GAMP Good Practice Guide:

A Risk-Based Approach to Compliant Electronic Records and Signatures

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Preface to the GAMP Good Practice Guide: A Risk-Based Approach to Compliant Electronic Records and Signatures

The appropriate management of electronic records and signatures is of current concern to both the regulated life science industry and its regulators. This *GAMP Good Practice Guide: A Risk-Based Approach to Compliant Electronic Records and Signatures* provides timely and much needed guidance on meeting current regulatory expectations for compliant electronic records and signatures, which include the need for record integrity, security, and availability throughout the required retention period.

It describes how a risk management approach may be used to ensure the compliance of regulated electronic records and signatures, through the application of appropriate controls commensurate with the impact of records and signatures and the identified risks. The Guide covers:

- New automated systems
- Existing automated systems
- Those systems that have already been subject to electronic record and signature assessments

This Guide is intended as a supplement to the *GAMP Guide for Validation of Automated Systems (GAMP 4)*. It has been designed so that it may be used in conjunction with guidance provided in GAMP 4 and other ISPE publications.

Disclaimer:
This Guide is meant to assist pharmaceutical manufacturing companies in managing systems which use and maintain regulated electronic records and signatures. The GAMP Forum cannot ensure and does not warrant that a system managed in accordance with this Guide will be acceptable to regulatory authorities. Further, this Guide does not replace the need for hiring professional engineers or technicians.

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1 Introduction

1.1 Overview

The increased use of information technology and computer systems in all aspects of business is leading to the automation of more and more processes. Key decisions and actions are routinely being taken using automated systems, with regulated records being generated electronically. Increasingly, confirmation and approval of these actions and decisions is also being provided electronically.

As a result, the appropriate management of electronic records and signatures is a very important topic for the life science industries.

This Guide has been developed by the GAMP Forum, a technical subcommittee of ISPE, to provide timely and much needed guidance in this area. It supplements the existing *GAMP 4, GAMP Guide for Validation of Automated Systems* (see Appendix 13, reference 1).

Good Automated Manufacturing Practice (GAMP) guidance aims to achieve validated and compliant automated systems meeting all current life science regulatory expectations, by building upon existing industry good practice in an efficient and effective manner.

1.2 Purpose

This Guide provides comprehensive new guidance on meeting current regulatory expectations for compliant electronic records and signatures, which includes the need for record integrity, security, and availability throughout the required retention period. This is achieved by well-documented, validated systems, and the application of appropriate operational controls.

The main drivers for this Guide are:

1. An increasing emphasis on the assessment and management of risk within the regulated environment

2. The need to consider and comply with all applicable international regulations

3. Recent regulatory activity and guidance, such as FDA guidance on 21 CFR Part 11 Scope and Application (see Appendix 13, reference 3).

This Guide supersedes previous guidance published jointly by ISPE and PDA, Complying with 21 CFR Part 11, Electronic Records and Electronic Signatures (see Appendix 13, reference 2).

The guidance is intended primarily for regulated companies, but will also be useful for suppliers of systems, products, or services in this area.

The intended audience for this Guide includes:

- Quality assurance (QA) and computer validation professionals responsible for defining and managing validation practices in regulated life science industries

- IT personnel, including IT compliance, who manage and support these systems

- Business owners, data owners, and system users
- System developers, engineers and suppliers

Some familiarity with GAMP and current international regulations is assumed.

1.3 Scope

This Guide addresses compliance with international regulations and guidelines for electronic records and signatures covering automated systems used within the regulated life science industries including pharmaceutical, biological, and medical devices. While not specifically targeted as such, this Guide may also be useful in other regulated areas such as cosmetics and food. Specific guidance is given for:

- New automated systems
- Existing automated systems
- Those systems that have already been subject to electronic record and signature assessments

Current international GxP life science requirements related to electronic records and signatures have been taken into account, and the following publications have been specifically considered:

- US Codes of Federal Regulations (CFRs) covering GCP, GLP, GMP, and medical devices
- US CFR regulation 21 CFR Part 11, and associated guidance documents
- Relevant sections of EU regulations
- PIC/S (Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-operation Scheme) Guidance
- Proposed Japan MHLW (Ministry of Health, Labour and Welfare) guidelines
- European Medicines Agency (EMEA) guidance
- World Health Organization (WHO) guidelines
- International Conference on Harmonization (ICH) guidelines
- International Society of Blood Transfusion (ISBT) guidelines
- Relevant ISO documents, such as ISO 14971 Medical devices - Application of risk management to medical devices and ISO 17799:2000 Information technology - Code of practice for information security management

This Guide covers electronic records, electronic signatures, handwritten signatures captured electronically, and handwritten signatures applied to electronic records. The Risk Management approach described applies to records generally. While paper, electronic and hybrid situations are considered, the detailed activities described are focused on the electronic aspects.

This Guide provides a method for managing risk to electronic records and signatures. Organizations may already have established risk management activities, including the use of methods such as HAZOP, CHAZOP, FMEA, FMECA, FTA, and HACCP. While the Guide may encourage organizations to perform new activities, it does not intend or imply that these existing methods should be discarded, rather that they continue to be used as appropriate within the context of the overall risk management process described.

While not within the scope of this Guide, it is recognized that aspects such as business criticality, health and safety, and environmental requirements may require specific assessment and control. Legal admissibility of information stored electronically should also be considered.

Note that this Guide provides one method of managing risk. It is not intended to imply that this is the only acceptable method of managing risks associated with regulated electronic records, or that companies not using the process will be failing to comply with regulations. Other methods or techniques giving documented evidence of adequate record control, ensuring appropriate record security and integrity, may also be acceptable.

1.4 Benefits

This GAMP Good Practice Guide applies a risk management approach to the identification, management, and control of electronic records and signatures in a regulated GxP context. This allows the implementation of technical and procedural controls appropriate to the impact of records, and to the risks to those records. As a result, a simple and pragmatic approach is described that can be applied to any automated system required to meet international regulations.

The approach allows measures aimed at a high degree of integrity, availability, and confidentiality (where required) to be established for records that have a high potential impact on product quality or patient safety, while permitting a less rigorous approach for records of lower impact, or those with lower levels of associated risk.

This overall philosophy is intended to encourage innovation and technological advances while avoiding unacceptable risk to product quality, patient safety, and public health.

1.5 Objectives

Risk management practices for electronic record and signature controls must protect public health. In order to be effective, however, risk management practices must also be practical and efficient. To this end the GAMP Council defined the following guiding principles for this Guide:

- Provide a consistent risk management approach to electronic records and signatures to address what are now similar expectations from international agencies.
- Adopt the philosophy of managing risk by defining minimum acceptable requirements to address electronic records and signatures. Any additional controls should be justified on the basis of tangible business benefit.
- Ensure the risk management approach to electronic records and signatures is simple and effective. The effort required to assess and manage risk must not outweigh the benefit of its application.
- Facilitate ready and meaningful access to international regulations identifying regulated records and signatures. It is important to focus on records and signatures with significant potential impact on product quality or patient safety.

- Ensure the new risk management approach to achieving compliant electronic records and signatures recognizes the need to minimize transition issues with any existing programs of remediation work.

- Emphasize the benefits, and encourage the use of technology, rather than introduce discouraging barriers.

The GAMP Council believes that the guidance developed has met these criteria. A single approach to risk management for electronic records and signatures is described that should be acceptable in all main regulated markets. The approach permits the adoption of electronic record and signature controls appropriate to the market supported.

1.6 Structure of this Guide

This Guide consists of a Main Body and a set of supporting Appendices.

Following the introductory and background material, the Main Body describes a process for managing risks to electronic records and signatures. It then explains how the process should be applied to existing and new systems, and provides particular guidance for those organizations who have already undertaken remediation programs to comply with 21 CFR Part 11. Finally, the Main Body considers the various controls that may be used to manage identified risks.

The Appendices cover a range of common issues of concern, as well as reference and supporting materials. These include:

- Validation

- Audit trail and data security

- Record retention and archiving

- Copies of records

- Legacy systems

- Examples of records required by GxP regulations

- Examples of signatures required by GxP regulations

- Case studies

- Template forms to support the processes described

- Current regulatory situation

1.7 Key Concepts

The term *GxP regulation* refers to the underlying international life science requirements such as those set forth in the US FD&C Act, US PHS Act, FDA regulations, EU Directives, Japanese MHLW regulations, or other applicable national legislation or regulations under which a company operates.

A *regulated record* is one required to be maintained or submitted by GxP regulations. A regulated record may be held in different formats, for example, electronic, paper, or both.

Electronic record refers to records required by GxP regulations such as clinical study reports, training records, or batch records when maintained in electronic format. Where emphasis is needed in order to avoid possible misunderstanding, the term *regulated electronic record* is used. Regulated electronic records include Part 11 records as defined by FDA. Appendix 6 of this Guide provides examples of records required by GxP regulations.

Note that some records are required to support regulated activities, despite them not being explicitly specified in the regulations. For example, monitoring records are not required by all regulations. However, monitoring is a regulated activity and reports are relied upon for performing this regulated activity.

A *regulated signature* is a signature required by a GxP regulation. The terms *signature* and *signed* are defined as *"The record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature."* (ICH Guideline Q7A, (see Appendix 13, reference 12)). Appendix 6 of this Guide provides an interpretation with examples of signatures and identifications required by GxP regulations.

Company is used in this Guide to refer to the regulated entity (such as company, partnership, corporation, or association). It is synonymous with the term "firm", as used by the FDA, and "User Company" as used in *GAMP 4* (see Appendix 13, reference 1).

Impact is a measure of the possible consequences of loss or corruption of a record.

The following terms used in this Guide are taken from ISO 14971 Medical Devices - Application of risk management to medical devices (see Appendix 13, reference 4) except where specified:

- **Harm:** physical injury or damage to the health of people, or damage to property or the environment
- **Hazard:** potential source of harm
- **Risk:** combination of the probability of occurrence of harm and the severity of that harm
- **Risk assessment:** overall process comprising a risk analysis and a risk evaluation:
  - **Risk analysis:** systematic use of available information to identify hazards and to estimate the risk
  - **Risk evaluation:** judgment, on the basis of risk analysis, of whether a risk which is acceptable has been achieved in a given context (ISO 14971 definition modified by GAMP)
- **Risk control:** process through which decisions are reached and protective measures are implemented for reducing risks to, or maintaining risks within, specified levels
- **Risk management:** systematic application of management policies, procedures and practices to the tasks of analyzing, evaluating, and controlling risk
- **Severity:** measure of the possible consequences of a hazard

Appendix 12 (Glossary) of this Guide contains further definitions and acronyms.

1.8 Current Regulatory Situation

Since the effective date of 21 CFR Part 11 in August 1997, there has been much discussion and debate among regulated life science companies, their regulators, and suppliers regarding the effective implementation of compliant electronic records and signatures.

Recent regulatory developments in Europe, Japan, and the US will fundamentally alter the way industry approaches this subject.

The US FDA are currently (at time of printing) re-examining 21 CFR Part 11 and may propose changes to the regulation as a result. FDA's most recent thinking on 21 CFR Part 11 is reflected in the guidance document on the scope and application of 21 CFR Part 11 (see Appendix 13, reference 3), published on 3 September 2003. The guidance describes how FDA intends to interpret the scope of 21 CFR Part 11 narrowly, and intends to exercise enforcement discretion with respect to certain 21 CFR Part 11 requirements during the re-examination period. The guidance also describes the current FDA thinking on key topics in this area, such as validation, audit trails, record copying, and record retention, and describes the role of justified and documented risk assessment in selecting appropriate controls.

Similarly, European, Japanese, and other international regulators and agencies have been active in this area (see Appendix 13, references 5, 9, 11).

2 Risk Management Process

2.1 Overview of Process

2.1.1 Current Risk Management Practices

Risk management is an integral element of good project management practice. Initial risk assessments are carried out during project start-up phases, when project scope is being defined, initial requirements and plans are being drafted, project sponsors are being identified, and budgetary approval is being sought. Risks to the overall project that might affect the capability to meet objectives, timescales, cost, quality, and safety are identified and considered. Following assessment, risks are then prioritized, monitored, and managed on an on-going basis as the project proceeds. Depending upon criticality and nature, some projects schedule further detailed risk assessments (e.g., hazard and operability studies, threats and controls studies, or failure mode and effect analysis) as functionality and design is developed.

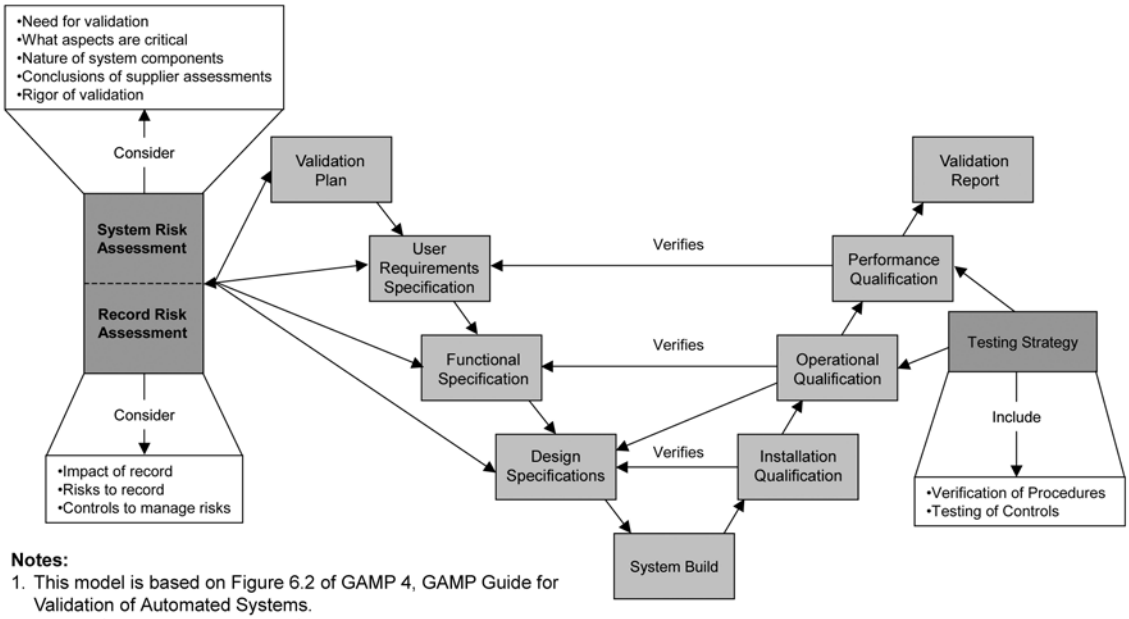
Risks to product quality and patient safety are particularly important for life science industries. These risks have typically been assessed at the system level and the following topics considered:

- Need for validation based upon the processes being managed and supported
- Criticality of the system based upon functionality and operation
- Nature of system components (e.g., custom software, configurable software packages, standard software packages)
- Outcomes and conclusions of supplier assessments
- Rigor of validation based upon system criticality and vulnerability

These activities may be incorporated within a typical validation process as shown in Figure 2.1. While the approaches to system level assessments vary from company to company, the guidance provided in Appendix M3 of *GAMP 4, GAMP Guide for Validation of Automated Systems* (see Appendix 13, reference 1) describes one approach. See also IEEE 1540 Standard for Software Lifecycle Processes - Risk Management (see Appendix 13, reference 13) for further guidance on this topic. In all cases, the conclusions of these assessments influence the validation strategy for the system.

To date the assessment and management of risks specific to electronic records and signatures have not typically formed part of this process. Figure 2.1 shows how these activities may be added to the typical validation process. It should be noted that this Guide does not intend or imply that any existing methods such as HAZOP, CHAZOP, FMEA, FMECA, FTA, and HACCP already used by organizations should be discarded, but rather that they continue to be used as appropriate within the context of the overall risk management process described.

Figure 2.1: Risk Management as part of the Validation Process



Notes:
1. This model is based on Figure 6.2 of GAMP 4, GAMP Guide for Validation of Automated Systems.
2. The URS may be developed before the Validation Plan, or in parallel.
3. Controls should also be considered during design reviews and code reviews, where applicable.

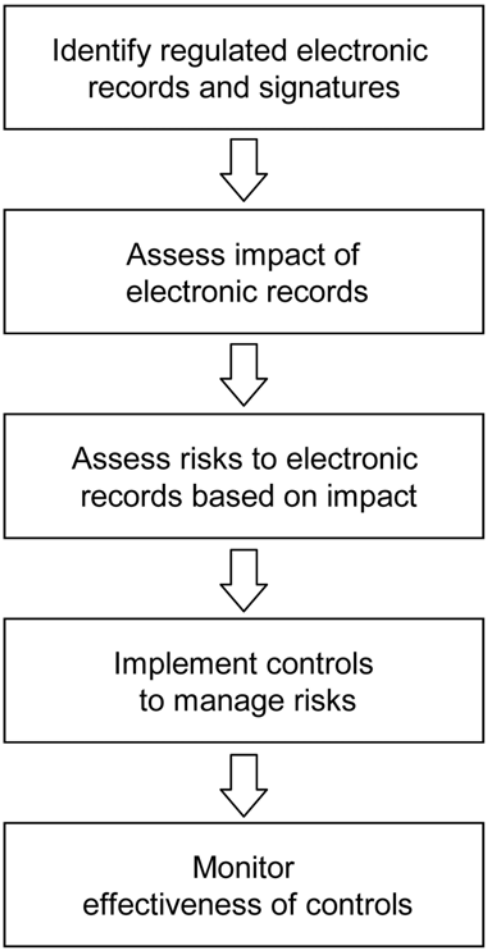
2.1.2 Managing Risks to Electronic Records

Managing risks to electronic records and signatures involves the following activities:

- Identifying which regulated electronic records are maintained in the system and where signatures are applied to those records, based on an analysis of the processes, and the applicable regulations.
- Assessing the impact of the electronic records on product quality or patient safety.
- Assessing the risks to the electronic records using a scaleable approach based on the impact of the records.
- Implementing controls to manage the identified risks, and verifying that the controls have been successfully implemented.
- Monitoring the effectiveness of controls during operation.

The objective of these activities is to reduce risks to product quality or patient safety to an acceptable level and to comply fully with GxP regulations. These activities are shown as a series of steps in Figure 2.2:

Figure 2.2: Managing Risks to Electronic Records



Where appropriate, during development of User Requirements and then Functional Specifications, business processes should be defined and the associated electronic records and signatures identified. The impact of the electronic records can then be established, risks assessed, and controls identified. More detailed assessments may be performed as the life cycle progresses and more information becomes available.

Similar records (e.g., training records) may be grouped by type, so that a consistent risk management approach can be applied to all records of that type either within individual projects or across the organization.

Controls may be technical or procedural in nature. Technical controls should be included in the relevant specification and identified procedures should be developed for the system.

Verification of the installation and correct operation of controls occurs during qualification.

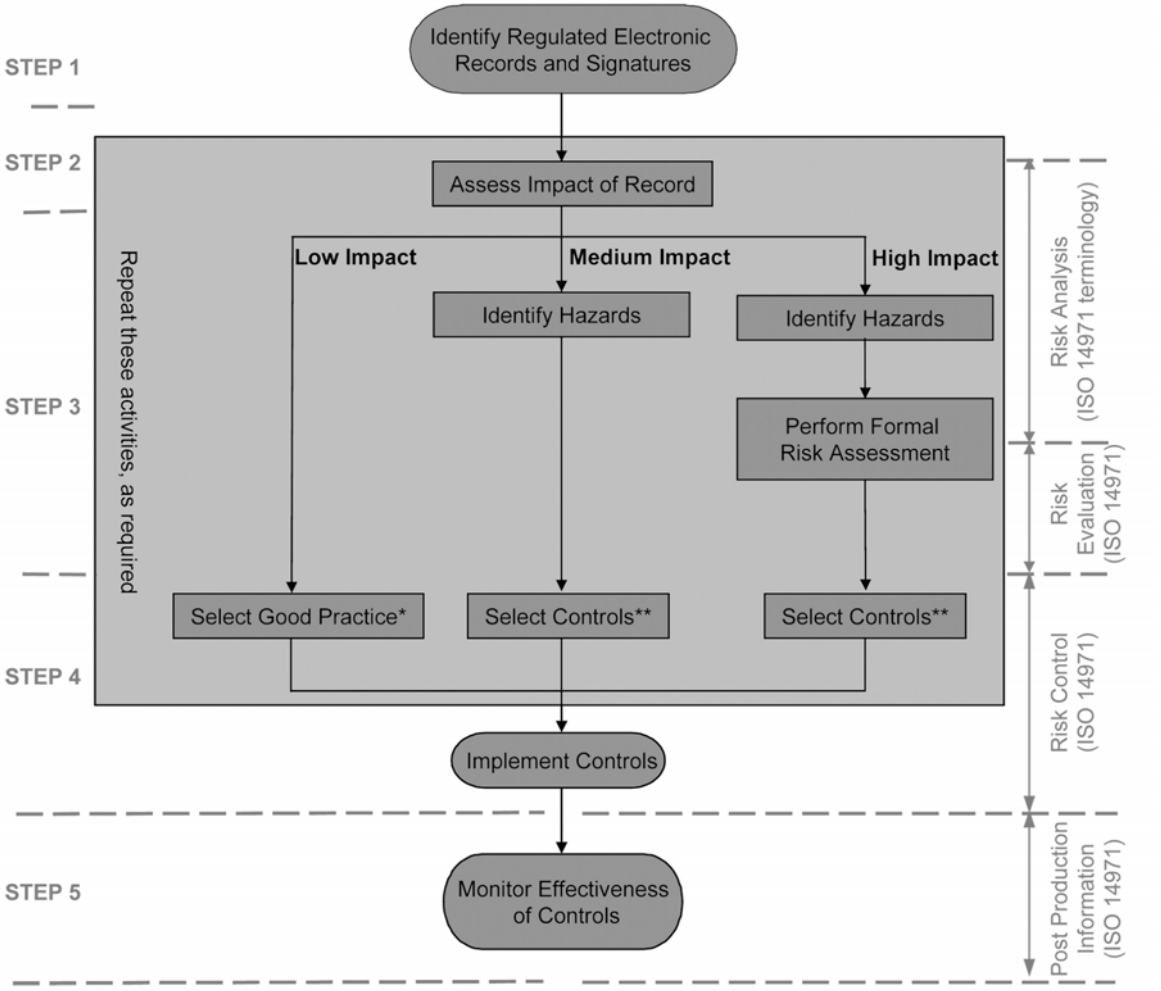
It is recommended that the activities to manage specific risks associated with regulated electronic records and signatures be incorporated into the company's overall quality and project management system, and validation planning strategy.

2.1.3 Risk Management Based on the Impact of Records

This Guide describes a risk management process based on the impact of the record, or type of record, on product quality or patient safety.

Depending upon the impact, a suitable risk management approach is taken, as shown in Figure 2.3. The purpose of this approach is to allow selection of appropriate controls while ensuring that the effort to assess and manage risk does not outweigh the benefit of its application.

Figure 2.3: Risk Management Approach based on Record Impact



* Good Practice covers Good IT Practice and Good Engineering Practice, such as backup and restore, and security management.
** In addition to Good Practice.

Subsequent sections provide more detailed guidance on each of the steps shown in Figure 2.3:

Step 1: Identify regulated electronic records and signatures

Step 2: Assess impact of electronic records

Step 3: Assess risks to electronic records based on impact

Step 4: Implement controls to manage identified risks

Step 5: Monitor effectiveness of controls during operation

A suitable cross-functional team, made up of individuals representing QA, system owner and users, IT, and engineering, as appropriate, should perform these activities. The team should include the electronic record or data owners, where these have been defined.

2.2 Step 1: Identify Regulated Electronic Records and Signatures

Each regulated record or record type in the system should be identified and documented. A data flow analysis is useful in supporting this activity and in determining the role of each record in regulated processes. The emphasis should be on identifying records required by regulations such as clinical study reports, training records, or batch records, rather than physical database records, or table fields. Some electronic records may be created and maintained on one system and electronic copies transferred and used by other systems. Companies should ensure that the approach taken with these copies makes maximum use of existing assessments in order to avoid unnecessary repetition.

Each signature or signature type (e.g., preclinical study approval) should also be identified. Whether or not the signed record is used for regulatory purposes should be decided and the conclusion documented.

Appendix 6 gives examples of records and signatures required by GxP regulations.

It should be noted that many systems, such as typical microprocessor or PLC controlled manufacturing equipment or laboratory equipment, do not generate or hold any regulated electronic records. Such determinations should be documented and no further analysis is required.

Other systems do not maintain electronic records required by GxP regulations although data relating to regulated records is processed. An example might be a measurement device or system capturing data to be passed on to another system, where it is later incorporated into a regulated record. Again, such determinations should be documented and no further analysis is required.

Some systems generate large amounts of intermediate data which is used to generate the regulated records upon which quality decisions are based. Only those records required to meet GxP regulations, or submitted to regulators, should be identified as regulated electronic records and not all data captured, generated, or held by such systems. For example, a validated system measures two million capsule weights for a single batch. The system generates a curve showing that batch weight distribution falls within validated norms. The individual data points would not be considered as regulated records.

Some systems are used to generate a record which is subsequently printed out, and it is the printed paper copy that is retained and used as the regulated record. It may be that the electronic record is only being used as a transitional phase in the creation of the paper record. A documented determination should be made of whether the electronic or paper record (or both) will be relied upon to perform regulated activities.

Software code, internal system configurations, and technical parameters are not regulated electronic records as described in this Guide. These are controlled by validation, change control, and configuration management.

2.3 Step 2: Assess Impact of Electronic Records

Impact assessment allows the selection of the appropriate approach to risk management for an identified record or record type. The conclusions of the impact assessment should be documented.

Impact should not be determined solely by the requirement for a record in a GxP regulation, but by an assessment of the potential impact of the record on patient safety or product quality. Regulated electronic records should be classified as one of High, Medium, or Low. While there is a continuous scale of impact, the following provides an indication:

- **High impact** records typically have a direct impact on product quality or patient safety, such as batch release or adverse event records.

- **Medium impact** records typically have an indirect impact on product quality or patient safety. These records are used as supporting evidence of compliance, such as validation documentation or training records.

- **Low impact** records typically have negligible impact on product quality or patient safety. Such records may be used to support regulated activities, but are not key evidence of compliance. For example, calibration scheduling records are typically low impact; the key records being the standards defining the required frequency and the records showing calibration has been performed in accordance with those standards.

Examples of record types specifically identified in GxP regulations with an indication of their typical impact are given in Table 2.1. It is important to note that this list of records is for guidance only. It is not intended to be definite or an all-inclusive list of possible record types. Companies should make a documented judgment of the impact of records or types of records based on their own processes and circumstances.

This judgment should be driven by an overall risk assessment of the business or facility aimed at identifying the overall undesirable outcomes that may occur independently of whether electronic records are involved. These can then be assessed against the primary, and related, risks to product quality or public safety. Different facilities and products will have very different profiles in this respect.

For example, a medical device company making tongue depressors is likely to focus on issues associated with direct contamination and failures of sterility, while an oncology drug manufacturer would typically focus on potency, stability, composition, and lab assay.

Table 2.1: Typical Impact of Records by Record Type

H: High Impact
M: Medium Impact
L: Low Impact

Type of Record	Typical Impact	Considerations
Training/personnel record, job descriptions, incl. roles and responsibilities of QA	**M**	While required by some GxP regulations these records do not have direct impact on product quality or patient safety.
QA Audits and Investigations (including Deviations)	**M-H**	QA investigations are often used for internal control, but if the record is used in a study report or for a product release decision then the impact is higher.
Equipment cleaning records	**M-H**	Cleaning records may impact product quality or patient safety (for example risk of cross-contamination). The impact will depend upon materials & products concerned and detectability.
Calibration records	**M-H**	Calibration records may impact product quality or patient safety (for example risk of incorrectly processed products). The impact will depend upon materials & products concerned and detectability.
Planning documents	**L**	Documents such as cleaning, calibration, or maintenance schedules may be requested by inspectors as a sign of compliance with GxP requirements, when considered as part of a quality system. While the absence of such plans may increase the risk of companies not having the required results available for inspection the key records are the results of executing such plans. Management information, such as project plans would have low impact.
Validation documentation	**M**	E.g., Validation Plan, Specifications, Traceability Matrix, Qualification Protocols and Results, Validation Reports.
Financial Disclosure by Clinical Investigators	**M**	Required by GxP regulations.
Inspection Records	**M**	Records of inspections of laboratories or facilities.
Review and approval of reports	**M**	Records which show that reports have been reviewed by knowledgeable responsible persons.

Table 2.1: Typical Impact of Records by Record Type (continued)

H: High Impact
M: Medium Impact
L: Low Impact

Type of Record	Typical Impact	Considerations
Monitoring records	**L-M-H**	This encompasses many types of record.Impact will vary depending on the criticality of parameters being monitored. For example, microbiological and environmental performance of a sterile area may be high impact. Another example may be monitoring records from clinical trials studies. Secondary packaging and warehousing areas may be medium impact depending on the product, while building management records of office environments would have negligible impact. Management information such as progress of validation, progress of internal audits or other internal investigations would have low impact.
SOPs	**L-M**	SOPs used in electronic form constitute electronic records. The impact of SOPs will depend on the nature of the SOP or set of SOPs concerned. For example, a set of SOPs that are used to govern the validation of automated systems should not be considered as critical as SOPs that are used to govern QC operations including final batch release.
Material and finished product specifications	**M-H**	These are the specifications used to release product. Material can range from finished product to shipping boxes.
Distribution records	**H**	These affect product recall and product return.
Clinical and Non-clinical studies	**M-H**	Indicate the methods and content of the study to be carried out and include: non-clinical study protocols, clinical study protocols, Institutional Review Board (IRB) documentation
Clinical and Non-clinical study report	**H**	Contains patient safety data.
Informed consent documentation	**M**	Required for clinical trials.
Investigational New Drug applications (INDs)	**H**	An IND is a compilation of documentation. These records contain patient safety data and information about process and product specifications.
Disposition of investigational drug	**H**	Affects the ability to recall investigational product.
New Drug Applications (NDAs)	**H**	An NDA is a compilation of documentation. These records contain patient safety data and information about process and product specifications.

