compliant.
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SUBPART C – ELECTRONIC SIGNATURES

11.100 – General Requirements

11.100(a) Each electronic signature shall be unique to one individual and shall not be reused by, or reassigned to, anyone else.

Observed, tested, and fully confirmed as compliant.
Dr. Sandy Weinberg

11.200 – Electronic signature components and controls

11.200(a)(1) Electronic signatures shall employ at least two distinct components such as an identification code and password.

Observed, tested, and fully confirmed as compliant.
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11.200(a)(2) Electronic signatures shall be used only by their genuine owners. No two users can have the same username and password. The system does not accept redundant user IDs.

Observed, tested, and fully confirmed as compliant.
Dr. Sandy Weinberg

11.200(a)(3) Electronic signatures shall be administered and executed to ensure that attempted use of an individual's electronic signature by anyone other than its genuine owner requires collaboration of two or more individuals.

Observed, tested, and fully confirmed as compliant.
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11.300 – Controls for identification codes / passwords

11.300(a) Identification codes/passwords controls shall include maintaining the uniqueness of each combined identification code and password, such that no two individuals have the same combination of identification code and password.

Observed, tested, and fully confirmed as compliant.
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11.300(b) Identification codes/passwords controls shall include ensuring that identification code and password issuances are periodically checked, recalled, or revised (e.g.,to cover such events as password aging).

Observed, tested, and fully confirmed as compliant.
Dr. Sandy Weinberg

11.300(d) Identification codes/passwords controls shall include use of transaction safeguards to prevent unauthorized use of passwords and/or identification codes, and to detect and report in an immediate and urgent manner any attempts at their unauthorized use to the system security unit, and, as appropriate, to organizational management.

Observed, tested, and fully confirmed as compliant.
Dr. Sandy Weinberg

11.300(e) Identification codes/passwords controls shall include initial and periodic testing of devices that bear or generate identification code or password information to ensure that they function properly and have not been altered in an unauthorized manner.

Observed, tested, and fully confirmed as compliant.
Dr. Sandy Weinberg

SUMMARY

Unicorn 5.0 provides all features to comply with the letter and spirit of 21 CFR Part 11 and other relevant FDA and EPA guidelines and regulations. Users of the system may should have no difficulty demonstrating 21 CFR Part 11compliance.

Based upon this analysis and the document reviews, interviews, demonstrations, and tests conducted, I am fully prepared to serve as an expert witness testifying complete compliance with 21 CFR Part 11 and related relevant FDA and EPA guidelines

Dr. Sandy Weinberg