Table 2.1: Typical Impact of Records by Record Type (continued)

H: High Impact
M: Medium Impact
L: Low Impact

Type of Record	Typical Impact	Considerations
Adverse Events (AEs) and Adverse Drug Reactions (ADRs)	**H**	Contains patient safety data.
Bioequivalency Study Reports	**H**	Contains patient safety data.
QC Analysis results	**M-H**	High if used for final product release decisions.
Batch records	**H**	These records document production and product quality.
Component, drug product container, closure, and labeling records	**H**	These records enable component traceability and batch recall.
Patient information leaflets	**H**	Contains information such as usage instructions and contraindications
Master production and control records	**H**	Contain specifications on which release decisions are based.
Complaint files	**H**	These are an important measure of product quality.

Not all records are specifically identified in GxP regulations. Some are maintained in order to provide evidence of GxP compliance or GxP decision making. A standard approach should be adopted to determine the impact of records, using a checklist of questions, such as the following:

- Can corruption or loss of the record lead to misinterpretation of product quality, safety, or efficacy?
- Can corruption or loss of the record cause the product to be adulterated or result in the release of adulterated or quarantined product?
- Can corruption or loss of the record cause the product to be misbranded?
- Can corruption or loss of the record affect the ability to recall product?
- Can corruption or loss of the record affect product quality or patient safety decisions?
- Does the record have an impact on patient safety decisions? (E.g., impact on pre-clinical or clinical safety results, impact on Adverse Drug Reactions (ADR) and Adverse Events (AE)).
- Is the record required by, or submitted to, a regulatory agency and could it relate to decisions on product quality or patient safety?

Impact classification will vary from case to case depending on factors such as the nature of the product, and company procedures and processes. The initial tendency of organizations may be to define the majority of records in the high impact group rather than in the low to middle groups. However, with improved understanding over time the interpretation of degrees of risk associated with records may start to decrease.

Typically, most regulated electronic records across an organization will be used within an overall management process with independent safeguards against failure (e.g., final QC testing and QA release of product). Therefore, while electronic records such as QA release decisions will be high impact, the majority of electronic records across the organization should have medium impact on product quality or patient safety. Classifying records as high when they are more realistically medium may lead to unnecessary work and controls which are not justified by the risks to product quality or patient safety.

It may also be appropriate to consider records associated with rules or regulations other than GxP regulations when identifying record types. These may include records relating to the handling of controlled substances or occupational health and safety. Issues of legal admissibility should also be considered (for an example, see Appendix 13, reference 14).

2.4 Step 3: Assess Risks to Electronic Records Based on Impact

Following the identification of electronic records and their impact, the next step is to select the appropriate risk management approach.

The risk management approach depends upon the impact, becoming increasingly more rigorous with greater impact.

2.4.1 Approach for Records Identified as Low Impact

Systems maintaining these records and any associated signatures should be subjected to standard validation practices supported by infrastructure qualification, project management, and operational controls. Such controls will involve good IT or engineering practice such as backup and restore, and security management.

For further information on these and related good practice topics see *GAMP 4* (see Appendix 13, reference 1).

2.4.2 Approach for Records Identified as Medium Impact

In addition to implementation of good practice, potential hazards to medium impact records and any associated signatures should be identified and appropriate controls should be designed and implemented to counter these threats (see Section 4 of this Guide).

This analysis should be documented and companies may decide to include the results of the analysis in an existing specification or in a standalone document. The use of a list of generic hazards should be considered. An example template form for recording an assessment of generic hazards and the implementation of appropriate controls is provided in Appendix 9 of this Guide.

2.4.3 Approach for Records Identified as High Impact

In addition to implementation of good practice, high impact records and any associated signatures should be subjected to more formal risk assessment as part of the overall risk management approach.

Potential hazards should be identified and the associated risks assessed. The following aspects should be considered during the assessment:

- Severity of the consequence
- Probability of occurrence
- Likelihood of detection prior to harm occurring

Hazards to high impact records should be formally identified and analyzed by a cross-functional team, including QA. Consideration should also be given to performing a more rigorous assessment, such as that provided by Appendix M3, Guideline for Risk Assessment of *GAMP 4, GAMP Guide for Validation of Automated Systems* (see Appendix 13, reference 1).

For ease of reference, Appendix M3 of *GAMP 4, GAMP Guide for Validation of Automated Systems* is reproduced in Appendix 8 of this Guide.

2.4.4 Hazards

The approach for medium and high impact records involves the evaluation of hazards during specification and design.

Potential hazards to records and associated signatures may be classified as *human-related, computer-related, or physical/environmental.*

Table 2.2 provides some examples of potential hazards to records and signatures. Note that the focus here is on hazards to the record rather than to the system. These examples are not intended to be definitive or all-inclusive.

There are several well established techniques for identifying hazards including HAZOP, CHAZOP, FMEA, FMECA, FTA, and HACCP (see Appendix 13, reference 8 for further details).

Table 2.2: Examples of Hazards to Records and Signatures

Hazard	**Consequence**
Human-related (accidental or deliberate)	
Human error (includes errors of judgment and errors in carrying out required actions)	• Wrong record/signature displayed • Accidental corrupted record/signature • Invalid contents of record/signature • Incorrect copy of record
Change error	Invalid contents of record
Unauthorized change	Invalid contents of record/signature
Undetectable change	Invalid contents of record/signature
Wrong access rights	• Wrong record/signature displayed • Invalid contents of record/signature
Computer-related	
Hardware undersized	Loss or corruption of record(s) or signature(s)
Hardware loss (e.g., disk crash)	Loss or corruption of record(s) or signature(s)
Data loss (e.g., backup failure)	Loss or corruption of record(s) or signature(s)
Software terminates	Loss or corruption of record(s) or signature(s)
Wrong version of software	Loss or corruption of record(s) or signature(s)
Multiple versions of software	Loss or corruption of record(s) or signature(s)
Software lost or deleted	Loss or corruption of record(s) or signature(s)
Software failure**	• Invalid contents of record/signature • Wrong record/signature displayed • Accidental corrupted record/signature
Printer error or failure	Incorrect copy of record/signature
Physical/Environmental	
Power surge	Loss or corruption of record(s) or signature(s)
Power failure	Loss or corruption of record(s) or signature(s)
Fire and/or smoke	Loss or corruption of record(s) or signature(s)
Environment problem	Loss or corruption of record(s) or signature(s)
Theft of hardware/software	Loss of record(s) or signature(s)
** Includes incorrect manifestation and incorrect link to the appropriate record	

2.5 Step 4: Implement Controls to Manage Identified Risks

The company should identify risk control measures that are appropriate for reducing risks to an acceptable level. Risk control involves eliminating or managing the hazard and may be achieved by one or more of the following:

- Modifying the process
- Modifying the system design
- Applying technical controls
- Applying procedural controls

The control measures should be aimed at eliminating or reducing the probability of occurrence of the harm, reducing the severity of harm, or increasing the probability of detection. The selected control measures should be documented and justified with reference to the identified risks, and implemented and verified. The rigor and extent of controls will depend upon the impact of the electronic record and identified risks.

The company should consider any residual risks to records that remain after the risk control measures are applied. If these risks are not acceptable, further risk control measures should be considered and applied. The risk control measures may also introduce new hazards. If so, risks associated with these new hazards should be assessed.

Finally, the company should satisfy themselves that risks from all identified hazards have been evaluated. This judgment should be documented.

There should be traceability between the identified hazards and the implemented and verified control measures.

The range of electronic record controls that may be applied is discussed in detail in Section 4. For further guidance on physical, logical, and procedural security measures see ISO 17799 (see Appendix 13, reference 14).

2.6 Step 5: Monitor Effectiveness of Controls

During periodic review of systems, or at other defined points, the company should review the risks to records. It should be verified that controls established during system development and validation are still effective, and corrective action taken if deficiencies are found. The company should also consider:

- If previously unrecognized hazards are present
- If the estimated risk associated with a hazard is no longer acceptable
- If the original assessment is otherwise invalidated (e.g., following changes to applicable regulations or change of system use)

Where necessary, the results of the evaluation should be fed back into the risk management process, and a review of the appropriate steps for the affected records should be considered. If there is a potential that the residual risk or its acceptability has changed, the impact on previously implemented risk control measures should be considered, and results of the evaluation documented. It should be noted that some changes may justify relaxation of existing controls.

2.7 Points to Consider

Organizations applying the risk management approach as described in this Guide should consider the following potential pitfalls.

Organizational Assumptions

Some organizations may assume that carrying out risk assessments will lead to less validation, others may see this as more work, and others may believe that the existence of risk assessments will guarantee inspection success.

Organizations may implement the risk management approach described in this Guide without considering how this integrates with their existing project management methodologies, which may include risk management techniques.

This may lead to friction between project groups, validation groups, and QA.

The risk based approach is a powerful tool for allocating priority and focusing effort. However, the process must be thought about carefully before being implemented by organizations, in particular:

- Emphasis should be to encourage innovation and technological advances without leading to over-engineered solutions that adversely impact the productivity of the process and without providing added benefit to patient health.

- Management may see record risk assessment as an extra overhead with no benefit. Organizations should ensure that the methodology is introduced in a way that demonstrates the benefits of the approach.

- The approach is not a one-off activity but an ongoing process throughout the system life cycle (as an integral part of change control).

- Presentation during regulatory inspections of the risk based approach, and outputs such as assessment results and implementation of controls based on justified conclusions, should be considered in advance.

Incorrect Assessment

The result of the impact and risk assessments could be either too high, or too low, leading to inappropriate, ineffective, or inconsistent conclusions. Possible reasons for this could be:

- Lack of adequate knowledge of either the system or the business process

- Lack of knowledge or understanding of the applicable regulations

- The participants do not understand the assessment process

- Too much focus on how the business process may fail, rather than on how the record may be affected throughout the process

- Constraints, such as timelines, resources

- Lack of clear guidance or interpretation within the company

- Failure to establish separation of authorities

It is therefore essential to ensure that the participants in the assessment bring with them the required project knowledge, business process knowledge, operational experience, and training.

Inappropriate use of controls

The controls implemented to address risks identified during the assessment may be either too rigorous or insufficient. The balance of technical and procedural controls may be inappropriate, leading to extra costs and difficulties either during project development or during operation.

Again, it is essential to ensure that the participants determining the controls have the necessary project knowledge, business process knowledge, operational experience, and training. Organizations should ensure there are adequate policies, procedures, and standards in place to support the required controls.

3 Applying the Risk Management Process

This section explains how the risk management process described in Section 2 may be applied to:

- New systems (including systems where implementation is not yet complete)
- Existing systems (either un-assessed or previously assessed)

Regulated companies may be at different stages in their response to 21 CFR Part 11, and electronic record and signature regulations in general. Section 3.4 considers the implications of the risk management process on existing systems that have already been assessed against 21 CFR Part 11, and offers guidance on how to deal with these systems.

Applying the risk management process involves initial activities that should be carried out at the company or department level, followed by other activities that should be performed at the individual system level. These activities are described in detail in subsequent sections and are summarized in Table 3.1.

Table 3.1: Summary of Activities Required to Apply Risk Management Process

Corporate Level Activities		
Stage	**Activity**	**Comments**
1	Agree Objectives	Ensure objectives agreed by senior management
2	Create an interpretation of GxP regulations for ER&S (that subset of regulations that apply to the company)	Interpretation should be risk based and should consider new and existing systems. In many cases this will involve updating existing interpretation.
3	If not already done, the company should certify to FDA, in writing, that they regard electronic signatures as legally binding equivalents of traditional handwritten signatures (if appropriate)	Important for new companies or companies implementing new systems who may not have used electronic signatures previously.
	Communicate interpretation to all	Provide clarity on identity and location of electronic record and signatures Emphasize importance of ensuring integrity of electronic record and signatures Describe how new interpretation affects new and existing systems

For New Systems		
Stage	**Activity**	**Comments**
1	Educate project team	Provide understanding of company policies interpreting GxP regulations
2	Determine whether ER&S regulations apply	If they do apply, ensure that an accurate and up-to-date user requirements specification is available, and that all requirements including ER&S are communicated to the supplier
3	Assess system	Identify and assess records required by GxP regulations, and determine required technical and procedural controls based on risk. Supplier assessments may include technical assessment of proposed system versus agreed ER&S requirements
4	Implement controls - Update Validation Plan	Identify those activities and procedures required to ensure compliance - this may involve updating the appropriate specifications
	- Execute the plan - Produce reports	Implement, test and document required technical and procedural controls
5	Monitor effectiveness of controls during operation	Implement periodic review and evaluation procedures

For Unassessed Existing Systems		
Stage	**Activity**	**Comments**
1	Establish and educate project team to assess existing systems	Educate to provide understanding of company policies interpreting GxP regulations
2	Establish list of systems For each system, determine whether ER&S regulations apply	If in scope need to carry out an assessment of compliance with GxP regulations and company procedures
3	Assess in scope systems	Identify and assess records required by GxP regulations, and determine required technical and procedural controls based on risk
4	Carry out remediation - Develop Remediation Plans - Execute the plan - Produce reports	Identify those activities and procedures required to ensure compliance. Prioritize remediation of systems based on risk Implement, test, and document required technical and procedural controls
5	Monitor effectiveness of controls during operation	Implement periodic review and evaluation procedures

For Systems Previously Assessed Against 21 CFR Part 11		
Stage	**Activity**	**Comments**
1	Determine company approach to previously assessed systems in light of current regulations	Can either: - Continue with existing remediation plans - Carry out full reassessment of each system - Consider specific points in the latest FDA guidance, e.g., audit trails
2	If required, based on company approach, establish and educate project team to carry out assessment Establish list of systems to reassess	Educate to provide understanding of company policies interpreting GxP regulations
3	Carry out assessment	Reassess required technical and procedural controls based on risk
4	Carry out remediation - Reconsider existing Remediation Plans in light of assessment - Execute the plan - Produce reports	Identify changes to activities and procedures required to ensure compliance Prioritize remediation of systems based on risk Implement, test, and document required technical and procedural controls
5	Monitor effectiveness of controls during operation	Implement periodic review and evaluation procedures

3.1 Corporate Level Activities

The initial stages are applicable to all regulated companies, regardless of previous work performed toward compliance with ER&S regulations. These should be completed before carrying out any system assessments.

Stage 1: Agree Objectives

A set of new, or revised, objectives should be agreed by senior management, based on the approach described in this Guide. A clear policy should exist, and the implications for company plans, activities, and organization at the global, regional, functional, and site level should be considered.

The objectives may include:

- To understand the applicable regulations
- To gain management commitment for resources and budgets
- To educate users in their responsibilities
- To ensure each new system is compliant when operational, or to establish controls and action plans to address any non-compliance
- To bring existing systems into compliance in the most cost-effective way taking into account work already completed or in progress
- To use a risk-based approach aimed at achieving compliance, while delivering business benefits
- To maximize compliance within existing constraints
- To set up an appropriate Information Security Management System (ISMS)

Stage 2: Agree An Interpretation

This is a documented interpretation of what the electronic record and signature regulations mean for the company, based on the approach described in this Guide. This should include representation from GCP, GLP, GMP, and GDP areas as appropriate so that a common approach is developed. This interpretation should then be communicated across the organization to ensure a common understanding.

Key points to consider as part of the interpretation are:

- Risk management
- Security management
- Backup and restore
- Disaster recovery
- Documentation standards

- Change control
- Training
- Validation
- Audit trail
- Record retention
- Copies of records
- Legacy systems
- Hybrid systems
- Use of electronic signatures
- Classification of record types (e.g., confidential, registered, private)

The interpretation should take into account all applicable regulations and guidance (e.g., 21 CFR Part 11, EU regulations, MHLW regulations, and PIC/S guidance) and this Guide.

Based on this interpretation, company standards, procedures, and guidelines should be written or revised if necessary.

The next stages will depend on whether the system under review is new or existing, and whether assessment, planning, or remediation activities are already underway. The management approaches for new and existing systems are described in subsequent sections.

Stage 3: Communicate To Everyone

Everyone involved should understand the implications of ER&S compliance, and the company policy. Commitment should be sought to resolve non-compliance in line with policy.

If the company intends to use electronic signatures, and has not already done so, the company should certify to FDA, in writing, that they regard electronic signatures as the legally binding equivalent of traditional handwritten signatures. This may not have been previously done if the company is new, or a company did not previously supply the US market, or if a company has not previously implemented a policy of allowing electronic signatures.

While this requirement can cause confusion the process is not complicated. An organization simply needs to notify the FDA that they intend to use electronic signatures as part of their regulated activities. It is not necessary to notify FDA about each employee who will use an electronic signature.

Note that as of the publication date there are no similar certification requirements for other regulatory authorities.

3.2 Applying the Process to New Systems

The following stages should be incorporated into the project life cycle for new systems:

Stage 1: Educate Team

Educate project teams in the new company approach, ensuring an understanding of how compliance and benefits are to be achieved, and a commitment to resolve any non-compliance.

Stage 2: Determine Whether ER&S Regulations Apply

If they do apply, ensure the User Requirements Specification contains requirements for electronic records and signatures that meet current company policies and standards. An initial identification of which electronic records and signatures will exist within the system should be included in the URS. Use of the system to generate regulated paper records should also be covered by the URS to avoid any ambiguity. Examples of systems where GxP regulations may apply are given in Appendix 7 of this Guide.

Stage 3: Assess System

Identify and assess records required by GxP regulations, by using the risk management process provided in Section 2. The assessment should consider:

- The business processes that create and update records
- The purpose of any electronic signatures
- Which records are being signed
- Any data supporting the electronic records or signatures

Appropriate technological and procedural controls should be selected using guidance provided in Section 4.

Where an external supplier is involved, an assessment of the proposed technology's compliance with customer requirements for electronic records and signatures should be performed. This may form part of the supplier audit, which should be carried out prior to contract placement.

Stage 4: Implement Controls

- Document and justify decisions
- Update Validation Plan
- Create or update system specifications
- Apply technical and procedural controls
- Test technical controls and verify procedural controls
- Produce Validation Report

Stage 5: Monitor Effectiveness of Controls During Operation

Key points to consider to ensure continuing compliance during operation are given in Section 2.6.

3.3 Applying the Process to Existing Systems

The following stages should be followed for existing systems that have not already been assessed. See Section 3.4 of this Guide for further information related to previously assessed systems.

Stage 1: Establish and Educate Team

Establish and educate project teams in the new company approach, ensuring an understanding of how compliance and benefits are to be achieved, and a commitment to resolve any non-compliance.

Stage 2: Determine Whether ER&S Regulations Apply

Using a master list of systems, determine which systems are in scope. This can be achieved by considering whether each system maintains an electronic record or captures electronic signatures. Examples are given in Appendix 7 of this Guide.

Stage 3: Assess In Scope Systems

Identify and assess records required by GxP regulations, by using the risk management process provided in Section 2. The assessment should consider:

- The business processes that create and update records
- The purpose of any electronic signatures
- Which records are being signed
- Any data supporting the electronic records or signatures

Where issues are identified, possible remediation should be considered and appropriate technological and procedural controls should be selected using guidance provided in Section 4. The next stage involves implementing the selected controls.

Stage 4: Carry Out Remediation

- Document and justify decisions
- Develop Remediation Plan: this should be prioritized against other systems based on risk to product quality or patient safety. The extent of non-compliance and useful life of system (when system is expected to be retired) should also be taken into account.
- Apply technical and procedural controls.
- Test technical controls and verify procedural controls
- Produce Remediation Report

Stage 5: Monitor Effectiveness of Controls During Operation

Key points to consider to ensure continuing compliance during operation are given in Section 2.6.

3.4 Systems Previously Assessed Against 21 CFR Part 11

The following stages can be followed for existing systems that have previously been assessed against 21 CFR Part 11 requirements.

Stage 1: Determine Company Approach

Current regulatory expectations give an opportunity for companies to:

- Re-think their initial or current approach
- Apply risk based management
- Achieve compliance more cost effectively

Most regulated companies have already undertaken programs in response to 21 CFR Part 11 and electronic records and signatures in general, though how far advanced these programs are will vary.

The following options exist for systems that have already been assessed:

- Continue with existing remediation plans
- Carry out a full reassessment of each system or group of system(s)
- Consider the impact of specific points raised in the FDA guidance on existing remediation plans for each system or group of system(s)

While all the above options are valid, continuing with existing remediation plans may result in the implementation of unnecessary controls, but carrying out a full reassessment of the records in each system using the detailed risk assessment process described in this Guide will be prohibitively expensive for many. One approach might be to complete the work on systems where remediation is underway but to re-assess the systems for which remediation has not yet started.

Evaluating the continuing applicability of 21 CFR Part 11 based on the specific points raised in the FDA guidance may be another practical way of dealing with previously assessed systems.

Companies should make a documented interpretation of what the new 21 CFR Part 11 guidance means to them in the context of their business. They should consider in particular:

- Validation
- Audit trail
- Record retention
- Copies of records
- Legacy systems

These points are considered fully in Appendices 1 to 5.

All other 21 CFR Part 11 controls not under enforcement discretion as per the guidance are still required for existing systems, unless those systems are legacy systems.

Stage 2: Establish and Educate Team

If a reassessment is to be carried out, establish project teams and educate in the new company approach, ensuring an understanding of how compliance and benefits are to be achieved, and a commitment to resolve any non-compliance.

The list of systems to be reassessed should be defined.

Stage 3: Carry Out Assessment

If the company approach is to carry out a full reassessment, then the process given in Section 3.3 should be followed.

However, if a reassessment of the continuing applicability of 21 CFR Part 11 based on the specific points raised in the FDA guidance is required, this may be documented using the example form provided in Appendix 10 of this Guide. This form documents whether 21 CFR Part 11 still applies, based on the narrow scope and definition of legacy system provided by the FDA guidance. The form also documents the reassessment of existing remediation plans with regard to specific 21 CFR Part 11 expectations, namely:

- Meeting predicate rules
- An assessment of risk
- The potential of the system to affect product quality or patient safety
- Record integrity

The form can be applied to individual systems or to groups of systems, as appropriate.

Stage 4: Carry Out Remediation

- Changes to existing remediation plans, activities, and procedures should be identified.
- These should be prioritized against other systems based on risk to product quality or patient safety. The extent of non-compliance and useful life of system (when system is expected to be retired) should also be taken into account.
- Apply technical and procedural controls. Note: procedural controls should already be in place.
- Test technical controls and verify procedural controls
- Produce Remediation Report

Stage 5: Monitor Effectiveness of Controls During Operation

Key points to consider to ensure continuing compliance during operation are given in Section 2.6.

4 Controls

This section discusses various risk control measures that can be used to manage risks, as identified by the process described in Section 2 of this guide. The control measures should be aimed at eliminating or reducing the probability of occurrence of the harm, reducing the severity of harm, or increasing the probability of detection. The rigor and extent of controls will depend upon the impact of the electronic record and identified risks.

4.1 Record Controls

Procedural and technical controls available to reduce risks to an acceptable level include:

- Security management
- Backup and restore
- Disaster recovery and business continuity
- Change control
- Validation
- Audit trail
- Record copying controls
- Record retention controls
- Software controls
- Hardware controls
- Policies and procedures
- Training and experience

A combination of these controls may be necessary to adequately manage the risk. The selected measures should be implemented and documented. Many of these controls will be implemented at the system level (e.g., audit trail). The implementation of procedural controls should be considered at a corporate, site, or department level as appropriate, to minimize unnecessary duplication of procedures.

4.1.1 Implementation of Controls

Controls may be implemented in different ways and with differing degrees of rigor. Table 4.1 shows how various types of controls may be implemented.

Table 4.1: Possible Implementation of Record Controls

Control	Possible Implementation
Security Management	• Physical access security • Formal access authorization • Confirming identity of new user before granting access • Unique user identification • Different user-id/password combinations for logon and signatures • Providing defined profiles for individual users or groups • Clear separation of server administration, application administration and user roles and responsibilities • Limiting Write, Update, Delete access (e.g., to key users) • Enforced password changing • Enforced minimum password length and format • Idle time logout • Management of lost or compromised passwords • Group access (sharing of access accounts) • Proactive monitoring for attempted breaches • Automated measures on attempted unauthorized access (e.g., lock account, notify management) • Use of super-user accounts • Changing user rights • Revoking access from users without losing record of their historical use • Testing and renewal of identity devices or tokens • Amount of documentation retained
Backup and Restore	• Formality of process • Documented testing of process • Frequency • Redundancy (e.g., number of tapes in cycle) • Auto or manual processes • Backup verification • Backup media • Storage conditions • Storage location(s) including remote storage locations • Media refresh • High availability system architecture if required • periodic testing throughout retention time • Amount of documentation retained
Disaster Recovery and Business Continuity (No IT service available)	• Service level agreements • Formal contracts for restoration of service • Defined allowable time of outage • Recovery mechanisms (e.g., hot standby, procedural) • Documented testing of the plan • Definition of defined recovery point • Documented procedures for business continuity and number of personnel trained in these procedures

Table 4.1: Possible Implementation of Record Controls (continued)

Control	Possible Implementation
Change Control	• Extent of QA involvement (e.g., Procedural authorization vs. individual approval vs. audit verification) • Defined roles and responsibilities for change assessment, authorization, review and approval • Formality and roles involved in authorization • Formality and roles involved in different types of review (which can include design review/risk assessment) • Formality and roles involved in approval • Amount of testing carried out • Formality of go live process after upgrade • Amount of documentary evidence retained
Validation	• Extent of QA involvement • Formality of process with defined roles and responsibilities • Degree of specification • Degree of review • Nature, scope & degree of testing, including controls implemented in support of electronic records and signatures • Roles involved in review • Roles involved in approval • Amount of documentary evidence retained
Audit Trail	• Type (automatic, manual, combination) • Date and time stamped • Identification of time zone • Amount of information retained (who/what/when) • Access control and security of the audit trail • Ability to change the audit trail • Retention of the audit trail • Backup and restore of the audit trail • Procedures for managing the audit trail • Retention of previous versions of data • Purpose: e.g., for auditing of planned authorized changes to data or for detecting unauthorized change (fraud attempts)
Record Copying Controls (see also retention below)	• Format of copy (common portable electronic, paper) • Reference to original on copy • Relationship with original (e.g., exact copy, summary) • Preservation of meaning and content • Search, sort, and trend capabilities • Process for producing copies (time required, access levels) • The method for controlling the exact copy, e.g., use of cyclic redundancy check (CRC-32) or message digest (MD5)

Table 4.1: Possible Implementation of Record Controls (continued)

Control	Possible Implementation
Record Retention Controls	• Retention periods • Definition of what is being retained • Retention of associated data (e.g., audit trails, configuration information) • Capacity limits • Automatic or requiring human intervention • Ability to reprocess data • Involvement of QA • Formal disposal procedure • Periodically test ability to retrieve records throughout retention period. • Media maintenance procedures throughout retention period - Ability to read physical media - Dependence on original version of software application - Dependence on original version of operating system - Dependence on original configuration of hardware
Software Controls	• User identity checks • Checksums and other verification of data transfer • Standard network protocols for data transfer • Automatic functionality to reduce human error, e.g., - use of barcodes - sequence enforcement • Measurement redundancy in critical applications • Data entry checking • Error handling • Alarms • Notification of software failure • Audit trail (treated separately, see above) • Prompting for confirmation of action • Monitoring tools (e.g., event logs)
Hardware Controls	• Mirrored or RAID drives • UPS • Stress testing • Contingency in sizing of hardware • Network monitoring (could be also software control)

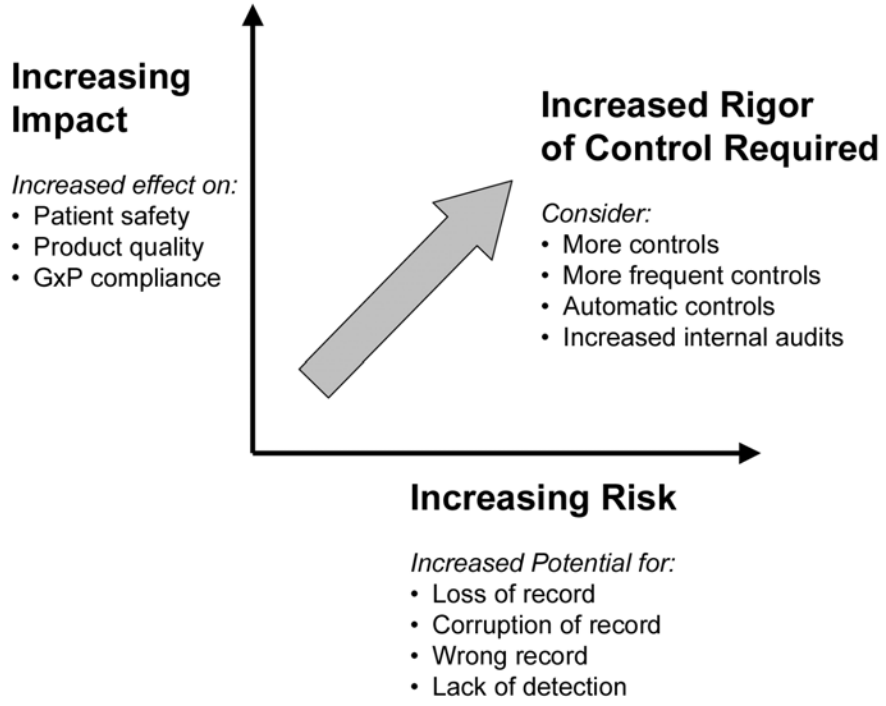
Table 4.1: Possible Implementation of Record Controls (continued)

Control	Possible Implementation
Policies and Procedures	• Formality of policies and procedures • Extent of QA involvement • Formality and roles involved in authorization • Formality and roles involved in review • Formality and roles involved in approval • Internal audit processes to confirm adherence to procedures Policies and Procedures to cover topics such as the following where appropriate: • Validation • Risk management • System documentation management • Change management • Taking copies of electronic records • Backup and restore • Access management • Audit trail management • Signature management • Usage of electronic signature • Operation of automated software controls • Record retention periods • Significance of electronic signatures in terms of individual responsibility • Consequence of falsification • Data archiving and deletion • Application archiving
Training and Experience	• Training and experience of users of systems containing electronic records • Training and experience of developers of systems (both pharmaceutical organizations and suppliers) • Amount of documentation retained • Significance of electronic signatures in terms of individual responsibility • Consequence of falsification • Usage of electronic signature

4.1.2 Rigor of Controls

The rigor with which the controls are applied should take into account both the impact of the record and the risks identified. As the impact and risk increase then more rigorous control is required, as shown in Figure 4.1.

Figure 4.1: Relationship between Impact, Risk, and Rigor of Controls



Companies should take into account the need for authenticity, integrity, accuracy, reliability, and where appropriate the confidentiality of the electronic records.

A combination of several technical and procedural controls may be required to achieve an adequate level of protection. For further information see National Institute of Standards and Technology (NIST) Engineering Principles for IT Security <SP 800-27> (see Appendix 13, reference 15).

For systems containing multiple types of records, there are two approaches to applying the controls.

1. Apply controls to all records appropriate to the highest identified risk

2. Apply controls to individual record types appropriate to the identified risk for each type

4.2 Signature Controls

Electronic signatures should be applied where a record is required to be signed by a GxP regulation and the record is maintained in electronic format. Electronic signatures are defined in 21 CFR Part 11 as "a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature."

Companies should define when signatures are required in light of their own processes and circumstances. Examples of GxP regulations for electronic signatures and identifications are provided in Appendix 6 of this Guide.

21 CFR Part 11 provides clear instruction on the information associated with a signing that needs to form part of a signed electronic record:

- The printed name of the signer
- Date and time when the signature was executed
- Meaning (such as review, approval, responsibility, or authorship) associated with the signature

This information must be included as part of any human readable form of the signed record (e.g., displayed on the screen or a printout of the record). Note that the information need not be physically stored in the same file but must be linked in a way that ensures it cannot be removed, altered, or copied by ordinary means.

The European Union has also provided requirements regarding the use of Advanced Electronic Signatures (EU Directive 1999/93/EC 13 Dec 1999, see Appendix 13, reference 11). EU advanced e-signatures security certificates are based on a secure 'signature creation device' (i.e., the signature creation data can practically occur only once; their secrecy is reasonably assured; the signature generation cannot, with reasonable assurance, be derived; the signature is protected against forgery using currently available technology; and can be reliably protected by the legitimate signatory against the use of others). The EU advanced e-signature has the following characteristics:

- It is uniquely linked to the signatory
- It is capable of identifying the signatory
- It is created using means that the signatory can maintain under their sole control
- It is linked to the data to which it relates in such a manner that any subsequent change of the data is detectable

Only authorized certification organizations are allowed to administer this type of electronic signature.

It is possible to meet the requirements of the controls required for both markets if systems are designed with forethought. The intent is to ensure that electronic signatures are equivalent to handwritten signatures and are legally binding.

The integrity of the electronic signature is vital. Companies should ensure that if individuals use the same electronic signature on both regulated and unregulated systems, that the controls on the unregulated systems are sufficient so as not to potentially compromise the use of the electronic signature on the regulated system.

The following signature controls should be considered when deciding upon a suitable approach to ensuring compliant signatures. The appropriate controls will depend upon the impact of, and risks to, the signed electronic record in question.

- Method for ensuring uniqueness of signature, including prohibition of reallocation
- Prevention of deletion of signature related information after the signature is applied
- Biometric methods

- Information recorded on signing (e.g., name, date and time, meaning of signature)
- Integrity of link between signature and record
- Method of display or print of signed records
- Procedure for delegation of signature responsibilities (e.g., holidays, periods of absence)
- Entry of all or some components of multiple component signatures
- Storage of password used in the act of signing (e.g., not in signed record)
- Use of certified providers of electronic signatures

4.3 Managing Hybrid Records

Hybrid records are commonly found in automated systems. Examples include:

- Records that are maintained electronically and handwritten signatures applied
- An electronic representation of a signed paper record and both are maintained

Existing technology may not allow the use of electronic signatures with electronic records in a particular system. An example could be the release of a manufacturing batch that has been compiled using electronically created records with no facility for electronic signature. These batch records would typically be identified as high impact and the risk assessment would likely highlight the issue of establishing and maintaining the link between the electronic and signed paper copies (since maintaining records synchronized in a hybrid system carries a significant risk). Companies should decide and document which is the regulated record (may be both).

Suitable controls should be established and verified. These may include standard operating procedures that define the process of controlling the signed paper record, and for making modifications to the paper and electronic records if required. The procedure should provide a process that prevents incorrect or out of date versions of records from being used.

Another example is a master batch record maintained in electronic form which is used to generate a blank paper batch record (including manufacturing instructions) which is completed manually. The original printout of the master batch record is signed on paper by head of manufacturing and QA. Subsequent printouts (i.e., working copies) are signed by QA to confirm that this is a true copy of the master batch record. In this case the electronic version of the signed paper master batch record is used to produce copies of the master batch record. Companies should have controls established to ensure that the electronic record used for printing is the same as the approved paper record.

A third example is a paper record, scanned into an electronic system and stored in PDF format. The assessment and resulting controls would be dependent upon the usage of the record.

4.4 User/Supplier Responsibilities

4.4.1 Procedural Requirements (responsibility of user)

The following list defines procedural requirements to support the use of compliant electronic record and signature systems. The procedures implemented should be commensurate with the identified risk:

1. Systems should be validated according to defined procedures.

2. Systems, records, and documentation should be developed according to defined procedures and should be managed under change control procedures.

3. Provision of data to external parties should be formally managed.

4. When copies of records with any associated audit trails and signatures are created for regulatory inspection, there should be controls to ensure legal compliance and that confidentiality is maintained.

5. Retention periods, and responsibilities for complying with these periods, should be documented. Document management procedures should ensure that handwritten signatures linked to electronic records are maintained for the same retention period.

6. Backup and recovery, and archive and retrieval of data should be formally documented.

7. Procedures should define how access to systems is limited to authorized individuals.

8. Evidence should be available to demonstrate that persons who develop, maintain, or use electronic record and signature systems have the education, training, and experience to perform their assigned tasks. There should be training records and a procedure that addresses this requirement. Refer to local SOPs for Staff and Training Records.

9. Unsuccessful attempts to access the system should be monitored - this is a system control and may not be possible on some systems.

10. There should be a system of self-inspection to demonstrate compliance with the procedures and controls.

The following procedural requirements relate to systems that utilize electronic signatures:

1. The significance of electronic signatures, in terms of individual responsibility, and the consequences of misuse or falsification should be documented. Procedures should be established to ensure individuals understand they are accountable and responsible for actions initiated under their electronic signatures, and that electronic signatures must not be made known to others. Particular attention is needed when electronic signature components are used on multiple systems, or for other activities such as logging into a system, to ensure that the integrity of the signature components is not compromised.

2. Security procedures should be established that ensure electronic signatures are unique to an individual. The user id should never be reassigned to another individual.

3. Procedures should be established to verify the identity of an individual before the assignment of their electronic signature, or any component of an electronic signature (such as the user ID).

4. Security procedures should ensure that the ability to apply electronic signatures is withdrawn for individuals whose responsibilities change and make the original assignment no longer applicable, without the loss of information relating to signatures already executed.

5. There should be initial and, where applicable, periodic testing of devices that bear or generate the confidential component of an electronic signature to ensure that they function properly and have not been altered in an unauthorized manner.

6. Procedures should be established to manage signature loss (e.g., token, password), and periodic changing where applicable (e.g., passwords).

7. Procedures should cover the delegation of signature responsibilities (e.g., holidays, periods of absence).

4.4.2 Technical Requirements (largely the responsibility of supplier)

Many of the controls identified in Table 4.1 in Section 4.1.1, and signature controls identified in Section 4.2, are technical in nature and will form part of the functionality of the supplied system. Suppliers of such systems should be aware that these controls will likely be standard requirements for systems supplied to the regulated life science industries, consistent with their applicability as shown in Table 4.1. Suppliers are liable to assessment, including audit, to ascertain that technical controls have been implemented appropriately, since user companies have ultimate responsibility for the system in use.

Suppliers should provide documentation that defines which electronic records and signatures a system is capable of maintaining. The controls available to help manage these records and any associated signatures should also be described. The user can then use this information during the risk management process.

It may not be possible to implement certain technical controls due to the required functionality not being currently available in the automated system. If it is determined that including the required technical control would not be practical, then the use of alternative technical controls, or failing that procedural controls, should be considered for acceptability by the user. The use of multiple procedural controls may together produce sufficient collaborative information to support the evidence of record control.

Suppliers may also provide administrative features and utilities in their applications and systems to make the user implementation of procedural controls more efficient, consistent, and secure. An example of this would be the inclusion of a system workflow to route lists of authorized users to the System Owners on a periodic basis for review.

Appendices

Appendix 1
Validation

1 Introduction

The regulated company should have established policies and procedures for the validation of systems, including those that generate or maintain regulated electronic records and signatures. Security and integrity of regulated records should be considered when planning validation activities.

Factors to be taken into account should include:

- GxP regulatory requirements for validation
- Potential impact and risk to product quality or patient safety
- Complexity, system size, and degree of standardization or novelty
- Nature and source of software and hardware components

2 Examples of Relevant GxP Regulations

21 CFR Part 820 Quality System Regulation, Subpart G, §820.70 Production and process controls:

"(i) Automated processes. When computers or automated data processing systems are used as part of production or the quality system, the manufacturer shall validate computer software for its intended use according to an established protocol...These validation activities and results shall be documented."

21 CFR Part 211, Subpart D, §211.68 Automatic, mechanical, and electronic equipment:

"(a) Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, and holding of a drug product. If such equipment is so used, it shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained."

EU GMP, Annex 11, Computerised Systems, Paragraph 2, Validation:

"The extent of validation necessary will depend on a number of factors including the use to which the system is to be put, whether the validation is to be prospective or retrospective and whether or not novel elements are incorporated. Validation should be considered as part of the complete life cycle of a computer system. This cycle includes the stages of planning, specification, programming, testing, commissioning, documentation, operation, monitoring and modifying."

Annex 15, Section 1, Principle:

"Significant changes to the facilities, the equipment and the processes, which may affect the quality of the product, should be validated. A risk assessment approach should be used to determine the extent and scope of validation."

Annex 18, Ref 5.40:

"GMP related computerised systems should be validated. The depth and scope of validation depends on the diversity, complexity and criticality of the computerised application."

3 Validation of Electronic Records and Signatures

Controls for regulated electronic records and associated signatures should be validated. This should happen as part of the overall validation strategy for the system, following a process such as that described in *GAMP 4* (Appendix 13, reference 1). Relevant material may also be found in:

General Principles of Software Validation; Final Guidance for Industry and FDA Staff (Appendix 13, reference 6)

Good Practices for Computerised Systems in Regulated 'GxP' Environments (Appendix 13, reference 5)

"Guideline on Control of Computerized Systems in Drug Manufacturing" (Appendix 13, reference 7)

Trial Management, Data Handling and Record Keeping (Appendix 13, reference 16)

The Good Laboratory Practice Regulations, Statutory Instrument 1999 No. 3106 - Part X, Section 1(e) (Appendix 13, reference 17)

Appendix 2
Audit Trail and Data Security

1 Introduction

Audit trails are being increasingly applied to industrial and commercial data to improve information quality and to reduce information loss from activities such as overwriting of data attributes.

For electronic records and signatures, the decision on whether to apply audit trails should be based on a combination of GxP regulatory requirements and assessment of risk to the trustworthiness and reliability of records, including the risk of unauthorized or undetectable changes to records. Suitable controls to manage risk and meet GxP requirements include audit trails, and other physical, logical, and procedural security measures as appropriate. Audit trails may be particularly appropriate where the users are expected to create, modify, or delete regulated records during normal operation.

An audit trail is typically used to provide two functions:

- Attribution of action or change
- Traceability of changes

In a wider context, audit trails may also be used as one safeguard to deter, prevent, and detect unauthorized record creation, modification, or deletion.

Audit trails themselves should be secure from change. For enhanced usability, facilities should be available to search, sort and filter audit trail data.

2 Attribution of Action or Change

Requirements for identifying who performed an action, and when, are traditionally met in paper-based systems by initialing (or signing) and dating the relevant record, even though there may be no associated GxP requirement for a signature.

In an electronic system, an audit trail is one suitable way of meeting such requirements for identification where there is no need for a regulated signature. The accuracy and reliability of the audit trail should be verified during validation testing.

3 Traceability of Changes

Some GxP regulations require traceability of creation, modification, or deletion of regulated records.

In a traditional paper-based system, such a requirement would typically be implemented as follows: if a user recognizes that a certain data entry is wrong they strike out the wrong data in a way that it is still readable and put the correct value next to it with their initials, the date, and in some cases the reason.

In an electronic system, an audit trail can be a good way of providing this traceability. Again, the accuracy and reliability of the audit trail should be verified during validation testing.

4 Examples of Relevant GxP Regulations

The following example regulations require changes to be documented. Adequate documentary evidence may be achieved using change control, security management, paper logs, electronic audit trails, or a combination thereof.

21 CFR Part 58, §58.120 Protocol:

"(b) All changes in or revisions of an approved protocol and the reasons therefore shall be documented, signed by the study director, dated, and maintained with the protocol."

21 CFR Part 58, §58.130 Conduct of a non-clinical laboratory study:

"(e) Any change in entries shall be made so as not to obscure the original entry, shall indicate the reason for such change, and shall be dated and signed or identified at the time of the change. In automated data collection systems, the individual responsible for direct data input shall be identified at the time of data input. Any change in automated data entries shall be made so as not to obscure the original entry, shall indicate the reason for change, shall be dated, and the responsible individual shall be identified."

21 CFR Part 820, §820.40 Document controls:

"(b) Document changes. Changes to documents shall be reviewed and approved by an individual(s) in the same function or organization that performed the original review and approval, unless specifically designated otherwise. Approved changes shall be communicated to the appropriate personnel in a timely manner. Each manufacturer shall maintain records of changes to documents. Change records shall include a description of the change, identification of the affected documents, the signature of the approving individual(s), the approval date, and when the change becomes effective"

EU GMP, Annex 11, Computerised Systems, Paragraph 10, System:

"The system should record the identity of operators entering or confirming critical data. Authority to amend entered data should be restricted to nominated persons. Any alteration to an entry of critical data should be authorized and recorded with the reason for the change. Consideration should be given to building into the system the creation of a complete record of all entries and amendments (an "audit trail").

5 Examples of Cases Not Requiring Audit Trails

In some systems a risk assessment may determine that an audit trail is not required. Examples include:

- A data warehouse, where data is not changed (read only). While a record is required of data loading into the warehouse, each read operation of the data need not be audit trailed.
- An instrument that passes raw data to a Laboratory Information System (LIMS) for storage. If the data were sent directly to the LIMS, without local manipulation by operators, then an audit trail within the instrument would not serve any purpose.
- The day to day operation of simple PLC or microprocessor controlled equipment, for example a pre-set program of a washing machine, whose output is recorded on a paper chart. Again, an audit trail would not be relevant.

A risk assessment may determine that an audit trail is not necessary due to GxP requirements being met by other adequate controls. These may include:

- The application of rigorous, documented, change control or version control, tied to access control
- Security measures to avoid unauthorized changes to regulated records (e.g., by storage on a read-only medium or directory)

Case studies which consider the relevance of audit trails among other aspects are included in Appendix 7.

Appendix 3
Record Retention, Archiving, and Migration

1 Introduction

This Appendix describes how to manage electronic records in order to comply with GxP regulations for record retention. It specifically does not discuss *defining* the retention period for various types of records, which is based on the relevant GxP regulations and company policy, and is outside the scope of this Guide. The primary focus will be on issues relating to choices a firm may wish to make regarding the logical or physical nature of the retention process concerning ERS compliance. While this includes consideration of issues related to migrating records to non-processible formats, it is also not intended to be a complete guide to GxP-compliant data migration or archiving practices.

The terms "record retention" and "archiving" describe separate issues. While an archive is often the best approach to meeting record retention requirements, it has additional meaning in that the archive process generally involves removing the record from the system that produced it, e.g., a production data base. There are "near-line" solutions that do this invisibly to the users where, for example, older records may be moved to another database that is also accessible through the main application. There are also "off-line" solutions that involve storage to different media, which typically will require more effort to retrieve archived records. Near-line solutions have the advantage of rapid access; off-line solutions trade rapid access for less costly storage solutions. Any of these options, or retaining records in the production database[1], is acceptable as long as the records are retained in accordance with relevant GxP regulations.

Use of non-electronic media such as microfilm, microfiche, and paper, or a standard electronic file format, such as PDF, SGML, or XML is also acceptable as long as all GxP regulations are satisfied, and copies of records preserve their content and meaning. Paper and electronic record and signature components can co-exist (i.e., a hybrid situation) provided the same GxP regulations are met.

For any data, the approach to data retention should be based upon an assessment of the risk associated with the data format, physical media, and future expected use of the data. Data management activities (including security, disaster recovery, etc.) must also be considered.

2 Management of Electronic Records

Measures required to support electronic records, whether on-line or archived, are discussed in *GAMP 4* (Appendix O6). For on-line records, such measures include logical and physical security, and back-up. When system upgrades are performed, data migration plans must ensure the integrity of the records already in the database. For archived electronic records, additional considerations include exercise of the media[2], refresh of the media[3], and storage

[1] 21 CFR 58.190 requires that the results of pre-clinical studies be archived (and under the control of an archivist) at the completion of the study. In such cases, if the records are to be retained on-line in a production database, measures need to be taken to protect them from alteration in order to comply with this predicate rule.
[2] For example, magnetic tape may delaminate if it is not periodically wound/rewound
[3] The lifetime of magnetic media varies, but in all cases is prone to degradation over time. CDs probably have a longer, although still finite, useful lifetime. The typical solution is to copy the data to new media of the same type.

conditions. For older records, it may occasionally be necessary to "technically refresh" archived data, converting it to a new format that is compatible with an upgraded production system.[4] It may also be necessary to develop new rendering software solutions to view records from obsolete systems after those systems are retired. Typically, rendering software will not feature significant abilities to manipulate data, so if there is a clear need to be able to process the data the "technical refresh" approach would be preferable.

3 Hybrid Records and Archives

Regulated companies should base their approach to data retention upon an assessment of the risk associated with the data format. The ability to retain records in processible form throughout the retention period is not always required. Companies may choose to retain records in formats other than the original electronic record if content and meaning are preserved, and GxP regulations are met.

If it is highly unlikely that data will have to be processed, then paper or other options may be an adequate solution. Factors to consider include:

- Data integrity
- Future use of the record, including prospective needs to sort or trend data
- The risk assumed with moving the records to a non-processible format or media
- Availability of the record to regulators

If GxP regulations are fully satisfied and the content and meaning of the records are preserved and archived, then the original version of the records may be deleted. Retaining the original record in an accessible format opens the possibility that the original record may improperly become the basis for further regulated activity. Firms need to be aware that regulators will base their assessment on the records that are actually used in their business processes. If a firm has signed paper copies in a locked file cabinet and the staff uses an electronic database, regulators are going to expect to see controls on the database and not the file cabinet.

Since archival typically involves removal of the record from the production system, this data conversion should be treated as creation of an archive copy and the electronic record should be eliminated. Note also that if a company's processes require keeping the original data, it is likely that conversion to an alternative format would not be considered acceptable by regulators.[5]

[4] Technically refreshing the records can also be a complex problem. For example, there may be floating point issues, rounding versus truncating, etc. Validation activities may therefore be important.

[5] If a firm feels the need to retain the original electronic record it will appear as though they either have lower confidence in the alternative format or that they anticipate needing the original. Neither is likely to instil regulatory confidence.

4 Audit Trail Considerations

When converting records to an alternative format, companies should make an informed decision regarding whether to migrate audit trail information with the data. If the audit trail is integral to understanding the record, for example, changing a GLP or GMP lab test result based on re-integration of a chromatogram, it should be part of the migrated record as well. It may not, however, be necessary if the audit trail is not required by GxP regulation and the data was used only for purposes like statistical process optimization within validated parameters, or for workflow tracking, and thus has at most low GxP impact. A decision not to migrate an audit trail should be justified, based on risk, and documented.

5 Alternative Systems

Occasionally, it may be advantageous or necessary to convert electronic records to a different electronic form, while preserving the ability to reprocess them. Records may be collected and managed on different systems.

For example, it may make sense to leverage superior data management capabilities (e.g., audit trailing, consolidated back-up, etc.) in a higher level system as opposed to trying to build the same capabilities into several lab instruments. Assuming that the content and meaning of the record is fully preserved, and all future uses and manipulations of the data are intended to be in the higher system, this approach should generally preclude any future manipulation *of the original "raw" data file* through the instrument. This can be enforced by removal of the record from the instrument as advocated above.[6]

Instrument records being managed in this manner would be handled more consistently, as all data would be managed via the same procedures. Searchability is likely to be improved, as all lab records would be accessible through one database, with more sophisticated data management tools.

Firms need to consider that many instruments or other systems use proprietary data formats that will not convert cleanly while preserving content and meaning of the record. It may be possible to manage data files through the higher level system, but the records may not be viewable without the use of the originating system. In such cases a decision must be made whether processibility is critical; the need for this may decrease as the record ages.

Finally, whenever migrating records from a computer system to another system, measures should be undertaken to ensure that the content and meaning are preserved. This generally entails either validating the conversion or verifying the accuracy of the new version.[7]

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[6] Firms need to understand the risks as well as benefits of such a solution. For example *EU* Volume 4 in 6.9 states *'for some kinds of data [e.g. analytical test results, yields, environmental controls]… it is recommended that records be kept in a manner permitting trend evaluation.'* If a firm interprets this as requiring the ability to reprocess the data, transferral to a LIMS may not be the right choice unless the LIMS can actually be used to manage raw data files that could be exported back to the original software. However, it may not even be necessary to be able to reprocess data to do trend analysis. All foreseeable scenarios for manipulating the data need to be considered in evaluating the risk of this solution. The risks and costs associated with validating or verifying the data migration also must be considered.

[7] A statistical method for verification of accuracy like AQL can be useful if the number of records is large.

6 Converting Electronic To Alternative Format/Media Hybrids

Under certain circumstances it may be acceptable to retain records in a format other than electronic (paper, microfilm/microfiche, etc.), or in an alternative "standard" electronic format like PDF[8], depending on the manner the record will be used. If a company uses a record in electronic format to support regulated activities or decisions, it cannot arbitrarily designate a printed copy as the official record. However, if the employees actually reference only the paper copy, it may be acceptable to retain the record on paper, and in this case, the electronic record should be deleted.

All possible scenarios should be considered. For drug product distribution records, for example, the speed of response is critical. The ability to search and access distribution records quickly is best suited to a computerized system, so it may be decided that distribution records are not well suited for immediate conversion to paper. The risk would be substantially lower, however, after the expiration of a lot of drug product, so conversion to paper at that point might be justified.

6.1 When Conversion Might Be Considered

The primary driver for any decision to convert records to other formats should be business need. Some of the logical points for considering such a move include:

- Creation of the record
- The point at which a record is to be archived
- At system upgrade, especially if data conversion is otherwise necessary
- At system retirement, especially if data conversion or development of rendering software is otherwise necessary
- The point at which a media refresh is necessary

6.2 Changing Repositories without Altering Format

Although the risks are lower, there are some risks associated with moving records from one repository to another, as is usually the case for simple archiving. Such risks might include media degradation, accidental loss, failure to retain software capable of viewing the records, etc.

[8] While PDF is an electronic format, and does offer some possibility to manage records using audit trails and digital signature, it is considered an alternative format because conversion to PDF generally sacrifices the ability to process the data. However, PDF carries the advantage of being able to execute some limited searches within documents, and depending on how the files are stored, also may offer searchability on the documents themselves. This should be considered when selecting to what format to convert records. PDF is editable with certain software, so controls should be in place relative to this.

6.3 Risk Assessment for Conversion

Decisions to convert records to an alternative media, format, or repository should be justified with a risk assessment showing no unacceptable risk to data integrity, product quality, and patient safety. However, the risk assessment process should be made as facile as possible by doing the assessment on groups of related records. For a small to moderate sized system, it is even conceivable that all of the records produced by a system could be assessed as a single group (e.g., a chromatography data system). However, large complex systems like ERP will clearly have several such groups of records that should be evaluated independently.

The approach to this risk assessment should be multi-tiered. First, it must be determined what the overall impact of the record is according to the scheme discussed in Section 2.1.3 of this Guide. For low and medium impact records the approach to archiving (i.e., transferring records to different media while retaining the original architecture of the record) should simply follow good IT practices. For archiving of high-impact records, risks such as those in Table 2 should be evaluated.

When considering conversion of regulated records to another format, risks such as those presented in Table 1 should be considered for high impact records. Companies should determine the degree to which this approach should be applied to medium impact records.

These assessments should consider the manner in which the data is accessed and used. Whilst the “potential effects” noted in Table 1 and Table 2 are generic, firms would have to consider them in the context of each unique set of records. For example, if accuracy and completeness of records in a drug safety database could be compromised by conversion, and the converted record could then be interpreted incorrectly, there could be significant risk to patient safety based on erroneous clinical study conclusions. The same occurrence to records in a training database would clearly have a much less immediate and severe impact.

Table 1: Risk Factors for Conversion of Electronic Records to an Alternative Format

Risk Factor	Considerations	Potential Effects	
Conversion may change the accuracy and completeness of the record in a manner that would effect the interpretation of the data	If the converted record is considered the “raw” data, the possibility of changing the interpretation of the data would be unacceptable.	Interpretation of the converted record leads to a different conclusion than before conversion	
Users may have to execute a rapid search of the data across records	If rapid retrieval is necessary, .e.g., to support a product recall, conversion may be ill-advised since cross-record searching is far easier using database technology.	Unable to rapidly search	Inadequate/incomplete searches
Users may have to execute large or frequent searches on the records	Frequent or large searches introduce increased probability that the searches will be incomplete.	Spend inordinate resources on searches or unable to execute search	Inadequate/incomplete searches
Users may have to search the records based on a wide range of keys	Most filing systems for non-electronic records have limited searchable keys.	Spend inordinate resources on searches	Inadequate/incomplete searches
Retention of original record after conversion to an alternative format	Why retain the original? How will it be kept consistent with the master copy?	Inconsistency of records	“Master copy” inaccurate
After being committed to its new format, the original electronic record is modifiable	Changes may become unsynchronized and confusion as to which is correct may result.	E-record used as master instead	Record integrity becomes questionable
Record may be used in electronic format to support GxP-regulated activities or decisions?	Use of the original electronic record to support GxP-regulated activities/decisions may preclude a claim that the alternative format record is the master copy.	Originating system may need to comply with additional regulations (e.g., 21 CFR Part 11)	
Record may have to be modified after it is committed to alternative format	Changes may be harder to execute and to track in the alternative format.	Audit trail inadequate	Paper audit trail may be required (possible regulatory exposure)

Table 1: Risk Factors for Conversion of Electronic Records to an Alternative Format (continued)

Risk Factor	Considerations	Potential Effects	
Employees who need it do not have ready access to the record in the new format in order to carry out their job responsibilities	If they are expected to use the alternative format record, it needs to be accessible. This can be problematic due to geographic or technical factors (e.g., a reader needed for microfilm/microfiche).	Inefficiency	Actions taken based on insufficient data
Employees who need the record have easier access to the original electronic record than official copy	People do what it easiest.	E-record is de facto master	Regulators will expect ERS compliance in the originating system.
An audit trail needs to be retained as part of the record in the alternative format	Is the record history retained in the audit trail critical to the value of the record? Is the audit trail integral to data integrity? Is an audit trail required by GxP regulation? An audit trail in an alternative format may double (or worse) the size of each record.	Audit trail inadequately shows subsequent changes, with the result that data integrity may be considered compromised by regulators	Size of archive may become unwieldy if audit trail retention is handled ineffectively
A signature is associated with the record	Is the alternative format adequate evidence of authenticity? Is the link between signature and record preserved?	Hybrid manifestation of e-sig loses legal meaning/ weight	Linkage of record with signature is broken

Table 2: Risk Factors for Transfer of Electronic Records to Alternative Media (Archiving)

Risk Factor	Considerations	Potential Effects	
Users may have to execute a rapid search of the data across records	If rapid retrieval is necessary, .e.g., to support a product recall, search capabilities on the new media may be limited and restoration of the records to a searchable platform may cause delay	Unable to rapidly search	
Users may have to execute large, complex, or frequent searches	Search capabilities on the new media may be limited. Frequent restoration of archived data would be resource-intensive and expensive.	Spend inordinate resources on searches	
Retention of original record after conversion to an alternative media	Why retain the original? How will it be kept consistent with the master copy?	Inconsistency of records	
Record may have to be modified after it is committed to alternative media	Changes may be harder to execute and to track on the new media.	Required changes not executed or not executed in a timely fashion	Audit trail inadequate
An audit trail needs to be retained as part of the record	Is the record history retained in the audit trail critical to the value of the record? Is the audit trail integral to data integrity? Is an audit trail required by GxP regulation? Depending on architecture of the audit trail, changes after commitment to different media may multiply record size several-fold.	Size of archive may become unwieldy if audit trail retention is handled ineffectively	

Based on the identification of risk factors such as those in Table 1 and Table 2, the *GAMP 4* risk assessment methodology can be applied. The first step is to identify potential effects for the risk factors, such as those shown in the two right-hand columns of these tables. For each possible effect the *GAMP 4* methodology relates likelihood of occurrence to the severity of harm then takes that result and relates it to the probability of detection of a fault.

The traditional application of the *GAMP 4* model to risk assessment is for the purpose of validation planning, and is geared toward system failure. Using the model to assess risk to record integrity, probability of detection is a little more complex. This is because of the additional mode of 'loss of record integrity' which involves alteration or deletion of the record through knowledgeable human actions. These will inevitably be harder to detect through electronic means; indeed, this is a major principle by which the need for an audit trail should be judged. Hence, in many cases one of the identified hazards related to a record should be undetectable change by normal means. Clearly, if a system has an audit trail or checksum verification built in, detectability will be high; if detectability is dependent upon human observation, it will be low. See Appendix 8 for a detailed discussion of the *GAMP 4* risk assessment methodology.

7 Examples of Application of *GAMP 4* Risk Assessment To Records Management

The following examples describe a variety of risk management scenarios related to record retention, covering such issues as:

- Risk related to deciding what data should actually be retained as records
- Risk related converting records from processible to non-processible format
- Age-dependent risk

Example 1: Raw Data from a GLP Environmental Monitor to Be Retained only as Processed Hourly Average and Alarm Records

This case presupposes a new system collecting temperature and humidity data with a high frequency (e.g., every 5 seconds). The system has a validated alarm function for reporting excursions. Only the system can write to the data files, which are accumulated in a logically protected directory.

The GxP regulations only offer an expectation that monitoring be in place. The practice before installing the new system was to report hourly averages based on a continuous analog chart recorder, with the charts retained as evidence of control. However, in the new system there is no compelling driver for retaining anything beyond the hourly averages and the excursion alarm history, since these give an adequate description of the environmental conditions and the controls on them. Because the data is secure and there are validated safeguards ensuring that excursions are recorded and acknowledged, there are reasonable controls in place to warrant a strategy of discarding the detailed raw data and retaining only the processed hourly averages and the alarm history as the GxP record. (See Table 3 for details of the risk assessment.)

Example 2: A Database Containing the Results of a Recently Completed Clinical Study

Each of the effects is assessed using the grids in Appendix 8 in reference to the proposed new format. One of the possible risks is undetectable change, as the proposed new record format is not supported by an audit trail. In this case there is a reasonable probability that some of the data may need to be altered, and it is possible that further manipulation of the data may be required prior to significant decisions which have regulatory impact. Without the audit trail functionality, detectability will be an issue, and when the GAMP risk assessment methodology is applied most of the risk priorities turn out medium to high, which indicates this database is not a good candidate for conversion. (See Table 4 for details of the risk assessment.)

Example 3: The Same Clinical Study Database System Ten Years Later

In this case a software upgrade forces us to consider whether we wish to spend considerable resources migrating this data. While the data is still useful, and may in fact have been used to support a recent application for a new therapeutic indication, the data has essentially been static for a considerable period.

There is no foreseeable need to search or manipulate the data through its native application, although it still retains business value; the statistical analysis data sets would be used to answer any additional regulatory queries that might arise from the recent application. Applying the same risk assessment shows that the risk level for conversion to paper/non-electronic format has dropped substantially, with all risk priority values coming out low-medium, making the case that conversion to paper or PDF from the clinical database at this point is reasonable (see Table 5 for details of the risk assessment.)

Example 4: Distribution Records Considered for Conversion to "Official" Paper, Deleting Original e-Record

The key risk factors associated with retaining distribution records only on paper is the searchability factor. In case of product recall, speed may be essential to protecting public health; a dangerous product must be removed from the market quickly, and the danger with converting such records to paper involves inefficiency of the search process. It is possible that the search might yield incomplete results, or that obtaining complete and reliable results would take too long. (See Table 6 for details of the risk assessment.)

Example 5: Distribution Records Considered for Conversion to "Official" Paper, Maintaining Original e-Record

Inconsistency would be a problem inherent in this approach. Every change to a record would have to be made in two places, a process bound to fail at some point. The proposition that the paper copy is official would be difficult to argue with a regulator as well, since the electronic record would be maintained to meet an important GMP requirement. (See Table 7 for details of the risk assessment.) Neither of the previous two approaches for managing distribution records can be supported based on these risk analyses.

Examples 2 and 3 show how judgments and factors affecting a decision to convert regulated records to a different format can change as the record advances through its life cycle. No specific defined value or cut-off point for a go/no go decision can be predefined in the context of this risk assessment process because many other variables, especially the nature of the product and risk to patient safety, and a company's risk tolerance, must be considered.

Example 1, on the other hand, shows a case where conversion is very safe from the start, while 4 and 5 demonstrate a type of record where conversion appears to be a poor idea laced with high assumed risks. Firms will have to decide for themselves exactly how much medium to high risks they can tolerate. Such decisions must account for a number of factors including regulatory compliance, cost, staffing, etc.

Note also that even in the context of a decision whether to convert records based on a risk assessment, one individual factor may be so important, that despite a favorable risk assessment it may be decided not to convert the data. A risk assessment tool provides objective criteria to support such decisions, but in specific cases there may be over-riding considerations unique to the circumstances. If a particular e-records management decision seems fundamentally unwise, it probably is.

Reading these tables: These tables summarize application of the *GAMP 4* risk assessment methodology to issues related to record retention, archiving, and conversion. For each risk factor there is one likelihood of occurrence. Two possible effects are evaluated for each risk factor. This is not to imply that there will always be exactly two possible effects. For each effect there is a severity of impact, and from these two values is derived the risk level. Risk level then is plotted against the probability of detection to give the final risk priority values. Not all risk factors from Table 1 and Table 2 appear in these examples, and others could apply. These must be derived based on business practice and regulatory requirements.

Table 3: Raw Data from a GLP Environmental Monitoring Device

Raw Data from Environmental Monitor to be Retained only as Processed Hourly Average and Alarm Records									
		Effect 1 Assessment				Effect 2 Assessment			
Risk Factor	**Likelihood**	**Effect**	**Impact**	**Det.**	**Risk 1 Priority**	**Effect**	**Impact**	**Det.**	**Risk 2 Priority**
Need to execute a rapid search of the data?	**L**	Unable to perform rapid search	**L**	**H**	**L**	Weak response to GLP emergency	**L**	**H**	**L**
Need to execute large or frequent searches on your records?	**L**	Unable to perform large searches	**L**	**H**	**L**	Search doesn't find all records	**L**	**H**	**L**
Need to search your records based on a wide range of keys?	**L**	Unable to execute sophisticated searches	**L**	**H**	**L**	Manual intervention	**L**	**H**	**L**
Managing change: only *e*-rec changed after alternative declared "master"	**L**	Inconsistency of records	**M**	**H**	**L**	Inadequate data for GLP decision	**M**	**H**	**L**
Managing change: Primary e-record is master, alternative copy also saved	**L**	Inconsistency of records	**M**	**H**	**L**	Master copy becomes corrupt	**M**	**H**	**L**
Managing change: Record will have to be modified after it is converted	**L**	Audit trail for changes after conversion lost	**L**	**H**	**L**	Compliance compromised	**M**	**H**	**L**
Managing change: Audit trail is required by predicate rule	**L**	Audit trail inadequate	**L**	**H**	**L**	Audit trail data difficult to evaluate	**L**	**H**	**L**
Employees don't have convenient access to alternative format records	**L**	Inefficiency	**L**	**H**	**L**	Actions based on insufficient data	**L**	**H**	**L**
Employees have access to record in its original electronic form	**L**	E-record used as master	**L**	**H**	**L**	Compliance compromised	**L**	**H**	**L**

Table 4: Risk Assessment for a Recently Populated Clinical Database

Clinical Study Database for a New Drug Entity										
		Effect 1 Assessment				Effect 2 Assessment				
Risk Factor	**Likelihood**	**Effect**	**Impact**	**Det.**	**Risk 1 Priority**	**Effect**	**Impact**	**Det.**	**Risk 2 Priority**
Need to execute a rapid search of the data?	**H**	Unable to perform rapid search	**M**	**H**	**M**	Weak response to GCP emergency	**H**	**H**	**M**
Need to execute large or frequent searches on your records?	**H**	Unable to perform large searches	**H**	**H**	**M**	Search doesn't find all records	**H**	**L**	**H**
Need to search your records based on a wide range of keys?	**H**	Unable to execute sophisticated searches	**H**	**H**	**M**	Manual intervention	**L**	**H**	**L**
Managing change: only *e*-rec changed after alternative declared "master"	**M**	Inconsistency of records	**M**	**L**	**H**	Inadequate data for GCP decision	**H**	**L**	**H**
Managing change: Primary e-record is master, alternative copy also saved	**L**	Inconsistency of records	**M**	**L**	**M**	Master copy becomes corrupt	**H**	**L**	**H**
Managing change: Record will have to be modified after it is converted	**L**	Audit trail for changes after conversion lost	**M**	**L**	**M**	Compliance compromised	**M**	**L**	**M**
Managing change: Audit trail is required by predicate rule	**H**	Audit trail inadequate	**M**	**L**	**H**	Audit trail data difficult to evaluate	**L**	**L**	**H**
Employees don't have convenient access to alternative format records	**L**	Inefficiency	**L**	**L**	**M**	Actions based on insufficient data	**H**	**L**	**H**
Employees have access to record in its original electronic form	**L**	E-record used as master	**M**	**L**	**M**	Compliance compromised	**M**	**L**	**M**

Table 5: Risk Assessment for an Old Clinical Database

10-Year-Old Clinical Study Database for a Drug Entity									
		Effect 1 Assessment				Effect 2 Assessment			
Risk Factor	**Likelihood**	**Effect**	**Impact**	**Det.**	**Risk 1 Priority**	**Effect**	**Impact**	**Det.**	**Risk 2 Priority**
Need to execute a rapid search of the data?	**L**	Unable to perform rapid search	**L**	**H**	**L**	Weak response to GCP emergency	**L**	**H**	**L**
Need to execute large or frequent searches on your records?	**L**	Unable to perform large searches	**M**	**H**	**L**	Search doesn't find all records	**L**	**M**	**L**
Need to search your records based on a wide range of keys?	**M**	Unable to execute sophisticated searches	**M**	**H**	**L**	Manual intervention	**L**	**H**	**L**
Managing change: only e-rec changed after alternative declared "master"	**L**	Inconsistency of records	**M**	**L**	**M**	Inadequate data for GCP decision	**L**	**M**	**L**
Managing change: Primary e-record is master, alternative copy also saved	**L**	Inconsistency of records	**M**	**L**	**M**	Master copy becomes corrupt	**L**	**H**	**L**
Managing change: Record will have to be modified after it is converted	**L**	Audit trail for changes after conversion lost	**M**	**L**	**M**	Compliance compromised	**L**	**M**	**L**
Managing change: Audit trail is required by predicate rule	**H**	Audit trail inadequate	**M**	**L**	**H**	Audit trail data difficult to evaluate	**L**	**M**	**M**
Employees don't have convenient access to alternative format records	**L**	Inefficiency	**L**	**L**	**M**	Actions based on insufficient data	**L**	**M**	**L**
Employees have access to record in its original electronic form	**L**	E-record used as master	**L**	**L**	**M**	Compliance compromised	**L**	**H**	**L**

Table 6: Distribution Records, Deleting Original

Distribution Records Considered for Conversion to "Official" Paper, Deleting Original e-Record									
		Effect 1 Assessment				Effect 2 Assessment			
Risk Factor	**Likelihood**	**Effect**	**Impact**	**Det.**	**Risk 1 Priority**	**Effect**	**Impact**	**Det.**	**Risk 2 Priority**
Need to execute a rapid search of the data?	**M**	Unable to perform rapid search	**H**	**M**	**H**	Weak response to GMP emergency	**H**	**M**	**H**
Need to execute large or frequent searches on your records?	**H**	Unable to perform large searches	**H**	**H**	**M**	Search doesn't find all records	**H**	**L**	**H**
Need to search your records based on a wide range of keys?	**H**	Unable to execute sophisticated searches	**H**	**M**	**H**	Manual intervention	**M**	**H**	**M**
Managing change: only *e*-rec changed after alternative declared "master"	**L**	Inconsistency of records	**L**	**L**	**M**	Inadequate data for GMP decision	**H**	**L**	**H**
Managing change: Primary e-record is master, alternative copy also saved	**L**	Inconsistency of records	**L**	**L**	**M**	Master copy becomes corrupt	**L**	**M**	**L**
Managing change: Record will have to be modified after it is converted	**M**	Audit trail for changes after conversion lost	**L**	**L**	**M**	Compliance compromised	**M**	**L**	**H**
Managing change: Audit trail is required by predicate rule	**L**	Audit trail inadequate	**L**	**M**	**L**	Audit trail data difficult to evaluate	**L**	**L**	**M**
Employees don't have convenient access to alternative format records	**L**	Inefficiency	**L**	**H**	**L**	Actions based on insufficient data	**L**	**H**	**L**
Employees have access to record in its original electronic form	**L**	E-record used as master	**L**	**H**	**L**	Compliance compromised	**L**	**H**	**L**

Table 7: Distribution Records, Retaining Original

Distribution Records Considered for Conversion to "Official" Paper, Retaining Original e-Record									
		Effect 1 Assessment				**Effect 2 Assessment**			
Risk Factor	**Likelihood**	**Effect**	**Impact**	**Det.**	**Risk 1 Priority**	**Effect**	**Impact**	**Det.**	**Risk 2 Priority**
Need to execute a rapid search of the data?	**M**	Unable to perform rapid search	**L**	**M**	**L**	Weak response to GMP emergency	**M**	**M**	**M**
Need to execute large or frequent searches on your records?	**H**	Unable to perform large searches	**L**	**H**	**L**	Search doesn't find all records	**L**	**L**	**H**
Need to search your records based on a wide range of keys?	**H**	Unable to execute sophisticated searches	**L**	**M**	**M**	Manual intervention	**L**	**H**	**L**
Managing change: only e-rec changed after alternative declared "master"	**M**	Inconsistency of records	**H**	**L**	**H**	Inadequate data for GMP decision	**H**	**L**	**H**
Managing change: Primary e-record is master, alternative copy also saved	**M**	Inconsistency of records	**H**	**L**	**H**	Master copy becomes corrupt	**H**	**M**	**H**
Managing change: Record will have to be modified after it is converted	**M**	Audit trail for changes after conversion lost	**L**	**L**	**M**	Compliance compromised	**M**	**L**	**H**
Managing change: Audit trail is required by predicate rule	**L**	Audit trail inadequate	**L**	**M**	**L**	Audit trail data difficult to evaluate	**L**	**L**	**M**
Employees don't have convenient access to alternative format records	**M**	Inefficiency	**M**	**M**	**M**	Actions based on insufficient data	**M**	**M**	**M**
Employees have access to record in its original electronic form	**M**	E-record used as master	**M**	**L**	**H**	Compliance compromised	**M**	**L**	**H**

Appendix 4
Copies of Records

1 Introduction

Regulated companies should provide an investigator with reasonable and useful access to records during an inspection. All records held in whatever form are subject to inspection as specified by the applicable GxP regulations.

Regulated companies should supply copies of electronic records by:

- Producing copies of records held in common portable formats when records are maintained in these formats
- Using established automated conversion or export methods, where available, to make copies in a more common format such as, but not limited to, PDF, XML, or SGML

The company should ensure that the copying process used produces copies that preserve the content and meaning of the record. Regulators should be informed that ad-hoc query processes are not as robust as validated processes.

If the company has the ability to search, sort, or trend electronic regulated records, then copies given to regulators should provide the same capability if it is reasonable and technically feasible. If this is not possible or reasonable, the company should be able and willing to explain why.

Companies should allow inspection, review, and copying of records in a human readable form at their site using their hardware and following established procedures and techniques for accessing records (i.e., under the company's control). It is therefore recommended that a general procedure on provision of electronic copies of records to regulators be established (this could be an addendum to existing procedures for providing paper copies).

For an example of a GxP regulation requirement for Copies of Records, see Appendix 6, 21 CFR Part 58, §58.195 (g).

Case studies which consider the copying of records and the provision of records to regulatory authorities are given in Appendix 7.

2 Risks to Records

When making copies of records available to regulators, the regulated company should consider the following aspects:

- Confidentiality
- Authenticity features
- Links

- Calculations and macros
- Proprietary software

These are discussed in the following sections. To overcome some of the potential issues listed below, companies should consider supplying regulated records in common portable formats such as PDF wherever possible. Alternatively, well established formats such as ASCII may be considered.

2.1 Confidentiality

When giving paper records to a regulator these may be stamped as CONFIDENTIAL if the material included in these records is not to be disclosed. For electronic records given to regulators, specific arrangements may need to be made. For example, the FDA has to ensure that such records are not publicly available. (§20.44 – Pre-submission review of request for confidentiality of voluntarily submitted data or information.)

If confidentiality is a major concern then data transmitted to regulators may be encrypted, to flag that a record is confidential. The message header should state the confidentiality status of the transmitted data. If encryption tools are not available the information should be given in paper format, or alternative arrangements must be agreed.

2.2 Records Containing Authenticity Features

Some records may be inspected at the manufacturer site. Readability in the original format might be only possible while the records are kept in the native environment. Records may contain security features that prevent or hinder reading the content if not in the native environment.

2.3 Records Containing Links

Records such as documents or spreadsheets might contain links or embedded files which will not be visible or fail if the document is read outside its original location or environment.

2.4 Calculations, Macros or Other Functions

Records containing calculation, trending, or sorting capabilities require the use of procedures and training. If such records are given to a regulator, they may need to follow the same procedures and training depending on their use of the data. In addition, if the regulator finds a discrepancy in the results, the regulator should contact the pharmaceutical company and follow its discrepancy procedure.

2.5 Proprietary Software

Licensing agreements should be considered in cases where records that need proprietary software for their review are supplied to regulators.

Appendix 5
21 CFR Part 11 Legacy Systems

1 Introduction

In the FDA Guidance on Scope and Application of 21 CFR Part 11 (Appendix 13, reference 3), the term legacy system refers to those systems which were operational before 20 August 1997, the effective date of 21 CFR Part 11.

This Appendix applies to systems exclusively supporting the US market. Systems that support other markets should meet the respective regulations of those markets.

2 Principle

Any systems used by regulated companies for the generation, maintenance, or submission of regulated records that have an impact on product quality or patient safety, should comply with all applicable predicate rules. The regulated company should have documented evidence that the system meets these requirements.

In the Guidance on Scope and Application the agency stated that it intends to exercise enforcement discretion with regard to all 21 CFR Part 11 requirements for systems that were operational before the effective date of 21 CFR Part 11 (also known as legacy systems).

For such systems, the company should make a documented judgment on the need for remediation, based on the following criteria:

- Is there documented evidence and justification that the system meets all applicable predicate rule requirements?
- Is there documented evidence and justification that the system has an acceptable level of record security and integrity?
- Have any modifications been made since implementation that may have caused additional risks that warrant application of 21 CFR Part 11 controls?

3 Legacy Records

Records contained within these legacy systems, regardless of the date of creation, transmission, modification etc, should be considered acceptable for regulatory use once predicate rules have been met and their integrity and security are maintained according to predicate rule requirements (e.g.: ensuring that any copies are true copies as required by 21 CFR Part 58, §58.195 (g)). This would be achieved through the application of the relevant operational controls, including security management, backup controls and a procedure describing the production and verification of copies that preserve content and meaning.

4 Management of 21 CFR Part 11 Legacy Systems

This section describes a structured approach to managing changes to operational systems in a consistent manner. The approach focuses on the potential risk to record security and integrity posed by the modifications.

A legacy system may use hybrid controls, especially for handling signatures. A typical hybrid situation is a system where the electronic records are presented for approval as printed reports requiring handwritten signatures. The application of a signature by a suitably qualified individual implicitly establishes the integrity of the records presented in the report. A procedure should define the process of creation, review and approval of the paper record and the relationship between the electronic and paper records.

For legacy systems the focus of activity should be to implement procedural controls and to consider introduction of suitable technical controls as technology permits, based upon risk. Improved technical controls can be applied to systems incrementally under change control. Examples of suitable technical controls are improved security management and access controls applied through application and configuration of the underlying operating system controls.

The net effect of these remedial actions at a minimum should be to ensure these systems are in compliance with the predicate rules and have an acceptable level of record security and integrity.

Table 1: Managing Changes to Operational Systems

Nature of Change	Change Strategy
Minor change, example, version upgrade with minor enhancements to functionality and patches for bugs, configuration change, changes to improve 21 CFR Part 11 compliance such as introduction of an audit trail.	Compliance with the predicate rules is mandatory. Procedural controls to ensure an acceptable level of record security and integrity should be operational.
Upgrade to infrastructure, e.g., operating system or network.	As above. Consider also whether changes to the infrastructure could impact the application.
No change, example a bio reactor control system which has had no code change since 1985.	Compliance with the predicate rules is mandatory. Procedural controls to ensure an acceptable level of record security and integrity should be operational.
New release of existing installed application where the release introduces significant extra functionality.	Compliance with the predicate rules is mandatory. Assess potential risk to record security and integrity. Demonstrate compliance by validating the application including the 21 CFR Part 11 requirements (for records to be maintained or submitted to the agency). If the new release is not fully 21 CFR Part 11 compliant, assess the risk of non-compliance with 21 CFR Part 11 of the relevant records and implement mitigation strategies (alternative technical controls or otherwise procedural controls). Validate those controls.
First installation (within an organization) of an application which is not technically 21 CFR Part 11 compliant (but it is the only solution available in the market).	1. Do install it and meet predicate rule requirements. Assess risk to product quality or patient safety of not having the system at all. If risk is reduced by having it even if it is non-compliant, then the overall position is improved. In this case sufficient controls should be immediately introduced to ensure compliance with predicate rules. 2. Don't install it because it is not compliant.
The use of the system has changed to bring it within the scope of 21 CFR Part 11.	Assess risk to product quality or patient safety of not having the system at all. If risk is reduced by having it even if it is non-compliant, then the overall position is improved. In this case sufficient controls should be immediately introduced to ensure compliance with predicate rules.

Appendix 6
Examples of Records and Signatures Required by GxP Regulations

This Appendix contains examples of records and signatures required by various US and EU regulations, and by ICH Q7A. It is not, however, intended to be a complete review of all GxP regulations. The material provided in this Appendix has been supplied by various GAMP steering committees and individuals worldwide, using different approaches. While every effort has been made to ensure accuracy at time of publication, neither ISPE nor the GAMP Forum can be held responsible for any errors or omissions in the text. **In no event shall ISPE or any of its affiliates (including the GAMP Forum), or the officers, directors, employees, members, or agents of each of them, be liable for any damages of any kind, including without limitation any special, incidental, indirect, or consequential damages, whether or not advised of the possibility of such damages, and on any theory of liability whatsoever, arising out of or in connection with the use of this information.** Readers are strongly recommended to refer to current regulations when reviewing and deciding on policies, procedures, and processes.

This Appendix is divided into three Sections:

1 Examples from US Regulations

1.1 Examples from US Regulations CFR Parts 50, 54, 56, 58, 211, 312, 314

1.1.1 Electronic Records

Good Laboratory Practice (GLP)
Code of Federal Regulations, Part 58

58.3 Definitions.

58.3(k) **Raw data** means any **laboratory worksheets, records, memoranda, notes, or exact copies** thereof, that are the result of original observations and activities of a nonclinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study. In the event that exact transcripts of raw data have been prepared (e.g., tapes which have been transcribed verbatim, dated, and verified accurate by signature), **the exact copy or exact transcript** may be substituted for the original source as raw data. Raw data may include **photographs, microfilm or microfiche copies, computer printouts, magnetic media, including dictated observations, and recorded data from automated instruments**.

58.29 Personnel.

58.29(b) Each testing facility shall maintain a current **summary of training** and **experience** and **job description** for each individual engaged in or supervising the conduct of a nonclinical laboratory study.

58.31 Testing facility management.

58.31(g) For each nonclinical laboratory study, testing facility management shall assure that any **deviations from these regulations** reported by the quality assurance unit are communicated to the study director and corrective actions are taken and documented.

58.33 Study Director.

The study director shall assure that:

58.33(a) The **protocol**, including any **change**, is approved as provided by Sec. 58.120 and is followed.

58.33(b) All **experimental data**, including observations of unanticipated responses of the test system are accurately recorded and verified.

58.33(c) **Unforeseen circumstances** that may affect the quality and integrity of the nonclinical laboratory study are noted when they occur, and **corrective action** is taken and documented.

58.35 Quality assurance unit.

58.35(b) The quality assurance unit shall:

58.35(b)(1) Maintain a **copy of a master schedule sheet** of all nonclinical laboratory studies conducted at the testing facility **indexed by test article** and containing the **test system, nature of study, date study was initiated, current status of each study, identity of the sponsor, and name of study director**.

58.35(b)(2) Maintain copies of all **protocols** pertaining to all nonclinical laboratory studies for which the unit is responsible.

58.35(b)(3) Inspect each nonclinical laboratory study at intervals adequate to assure the integrity of the study and maintain written and properly signed records of each **periodic inspection** showing the **date of the inspection, the study inspecetd, the phase or segment of the study inspected, the person performing the inspection, findings and problems, action recommended and taken to resolve existing problems, and any scheduled date of reinspection**. Any problems found during the course of an inspection which are likely to affect study integrity shall be brought to the attention of the study director and management immediately.

58.35(b)(4) Periodically submit to management and the study director **written status reports** on each study, **noting any problems and the corrective actions taken**.

58.35(b)(5) Determine that no **deviations from approved protocols or standard operating procedures** were made without proper authorization and **documentation**.

58.35(b)(7) Prepare and sign a **statement** to be included with the **final study report** which shall specify the **dates inspections were made and findings** reported to management and to the study director.

58.35(c) The **responsibilities and procedures applicable to the quality assurance unit**, **the records maintained by the quality assurance unit, and the method of indexing such records** shall be in writing and shall be maintained. These items including **inspection dates, the study inspected, the phase or segment of the study inspected, and the name of the individual performing the inspection** shall be made available for inspection to authorized employees of the Food and Drug Administration.

58.63 Maintenance and calibration of equipment.

58.63(b) The written **standard operating procedures** required under Sec. 58.81 (b) (11) shall set forth in sufficient detail the **methods, materials, and schedules** to be used in the routine inspection, cleaning, maintenance, testing, calibration, and/or standardization of equipment, and shall specify, when appropriate, **remedial action to be taken in the event of failure or malfunction of equipment**. The written standard operating procedures shall designate the **person responsible for the performance of each operation**.

58.63(c) Written **records shall be maintained of all inspection, maintenance, testing, calibrating, and/or standardizing operations**. These records, containing the **date of the operation**, shall **describe whether the maintenance operations were routine and followed the written standard operating procedures**. Written **records shall be kept of nonroutine repairs** performed on equipment as a result of failure and malfunction. Such records shall document the **nature of the defect, how and when the defect was discovered, and any remedial action taken in response to the defect**.

58.81 Standard operating procedures.

58.81(a) A testing facility shall have **standard operating procedures** in writing setting forth nonclinical laboratory study methods that management is satisfied are adequate to insure the quality and integrity of the data generated in the course of a study. All **deviations in a study from standard operating procedures** shall be authorized by the study director and shall be documented in the raw data. **Significant changes in established standard operating procedures** shall be properly authorized in writing by management.

58.81(b) **Standard operating procedures** shall be established for, but not limited to, the following:

(1) **Animal room preparation.**

(2) **Animal care.**

(3) **Receipt, identification, storage, handling, mixing, and method of sampling of the test and control articles.**

(4) **Test system observations**.

(5) **Laboratory tests.**

(6) **Handling of animals found moribund or dead during study.**

(7) **Necropsy of animals or postmortem of animals.**

(8) **Collection and identification of specimens.**

(9) **Histopathology.**

(10) **Data handling, storage, and retrieval.**

(11) **Maintenance and calibration of equipment.**

(12) **Transfer, proper placement, and identification of animals.**

58.81(c) Each laboratory area shall have immediately available **laboratory manuals** and **standard operating procedures relative to the laboratory procedures being performed**. Published literature may be used as a supplement to standard operating procedures.

58.81(d) A historical file **of standard operating procedures**, and all revisions thereof, including the **dates of such revisions**, shall be maintained.

58.83 Reagents and solutions.

All reagents and solutions in the laboratory areas shall be **labeled** to indicate **identity, titer or concentration, storage requirements, and expiration date**. Deteriorated or outdated reagents and solutions shall not be used.

58.90 Animal care.

58.90(a) There shall be **standard operating procedures for the housing, feeding, handling, and care of animals**.

58.90(c) At the initiation of a nonclinical laboratory study, animals shall be free of any disease or condition that might interfere with the purpose or conduct of the study. If, during the course of the study, the animals contract such a disease or condition, the diseased animals shall be isolated, if necessary. These animals may be treated for disease or signs of disease provided that such treatment does not interfere with the study. The **diagnosis, authorizations of treatment, description of treatment, and each date of treatment** shall be documented and shall be retained.

58.90(d) Warm-blooded animals, excluding suckling rodents, used in laboratory procedures that require manipulations and observations over an extended period of time or in studies that require the animals to be removed from and returned to their home cages for any reason (e.g., cage cleaning, treatment, etc.), **shall receive appropriate identification**. **All information needed to specifically identify each animal within an animal-housing unit shall appear on the outside of that unit**.

58.90(g) Feed and water used for the animals shall be analyzed periodically to ensure that contaminants known to be capable of interfering with the study and reasonably expected to be present in such feed or water are not present at levels above those specified in the protocol. **Documentation of such analyses shall be maintained as raw data.**

58.90(i) If any **pest control materials are used, the use shall be documented**. Cleaning and pest control materials that interfere with the study shall not be used.

58.105 Test and control article characterization.

58.105(a) The **identity, strength, purity, and composition or other characteristics which will appropriately define the test or control article** shall be determined for each batch and shall be documented. **Methods of synthesis, fabrication, or derivation of the test and control articles shall be documented by the sponsor or the testing facility**. In those cases where **marketed products are used as control articles, such products will be characterized by their labeling**.

58.105(b) The **stability** of each test or control article shall be determined by the testing facility or by the sponsor either: (1) Before study initiation, or (2) concomitantly according to **written standard operating procedures, which provide for periodic analysis of each batch.**

58.105(c) Each **storage container** for a test or control article shall be **labeled by name, chemical abstract number or code number, batch number, expiration date, if any, and, where appropriate, storage conditions** necessary to maintain the identity, strength, purity, and composition of the test or control article. Storage containers shall be assigned to a particular test article for the duration of the study.

58.107 Test and control articles handling.

Procedures shall be established for a system for the handling of the test and control articles to ensure that:

58.107(c) **Proper identification is maintained throughout the distribution process**.

58.107(d) The **receipt and distribution of each batch** is documented. Such documentation shall include the **date and quantity of each batch distributed or returned**.

58.113 Mixtures of articles with carriers.

58.113(a) For each test or control article that is mixed with a carrier, **tests by appropriate analytical methods shall be conducted**:

(1) To determine the **uniformity** of the mixture and to determine, periodically, the **concentration** of the test or control article in the mixture.

(2) To determine the **stability** of the test and control articles in the mixture as required by the conditions of the study either: (i) Before study initiation, or (ii) Concomitantly according to written standard operating procedures which provide for periodic analysis of the test and control articles in the mixture.

58.120 Protocol.

58.120(a) Each study shall have an approved written **protocol** that clearly indicates the **objectives and all methods for the conduct of the study**. The protocol shall contain, as applicable, the following information:

(1) A **descriptive title and statement of the purpose** of the study.

(2) **Identification of the test and control articles by name, chemical abstract number, or code number**.

(3) The **name of the sponsor and the name and address of the testing facility** at which the study is being conducted.

(4) The **number, body weight range, sex, source of supply, species, strain, and age of the test system**.

(5) The **procedure for identification of the test system**.

(6) A **description of the experimental design, including the methods for the control of bias**.

(7) A **description and/or identification of the diet** used in the study as well as **solvents, emulsifiers, and/or other materials used to solubilize or suspend the test or control articles before mixing with the carrier**. The description shall include **specifications for acceptable levels of contaminants** that are reasonably expected to be present in the dietary materials and are known to be capable of interfering with the purpose or conduct of the study if present at levels greater than established by the specifications.

(8) **Each dosage level, expressed in milligrams per kilogram of body weight or other appropriate units, of the test or control article to be administered and the method and frequency of administration**.

(9) The **type and frequency of tests, analyses, and measurements to be made**.

(10) The **records** to be maintained.

(11) The **date of approval of the protocol** by the sponsor and the **dated signature of the study director**.

(12) A **statement of the proposed statistical methods** to be used.

58.120(b) All **changes in or revisions of an approved protocol** and the reasons therefore shall be documented, **signed by the study director, dated**, and maintained with the protocol.

58.130 Conduct of a nonclinical laboratory study.

58.130(c) Specimens shall be **identified** by **test system, study, nature, and date of collection**. This information shall be located on the specimen container or shall accompany the specimen in a manner that precludes error in the recording and storage of data.

58.130(d) Records of **gross findings for a specimen from postmortem observations** should be available to a pathologist when examining that specimen histopathologically.

58.130(e) All data generated during the conduct of a nonclinical laboratory study, except those that are generated by automated data collection systems, shall be recorded directly, promptly, and legibly in ink. **All data entries shall be dated on the date of entry and signed or initialed by the person entering the data**. Any **change in entries** shall be made so as not to obscure the original entry, shall indicate the **reason for such change, and shall be dated and signed or identified at the time of the change**. In automated data collection systems, the **individual responsible for direct data input shall be identified** at the time of data input. **Any change** in automated data entries shall be made so as not to obscure the original entry, shall **indicate the reason for change, shall be dated, and the responsible individual shall be identified**.

58.185 Reporting of nonclinical laboratory study results.

58.185(a) A **final report** shall be prepared for each nonclinical laboratory study and shall include, but not necessarily be limited to, the following:

(1) **Name and address of the facility performing the study and the dates on which the study was initiated and completed**.

(2) **Objectives and procedures** stated in the approved protocol, including any changes in the original protocol.

(3) **Statistical methods employed** for analyzing the data.

(4) The **test and control articles identified by name, chemical abstracts number or code number, strength, purity, and composition or other appropriate characteristics**.

(5) **Stability** of the test and control articles under the conditions of administration.

(6) A **description of the methods** used.

(7) A **description of the test system used**. Where applicable, the final report shall include the **number of animals used, sex, body weight range, source of supply, species, strain and substrain, age, and procedure used for identification**.

(8) A **description of the dosage, dosage regimen, route of administration, and duration**.

(9) A **description of all circumstances that may have affected the quality or integrity of the data**.

(10) The **name of the study director, the names of other scientists or professionals, and the names of all supervisory personnel, involved in the study**.

(11) A **description of the transformations, calculations, or operations performed on the data, a summary and analysis of the data, and a statement of the conclusions drawn from the analysis**.

(12) The **signed and dated reports of each of the individual scientists or other professionals involved in the study**.

(13) The **locations where all specimens, raw data, and the final report are to be stored**.

(14) The **statement prepared and signed by the quality assurance unit** as described in Sec. 58.35(b)(7).

58.185(b) The **final report** shall be **signed and dated by the study director**.

58.185(c) **Corrections or additions** to a final report shall be in the form of an **amendment** by the study director. The amendment shall clearly **identify that part of the final report that is being added to or corrected and the reasons for the correction or addition, and shall be signed and dated by the person responsible**.

58.190 Storage and retrieval of records and data.

58.190(a) **All raw data, documentation, protocols, final reports, and specimens** (except those specimens obtained from mutagenicity tests and wet specimens of blood, urine, feces, and biological fluids) generated as a result of a nonclinical study **shall be retained**.

58.190(b) There shall be **archives for orderly storage and expedient retrieval of all raw data, documentation, protocols, specimens, and interim and final reports**. Conditions of storage shall minimize deterioration of the documents or specimens in accordance with the requirements for the time period of their retention and the nature of the documents or specimens. A testing facility may contract with commercial archives to provide a repository for all material to be retained. Raw data and specimens may be retained elsewhere provided that the **archives have specific reference to those other locations**.

58.190(e) Material retained or referred to in the archives shall be **indexed** to permit expedient retrieval.

58.195 Retention of records.

58.195(b) Except as provided in paragraph (c) of this section, documentation records, raw data and specimens pertaining to a nonclinical laboratory study and required to be made by this part shall be retained in the archive(s) for whichever of the following periods is shortest:

(1) A period of at least 2 years following the date on which an application for a research or marketing permit, in support of which the results of the nonclinical laboratory study were submitted, is approved by the Food and Drug Administration. This requirement does not apply to studies supporting investigational new drug applications (IND's) or applications for investigational device exemptions (IDE's), records of which shall be governed by the provisions of paragraph (b)(2) of this section.

(2) A period of at least 5 years following the date on which the results of the nonclinical laboratory study are submitted to the Food and Drug Administration in support of an application for a research or marketing permit.

(3) In other situations (e.g., where the nonclinical laboratory study does not result in the submission of the study in support of an application for a research or marketing permit), a period of at least 2 years following the date on which the study is completed, terminated, or discontinued.

58.195(d) The **master schedule sheet, copies of protocols, and records of quality assurance inspections**, as required by Sec. 58.35(c) shall be maintained by the quality assurance unit as an easily accessible system of records for the period of time specified in paragraphs (a) and (b) of this section.

58.195(e) Summaries of **training** and **experience** and **job descriptions** required to be maintained by Sec. 58.29(b) may be retained along with all other testing facility **employment records** for the length of time specified in paragraphs (a) and (b) of this section.

58.195(f) **Records and reports of the maintenance and calibration and inspection of equipment**, as required by Sec. 58.63(b) and (c), shall be retained for the length of time specified in paragraph (b) of this section.

58.195(g) **Records required by this part may be retained either as original records or as true copies such as photocopies, microfilm, microfiche**, or other accurate reproductions of the original records.

58.195(h) If a facility conducting nonclinical testing goes out of business, all **raw data, documentation, and other material specified in this section shall be transferred to the archives of the sponsor** of the study. The **Food and Drug Administration shall be notified in writing of such a transfer**.

Good Clinical Practice (GCP)
Code of Federal Regulations, Parts 50, 56, 312, 314
Part 50 Consent

50.3 Definitions.

50.3 (b) Application for research or marketing permit includes:

(1) A **color additive petition**, described in part 71.

(2) A **food additive petition**, described in parts 171 and 571.

(3) **Data and information about a substance** submitted as part of the procedures for establishing that the substance is generally recognized as safe for use that results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in Secs. 170.30 and 570.30.

(4) **Data and information about a food additive** submitted as part of the procedures for food additives permitted to be used on an interim basis pending additional study, described in Sec. 180.1.

(5) **Data and information about a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials**, described in section 406 of the act.

(6) An **investigational new drug application**, described in part 312 of this chapter.

(7) A **new drug application**, described in part 314.

(8) **Data and information about the bioavailability or bioequivalence of drugs** for human use submitted as part of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in part 320.

(9) **Data and information about an over-the-counter drug** for human use submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in part 330.

(10) **Data and information about a prescription drug for human use** submitted as part of the procedures for classifying these drugs as generally recognized as safe and effective and not misbranded, described in this chapter.

(11) [Reserved]

(12) An **application for a biologics license**, described in part 601 of this chapter.

(13) **Data and information about a biological product** submitted as part of the procedures for determining that licensed biological products are safe and effective and not misbranded, described in part 601.

(14) **Data and information about an in vitro diagnostic product** submitted as part of the procedures for establishing, amending, or repealing a standard for these products, described in part 809.

(15) An **Application for an Investigational Device Exemption**, described in part 812.

(16) **Data and information about a medical device** submitted as part of the procedures for classifying these devices, described in section 513.

(17) **Data and information about a medical device** submitted as part of the procedures for establishing, amending, or repealing a standard for these devices, described in section 514.

(18) An **application for premarket approval of a medical device**, described in section 515.

(19) A **product development protocol for a medical device**, described in section 515.

(20) **Data and information about an electronic product** submitted as part of the procedures for establishing, amending, or repealing a standard for these products, described in section 358 of the Public Health Service Act.

(21) **Data and information about an electronic product** submitted as part of the procedures for obtaining a variance from any electronic product performance standard, as described in Sec. 1010.4.

(22) **Data and information about an electronic product** submitted as part of the procedures for granting, amending, or extending an exemption from a radiation safety performance standard, as described in Sec. 1010.5.

(23) **Data and information about a clinical study of an infant formula** when submitted as part of an infant formula notification under section 412(c) of the Federal Food, Drug, and Cosmetic Act.

(24) **Data and information submitted in a petition for a nutrient content claim**, described in Sec. 101.69 of this chapter, or for a health claim, described in Sec. 101.70 of this chapter.

(25) **Data and information from investigations involving children** submitted in a new dietary ingredient notification, described in Sec. 190.6 of this chapter.

50.3 (c) Clinical investigation means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the **results** of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies.

50.20 General requirements for informed consent.

Except as provided in Secs. 50.23 and 50.24, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the **legally effective informed consent** of the subject or the subject's legally authorizes representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language that is understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

50.23 Exception from general requirements.

50.23(a) The obtaining of informed consent shall be deemed feasible unless, before the use of the test article (except as provided in paragraph (b) of this section), both the investigator and a physician who is not otherwise participating in the clinical investigation **certify in writing** all of the following:

(1) The human subject is confronted by a life-threatening situation necessitating the use of the test article.

(2) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent, from the subject.

(3) Time is not sufficient to obtain consent from the subject's legal representative.

(4) There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

50.23(b) If immediate use of the test article is, in the investigator's opinion, required to preserve the life to the subject, and time is not sufficient to obtain the independent determination required in paragraph (a) of this section in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and **evaluated in writing** by a physician who is not participating in the clinical investigation.

50.23(c) The **documentation** required in paragraph (a) or (b) of this section shall be submitted to the IRB within 5 working days after the use of the test article.

50.25 Elements of informed consent.

50.25(a)(5) A **statement describing the extent, if any, to which confidentiality of records identifying the subject** will be maintained and that notes the possibility that Food and Drug Administration may inspect the **records**.

50.27 Documentation of informed consent.

50.27(a) Except as provided in Sec. 56.109(c), informed consent shall be documented by the use of a **written consent form** approved by the IRB and **signed and dated by the subject or the subject's legally authorized representative** at the time of consent. A **copy shall be given to the person signing the form**.

50.27(b) Except as provided in Sec. 56.109(c), the consent form may be either of the following:

(b)(1) A **written consent document** that embodies the elements of informed consent required by Sec. 50.25. This form may be read to the subject or the subject's legally authorized representative, but, in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed.

(b)(2) A short form **written consent document** stating that the elements of informed consent required by Sec. 50.25 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a **witness** to the oral presentation. Also, the IRB shall **approve a written summary** of what is to be said to the subject or the representative. Only the short form itself is to be **signed by the subject or the representative**. However, the witness shall **sign both the short form and a copy of the summary**, and the person actually obtaining the consent shall **sign a copy of the summary**. A **copy of the summary shall be given to the subject or the representative in addition to a copy of the short form**.

Part 56 Institutional Review Boards

56.103 Circumstances in which IRB review is required.

56.103(a) Except as provided in Secs. 56.104 and 56.105, any clinical investigation which must meet the requirements for prior submission (as required in parts 312, 812, and 813) to the Food and Drug Administration shall not be initiated unless that **investigation has been reviewed and approved by,** and remains subject to continuing review by, **an IRB** meeting the requirements of this part.

56.104 Exemptions from IRB requirement.

56.104(c) Emergency use of a test article, provided that such emergency use is **reported to the IRB** within 5 working days. Any subsequent use of the test article at the institution is subject to **IRB review**.

56.108 IRB functions and operations.

In order to fulfill the requirements of these regulations, each IRB shall:

56.108(a) Follow **written procedures**:

(1) For conducting its initial and continuing **review of research** and for **reporting its findings and actions** to the investigator and the institution;

(4) for ensuring that **changes in approved** research, during the period for which IRB approval has already been given, may not be initiated without IRB **review and approval** except where necessary to eliminate apparent immediate hazards to the human subjects.

56.108(c) Except when an expedited review procedure is used (see Sec. 56.110), **review proposed research at convened meetings** at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the **approval of a majority of those members** present at a meeting.

56.109 IRB review of research.

56.109(a) An IRB shall **review and have authority to approve**, **require modifications in (to secure approval), or disapprove** all research activities covered by these regulations.

56.109(c) An IRB shall require **documentation of informed consent** in accordance with Sec. 50.27 of this chapter, except as follows:

(1) The IRB may, for some or all subjects, **waive the requirement** that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context; or

(2) The IRB may, for some or all subjects, find that the requirements in Sec. 50.24 of this chapter for an **exemption from informed consent for emergency research** are met.

56.109(e) An IRB shall **notify investigators and the institution in writing of its decision to approve or disapprove** the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its **written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing**. For investigations involving an exception to informed consent under Sec. 50.24 of this chapter, an IRB shall promptly **notify in writing the investigator and the sponsor of the research when an IRB determines that it cannot approve the research** because it does not meet the criteria in the exception provided under Sec. 50.24(a) of this chapter or because of other relevant ethical concerns. The **written notification shall include a statement of the reasons** for the IRB's determination.

56.111 Criteria for IRB approval of research.

56.111(a)(6) Where appropriate, the **research plan** makes adequate provision for monitoring the data collected to ensure the safety of subjects.

56.113 Suspension or termination of IRB approval of research.

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include **a statement of the reasons** for the IRB's action and shall be **reported** promptly to the investigator, appropriate institutional officials, and the Food and Drug Administration.

56.115 IRB records.

56.115(a) An institution, or where appropriate an IRB, shall prepare and maintain **adequate documentation of IRB activities**, including the following:

(1) **Copies of all research proposals reviewed, scientific evaluations**, if any, that accompany the proposals, **approved sample consent documents, progress reports** submitted by investigators**,** and **reports of injuries to subjects**.

(2) **Minutes of IRB meetings** which shall be in sufficient detail to show **attendance** at meetings; **actions** taken by the IRB; the vote on these actions including **the number of members voting for, against, and abstaining**; the **basis for requiring changes in or disapproving research; and a written summary of the discussion of controversial issues and their resolution**.

(3) **Records of continuing review activities**.

(4) **Copies of all correspondence** between the IRB and the investigators.

(5) A **list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant**.

(6) **Written procedures** for the IRB as required by Sec. 56.108 (a) and (b).

(7) **Statements of significant new findings provided to subjects**, as required by Sec. 50.25.

56.115(b) The **records required** by this regulation shall be retained for at least 3 years after completion of the research, and the **records** shall be accessible for **inspection and copying** by authorized representatives of the Food and Drug Administration at reasonable times and in a reasonable manner.

Part 312 Investigational New Drug Application

312.7 Promotion and charging for investigational drugs.

312.7(d) Charging for and commercialization of investigational drugs—(1) Clinical trials under an IND. Charging for an investigational drug in a clinical trial under an IND is not permitted without the **prior written approval of FDA**. In requesting such approval, the sponsor shall provide a **full written explanation** of why charging is necessary in order for the sponsor to undertake or continue the clinical trial, e.g., why distribution of the drug to test subjects should not be considered part of the normal cost of doing business.

312.10 Waivers.

312.10(a) A sponsor may request FDA to waive applicable requirement under this part. A **waiver request** may be submitted either in an IND or in an information amendment to an IND. In an emergency, a **request may be made by telephone or other rapid communication means**. A waiver request is required to contain at least one of the following:

(1) An **explanation why the sponsor's compliance with the requirement is unnecessary or cannot be achieved**;

(2) A **description of an alternative submission or course of action** that satisfies the purpose of the requirement; or

(3) **Other information justifying a waiver**.

312.23 IND content and format.

312.23(a) A sponsor who intends to conduct a clinical investigation subject to this part shall **submit an "Investigational New Drug Application" (IND)** including, in the following order:

(1)(ix) The **signature of the sponsor** or the sponsor's authorized representative. If the person signing the application does not reside or have a place of business within the United States, the IND is required to contain the name and address of, and be countersigned by, an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

(5) **Investigator's brochure**. If required under Sec. 312.55, a copy of the investigator's brochure, containing the following information:

(5)(ii) A **summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans**.

(5)(iii) A **summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans**.

(5)(iv) A **summary of information related(relating) to safety and effectiveness in humans obtained from prior clinical studies.** (Reprints of published articles on such studies may be appended when useful.)

(6) **Protocols**. (i) A protocol for **each planned study**. (Protocols for studies not submitted initially in the IND should be submitted in accordance with Sec. 312.30(a).) In general, protocols for Phase 1 studies may be less detailed and more flexible than protocols for Phase 2 and 3 studies. Phase 1 protocols should be directed primarily at providing an outline of the investigation**—**an **estimate of the number of patients to be involved, a description of safety exclusions, and a description of the dosing plan including duration, dose, or method to be used in determining dose—and should specify in detail only those elements of the study that are critical to safety**, such as necessary monitoring of vital signs and blood chemistries. **Modifications** of the experimental design of Phase I studies that do not affect critical safety assessments are **required to be reported** to FDA only in the **annual report**.

(7) Chemistry, manufacturing, and control information.

(7)(i) As appropriate for the particular investigations covered by the IND, a **section describing the composition, manufacture, and control of the drug substance and the drug product**. Although in each phase of the investigation sufficient information is required to be submitted to assure the proper identification, quality, purity, and strength of the investigational drug, the amount of information needed to make that assurance will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information otherwise available. FDA recognizes that modifications to the method of preparation of the new drug substance and dosage form and changes in the dosage form itself are likely as the investigation progresses. Therefore, the emphasis in an initial Phase 1 submission should generally be placed on the identification and control of the raw materials and the new drug substance. Final specifications for the drug substance and drug product are not expected until the end of the investigational process.

(7)(ii) It should be emphasized that the amount of information to be submitted depends upon the scope of the proposed clinical investigation. For example, although stability data are required in all phases of the IND to demonstrate that the new drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation, if very short-term tests are proposed, the supporting stability data can be correspondingly limited.

(7)(iii) As drug development proceeds and as the scale or production is changed from the pilot-scale production appropriate for the limited initial clinical investigations to the larger-scale production needed for expanded clinical trials, the sponsor should **submit information amendments to supplement the initial information submitted** on the chemistry, manufacturing, and control processes with information appropriate to the expanded scope of the investigation.

(7) (iv) Reflecting the distinctions described in this paragraph (a)(7), and based on the phase(s) to be studied, the submission is required to contain the following:

(a) **Drug substance**. A description of the drug substance, including its **physical, chemical, or biological characteristics; the name and address of its manufacturer; the general method of preparation of the drug substance; the acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug substance; and information sufficient to support stability of the drug substance** during the toxicological studies and the planned clinical studies. Reference to the current edition of the United States Pharmacopeia-National Formulary may satisfy relevant requirements in this paragraph.

(b) **Drug product**. A **list of all components, which may include reasonable alternatives for inactive compounds, used in the manufacture of the investigational drug product, including both those components intended to appear in the drug product and those which may not appear but which are used in the manufacturing process, and, where applicable, the quantitative composition of the investigational drug product, including any reasonable variations that may be expected during the investigational stage; the name and address of the drug product manufacturer; a brief general description of the manufacturing and packaging procedure as appropriate for the product; the acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug product; and information sufficient to assure the product's stability** during the planned clinical studies. Reference to the current edition of the United States Pharmacopeia-National Formulary may satisfy certain requirements in this paragraph.

(c) A **brief general description of the composition, manufacture, and control of any placebo** used in a controlled clinical trial.

(d) **Labeling. A copy of all labels and labeling** to be provided to each investigator.

(e) **Environmental analysis requirements**. A claim for categorical exclusion under § 25.30 or 25.31 or an environmental assessment under § 25.40.

(8) **Pharmacology and toxicology information**. **Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro**, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations. Guidance documents are available from FDA that describe ways in which these requirements may be met. Such **information is required to include** the **identification and qualifications of the individuals who evaluated the results of such studies** and concluded that it is reasonably safe to begin the proposed investigations and a **statement of where the investigations were conducted** and **where the records are available for inspection**. As drug development proceeds, the sponsor is **required to submit informational amendments**, as appropriate, with additional information pertinent to safety.

(8)(ii) **Toxicology**. (a) An **integrated summary** of the toxicological effects of the drug in animals and in vitro. Depending on the nature of the drug and the phase of the investigation, the description is to include the **results of acute, subacute, and chronic toxicity tests**; **tests of the drug's effects on reproduction and the developing fetus; any special toxicity test related to the drug's particular mode of administration or conditions of use** (e.g., inhalation, dermal, or ocular toxicology); and **any in vitro studies intended to evaluate drug toxicity**. (b) **For each toxicology study that is intended primarily to support the safety of the proposed clinical investigation, a full tabulation of data** suitable for detailed review.

(9)(iii) If the drug has been marketed outside the United States, a **list of the countries in which the drug has been marketed and a list of the countries in which the drug has been withdrawn from marketing** for reasons potentially related to safety or effectiveness.

(10) **Additional information**. In certain applications, as described below, information on special topics may be needed. Such information shall be submitted in this section as follows:

(10)(i) **Drug dependence and abuse potential**. If the drug is a psychotropic substance or otherwise has abuse potential, **a section describing relevant clinical studies and experience and studies in test animals**.

(10)(ii) Radioactive drugs. If the drug is a radioactive drug, **sufficient data from animal or human studies to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to a human subject**. Phase 1 studies of radioactive drugs must include studies which will obtain sufficient data for dosimetry calculations.

312.23 (b) **Information previously submitted**. The sponsor ordinarily is not required to resubmit information previously submitted, but may incorporate the information by reference. A **reference to information submitted previously must identify the file by name, reference number, volume, and page number** where the information can be found. A **reference** to information submitted to the agency by a person other than the sponsor is **required to contain a written statement** that authorizes the reference and that is **signed** by the person who submitted the information.

312.30 Protocol amendments.

312.30(a) New protocol. Whenever a sponsor intends to conduct a study that is not covered by a protocol already contained in the IND, the sponsor shall **submit to FDA a protocol amendment containing the protocol** for the study. Such study may begin provided two conditions are met:

(1) The sponsor has submitted the protocol to FDA for its review; and

(2) the protocol has been **approved by the Institutional Review Board (IRB)** with responsibility for review and approval of the study in accordance with the requirements of part 56. The sponsor may comply with these two conditions in either order.

312.30(b)(2)(i) A protocol change under paragraph (b)(1) of this section may be made provided two conditions are met:

(a) The sponsor has **submitted the change to FDA** for its review and

(b) the change has been **approved by the IRB** with responsibility for review and approval.

312.30(c) New investigator. A sponsor shall **submit a protocol amendment when a new investigator is added** to carry out a previously submitted protocol, except that a protocol amendment is not required when a licensed practitioner is added in the case of a treatment protocol under Sec. 312.34. Once the investigator is added to the study, the investigational drug may be shipped to the investigator and the investigator may begin participating in the study. The sponsor shall **notify FDA of the new investigator within 30 days of the investigator being added**.

312.30(e) When submitted. A sponsor shall **submit a protocol amendment** for a new protocol or a change in protocol before its implementation. Protocol amendments to add a new investigator or to provide additional information about investigators may be grouped and submitted at 30-day intervals. When several submissions of new protocols or protocol changes are anticipated during a short period, the sponsor is encouraged, to the extent feasible, to include these all in a single submission.

312.31 Information amendments.

312.31(a) Requirement for information amendment. A sponsor shall **report in an information amendment essential information on the IND that is not within the scope of a protocol amendment**, IND safety reports, or annual report. Examples of information requiring an information amendment include:

(1) **New toxicology, chemistry, or other technical information**; or

(2) **A report regarding the discontinuance of a clinical investigation**.

312.32 IND safety reports.

312.32(b) **Review of safety information**. The sponsor shall promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source, foreign or domestic, including **information** derived from clinical investigations, animal investigations, commercial marketing experience, **reports** in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not already been previously reported to the agency by the sponsor.

312.32(c) IND safety reports.

(1) **Written reports** -

(i) The sponsor shall notify FDA and all participating investigators in **a written IND safety report** of:

(A) **Any adverse experience** associated with the use of the drug that is both serious and unexpected; or

(B) **Any finding from tests in laboratory animals that suggests a significant risk for human subjects** including reports of **mutagenicity**, **teratogenicity**, or **carcinogenicity**. Each notification shall be made as soon as possible and in no event later than 15 calendar days after the sponsor's initial receipt of the information. Each written notification may be submitted on FDA Form 3500A or in a narrative format (foreign events may be submitted either on an FDA Form 3500A or, if preferred, on a CIOMS I form; reports from animal or epidemiological studies shall be submitted in a narrative format) and shall bear prominent identification of its contents, i.e., "IND Safety Report." Each written notification to FDA shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. If FDA determines that additional data are needed, the agency may require further data to be submitted.

(ii) In each **written IND safety report**, the sponsor shall identify all **safety reports** previously filed with the IND concerning a similar adverse experience, and shall **analyze the significance of the adverse experience** in light of the previous, similar reports.

312.33 Annual Reports.

A sponsor shall within 60 days of the anniversary date that the IND went into effect, submit a brief **report** of the progress of the investigation that includes:

312.33 (a) Individual study information. A brief **summary of the status of each study in progress and each study completed during the previous year**. The summary is required to include the following information for each study:

(1) The **title of the study (with any appropriate study identifiers such as protocol number), its purpose, a brief statement identifying the patient population, and a statement as to whether the study is completed**.

(2) The **total number of subjects initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, gender, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason**.

(3) If the study has been completed, or if interim results are known, a **brief description of any available study results**.

312.35 Submissions for treatment use.

312.35(a) Treatment protocol submitted by IND sponsor. Any sponsor of a clinical investigation of a drug who intends to sponsor a treatment use for the drug shall **submit to FDA a treatment protocol** under Sec. 312.34 if the sponsor believes the criteria of Sec. 312.34 are satisfied. If a protocol is not submitted under Sec. 312.34, but FDA believes that the protocol should have been submitted under this section, FDA may deem the protocol submitted under Sec. 312.34. A treatment use under a treatment protocol may begin 30 days after FDA receives the protocol or on earlier notification by FDA that the treatment use described in the protocol may begin.

312.42 Clinical holds and requests for modification.

312.42(e) Resumption of clinical investigations. An investigation may only resume after FDA (usually the Division Director, or the Director's designee, with responsibility for review of the IND) has **notified the sponsor that the investigation may proceed**. Resumption of the affected investigation(s) will be authorized when the sponsor corrects the deficiency(ies) previously cited or otherwise satisfies the agency that the investigation(s) can proceed. FDA may notify a sponsor of its determination regarding the clinical hold by telephone or other means of rapid communication. If a sponsor of an IND that has been placed on clinical hold **requests in writing that the clinical hold be removed and submits a complete response to the issue(s) identified in the clinical hold order**, FDA shall respond in writing to the sponsor within 30-calendar days of receipt of the request and the complete response. FDA's response will either remove or maintain the clinical hold, and will state the reasons for such determination. Notwithstanding the 30-calendar day response time, a sponsor may not proceed with a clinical trial on which a clinical hold has been imposed until the sponsor has been notified by FDA that the hold has been lifted.

312.44 Termination.

312.44(a) General. This section describes the procedures under which FDA may terminate an IND. If an IND is terminated, the sponsor shall end all clinical investigations conducted under the IND and recall or otherwise provide for the disposition of all unused supplies of the drug. A termination action may be based on deficiencies in the IND or in the conduct of an investigation under an IND. Except as provided in paragraph (d) of this section, a termination shall be preceded by a proposal to terminate by FDA and an opportunity for the sponsor to respond. FDA will, in general, only initiate an action under this section after first attempting to resolve differences informally or, when appropriate, through the clinical hold procedures described in Sec. 312.42.

312.44(c) Opportunity for sponsor response.

(1) If FDA proposes to terminate an IND, **FDA will notify the sponsor in writing,** and invite correction or explanation within a period of 30 days.

(2) On such notification, the **sponsor may provide a written explanation or correction or may request a conference** with FDA to provide the requested explanation or correction. If the sponsor does not respond to the notification within the allocated time, the IND shall be terminated.

(3) If the sponsor responds but FDA does not accept the explanation or correction submitted, FDA shall inform the sponsor in **writing of the reason for the nonacceptance and provide the sponsor with an opportunity for a regulatory hearing** before FDA under part 16 on the question of whether the IND should be terminated. The sponsor's request for a regulatory hearing must be made within 10 days of the sponsor's receipt of FDA's notification of nonacceptance.

312.44(d) Immediate termination of IND. Notwithstanding paragraphs (a) through (c) of this section, if at any time FDA concludes that continuation of the investigation presents an immediate and substantial danger to the health of individuals, the agency shall immediately, by **written notice** to the sponsor from the Director of the Center for Drug Evaluation and Research or the Director of the Center for Biologics Evaluation and Research, terminate the IND. An IND so terminated is subject to reinstatement by the Director on the basis of additional submissions that eliminate such danger. If an IND is terminated under this paragraph, the agency will afford the sponsor an opportunity for a regulatory hearing under part 16 on the question of whether the IND should be reinstated.

312.45 Inactive status.

312.45(b) If an IND is placed on inactive status, all **investigators shall be so notified**, and all stocks of the drug shall be returned or otherwise disposed of in accordance with Sec. 213.59.

312.53 Selecting investigators and monitors.

312.53(c) Obtaining information from the investigator. Before permitting an investigator to begin participation in an investigation, the sponsor shall obtain the following:

(1) A **signed investigator statement (Form FDA-1572)** containing:

(i) The **name and address of the investigator**;

(ii) The **name and code number, if any, of the protocol(s)** in the IND identifying the study(ies) to be conducted by the investigator;

(iii) **The name and address of any medical school, hospital, or other research facility** where the clinical investigation(s) will be conducted;

(iv) **The name and address of any clinical laboratory facilities** to be used in the study;

(v) **The name and address of the IRB** that is responsible for review and approval of the study(ies);

(vi) A **commitment** by the investigator that he or she:

(a) **Will conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, the rights, or welfare of subjects;**

(b) **Will comply with all requirements regarding the obligations of clinical investigators and all other pertinent requirements in this part;**

(c) **Will personally conduct or supervise** the described investigation(s);

(d) **Will inform any potential subjects that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent (21 CFR part 50) and institutional review board review and approval (21 CFR part 56) are met;**

(e) **Will report to the sponsor adverse experiences** that occur in the course of the investigation(s) in accordance with Sec. 312.64;

(f) **Has read and understands the information in the investigator's brochure,** including the potential risks and side effects of the drug; and

(g) **Will ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations** in meeting the above commitments.

(vii) **A commitment by the investigator that, for an investigation subject to an institutional review requirement under part 56, an IRB that complies with the requirements of that part will be responsible for the initial and continuing review and approval of the clinical investigation and that the investigator will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to the human subjects.**

(viii) A **list of the names of the subinvestigators** (e.g., research fellows, residents) who will be assisting the investigator in the conduct of the investigation(s).

312.55 Informing investigators.

312.55(b) The sponsor shall, as the overall investigation proceeds, **keep each participating investigator informed of new observations discovered by or reported to the sponsor** on the drug, particularly with respect to adverse effects and safe use. Such information may be distributed to investigators by means of **periodically revised investigator brochures, reprints or published studies, reports, or letters to clinical investigators**, or other appropriate means. Important safety information is required to be relayed to investigators in accordance with Sec. 312.32.

312.56 Review of ongoing investigations.

312.56(c) The sponsor shall **review and evaluate the evidence** relating to the safety and effectiveness of the drug as it is obtained from the investigator. The **sponsors shall make such reports to FDA regarding information relevant to the safety of the drug** as are required under Sec. 312.32. The **sponsor shall make annual reports on the progress of the investigation** in accordance with Sec. 312.33.

312.57 Recordkeeping and record retention.

312.57(a) A sponsor shall maintain **adequate records showing the receipt, shipment, or other disposition of the investigational drug**. These **records are required to include, as appropriate, the name of the investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each such shipment**.

312.57(c) A sponsor shall **retain the records and reports required** by this part for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified.

312.58 Inspection of sponsor's records and reports.

312.58(a) FDA inspection. A sponsor shall upon request...permit such officer or employee to have **access to and copy and verify any records and reports** relating to a clinical investigation conducted under this part. Under written request by FDA, the sponsor shall **submit the records or reports (or copies of them) to FDA**. The sponsor shall discontinue shipments of the drug to any investigator who has failed to **maintain or make available records or reports of the investigation** as required by this part.

312.58(b) Controlled substances. If an investigational new drug is a substance listed in any schedule of the Controlled Substances Act (21 U.S.C. 801; 21 CFR part 1308), **records concerning shipment, delivery, receipt, and disposition of the drug**, which are required to be kept under this part or other applicable parts of this chapter shall, upon the request of a properly authorized employee of the Drug Enforcement Administration of the U.S. Department of Justice, be made available by the investigator or sponsor to whom the request is made, for **inspection and copying**. In addition, the sponsor shall assure that adequate precautions are taken, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

312.59 Disposition of unused supply of investigational drug.

The sponsor shall **maintain written records of any disposition of the drug** in accordance with Sec. 312.57.

312.60 General responsibilities of investigators.

An investigator is responsible for ensuring that an investigation is conducted according to the **signed investigator statement**, the **investigational plan**, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation. An investigator shall, in accordance with the provisions of part 50 of this chapter, **obtain the informed consent of each human subject** to whom the drug is administered, except as provided in Secs. 50.23 or 50.24 of this chapter. Additional specific responsibilities of clinical investigators are set forth in this part and in parts 50 and 56 of this chapter.

312.62 Investigator recordkeeping and record retention.

312.62(a) Disposition of drug. An investigator is required to maintain **adequate records of the disposition of the drug**, including **dates, quantity, and use by subjects**....

312.62(b) Case histories. An investigator is **required to prepare and maintain adequate and accurate case histories** that **record all observations and other data pertinent to the investigation** on each individual administered the investigational drug or employed as a control in the investigation. **Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes**. The case history for each individual shall document that **informed consent** was obtained prior to participation in the study.

312.62(c) Record retention. An investigator shall **retain records required to be maintained under this part** for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

312.68 Inspection of investigator's records and reports.

An investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have **access to, and copy and verify any records or reports made by the investigator** pursuant to Sec. 312.62. The investigator is not required to divulge subject names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.

312.120 Foreign clinical studies not conducted under an IND.

312.120(c)(3) When the research has been **approved by an independent review committee**, the sponsor shall **submit to FDA documentation of such review and approval, including the names and qualifications of the members of the committee**. In this regard, a "review committee" means a committee composed of scientists and, where practicable, individuals who are otherwise qualified (e.g., other health professionals or laymen). The investigator may not vote on any aspect of the review of his or her protocol by a review committee.

312.160 Drugs for investigational use in laboratory research animals or in vitro tests.

312.160(a)(3) A person who ships a drug under paragraph (a) of this section shall **maintain adequate records showing the name and post office address of the expert to whom the drug is shipped and the date, quantity, and batch or code mark of each shipment and delivery. Records of shipments** under paragraph (a)(1)(i) of this section are to be maintained for a period of 2 years after the shipment. **Records and reports of data and shipments** under paragraph (a)(1)(ii) of this section are to be maintained in accordance with Sec. 312.57(b). The person who ships the drug shall upon request from any properly authorized officer or employee of the Food and Drug Administration, at reasonable times, permit such officer or employee to have **access to and copy and verify records required to be maintained** under this section.

Part 314 Applications for FDA Approval to Market a New Drug

314.50 Content and format of an application.

Applications and supplements to approved applications are required to be submitted in the form and contain the information, as appropriate for the particular submission, required under this section. **Three copies of the application are required: An archival copy, a review copy, and a field copy.** An application for a new chemical entity will generally contain an application form, an index, a summary, five or six technical sections, case report tabulations of patient data, case report forms, drug samples, and labeling, including, if applicable, any Medication Guide required under part 208 of this chapter. Other applications will generally contain only some of those items, and information will be limited to that needed to support the particular submission. These include an application of the type described in section 505(b)(2) of the act, an amendment, and a supplement. The application is required to contain **reports of all investigations of the drug product sponsored by the applicant, and all other information about the drug pertinent** to an evaluation of the application that is received or otherwise obtained by the applicant from any source.

314.50(a) Application form. The applicant shall submit a completed and **signed application form** that contains the following:

(1) The **name and address of the applicant; the date of the application; the application number if previously issued** (for example, if the application is a resubmission, an amendment, or a supplement); the **name of the drug product, including its established, proprietary, code, and chemical names; the dosage form and strength; the route of administration; the identification numbers of all investigational new drug applications that are referenced in the application; the identification numbers of all drug master files and other applications under this part that are referenced in the application; and the drug product's proposed indications for use.**

(2) A **statement whether the submission is an original submission, a 505(b)(2) application, a resubmission, or a supplement to an application under Sec. 314.70.**

(3) A **statement whether the applicant proposes to market the drug product as a prescription or an over-the-counter product.**

(4) A **check-list identifying what enclosures** required under this section the applicant is submitting.

(5) The applicant, or the applicant's attorney, agent, or other authorized official shall **sign the application**. If the person signing the application does not reside or have a place of business within the United States, the application is required to contain the name and address of, and be **countersigned** by, an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

314.50(b) Index. The **archival copy** of the application is required to contain a **comprehensive index by volume number and page number** to the summary under paragraph (c) of this section, the **technical sections** under paragraph (d) of this section, and the **supporting information** under paragraph (f) of this section.

314.50(c) Summary.

314.50(c)(1) An application is required to contain a **summary of the application** in enough detail that the reader may gain a good general understanding of the data and information in the application, including an understanding of the quantitative aspects of the data. The summary is not required for supplements under Sec. 314.70. Resubmissions of an application should contain an updated summary, as appropriate. The summary should discuss all aspects of the application, and synthesize the information into a well-structured and unified document. The summary should be written at approximately the level of detail required for publication in, and meet the editorial standards generally applied by, refereed scientific and medical journals. In addition to the agency personnel reviewing the summary in the context of their review of the application, FDA may furnish the summary to FDA advisory committee members and agency officials whose duties require an understanding of the application. To the extent possible, data in the summary should be presented in tabular and graphic forms. FDA has prepared a guideline under Sec. 10.90(b) that provides information about how to prepare a summary. The summary required under this paragraph may be used by FDA or the applicant to prepare the Summary Basis of Approval document for public disclosure (under Sec. 314.430(e)(2)(ii)) when the application is approved.

314.50(d) Technical sections The application is required to contain the technical sections described below. Each technical section is required to contain **data and information in sufficient detail** to permit the agency to make a knowledgeable judgment about whether to approve the application The required technical sections are as follows:

(1) Chemistry, manufacturing, and controls section. A section **describing the composition, manufacture, and specification of the drug substance and the drug product**, including the following:

(i) Drug substance. A **full description of the drug substance including its physical and chemical characteristics and stability; the name and address of its manufacturer; the method of synthesis (or isolation) and purification of the drug substance; the process controls used during manufacture and packaging; and such specifications and analytical methods as are necessary to assure the identity, strength, quality, and purity of the drug substance and the bioavailability of the drug products made from the substance, including, for example, specifications relating to stability, sterility, particle size, and crystalline form**. The application may provide additionally for the use of alternatives to meet any of these requirements, including alternative sources, process controls, methods, and specifications. Reference to the current edition of the U.S. Pharmacopeia and the National Formulary may satisfy relevant requirements in this paragraph.

(ii)(a) Drug product. A **list of all components used in the manufacture of the drug product (regardless of whether they appear in the drug product); and a statement of the composition of the drug product; a statement of the specifications and analytical methods for each component; the name and address of each manufacturer the drug product; a description of the manufacturing and packaging procedures and in-process controls for the drug product; such specifications and analytical methods as are necessary to assure the identity, strength, quality, purity, and bioavailability of the drug product, including, for example, specifications relating to sterility, dissolution rate, containers and closure systems; and stability data with proposed expiration dating.** The application may provide additionally for the use of alternatives to meet any of these requirements, including alternative components, manufacturing and packaging procedures, in-process controls, methods, and specifications. Reference to the current edition of the U.S. Pharmacopeia and the National Formulary may satisfy relevant requirements in this paragraph.

(b) Unless provided by paragraph (d)(1)(ii)(a) of this section, for each batch of the drug product used to conduct a bioavailability or bioequivalence study described in Sec. 320.38 or Sec. 320.63 of this chapter or used to conduct a primary stability study: The **batch production record; the specifications and test procedures for each component and for the drug product; the names and addresses of the sources of the active and noncompendial inactive components and of the container and closure system for the drug product; the name and address of each contract facility involved in the manufacture, processing, packaging, or testing of the drug product and identification of the operation performed by each contract facility; and the results of any test performed on the components used in the manufacture** of the drug product as required by Sec. 211.84(d) of this chapter and on the drug product as required by Sec. 211.165 of this chapter.

(c) The proposed or actual **master production record**, **including a description of the equipment**, to be used for the manufacture of a commercial lot of the drug product or a comparably detailed description of the production process for a representative batch of the drug product.

(iii) Environmental impact. The application is required to **contain either a claim for categorical exclusion under Sec. 25.30 or 25.31 of this chapter or an environmental assessment under Sec. 25.40 of this chapter**.

(iv) The applicant may, at its option, submit a complete chemistry, manufacturing, and controls section 90 to 120 days before the anticipated submission of the remainder of the application. FDA will review such early submissions as resources permit.

(v) Except for a foreign applicant, the applicant shall include a **statement certifying that the field copy of the application has been provided to the applicant's home FDA district office**.

(3)(ii) If the application describes in the chemistry, manufacturing, and controls section specifications or analytical methods needed to assure the bioavailability of the drug product or drug substance, or both, a **statement in this section of the rationale for establishing the specification(s) or analytical methods, including data and information supporting the rationale**.

(5)(vi) A summary and updates of **safety information**, as follows:

(a) The applicant shall submit an **integrated summary of all available information about the safety of the drug product, including pertinent animal data, demonstrated or potential adverse effects of the drug, clinically significant drug/drug interactions, and other safety considerations, such as data from epidemiological studies of related drugs. The safety data shall be presented by gender, age, and racial subgroups. When appropriate, safety data from other subgroups of the population of patients treated also shall be presented, such as for patients with renal failure or patients with different levels of severity** of the disease. A description of any statistical analyses performed in analyzing safety data should also be included, unless already included under paragraph (d)(5)(ii) of this section.

(b) The applicant shall, under section 505(i) of the act, update periodically its pending application with **new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling and, if applicable, any Medication Guide required under part 208 of this chapter. These "safety update reports" are required to include the same kinds of information (from clinical studies, animal studies, and other sources) and are required to be submitted in the same format as the integrated summary in paragraph (d)(5)(vi)(a) of this section. In addition, the reports are required to include the case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event** (unless this requirement is waived). The applicant shall submit these reports (1) 4 months after the initial submission; (2) following receipt of an approvable letter; and (3) at other times as requested by FDA. Prior to the submission of the first such report, applicants are encouraged to consult with FDA regarding further details on its form and content.

314.50(f) Case report forms and tabulations. The archival copy of the application is required to contain the following case report tabulations and case report forms:

(1) Case report tabulations. The application is **required to contain tabulations of the data from each adequate and well-controlled study** under Sec. 314.126 (Phase 2 and Phase 3 studies as described in Secs. 312.21 (b) and (c) of this chapter), **tabulations of the data from the earliest clinical pharmacology studies** (Phase 1 studies as described in Sec. 312.21(a) of this chapter), and **tabulations of the safety data from other clinical studies.** Routine submission of other patient data from uncontrolled studies is not required. The **tabulations are required to include the data on each patient in each study**, except that the applicant may delete those tabulations which the agency agrees, in advance, are not pertinent to a review of the drug's safety or effectiveness. Upon request, FDA will discuss with the applicant in a "pre-NDA" conference those tabulations that may be appropriate for such deletion. Barring unforeseen circumstances, tabulations agreed to be deleted at such a conference will not be requested during the conduct of FDA's review of the application. If such unforeseen circumstances do occur, any request for deleted tabulations will be made by the director of the FDA division responsible for reviewing the application, in accordance with paragraph (f)(3) of this section.

(2) Case report forms. The application is required to contain **copies of individual case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event**, whether believed to be drug related or not, including patients receiving reference drugs or placebo.

314.50(g)(1) The applicant ordinarily is not required to resubmit information previously submitted, but may incorporate the information by reference. A **reference to information submitted previously is required to identify the file by name, reference number, volume, and page number in the agency's records where the information can be found. A reference to information submitted to the agency by a person other than the applicant is required to contain a written statement that authorizes the reference and that is signed by the person who submitted the information**.

(3) If an applicant who submits a new drug application under section 505(b) of the act obtains a "right of reference or use," as defined under Sec. 314.3(b), to an investigation described in clause (A) of section 505(b)(1) of the act, the applicant shall include in its application a **written statement signed by the owner of the data from each such investigation** that the applicant may rely on in support of the approval of its application, and provide FDA access to, the underlying raw data that provide the basis for the report of the investigation submitted in its application.

314.53 Submission of patent information.

314.53(c) Reporting requirements.

(4) Authorized signature. The **declarations required by this section shall be signed by the applicant** or patent owner, or the applicant's or patent owner's attorney, agent (representative), or other authorized official.

314.72 Change in ownership of an application.

314.72(a) The **new owner shall submit an application form signed by the new owner** and a letter or other document containing the following:

(i) The **new owner's commitment to agreements, promises, and conditions made by the former owner and contained in the application**;

(ii) The **date that the change in ownership is effective**; and

(iii) Either a **statement that the new owner has a complete copy of the approved application, including supplements and records that are required to be kept under Sec. 314.81, or a request for a copy of the application from FDA's files**. FDA will provide a copy of the application to the new owner under the fee schedule in Sec. 20.42 of FDA's public information regulations.

314.80 Postmarketing reporting of adverse drug experiences.

314.80(c)(1)(i) Postmarketing 15-day "Alert reports". The applicant shall **report each adverse drug experience that is both serious and unexpected**, whether foreign or domestic, as soon as possible but in no case later than 15 calendar days of initial receipt of the information by the applicant.

314.80(c)(2) Periodic adverse drug experience reports. (i) The applicant shall **report each adverse drug experience not reported under paragraph (c)(1)(i) of this section at quarterly intervals**, for 3 years from the date of approval of the application, and then at annual intervals. The applicant shall submit each quarterly report within 30 days of the close of the quarter (the first quarter beginning on the date of approval of the application) and each annual report within 60 days of the anniversary date of approval of the application. Upon written notice, FDA may extend or reestablish the requirement that an applicant submit quarterly reports, or require that the applicant submit reports under this section at different times than those stated. For example, the agency may reestablish a quarterly reporting requirement following the approval of a major supplement. Followup information to adverse drug experiences submitted in a periodic report may be submitted in the next periodic report.

314.80(f)(3) Instead of using FDA Form 3500A, an applicant may use a **computer-generated FDA 3500A or other alternative format** (e.g., a computer-generated tape or tabular listing) provided that: (i) The content of the alternative format is equivalent in all elements of information to those specified in FDA Form 3500A; and (ii) **The format is agreed to in advance by MedWatch**: The FDA Medical Products Reporting Program.

314.80(i) Recordkeeping. The applicant shall maintain for a period of 10 years **records of all adverse drug experiences known to the applicant, including raw data and any correspondence relating to adverse drug experiences.**

314.81 Other postmarketing reports.

314.81(b) Reporting requirements. The applicant shall submit to the Food and Drug Administration at the specified times two copies of the following reports:

(1) NDA—**Field alert report**. The applicant shall submit information of the following kinds about distributed drug products and articles to the FDA district office that is responsible for the facility involved within 3 working days of receipt by the applicant. The information may be provided by telephone or other rapid communication means, with prompt written followup. The report and its mailing cover should be plainly marked: "NDA—Field Alert Report."

(i) Information concerning any **incident that causes the drug product or its labeling to be mistaken for, or applied to, another article.**

(ii) Information concerning any **bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specifications established for it in the application**.

(2) **Annual report**. The applicant shall submit each year within 60 days of the anniversary date of U.S. approval of the application, two copies of the report to the FDA division responsible for reviewing the application. Each annual report is required to be accompanied by a completed transmittal **Form FDA 2252** (Transmittal of Periodic Reports for Drugs for Human Use), and must include all the information required under this section that the applicant received or otherwise obtained during the annual reporting interval that ends on the U.S. anniversary date. The **report is required to contain** in the order listed:

(i) Summary. A brief **summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling** of the drug product. The report is also required to contain a brief **description of actions the applicant has taken or intends to take as a result of this new information**, for example, submit a labeling supplement, add a warning to the labeling, or initiate a new study. The summary shall briefly **state whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated**. Where possible, an **estimate of patient exposure to the drug product, with special reference to the pediatric population (neonates, infants, children, and adolescents) shall be provided, including dosage form**.

(ii) Distribution data. Information about **the quantity of the drug product distributed under the approved application, including that distributed to distributors**. The information is required to include the **National Drug Code (NDC) number, the total number of dosage units of each strength or potency distributed** (e.g., 100,000/5 milligram tablets, 50,000/10 milliliter vials), and **the quantities distributed for domestic use and the quantities distributed for foreign use**. Disclosure of financial or pricing data is not required.

(3)(i) Advertisements and promotional labeling. The applicant shall submit **specimens of mailing pieces and any other labeling or advertising devised for promotion of the drug product** at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. Mailing pieces and labeling that are designed to contain samples of a drug product are required to be complete, except the sample of the drug product may be omitted. Each submission is required to be accompanied by a completed transmittal **Form FDA-2253** (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) and is required to include a copy of **the product's current professional labeling.** Form FDA-2253 may be obtained from the PHS Forms and Publications Distribution Center, 12100 Parklawn Dr., Rockville, MD 20857.

314.81(c) General requirements

(1) Multiple applications. For all reports required by this section, the applicant shall submit the information common to more than one application only to the application first approved, and shall not report separately on each application. The submission is required to identify all the applications to which the report applies.

(2) Patient identification. Applicants should not include in reports under this section the names and addresses of individual patients; instead, the applicant should code the patient names whenever possible and retain the code in the applicant's files. The applicant shall **maintain sufficient patient identification information** to permit FDA, by using that information alone or along with records maintained by the investigator of a study, to identify the name and address of individual patients; this will ordinarily occur only when the agency needs to investigate the reports further or when there is reason to believe that the reports do not represent actual results obtained.

314.90 Waivers.

314.90(a) An applicant may ask the Food and Drug Administration to waive under this section any requirement that applies to the applicant under Secs. 314.50 through 314.81. An applicant may ask FDA to waive under Sec. 314.126(c) any criteria of an adequate and well-controlled study described in Sec.

314.126(b) A waiver request under this section is required to be submitted with supporting documentation in an application, or in an amendment or supplement to an application. The **waiver request is required to contain one of the following**:

(1) An **explanation why the applicant's compliance with the requirement is unnecessary or cannot be achieved;**

(2) **A description of an alternative submission that satisfies the purpose of the requirement; or**

(3) **Other information justifying a waiver**.

314.93 Petition to request a change from a listed drug.

314.93(b) A person who wants to submit an abbreviated new drug application for a drug product which is not identical to a listed drug in route of administration, dosage form, and strength, or in which one active ingredient is substituted for one of the active ingredients in a listed combination drug, must first obtain permission from FDA to submit such an abbreviated application.

314.93(e)(3) If FDA approves a petition submitted under this section, the agency's response may describe what additional information, if any, will be required to support an abbreviated new drug application for the drug product. FDA may, at any time during the course of its review of an abbreviated new drug application, request additional information required to evaluate the change approved under the petition.

314.94 Content and format of an abbreviated application.

Abbreviated applications are required to be submitted in the form and contain the information required under this section. Three copies of the application are required, an archival copy, a review copy, and a field copy. FDA will maintain guidance documents on the format and content of applications to assist applicants in their preparation.

314.94(a) Abbreviated new drug applications. Except as provided in paragraph (b) of this section, the applicant shall submit a complete archival copy of the abbreviated new drug application that includes the following:

(1) Application form. The applicant shall submit a **completed and signed application form** that contains the information described under Sec. 314.50(a)(1), (a)(3), (a)(4), and (a)(5). The applicant shall **state whether the submission is an abbreviated application under this section or a supplement to an abbreviated application under Sec. 314.97**.

(2) Table of contents. the archival copy of the abbreviated new drug application is **required to contain a table of contents that shows the volume number and page number** of the contents of the submission.

(3) Basis for abbreviated new drug application submission. An abbreviated new drug application must refer to a listed drug. Ordinarily, that listed drug will be the drug product selected by the agency as the reference standard for conducting bioequivalence testing. The application shall contain:

(i) The **name of the reference listed drug, including its dosage form and strength**. For an abbreviated new drug application based on an approved petition under Sec. 10.30 of this chapter or Sec. 314.93, the reference listed drug must be the same as the listed drug approved in the petition.

(ii) A statement as to whether, according to the information published in the list, the **reference listed drug is entitled to a period of marketing exclusivity** under section 505(j)(4)(D) of the act.

(iii) For an abbreviated new drug application based on an approved petition under Sec. 10.30 of this chapter or Sec. 314.93, a **reference to FDA-assigned docket number for the petition and a copy of FDA's correspondence approving the petition**.

(7)(ii) If the abbreviated new drug application is submitted under a petition approved under Sec. 314.93, the **results of any bioavailability or bioequivalence testing required by the agency, or any other information required by the agency** to show that the active ingredients of the proposed drug product are of the same pharmacological or therapeutic class as those in the reference listed drug and that the proposed drug product can be expected to have the same therapeutic effect as the reference listed drug. If the proposed drug product contains a different active ingredient than the reference listed drug, FDA will consider the proposed drug product to have the same therapeutic effect as the reference listed drug if the applicant provides information demonstrating that:

(A) There is an **adequate scientific basis for determining that substitution** of the specific proposed dose of the different active ingredient for the dose of the member of the same pharmacological or therapeutic class in the reference listed drug will yield a resulting drug product whose safety and effectiveness have not been adversely affected.

(B) The **unchanged active ingredients in the proposed drug product are bioequivalent** to those in the reference listed drug.

(C) The **different active ingredient in the proposed drug product is bioequivalent** to an approved dosage form containing that ingredient and approved for the same indication as the proposed drug product or is bioequivalent to a drug product offered for that indication which does not meet the definition of "new drug" under section 201(p) of the act.

(11) Other. The **information required under Sec. 314.50(g).**

314.95 Notice of certification of invalidity or noninfringement of a patent.

314.95(a) Notice of **certification**. For each patent that claims the listed drug or that claims a use for such listed drug for which the applicant is seeking approval and that the applicant certifies under Sec. 314.94(a)(12) is invalid, unenforceable, or will not be infringed, **the applicant shall send notice of such certification** by registered or certified mail, return receipt requested to each of the following persons:

(1) Each owner of the patent which is the subject of the certification or the representative designated by the owner to receive the notice. The **name and address of the patent owner** or its representative may be obtained from the United States Patent and Trademark Office; and

(2) The holder of the approved application under section 505(b) of the act for the listed drug that is claimed by the patent and for which the applicant is seeking approval, or, if the application holder does not reside or maintain a place of business within the United States, the application holder's attorney, agent, or other authorized official. The **name and address of the application holder** or its attorney, agent, or authorized official may be obtained from the Division of Drug Information Resources (HFD-80), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

(3) This paragraph does not apply to a use patent that claims no uses for which the applicant is seeking approval.

314.95(e) **Documentation of receipt** of notice. The applicant shall amend its abbreviated application to document receipt of the notice required under paragraph (a) of this section by each person provided the notice. The applicant shall include a **copy of the return receipt** or other similar evidence of the **date the notification was received**. FDA will accept as adequate documentation of the date of receipt a return receipt or a letter acknowledging receipt by the person provided the notice. An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance. A copy of the notice itself need not be submitted to the agency.

314.98 Postmarketing reports.

314.98(b) Each applicant shall submit one copy of each **report required under Sec. 314.80** to the Division of Epidemiology and Surveillance (HFD-730), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

314.98(c) Each applicant shall make the **reports required under Sec. 314.81 and section 505(k)** of the act for each of its approved abbreviated applications.

314.102 Communications between FDA and applicants.

314.102(a) General principles. During the course of reviewing an application or an abbreviated application, FDA shall communicate with applicants about scientific, medical, and procedural issues that arise during the review process. Such communication may take the form of telephone conversations, letters, or meetings, whichever is most appropriate to discuss the particular issue at hand. **Communications shall be appropriately documented** in the application in accordance with Sec. 10.65 of this chapter. Further details on the procedures for communication between FDA and applicants are contained in a staff manual guide that is publicly available.

314.107 Effective date of approval of a 505(b)(2) application or abbreviated new drug application under section 505(j) of the act.

314.107(c)(2) For purposes of paragraph (c)(1) of this section, the "applicant submitting the first application" is the applicant that submits an **application that is both substantially complete and contains a certification that the patent was invalid, unenforceable, or not infringed** prior to the submission of any other application for the same listed drug that is both substantially complete and contains the same certification. A "substantially complete" application must contain the results of any **required bioequivalence studies, or, if applicable, a request for a waiver of such studies**.

314.107 (f)(2) The abbreviated new drug applicant or the 505(b)(2) applicant **shall notify FDA immediately of the filing of any legal action** filed within 45 days of receipt of the notice of certification. If the applicant submitting the abbreviated new drug application or the 505(b)(2) application or patent owner or its representative does not notify FDA in writing before the expiration of the 45-day time period or the completion of the agency's review of the application, whichever occurs later, that a legal action for patent infringement was filed within 45 days of receipt of the notice of certification, approval of the abbreviated new drug application or the 505(b)(2) application will be made effective immediately upon expiration of the 45 days or upon completion of the agency's review and approval of the application, whichever is later. The notification to FDA of the legal action shall include:

(i) The **abbreviated new drug application or 505(b)(2) application number**.

(ii) The **name of the abbreviated new drug or 505(b)(2) application applicant**.

(iii) The established **name of the drug product or, if no established name exists, the name(s) of the active ingredient(s), the drug product's strength, and dosage form**.

(iv) A **certification that an action for patent infringement identified by number, has been filed in an appropriate court on a specified date**. The applicant of an abbreviated new drug application shall send the notification to FDA's Office of Generic Drugs (HFD-600). A 505(b)(2) applicant shall send the notification to the appropriate division in the Center for Drug Evaluation and Research reviewing the application. A patent owner or its representative may also notify FDA of the filing of any legal action for patent infringement. The notice should contain the information and be sent to the offices or divisions described in this paragraph.

(f)(3) If the patent owner or approved application holder who is an exclusive patent licensee waives its opportunity to file a legal action for patent infringement within 45 days of a receipt of the notice of certification and the patent owner or approved application holder who is an exclusive patent licensee submits to FDA a valid waiver before the 45 days elapse, approval of the abbreviated new drug application or the 505(b)(2) application will be made effective upon completion of the agency's review and approval of the application. FDA will only accept a **waiver in the following form**: **(Name of patent owner or exclusive patent licensee) has received notice from (name of applicant) under (section 505(b)(3) or 505(j)(2)(B) of the act) and does not intend to file an action for patent infringement against (name of applicant) concerning the drug (name of drug) before (date on which 45 days elapses. (Name of patent owner or exclusive patent licensee) waives the opportunity provided by (section 505(c)(3)(C) or 505(j)(B)(iii) of the act) and does not object to FDA's approval of (name of applicant)'s (505(b)(2) or abbreviated new drug application) for (name of drug) with an immediate effective date on or after the date of this letter.**

314.126 Adequate and well-controlled studies.

314.126(a) The purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation. The characteristics described in paragraph (b) of this section have been developed over a period of years and are recognized by the scientific community as the essentials of an adequate and well-controlled clinical investigation. The Food and Drug Administration considers these characteristics in determining whether an investigation is adequate and well-controlled for purposes of section 505 of the act. Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is "substantial evidence" to support he claims... Therefore, the **study report should provide sufficient details of study design, conduct, and analysis** to allow critical evaluation and a determination of whether the characteristics of an adequate and well-controlled study are present.

314.126(b)(1) There is a **clear statement of the objectives of the investigation and a summary of the proposed or actual methods of analysis in the protocol for the study and in the report of its results**. In addition, the **protocol should contain a description of the proposed methods of analysis, and the study report should contain a description of the methods of analysis ultimately used**. If the protocol does not contain a description of the proposed methods of analysis, the **study report should describe how the methods used were selected.**

314.126(c) The Director of the Center for Drug Evaluation and Research may, on the Director's own initiative or on the petition of an interested person, waive in whole or in part any of the criteria in paragraph (b) of this section with respect to a specific clinical investigation, either prior to the investigation or in the evaluation of a completed study. A **petition for a waiver is required to set forth clearly and concisely the specific criteria from which waiver is sought, why the criteria are not reasonably applicable to the particular clinical investigation, what alternative procedures, if any, are to be, or have been employed, and what results have been obtained. The petition is also required to state why the clinical investigations so conducted will yield, or have yielded, substantial evidence of effectiveness**, notwithstanding nonconformance with the criteria for which waiver is requested.

314.150 Withdrawal of approval of an application or abbreviated application.

314.150(b)(1) That the applicant has failed to establish a system for **maintaining required records**, or has repeatedly or deliberately failed to **maintain required records** or to make **required reports** under section 505(k) or 507(g) of the act and Sec. 314.80, Sec. 314.81, or Sec. 314.98, or that the applicant has refused to **permit access to, or copying or verification of, its records**.

314.200 Notice of opportunity for hearing; notice of participation and request for hearing; grant or denial of hearing.

314.200(d) The person requesting a hearing is **required to submit** under paragraph (c)(1)(ii) of this section the studies (including **all protocols and underlying raw data**) on which the person relies to justify a hearing with respect to the drug product. Except, a person who requests a hearing on the refusal to approve an application is not required to submit additional studies and analyses if the studies upon which the person relies have been submitted in the application and in the format and containing the summaries required under Sec. 314.50.

(1) If the grounds for FDA's proposed action concern the effectiveness of the drug, each request for hearing is required to be supported only by adequate and well-controlled clinical studies meeting all of the precise requirements of Sec. 314.126 and, for combination drug products, Sec. 300.50, or by other studies not meeting those requirements for which a waiver has been previously granted by FDA under Sec. 314.126. **Each person requesting a hearing shall submit all adequate and well-controlled clinical studies on the drug product, including any unfavorable analyses, views, or judgments with respect to the studies.** No other data, information, or studies may be submitted.

(2) The submission is required to **include a factual analysis of all the studies submitted**. If the grounds for FDA's proposed action concern the effectiveness of the drug, the analysis is required to **specify how each study accords, on a point-by-point basis, with each criterion required for an adequate well-controlled clinical investigation** established under Sec. 314.126 and, if the product is a combination drug product, with each of the requirements for a combination drug established in Sec. 300.50, or the study is required to be accompanied by an appropriate waiver previously granted by FDA. **If a study concerns a drug or dosage form or condition of use or mode of administration other than the one in question, that fact is required to be clearly stated. Any study conducted on the final marketed form of the drug product is required to be clearly identified**.

314.200(e) Contentions that a drug product is not subject to the new drug requirements. A notice of opportunity for a hearing encompasses all issues relating to the legal status of each drug product subject to it, including identical, related, and similar drug products as defined in Sec. 310.6. A notice of appearance and request for a hearing under paragraph (c)(1)(i) of this section is required to contain any contention that the product is not a new drug because it is generally recognized as safe and effective within the meaning of section 201(p) of the act, or because it is exempt from part or all of the new drug provisions of the act under the exemption for products marketed before June 25, 1938, contained in section 201(p) of the act or under section 107(c) of the Drug Amendments of 1962, or for any other reason. Each contention is required to be supported by a submission under paragraph (c)(1)(ii) of this section and the Commissioner of Food and Drugs will make an administrative determination on each contention. The failure of any person subject to a notice of opportunity for a hearing, including any person who manufactures or distributes an identical, related, or similar drug product as defined in Sec. 310.6, to submit a notice of participation and request for hearing or to raise all such contentions constitutes a waiver of any contentions not raised.

314.200(e)(1) A **contention** that a drug product is generally recognized as safe and effective within the meaning of section 201(p) of the act is **required to be supported by submission of the same quantity and quality of scientific evidence** that is **required** to obtain approval of an application for the product, unless FDA has waived a requirement for effectiveness (under Sec. 314.126) or safety, or both. The **submission should be in the format and with the analyses required under paragraph (d)** of this section. A person who fails to submit the required scientific evidence required under paragraph (d) waives the contention. General recognition of safety and effectiveness shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data and information.

(4) A contention that a drug product is not a new drug for any other reason is **required to be supported by submission of the factual records, data, and information** that are necessary and appropriate to support the contention.

314.420 Drug master files.

314.420(b) An investigational new drug application or an application, abbreviated application, amendment, or supplement may incorporate by reference all or part of the contents of any drug master file in support of the submission if the **holder authorizes the incorporation in writing**. Each incorporation by reference is required to **describe the incorporated material by name, reference number, volume, and page number of the drug master file**.

314.420(c) A drug master file is required to be submitted in two copies. The agency has prepared guidance that provides information about how to prepare a well-organized drug master file. If the drug master file holder adds, changes, or deletes any information in the file, the **holder shall notify in writing, each person authorized to reference that information**. Any addition, change, or deletion of information in a drug master file (except the list required under paragraph (d) of this section) is required to be submitted in two copies and to **describe by name, reference number, volume, and page number the information affected in the drug master file**.

314.420(d) The drug master file is required to contain a **complete list of each person currently authorized to incorporate by reference any information in the file, identifying by name, reference number, volume, and page number the information that each person is authorized to incorporate**. If the holder restricts the authorization to particular drug products, the list is required to include the **name of each drug product and the application number**, if known, to which the authorization applies.

Good Manufacturing Practice (GMP)
Code of Federal Regulations, Part 211

211.22 Responsibilities of quality control unit.

211.22(a) There shall be a quality control unit that shall have the responsibility and authority to **approve or reject** all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to **review production records** to assure that no errors have occurred or, if errors have occurred, that they have been **fully investigated**. The quality control unit shall be responsible for **approving or rejecting** drug products manufactured, processed, packed, or held under contract by another company.

211.34 Consultants.

Consultants advising on the manufacture, processing, packing, or holding of drug products shall have **sufficient education, training, and experience, or any combination thereof**, to advise on the subject for which they are retained. Records shall be maintained stating the **name, address, and qualifications of any consultants and the type of service they provide**.

211.67 Equipment cleaning and maintenance.

211.67(c) **Records shall be kept of maintenance, cleaning, sanitizing, and inspection** as specified in Secs. 211.180 and 211.182.

211.68 Automatic, mechanical, and electronic equipment.

211.68(a) Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, and holding of a drug product. If such equipment is so used, it shall be **routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained**.

211.68(b) Appropriate controls shall be exercised over computer or related systems to assure that **changes in master production and control records or other records are instituted only by authorized personnel**. Input to and output from the computer or related system of formulas or other records or data shall be **checked for accuracy**. The degree and frequency of input/output verification shall be **based on the complexity and reliability of the computer or related system**. A **backup file of data entered into the computer or related system shall be maintained** except where certain data, such as calculations performed in connection with laboratory analysis, are eliminated by computerization or other automated processes. In such instances a **written record of the program shall be maintained along with appropriate validation data**. **Hard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that backup data are exact and complete and that it is secure from alteration, inadvertent erasures, or loss shall be maintained.**

211.80 General requirements.

211.80(d) Each container or grouping of containers for components or drug product containers, or closures shall be **identified with a distinctive code for each lot in each shipment received**. This code shall be used in recording the **disposition** of each lot. Each lot shall be appropriately identified as to its **status** (**i.e., quarantined, approved, or rejected**).

211.84 Testing and approval or rejection of components, drug product containers, and closures.

211.84(d)(2) Each component shall be tested for conformity with all appropriate **written specifications for purity, strength, and quality**. In lieu of such testing by the manufacturer, a **report of analysis** may be accepted from the supplier of a component, provided that at least one specific **identity test** is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through **appropriate validation of the supplier's test results at appropriate intervals**.

211.86 Use of approved components, drug product containers, and closures.

Components, drug product containers, and closures approved for use shall be rotated so that the **oldest approved stock is used first**. Deviation from this requirement is permitted if such **deviation is temporary and appropriate**.

211.100 Written procedures; deviations.

211.100(a) There shall be **written procedures** for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall include all requirements in this subpart. These written procedures, **including any changes**, shall be **drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit**.

211.101 Charge-in of components.

211.101(d) Each component shall be **added to the batch by one person** and **verified by a second person.**

211.103 Calculation of yield.

Actual yields and **percentages of theoretical yield** shall be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the drug product. Such calculations shall be **performed by one person** and **independently verified by a second person**.

211.105 Equipment identification.

211.105(b) Major equipment shall be **identified by a distinctive identification number or code** that shall be **recorded in the batch production record** to show the **specific equipment** used in the manufacture of each batch of a drug product. In cases where only one of a particular type of equipment exists in a manufacturing facility, the name of the equipment may be used in lieu of a distinctive identification number or code.

211.110 Sampling and testing of in-process materials and drug products.

211.110(c) In-process materials shall be **tested for identity, strength, quality, and purity** as appropriate, and **approved or rejected** by the quality control unit, during the production process, e.g., at commencement or completion of significant phases or after storage for long periods.

211.111 Time limitations on production.

When appropriate, time limits for the completion of each phase of production shall be established to assure the quality of the drug product. Deviation from established time limits may be acceptable if such deviation does not compromise the quality of the drug product. Such **deviation shall be justified and documented**.

211.122 Materials examination and usage criteria.

211.122(b) Any labeling or packaging materials meeting appropriate **written specifications** may be **approved** and **released** for use. Any labeling or packaging materials that do not meet such specifications shall be **rejected** to prevent their use in operations for which they are unsuitable.

211.122(c) **Records shall be maintained for each shipment received of each different labeling and packaging material indicating receipt, examination or testing, and whether accepted or rejected**.

211.122(g) If cut labeling is used, packaging and labeling operations shall include one of the following special control **procedures**:

(1) Dedication of labeling and packaging lines to each different strength of each different drug product;

(2) Use of appropriate electronic or electromechanical equipment to conduct a **100-percent examination for correct labeling** during or after completion of finishing operations; or

(3) Use of **visual inspection to conduct a 100-percent examination for correct labeling** during or after completion of finishing operations for hand-applied labeling. Such examination shall be **performed by one person and independently verified by a second person**.

211.130 Packaging and labeling operations.

211.130(d) **Examination of packaging and labeling materials for suitability and correctness** before packaging operations, and **documentation of such examination in the batch production record**.

211.130(e) **Inspection of the packaging and labeling facilities** immediately before use to assure that all drug products have been removed from previous operations. **Inspection shall also be made to assure that packaging and labeling materials not suitable for subsequent operations have been removed. Results of inspection shall be documented in the batch production records**.

211.134 Drug product inspection.

211.134(c) **Results of these examinations shall be recorded in the batch production or control records**.

211.150 Distribution procedures.

211.150(b) A system by which the **distribution of each lot of drug product can be readily determined to facilitate its recall if necessary**.

211.160 General requirements.

211.160(a) The establishment of any **specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit**. The requirements in this subpart shall be followed and shall be documented at the time of performance. Any **deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified**.

211.165 Testing and release for distribution.

211.165(e) The **accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented**. Such validation and documentation may be accomplished in accordance with Sec. 211.194(a)(2).

211.166 Stability testing.

211.166(b) **An adequate number of batches of each drug product shall be tested to determine an appropriate expiration date and a record of such data shall be maintained.** Accelerated studies, combined with basic stability information on the components, drug products, and container-closure system, may be used to support tentative expiration dates provided full shelf life studies are not available and are being conducted. Where **data from accelerated studies** are used to project a tentative expiration date that is beyond a date supported by actual shelf life studies, there must be **stability studies conducted**, including drug product testing at appropriate intervals, until the tentative expiration date is verified or the appropriate expiration date determined.

211.166(c) For homeopathic drug products, the requirements of this section are as follows:

(1) There shall be a **written assessment of stability based at least on testing or examination of the drug product for compatibility of the ingredients, and based on marketing experience with the drug product to indicate that there is no degradation** of the product for the normal or expected period of use.

211.167 Special testing requirements.

211.167(a) For each batch of drug product purporting to be sterile and/or pyrogen-free, there shall be **appropriate laboratory testing to determine conformance to such requirements**. The **test procedures shall be in writing and shall be followed**.

(b) For each batch of ophthalmic ointment, there shall be **appropriate testing to determine conformance to specifications regarding the presence of foreign particles and harsh or abrasive substances. The test procedures shall be in writing and shall be followed**.

(c) For each batch of controlled-release dosage form, **there shall be appropriate laboratory testing to determine conformance to the specifications for the rate of release of each active ingredient. The test procedures shall be in writing and shall be followed.**

211.170 Reserve samples.

211.170(b) An **appropriately identified reserve sample** that is representative of each lot or batch of drug product shall be retained and **stored under conditions consistent with product labeling**. The reserve sample shall be stored in the same immediate container-closure system in which the drug product is marketed or in one that has essentially the same characteristics. The reserve sample consists of at least twice the quantity necessary to perform all the required tests, except those for sterility and pyrogens. Except for those for drug products described in paragraph (b)(2) of this section, reserve samples from representative sample lots or batches selected by acceptable statistical procedures shall be **examined visually** at least once a year for evidence of deterioration unless visual examination would affect the integrity of the reserve sample. Any **evidence of reserve sample deterioration shall be investigated** in accordance with Sec. 211.192. **The results of the examination shall be recorded and maintained with other stability data on the drug product.** Reserve samples of compressed medical gases need not be retained. The retention time is as follows:

(1) For a drug product other than those described in paragraphs (b) (2) and (3) of this section, the reserve sample shall be **retained for 1 year after the expiration date** of the drug product.

(2) For a radioactive drug product, except for nonradioactive reagent kits, the reserve sample shall be retained for:

(i) **Three months after the expiration date** of the drug product if the expiration dating period of the drug product is 30 days or less; or

(ii) **Six months after the expiration date** of the drug product if the expiration dating period of the drug product is more than 30 days.

(3) For an OTC drug product that is exempt for bearing an expiration date under Sec. 211.137, the reserve sample must be retained for **3 years after the lot or batch of drug product is distributed**.

211.173 Laboratory animals.

211.173 Animals used in testing components, in-process materials, or drug products for compliance with established specifications shall be **maintained and controlled in a manner that assures their suitability for their intended use. They shall be identified, and adequate records shall be maintained showing the history of their use.**

211.180 General requirements.

211.180(a) Any **production, control, or distribution record that is required to be maintained in compliance with this part and is specifically associated with a batch of a drug product shall be retained for at least 1 year after the expiration date of the batch or, in the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under Sec. 211.137, 3 years after distribution of the batch.**

(b) Records shall be maintained for all **components, drug product containers, closures, and labeling for at least 1 year after the expiration date or, in the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under Sec. 211.137, 3 years after distribution of the last lot of drug product incorporating the component or using the container, closure, or labeling.**

(c) All records required under this part, or copies of such records, shall be **readily available for authorized inspection during the retention period at the establishment where the activities described in such records occurred**. These records or copies thereof shall be subject to photocopying or other means of reproduction as part of such inspection. Records that can be immediately retrieved from another location by computer or other electronic means shall be considered as meeting the requirements of this paragraph.

(d) Records required under this part may be retained either as **original records** or as **true copies** such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques, such as microfilming, are used, suitable reader and photocopying equipment shall be readily available.

(e) **Written records required by this part shall be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures**. **Written procedures shall be established and followed for such evaluations and shall include provisions for**:

(1) A **review of a representative number of batches**, whether approved or rejected, and, where applicable, records associated with the batch.

(2) A **review of complaints, recalls, returned or salvaged drug products, and investigations** conducted under Sec. 211.192 for each drug product.

(f) **Procedures shall be established to assure that the responsible officials of the firm, if they are not personally involved in or immediately aware of such actions, are notified in writing of any investigations conducted under Secs. 211.198, 211.204, or 211.208 of these regulations, any recalls, reports of inspectional observations issued by the Food and Drug Administration, or any regulatory actions relating to good manufacturing practices brought by the Food and Drug Administration**.

211.182 Equipment cleaning and use log.

A **written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use shall be included in individual equipment logs that show the date, time, product, and lot number of each batch processed**. If equipment is dedicated to manufacture of one product, then individual equipment logs are not required, provided that lots or batches of such product follow in numerical order and are manufactured in numerical sequence. In cases where dedicated equipment is employed, the **records of cleaning, maintenance, and use shall be part of the batch record**. The **persons performing and double-checking the cleaning and maintenance shall date and sign or initial the log indicating that the work was performed**. Entries in the log shall be in chronological order.

211.184 Component, drug product container, closure, and labeling records.

211.184 These **records shall include** the following:

(a) The **identity and quantity of each shipment of each lot of components, drug product containers, closures, and labeling; the name of the supplier; the supplier's lot number(s) if known; the receiving code as specified in Sec. 211.80; and the date of receipt. The name and location of the prime manufacturer, if different from the supplier, shall be listed if known**.

(b) **The results of any test or examination performed** (including those performed as required by Sec. 211.82(a), Sec. 211.84(d), or Sec. 211.122(a)) and the **conclusions derived therefrom**.

(c) **An individual inventory record of each component, drug product container, and closure and, for each component, a reconciliation of the use of each lot of such component. The inventory record shall contain sufficient information to allow determination of any batch or lot of drug product associated with the use of each component, drug product container, and closure**.

(d) Documentation of the **examination and review of labels and labeling for conformity with established specifications** in accord with Secs. 211.122(c) and 211.130(c).

(e) The **disposition of rejected components, drug product containers, closure, and labeling**.

211.186 Master production and control records.

211.186(a) To assure uniformity from batch to batch, **master production and control records for each drug product, including each batch size thereof, shall be prepared, dated, and signed** (full signature, handwritten) **by one person and independently checked, dated, and signed by a second person.** The preparation of master production and control records shall be described in a **written procedure and such written procedure shall be followed**.

211.186(b) **Master production and control records shall include**:

(3) A **complete list of components designated by names or codes sufficiently specific to indicate any special quality characteristic**;

(4) **An accurate statement of the weight or measure of each component, using the same weight system (metric, avoirdupois, or apothecary) for each component**. Reasonable variations may be permitted, however, in the amount of components necessary for the preparation in the dosage form, provided they are **justified in the master production and control records**;

(5) A **statement concerning any calculated excess of component**;

(6) A **statement of theoretical weight or measure at appropriate phases of processing**;

(7) A **statement of theoretical yield, including the maximum and minimum percentages of theoretical yield beyond which investigation according to Sec. 211.192 is required;**

(8) A **description of the drug product containers, closures, and packaging materials, including a specimen or copy of each label and all other labeling signed and dated by the person or persons responsible for approval of such labeling**;

211.188 Batch production and control records.

211.188 **Batch production and control records** shall be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch. These records shall include:

211.188(a) An **accurate reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed**;

211.188(b) **Documentation that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished**, including:

(1) **Dates**;

(2) **Identity of individual major equipment and lines used**;

(3) **Specific identification of each batch of component or in-process material used**;

(4) **Weights and measures of components** used in the course of processing;

(5) **In-process and laboratory control results**;

(6) **Inspection of the packaging and labeling area before and after use**;

(7) A **statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing**;

(8) **Complete labeling control records, including specimens or copies of all labeling used**;

(9) **Description of drug product containers and closures**;

(10) **Any sampling performed**;

(11) **Identification of the persons performing and directly supervising or checking each significant step in the operation**;

(12) **Any investigation made** according to Sec. 211.192.

(13) **Results of examinations made** in accordance with Sec. 211.134.

211.192 Production record review.

All drug product production and control records, including those for packaging and labeling, shall be reviewed and approved by the quality control unit to determine compliance with all established, **approved written procedures before a batch is released or distributed.** Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed. The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. A **written record of the investigation shall be made and shall include the conclusions and followup**.

211.194 Laboratory records.

211.194(a) **Laboratory records shall include complete data derived from all tests** necessary to assure compliance with established specifications and standards, including examinations and assays, as follows:

(1) A **description of the sample received for testing with identification of source (that is, location from where sample was obtained), quantity, lot number or other distinctive code, date sample was taken, and date sample was received for testing**.

(2) A **statement of each method used** in the testing of the sample. The **statement shall indicate the location of data** that establish that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested. (If the method employed is in the current revision of the United States Pharmacopeia, National Formulary, Association of Official Analytical Chemists, Book of Methods,\1\ or in other recognized standard references, or is detailed in an approved new drug application and the referenced method is not modified, a statement indicating the method and reference will suffice). The suitability of all testing methods used shall be verified under actual conditions of use.

(3) A **statement of the weight or measure of sample used for each test, where appropriate**.

(4) A **complete record of all data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, drug product container, closure, in-process material, or drug product, and lot tested**.

(5) A **record of all calculations performed in connection with the test, including units of measure, conversion factors, and equivalency factors**.

(6) A **statement of the results of tests and how the results compare with established standards of identity, strength, quality, and purity for the component, drug product container, closure, in-process material, or drug product tested**.

(7) The **initials or signature of the person who performs each test and the date(s) the tests were performed**.

(8) The **initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards**.

211.194(b) **Complete records shall be maintained of any modification of an established method** employed in testing. Such records shall include **the reason for the modification and data to verify that the modification produced results that are at leas**t as accurate and reliable for the material being tested as the established method.

(c) **Complete records shall be maintained of any testing and standardization of laboratory reference standards, reagents, and standard solutions**.

(d) **Complete records shall be maintained of the periodic calibration of laboratory instruments, apparatus, gauges, and recording devices** required by Sec. 211.160(b)(4).

(e) **Complete records shall be maintained of all stability testing performed** in accordance with Sec. 211.166.

211.196 Distribution records.

Distribution records shall contain the name and strength of the product and description of the dosage form, name and address of the consignee, date and quantity shipped, and lot or control number of the drug product. For compressed medical gas products, distribution records are not required to contain lot or control numbers.

211.198 Complaint files.

211.198(a) **Written procedures describing the handling of all written and oral complaints regarding a drug product shall be established and followed**. Such procedures shall include **provisions for review by the quality control unit**, of any complaint involving the possible failure of a drug product to meet any of its specifications and, for such drug products, a determination as to the need for an investigation in accordance with Sec. 211.192. Such **procedures shall include provisions for review to determine whether the complaint represents a serious and unexpected adverse drug experience** which is required to be reported to the Food and Drug Administration in accordance with Sec. 310.305 of this chapter.

211.198(b) A **written record of each complaint shall be maintained in a file designated for drug product complaints**. The file regarding such drug product complaints shall be maintained at the establishment where the drug product involved was manufactured, processed, or packed, or such file may be maintained at another facility if the written records in such files are **readily available for inspection** at that other facility. Written records involving a drug product shall be maintained until at least 1 year after the expiration date of the drug product, or 1 year after the date that the complaint was received, whichever is longer. In the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under Sec. 211.137, such written records shall be maintained for 3 years after distribution of the drug product.

(1) The **written record shall include the following information, where known: the name and strength of the drug product, lot number, name of complainant, nature of complaint, and reply to complainant**.

(2) Where an investigation under Sec. 211.192 is conducted, the **written record shall include the findings of the investigation and followup**. The record or copy of the record of the investigation shall be maintained at the establishment where the investigation occurred in accordance with Sec. 211.180(c).

(3) Where an investigation under Sec. 211.192 is not conducted, the **written record shall include the reason that an investigation was found not to be necessary and the name of the responsible person making such a determination.**

211.204 Returned drug products.

Returned drug products shall be identified as such and held. If the conditions under which returned drug products have been held, stored, or shipped before or during their return, or if the condition of the drug product, its container, carton, or labeling, as a result of storage or shipping, casts doubt on the safety, identity, strength, quality or purity of the drug product, the returned drug product shall be destroyed unless examination, testing, or other investigations prove the drug product meets appropriate standards of safety, identity, strength, quality, or purity. A drug product may be reprocessed provided the subsequent drug product meets appropriate standards, specifications, and characteristics. **Records of returned drug products shall be maintained and shall include the name and label potency of the drug product dosage form, lot number (or control number or batch number), reason for the return, quantity returned, date of disposition, and ultimate disposition of the returned drug product**. If the reason for a drug product being returned implicates associated batches, an appropriate investigation shall be conducted in accordance with the requirements of Sec. 211.192. **Procedures for the holding, testing, and reprocessing of returned drug products shall be in writing and shall be followed.**

211.208 Drug product salvaging.

Drug products that have been subjected to improper storage conditions including extremes in temperature, humidity, smoke, fumes, pressure, age, or radiation due to natural disasters, fires, accidents, or equipment failures shall not be salvaged and returned to the marketplace. Whenever there is a question whether drug products have been subjected to such conditions, salvaging operations may be conducted only if there is (a) **evidence from laboratory tests and assays** (including animal feeding studies where applicable) that the drug products meet all applicable standards of identity, strength, quality, and purity and (b) **evidence from inspection of the premises that the drug products and their associated packaging were not subjected to improper storage conditions as a result of the disaster or accident**. Organoleptic examinations shall be acceptable only as supplemental evidence that the drug products meet appropriate standards of identity, strength, quality, and purity. **Records including name, lot number, and disposition shall be maintained for drug products subject to this section**.

1.1.2 Electronic Signatures

This section contains interpretations of signature requirements, and readers are strongly recommended to refer to current regulations.

Introduction.

The preamble to 21 CFR Part 11 refers to electronic signatures that meet the requirements as being considered equivalent to full handwritten signatures, initials, and other "general signings" required by agency regulations.

Comment 28 of the preamble states: "The agency advises that current regulations that require records to be signed express those requirements in different ways depending upon the agency's intent and expectations. Some regulations **expressly** state that records must be signed using "full handwritten" signatures, whereas other regulations state that records must be "signed or initialed;" still other regulations **implicitly** call for some kind of signing by virtue of requiring record approvals or endorsements. This last broad category is addressed by the term "general signings" in Section 11.1(c)."

General signings implies that the use of the words "**initials**", or "**approved**", or "**rejected**", or "**authorized**" within FDA regulations equates to a general signing or signature requirement.

Regulations Covered.

FDA GxP Regulations shown at 21 CFR in the following parts as of April 2001:

Part 58 - GLP

Parts 50, 54, 56, 312, 314 - GCP (Part 50 as of June 2001)

Parts 211 - GMP

Definitions.

For the purpose of this guidance, the following terms have been defined in accordance with 21 CFR Part 11 (for "signature") or established custom (for other terms).

Term	Definition
General Signing:	An implied signature indicated by use of the words "initials", or "approved", or "rejected", or "authorized" within FDA regulations.
Signature:	The legal mark of an individual, executed by them, with the present intention of authenticating a written statement permanently.
Identification:	An attribute linked to a record that uniquely identifies the person originating or modifying that record. When used in the context of a computer system that needs to comply with 21 CFR Part 11, identification is not intended to meet the requirements for electronic signatures defined in 21 CFR Part 11.
Initials:	The abbreviated signature of an individual, and considered equivalent to a signature, if intended to meet FDA regulation for signature. Not an acceptable alternative if the regulation calls for full handwritten signature. Interpreted as a general signing.
Written:	Documented permanently and non-verbally. Can be applied to procedures, records, interpretations, authorizations, approvals, or rejections.
Approved:	Indication that a person has accepted a procedure, statement, item of data or conclusion as satisfactory. Interpreted as a general signing.
Rejected:	Indication that a person has rejected a procedure, statement, item of data or conclusion as not satisfactory. Interpreted as a general signing.
Authorized:	Indication that a person in authority has agreed an action or granted privileges. Interpreted as a general signing.
Authenticated:	Indication that information is genuine.

Good Laboratory Practice (GLP)

Summary.

GLP protocols, final reports, QA records and QA statements require ***signature***.

Protocols require sponsor's ***approval***.

Authorization is required for animal treatments and for changes to, and deviations from, standard operating procedures.

Data collected electronically under FDA GLP do not require signature, but personnel collecting data must be ***identified.***

Signatures.

58.3(k) Exact transcripts of raw data to be verified accurate by signature.

58.130(e) Manual data to be recorded in ink and signed or initialed by the individual entering the data. Changes to be signed or identified.

58.3(o), 58.120(a)(11), 58.120(b) Protocol and amendments to be signed by the study director.

58.120(a)(11), 58.33(a), 58.35(b)(5), 58.185(a)(2) Protocols to be approved by the sponsor.

58.3(p), 58.185(b), 58.185(c) Final report and amendments to be signed by study director.

58.90(c) Authorizations of animal treatment to be documented.

58.185(a)(12) Final report includes signed reports of contributing scientists.

58.35(b)(3) QA inspection records written and signed.

58.35(b)(7), 58.185(a)(14) Statement in final report prepared and signed by QA.

58.35(b)(5), 58.81(a) Deviations from standard operating procedures shall be authorized by study director.

58.81(a) Changes to standard operating procedures shall be authorized by management.

Identification.

58.130(e) The individual responsible for direct data input and changes on an automated system to be identified.

Good Clinical Practice (GCP)

Summary.

Under FDA GCP, informed consent and Institutional Review Board (IRB) documentation and Investigator Statement form require ***signature***.

No directly stated requirement to ***sign*** GCP data records.

Several documents related to the application processes for IND, NDA, or Abbreviated NDA submissions require ***signature***.

Signatures.

Required under Protection of Human Subjects and Institutional Review Boards.

50.23(d)(1)	IRB must review and approve use of investigational drug without informed consent when informed consent is not feasible.
50.24(a)(6), 50.27(a); 50.27(b)(1), 56.115(a)(1)	Informed consent document to be in writing and signed by subject or representative and approved by the IRB.
50.27(b)(2)	Short form written consent document to be signed by witness and subject or representative.
50.27(b)(2)	Written summary of elements of consent to be signed by witness and person obtaining consent and IRB to approve written summary.
56.102(m), 56.108(a)(4), 56.108(c), 56.109(a)	IRB reviews and approves the clinical investigation and changes.
312.120(c)(3)	For foreign studies [outside US], research is approved by an independent review committee.

Required under Financial Disclosure by Clinical Investigator.

54.4(a)(1)	Financial Disclosure Form FDA 3454 shall be dated and signed by the chief financial officer or other responsible corporate representative.

Required under Investigational New Drug Application and Applications for FDA Approval to Market a New Drug.

312.53(c)(1) Investigator Statement (Form FDA-1572) to be signed by investigator.

312.23(a)(1)(ix), 314.50(a)(5), 314.94(a)(1) IND cover sheet, NDA and abbreviated NDA application forms require signature of sponsor. Countersignature of US-based representative also required if sponsor has no US base.

314.72(a)(2) If ownership of NDA changes, new owner signs an application form.

312.23(b), 314.50(g)(1) Written statement signed by the original submitter is required to authorize references to information submitted previously by a person other than the applicant.

312.30(a), 312.30(b)(2)(i) Protocol amendments are approved by IRB.

312.59 Sponsor may authorize alternative disposition of unused supplies.

314.50(g)(3) Written statement signed by the data owner allowing use of data in an NDA if it is not owned by the applicant.

314.53(c)(2)(i), 314.53(c)(4) Statement signed by applicant or patent owner that a given patent applies to the NDA.

314.200(d)(3)IV Statement signed by person responsible for such submission that it includes all required studies and information.

314.200(e)(2)IV Statement signed by person responsible for such submission that all records have been searched and the submission is true and accurate.

314.420(b) NDA, abbreviated NDA application, amendment, or supplement may incorporate by reference all or part of any drug master file if the holder authorizes the incorporation in writing.

Identification.

No references.

Good Manufacturing Practice (GMP)

Summary.

Under FDA GMP, ***signatures*** required on master production/control records, master labels, and copy of production/control master placed in batch record.

Records of GMP equipment cleaning and maintenance, and laboratory testing need ***signatures*** or ***initials***.

All materials, components, production and control procedures, and records require ***approval***.

Personnel involved in batch production only need to be ***identified***.

Signatures.

211.182. Written records of major equipment cleaning, maintenance and use, to be signed or initialed by persons performing operation and persons checking.

211.186(a) Master production and control records to have full handwritten signature of person preparing the record and signature of an independent checker.

211.186(b)(8) Master production and control records to include copies of all labeling signed by the quality control unit.

211.194(a) Persons performing laboratory tests to initial or sign records. Checker to initial or sign the records.

211.188(a) Batch record includes signed copy of master record.

211.22(a), 211.22(c), 211.84(e), 211.87, 211.100(a), 211.110(c), 211.115(b), 211.122(b), 211.160(a), 211.192 The quality control unit is responsible for approving or rejecting use of all components, drug product containers, closures, in-process materials, packaging material, labeling, drug products, procedures and specifications, products from contractors, production records, and reprocessing of batches.

Identification.

211.188(b)(11) Batch record includes identification of persons performing and directly supervising or checking each significant step in the operation.

1.2 Examples from US Regulations CFR Parts 203 and 205

This subsection provides examples of records and signatures required by 21 CFR § 203 (Prescription Drug Marketing) and 21 CFR § 205 (Guidelines for State Licensing of Wholesale Prescription Drug Distributors) collectively known as the Prescription Drug Marketing Act.

Predicate Rule RECORDS for Part 203

203.3(z) *Representative* means an employee or agent of a drug manufacturer or distributor who promotes the sale of prescription drugs to **licensed practitioners** and who may solicit or receive **written requests** for the delivery of drug samples. A detailer is a representative.

203.11(a) **Applications** for reimportation for emergency medical care shall be submitted to the director of the FDA District Office in the district where reimportation is sought (addresses found in § 5.115 of this chapter).

203.11(b) **Applications** for reimportation to provide emergency medical care shall be reviewed and approved or disapproved by each district office.

203.23(a) The hospital, health care entity, or charitable institution **documents** the return by filling out a **credit memo** specifying:

(1) The name and address of the hospital, health care entity, or charitable institution;

(2) The name and address of the manufacturer or wholesale distributor from which it was acquired;

(3) The product name and lot or control number;

(4) The quantity returned; and

(5) The date of the return.

203.23(b) The hospital, health care entity, or charitable institution forwards a copy of each **credit memo** to the manufacturer and retains a copy of each **credit memo** for its **records**;

203.23(c) Any drugs returned to a manufacturer or wholesale distributor are kept under proper conditions for storage, handling, and shipping, and **written documentation** showing that proper conditions were maintained is provided to the manufacturer or wholesale distributor to which the drugs are returned.

203.30(a) *Requirements for drug sample distribution by mail or common carrier.* A manufacturer or authorized distributor of record may distribute a drug sample to a practitioner licensed to prescribe the drug that is to be sampled or, at the **written request** of a licensed practitioner, to the pharmacy of a hospital or other health care entity, by mail or common carrier, provided that: to contain, in addition to all of the information in paragraph (b)(l) of this section, the name and address of the pharmacy of the hospital or other health care entity to which the drug sample is to be delivered.

203.30(a)(1) The licensed practitioner **executes and submits a written request** to the manufacturer or authorized distributor of record, as set forth in paragraph (b) of this section, before the delivery of the drug sample;

203.30(a)(3) The recipient **executes a written receipt**, as set forth in paragraph (c) of this section, when the drug sample is delivered; and

203.30(a)(4) The **receipt is returned** to the manufacturer or distributor from which the drug sample was received

203.30(b)(1) *Contents of the written request form for delivery of samples by mail or common carrier.* A **written request** for a drug sample to be delivered by mail or common carrier to a licensed practitioner is required to contain the following:

(ii) The practitioner's State license or authorization number or, where a scheduled drug product is requested, the practitioner's Drug Enforcement Administration number.

(iii) The proprietary or established name and the strength of the drug sample requested;

(iv) The quantity requested;

(v) The name of the manufacturer and the authorized distributor of record, if the drug sample is requested from an authorized distributor of record; and

(vi) The date of the request.

203.30(b)(2) A **written request** for a drug sample to be delivered by mail or common carrier to the pharmacy of a hospital or other health care entity is required to contain, in addition to all of the information in paragraph (b)(l) of this section, the name and address of the pharmacy of the hospital or other health care entity to which the drug sample is to be delivered.

203.30(c) *Contents of the receipt to be completed upon delivery of a drug sample.* The **receipt** is to be on a form designated by the manufacturer or distributor, and is required to contain the following:

203.30(c)(1) If the drug sample is delivered to the licensed practitioner who requested it, the **receipt** is required to contain the name, address, professional title, and **signature** of the practitioner or the practitioner's designee who acknowledges delivery of the drug sample; the proprietary or established name and strength of the drug sample and the quantity of the drug sample delivered; and the date of the delivery.

203.30(c)(2) If the drug sample is delivered to the pharmacy of a hospital or other health care entity at the request of a licensed practitioner, the **receipt** is required to contain the name and address of the requesting licensed practitioner; the name and address of the hospital or health care entity pharmacy designated to receive the drug sample; the name, address, professional title, and **signature** of the person acknowledging delivery of the drug sample; the proprietary or established name and strength of the drug sample; the quantity of the drug sample delivered; and the date of the delivery.

203.31(a) *Requirements for drug sample distribution by means other than mail or common carrier.* A manufacturer or authorized distributor of record may distribute by means other than mail or common carrier, by a representative or detailer, a drug sample to a practitioner licensed to prescribe the drug to be sampled or, at the **written request** of such a licensed practitioner, to the pharmacy of a hospital or other health care entity, provided that:

203.31(a)(4) The **receipt** is returned to the manufacturer or distributor; and

203.31(b)(1) *Contents of the written request forms for delivery of samples by a representative.* (1) A **written request** for delivery of a drug sample by a representative to a licensed practitioner is required to contain the following:

(ii) The practitioner's State license or authorization number, or, where a scheduled drug product is requested, the practitioner's Drug Enforcement Administration number;

(iii) The proprietary or established name and the strength of the drug sample requested;

(iv) The quantity requested;

(v) The name of the manufacturer and the authorized distributor of record, if the drug sample is requested from an authorized distributor of record; and

(vi) The date of the request.

203.31(b)(2) A **written request** for delivery of a drug sample by a representative to the pharmacy of a hospital or other health care entity is required to contain, in addition to all of the information in paragraph (b) of this section, the name and address of the pharmacy of the hospital or other health care entity to which the drug sample is to be delivered.

203.31(c) A **written request** for delivery of a drug sample by a representative to the pharmacy of a hospital or other health care entity is required to contain, in addition to all of the information in paragraph (b) of this section, the name and address of the pharmacy of the hospital or other health care entity to which the drug sample is to be delivered.

203.31(c) *Contents of the receipt to be completed upon delivery of a drug sample.* The **receipt** is to be on a form designated by the manufacturer or distributor, and is required to contain the following:

203.31(c)(1) If the drug sample is received at the address of the licensed practitioner who requested it, the **receipt** is required to contain the name, address, professional title, and **signature** of the practitioner or the practitioner's designee who acknowledges delivery of the drug sample; the proprietary or established name and strength of the drug sample; the quantity of the drug sample delivered; and the date of the delivery.

203.31(c)(2) If the drug sample is received by the pharmacy of a hospital or other health care entity at the request of a licensed practitioner, the **receipt** is required to contain the name and address of the requesting licensed practitioner; the name and address of the hospital or health care entity pharmacy designated to receive the drug sample; the name, address, professional title, and **signature** of the person acknowledging delivery of the drug sample; the proprietary or established name and strength of the drug sample; the quantity of the drug sample delivered; and the date of the delivery.

203.31(d) *Inventory and reconciliation of drug samples of manufacturers' and distributors' representatives.* Each drug manufacturer or authorized distributor of record that distributes drug samples by means of representatives shall conduct, at least annually, a complete and accurate physical inventory of all drug samples. All drug samples in the possession or control of each manufacturer's and distributor's representatives are required to be inventoried and the results of the inventory are required to be recorded in an **inventory record**, as specified in paragraph (d)(1) of this section. In addition, manufacturers and distributors shall reconcile the results of the physical inventory with the most recently completed prior physical inventory and **create a report documenting the reconciliation process**, as specified in paragraph (d)(2) of this section.

203.31(d)(1) The **inventory record** is required to identify all drug samples in a representative's stock by the proprietary or established name, dosage strength, and number of units.

203.31(d)(2) The **reconciliation report** is required to include:

(i) The **inventory record** for the most recently completed prior inventory;

(ii) A **record** of each drug sample shipment received since the most recently completed prior inventory, including the sender and date of the shipment, and the proprietary or established name, dosage strength, and number of sample units received;

(iii) A **record** of drug sample distributions since the most recently completed inventory showing the name and address of each recipient of each sample unit shipped, the date of the shipment, and the proprietary or established name, dosage strength, and number of sample units shipped. For the purposes of this paragraph and paragraph (d)(2)(v) of this section, ''distributions'' includes distributions to health care practitioners or designated hospital or health care entity pharmacies, transfers or exchanges with other firm representatives, returns to the manufacturer or authorized distributor, destruction of drug samples by a sales representative, and other types of drug sample dispositions. The specific type of distribution must be specified in the record;

(iv) A **record** of drug sample thefts or significant losses reported by the representative since the most recently completed prior inventory, including the approximate date of the occurrence and the proprietary or established name, dosage strength, and number of sample units stolen or lost; and

(v) A **record** summarizing the information required by paragraphs (d)(2)(ii) through (d)(2)(iv) of this section. The **record** must show, for each type of sample unit (i.e., sample units having the same established or proprietary name and dosage strength), the total number of sample units received, distributed, lost, or stolen since the most recently completed prior inventory. For example, a typical entry in this record may read ''50 units risperidone (1 mg) returned to manufacturer'' or simply ''Risperidone (1 mg)/50/returned to manufacturer.''

203.31(d)(3) Each drug manufacturer or authorized distributor of record shall take appropriate internal control measures to guard against error and possible fraud in the conduct of the **physical inventory and reconciliation**, and in the preparation of the **inventory record and reconciliation report**.

203.31(e) Each drug manufacturer or authorized distributor of record who distributes drug samples by means of representatives shall **maintain a list** of the names and addresses of its representatives who distribute drug samples and of the sites where drug samples are stored.

203.33 **A sample request or receipt form** may be delivered by mail, common carrier, or private courier or may be transmitted photographically or electronically (i.e., by telephoto, wire photo, radiophoto, facsimile transmission (FAX), xerography, or electronic data transfer) or by any other system, provided that the method for transmission meets the security requirements set forth in § 203.60(c).

203.34 Each manufacturer or authorized distributor of record that distributes drug samples **shall establish, maintain,** and adhere to **written policies and procedures** describing its administrative systems for the following:

203.34(b)(2) Conducting the annual physical inventory and preparation of the **reconciliation report**;

203.35 Manufacturers or authorized distributors of record shall not distribute drug samples on the basis of open ended or standing requests, but shall require separate **written requests** for each drug sample or group of samples.

203.37(a)&(a)(1) (a) *Investigation of falsification of drug sample records.* A manufacturer or authorized distributor of record that has reason to believe that any person has falsified drug sample requests, receipts, or records, or is diverting drug samples, shall: (1) Notify FDA, by telephone or **in writing**, within 5 working days;

203.37(a)(3) **Provide FDA with a complete written report**, including the reason for and the results of the investigation, not later than 30 days after the date of the initial notification in paragraph (a)(1) of this section.

203.37(b)(1) (b) *Significant loss or known theft of drug samples.* A manufacturer or authorized distributor of record that distributes drug samples or a charitable institution that receives donated drug samples from a licensed practitioner shall:

(1) Notify FDA, by telephone or **in writing**, within 5 working days of becoming aware of a significant loss or known theft

203.37(b)(3) Provide FDA with a complete **written report**, including the reason for and the results of the investigation, not later than 30 days after the date of the initial notification in paragraph (b)(1) of this section.

203.37(c)(1) (c) *Conviction of a representative.* (1) A manufacturer or authorized distributor of record that distributes drug samples shall notify FDA, by telephone or **in writing**, within 30 days of becoming aware of the conviction of one or more of its representatives for a violation of section 503(c)(1) of the act or any State law involving the sale, purchase, or trade of a drug sample or the offer to sell, purchase, or trade a drug sample.

203.37(c)(2) A manufacturer or authorized distributor of record shall provide FDA with a complete **written report** not later than 30 days after the date of the initial notification

203.37(d) *Selection of individual responsible for drug sample information.* A manufacturer or authorized distributor of record that distributes drug samples shall inform FDA **in writing** within 30 days of selecting the individual responsible for responding to a request for information about drug samples of that individual's name, business address, and telephone number.

203.38(a) *Lot or control number required on drug sample labeling and sample unit label.* The manufacturer or authorized distributor of record of a drug sample shall include on the label of the sample unit and on the outside container or packaging of the sample unit, if any, an **identifying lot or control number** that will permit the tracking of the distribution of each drug sample unit.

203.38(b) *Records containing lot or control numbers required for all drug samples distributed.* A manufacturer or authorized distributor of record shall maintain for all samples distributed **records of drug sample distribution** containing lot or control numbers that are sufficient to permit the tracking of sample units to the point of the licensed practitioner.

203.38(c) *Labels of sample units.* Each **sample unit** shall bear a **label** that clearly denotes its status as a drug sample, e.g., ''sample,'' ''not for sale,'' ''professional courtesy package.''

(1) A drug that is labeled as a drug sample is deemed to be a drug sample within the meaning of the act.

(2) A drug product dosage unit that bears an imprint identifying the dosage form as a drug sample is deemed to be a drug sample within the meaning of the act.

(3) Notwithstanding paragraphs (c)(1) and (c)(2) of this section, any article that is a drug sample as defined in section 503(c)(1) of the act and § 203.3(i) that fails to bear the label required in this paragraph (c) is a drug sample.

203.39(c) A donated drug sample shall not be dispensed to a patient or be distributed to another charitable institution until it has been examined by a licensed practitioner or registered pharmacist at the recipient charitable institution to confirm that **the donation record** accurately describes the drug sample delivered and that no drug sample is adulterated or misbranded for any reason, including, but not limited to, the following:

(1) The drug sample is out of date;

(2) The labeling has become mutilated, obscured, or detached from the drug sample packaging;

(3) The drug sample shows evidence of having been stored or shipped under conditions that might adversely affect its stability, integrity, or effectiveness;

(4) The drug sample is for a prescription drug product that has been recalled or is no longer marketed;

(5) The drug sample is otherwise possibly contaminated, deteriorated, or adulterated.

203.39(d) The recipient charitable institution shall dispose of any drug sample found to be unsuitable by destroying it or by returning it to the manufacturer. The charitable institution shall maintain **complete records of the disposition** of all destroyed or returned drug samples.

203.39(e) The recipient charitable institution shall prepare at the time of collection or delivery of a drug sample a **complete and accurate donation record**, a copy of which shall be retained by the recipient charitable institution for at least 3 years, containing the following information:

(1) The name, address, and telephone number of the licensed practitioner (or donating charitable institution);

(2) The manufacturer, brand name, quantity, and lot or control number of the drug sample donated;

(3) The date of the donation.

203.39(f) Each recipient charitable institution shall **maintain complete and accurate records** of donation, receipt, inspection, inventory, dispensing, redistribution, destruction, and returns sufficient for complete accountability and auditing of drug sample stocks.

203.39(g) Each recipient charitable institution shall conduct, at least annually, an inventory of prescription drug sample stocks and shall prepare a **report reconciling the results of each inventory** with the most recent prior inventory. Drug sample inventory discrepancies and reconciliation problems shall be investigated by the charitable institution and **reported to FDA**.

203.50(a) Before the completion of any wholesale distribution by a wholesale distributor of a prescription drug for which the seller is not an authorized distributor of record to another wholesale distributor or retail pharmacy, the seller shall **provide to the purchaser a statement identifying each prior sale, purchase, or trade of such drug**. This identifying statement shall include:

(1) The proprietary and established name of the drug;

(2) Dosage;

(3) Container size;

(4) Number of containers;

(5) The drug's lot or control number(s);

(6) The business name and address of all parties to each prior transaction involving the drug, starting with the manufacturer;

(7) The date of each previous transaction.

203.50(b) The **drug origin statement** is subject to the record retention requirements of § 203.60 and must be retained by all wholesale distributors involved in the distribution of the drug product, whether authorized or unauthorized, for 3 years.

203.50(d) Each manufacturer shall maintain at the corporate offices a current **written list of all authorized distributors of record.**

(1) Each manufacturer's list of authorized distributors of record shall specify whether each distributor listed thereon is authorized to distribute the manufacturer's full product line or only particular, specified products.

(2) Each manufacturer shall update its list of authorized distributors of record on a continuing basis.

(3) Each manufacturer shall make its list of authorized distributors of record available on request to the public for inspection or copying. A manufacturer may impose reasonable copying charges for such requests from members of the public.

203.60(a)(1) *Use of electronic records, electronic signatures, and handwritten signatures executed to electronic records*. (1) Provided the requirements of part 11 of this chapter are met, electronic **records**, electronic **signatures**, and handwritten **signatures** executed to electronic records may be used as an alternative to paper records and handwritten signatures executed on paper to meet any of the record and signature requirements of PDMA, PDA, or this part.

203.60(a)(2)(i) The requirements of part 11 of this chapter are met for the **electronic records**, **electronic signatures**, **or handwritten signatures executed to electronic records**;

203.60(a)(2)(ii) **A reasonably secure link between the paper-based and electronic components exists** such that the **combined records and signatures** are trustworthy and reliable, and to ensure that the signer cannot readily repudiate the signed records as not genuine.

203.60(a)(3) For the purposes of this paragraph (a), the phrase ''**record and signature requirements of PDMA, PDA, or this part**'' includes drug sample request and receipt forms, reports, records, and other documents, and their associated signatures required by PDMA, PDA, and this part.

203.60(b) *Maintenance of request and receipt forms, reports, records, and other documents created on paper.* Request and receipt forms, reports, records, and other documents created on paper may be maintained on paper or by photographic imaging (i.e., photocopies or microfiche), provided that the security and authentication requirements described in paragraph (c) of this section are followed. Where a required **document** is created on paper and electronically scanned into a computer, the resulting **record** is an **electronic record** that must meet the requirements of part 11 of this chapter.

203.60(c) *Security and authentication requirements for request and receipt forms, reports, records, and other documents created on paper.* A **request or receipt form, report, record, or other document, and any signature appearing thereon,** that is created on paper and that is maintained by photographic imaging, or transmitted electronically (i.e., by facsimile) shall be maintained or transmitted in a form that provides reasonable assurance of being:

(1) Resistant to tampering, revision, modification, fraud, unauthorized use, or alteration;

(2) Preserved in accessible and retrievable fashion;

(3) Available to permit copying for purposes of review, analysis, verification, authentication, and reproduction by the person who executed the form or created the **record**, by the manufacturer or distributor, and by authorized personnel of FDA and other regulatory and law enforcement agencies.

203.60(d) *Retention of request and receipt forms, reports, lists, records, and other documents.* Any person required to create or maintain **reports, lists**, or other **records** under PDMA, PDA, or this part, including records relating to the distribution of drug samples, shall retain them for at least 3 years after the date of their creation.

203.60(e) *Availability of request and receipt forms, reports, lists, and records.* Any person required to create or maintain request and receipt **forms, reports, lists**, or other **records** under PDMA, PDA, or this part shall make them available, upon request, in a form that permits copying or other means of duplication, to FDA or other Federal, State, or local regulatory and law enforcement officials for review and reproduction. The records shall be made available within 2 business days of a request.

Predicate Rule SIGNATURES for Part 203

203.31(a)(1) The manufacturer or authorized distributor of record receives from the licensed practitioner a **written request signed by the licensed practitioner** before the delivery of the drug sample;

203.31(a)(3) A **receipt is signed by the recipient**, as set forth in paragraph (c) of this section, when the drug sample is delivered;

203.31(b)(1)(i) A **written request** for delivery of a drug sample by a representative to a licensed practitioner is required to contain the following:

(i) The name, address, professional title, and **signature of the practitioner making the request**;

203.31(c)(1) If the drug sample is received at the address of the licensed practitioner who requested it, the **receipt** is required to contain the name, address, professional title, and **signature of the practitioner or the practitioner's designee** who acknowledges delivery of the drug sample; the proprietary or established name and strength of the drug sample; the quantity of the drug sample delivered; and the date of the delivery.

203.31(c)(2) If the drug sample is received by the pharmacy of a hospital or other health care entity at the request of a licensed practitioner, the **receipt** is required to contain the name and address of the requesting licensed practitioner; the name and address of the hospital or health care entity pharmacy designated to receive the drug sample; the name, address, professional title, and **signature of the person** acknowledging delivery of the drug sample; the proprietary or established name and strength of the drug sample; the quantity of the drug sample delivered; and the date of the delivery.

203.60(a)(1) Provided the requirements of part 11 of this chapter are met, electronic records, **electronic signatures, and handwritten signatures executed to electronic records** may be used as an alternative to paper records and handwritten signatures executed on paper to meet any of the record and signature requirements of PDMA, PDA, or this part.

203.60(a)(2) Combinations of **paper records and electronic records**, **electronic records and handwritten signatures executed on paper**, or **paper records and electronic signatures or handwritten signatures executed to electronic records**, may be used to meet any of the record and signature requirements of PDMA, PDA, or this part, provided that:

203.60(a)(2)(i) The requirements of part 11 of this chapter are met for the electronic records, **electronic signatures**, or **handwritten signatures executed to electronic records;**

203.60(a)(2)(ii) A reasonably secure link between the paper-based and electronic components exists such that the combined records and **signatures** are trustworthy and reliable, and to ensure that the signer cannot readily repudiate the signed records as not genuine.

203.60(c) A request or receipt form, report, record, or other document, and any **signature appearing thereon**, that is created on paper and that is maintained by photographic imaging, or transmitted electronically (i.e., by facsimile) shall be maintained or transmitted in a form that provides reasonable assurance of being:

(1) Resistant to tampering, revision, modification, fraud, unauthorized use, or alteration;

(2) Preserved in accessible and retrievable fashion;

(3) Available to permit copying for purposes of review, analysis, verification, authentication, and reproduction by the person who executed the form or created the record, by the manufacturer or distributor, and by authorized personnel of FDA and other regulatory and law enforcement agencies.

Predicate Rule RECORDS for Part 205

205.5(c) Changes in any **information** in paragraph (a) of this section shall be submitted to the State licensing authority as required by such authority considers relevant to and consistent with the public health and safety.

205.6(a)(2) Any **felony convictions** of the applicant under Federal, State, or local laws;

205.6(a)(3) The **applicant's past experience** in the manufacture or distribution of prescription drugs, including controlled substances;

205.6(a)(7) Compliance with requirements to maintain and/or make available to the State licensing authority or to Federal, State, or local law enforcement officials those **records required** under this section;

205.50(f)(1) *Record keeping.* (1) Wholesale drug distributors **shall establish and maintain inventories and records of all transactions regarding the receipt and distribution or other disposition of prescription drugs.** These records shall include the following information:

(i) The source of the drugs, including the name and principal address of the seller or transferor, and the address of the location from which the drugs were shipped;

(ii) The identity and quantity of the drugs received and distributed or disposed of;

(iii) The dates of receipt and distribution or other disposition of the drugs.

205.50(f)(2) **Inventories and records** shall be made available for inspection and photocopying by authorized Federal, State, or local law enforcement agency officials for a period of 3 years after the date of their creation.

205.50(f)(3) **Records** described in this section that are kept at the inspection site or that can be immediately retrieved by computer or other electronic means shall be readily available for authorized inspection during the retention period. **Records** kept at a central location apart from the inspection site and not electronically retrievable shall be made available for inspection within 2 working days of a request by an authorized official of a Federal, State, or local law enforcement agency.

205.50(g) *Written policies and procedures*. Wholesale drug distributors shall **establish, maintain, and adhere to written policies and procedures**, which shall be followed for the receipt, security, storage, inventory, and distribution of prescription drugs, including policies and procedures for identifying, recording, and reporting losses or thefts, and for correcting all errors and inaccuracies in inventories. Wholesale drug distributors shall include in their written policies and procedures the following:

205.50(g)(1) A **procedure** whereby the oldest approved stock of a prescription drug product is distributed first. The **procedure** may permit deviation from this requirement, if such deviation is temporary and appropriate.

205.50(g)(2) A **procedure** to be followed for handling recalls and withdrawals of prescription drugs. Such **procedure** shall be adequate to deal with recalls and withdrawals due to:

(i) Any action initiated at the request of the Food and Drug Administration or other Federal, State, or local law enforcement or other government agency, including the State licensing agency;

(ii) Any voluntary action by the manufacturer to remove defective or potentially defective drugs from the market;

(iii) Any action undertaken to promote public health and safety by replacing of existing merchandise with an improved product or new package design.

205.50(g)(3) A **procedure** to ensure that wholesale drug distributors prepare for, protect against, and handle any crisis that affects security or operation of any facility in the event of strike, fire, flood, or other natural disaster, or other situations of local, State, or national emergency.

205.50(g)(4) A **procedure** to ensure that any outdated prescription drugs shall be segregated from other drugs and either returned to the manufacturer or destroyed. This **procedure** shall provide for **written documentation** of the disposition of outdated prescription drugs. This **documentation** shall be maintained for 2 years after disposition of the outdated drugs.

205.50(h) *Responsible persons*. Wholesale drug distributors **shall establish and maintain lists** of officers, directors, managers, and other persons in charge of wholesale drug distribution, storage, and handling, including a **description of their duties and a summary of their qualifications.**

1.3 Examples from US Regulations CFR Part 820

This subsection provides examples of records and signatures required by 21 CFR § 820 (Medical Device Quality System Regulation).

Predicate Rule Records Part 820

820.3(e) *Design history file* (*DHF*) means a compilation of **records** which describes the design history of a finished device.

820.3(i) *Device history record (DHR)* means a compilation of **records** containing the production history of a finished device.

820.3(j) *Device master record (DMR)* means a compilation of **records** containing the procedures and specifications for a finished device.

820.20(b)(3)(e) *Quality system procedures.* Each manufacturer shall establish quality system **procedures and instructions**. An outline of the structure of the **documentation** used in the quality system shall be established where appropriate.

820.25(b) *Training*. Each manufacturer shall establish **procedures** for identifying training needs and ensure that all personnel are trained to adequately perform their assigned responsibilities. Training shall be **documented**.

820.30 *Design controls.*

820.30(a) *General.* (1) Each manufacturer of any class III or class II device, and the class I devices listed in paragraph (a)(2) of this section, shall establish and maintain **procedures** to control the design of the device in order to ensure that specified design requirements are met.

820.30(b) *Design and development planning*. Each manufacturer shall establish and maintain **plans** that describe or reference the design and development activities and define responsibility for implementation. The **plans** shall identify and describe the interfaces with different groups or activities that provide, or result in, input to the design and development process. The **plans** shall be reviewed, updated, and approved as design and development evolves.

820.30(c) *Design input*. Each manufacturer shall establish and maintain **procedures** to ensure that the design requirements relating to a device are appropriate and address the intended use of the device, including the needs of the user and patient. The procedures shall include a mechanism for addressing incomplete, ambiguous, or conflicting requirements. The design input requirements shall be **documented** and shall be reviewed and approved by a designated individual(s). The approval, including the date and signature of the individual(s) approving the requirements, shall be documented.

820.30(d) *Design output*. Each manufacturer shall establish and maintain **procedures** for defining and documenting design output in terms that allow an adequate evaluation of conformance to design input requirements. Design output procedures shall contain or make reference to acceptance criteria and shall ensure that those design outputs that are essential for the proper functioning of the device are identified. Design output shall be **documented**, reviewed, and approved before release. The approval, including the date and signature of the individual(s) approving the output, shall be documented.

820.30(e) *Design review*. Each manufacturer shall establish and maintain **procedures** to ensure that formal **documented reviews** of the design results are planned and conducted at appropriate stages of the device's design development. The procedures shall ensure that participants at each design review include representatives of all functions concerned with the design stage being reviewed and an individual(s) who does not have direct responsibility for the design stage being reviewed, as well as any specialists needed. The results of a design review, including identification of the design, the date, and the individual(s) performing the review, shall be **documented** in the design history file (the DHF).

820.30(f) *Design verification*. Each manufacturer shall establish and maintain **procedures** for verifying the device design. Design verification shall confirm that the design output meets the design input requirements. The results of the design verification, including identification of the design, method(s), the date, and the individual(s) performing the verification, shall be **documented** in the DHF.

820.30(g) *Design validation*. Each manufacturer shall establish and maintain **procedures** for validating the device design. Design validation shall be performed under defined operating conditions on initial production units, lots, or batches, or their equivalents. Design validation shall ensure that devices conform to defined user needs and intended uses and shall include testing of production units under actual or simulated use conditions. Design validation shall include software validation and risk analysis, where appropriate. The results of the design validation, including identification of the design, method(s), the date, and the individual(s) performing the validation, shall be **documented** in the DHF.

820.30(h) *Design transfer*. Each manufacturer shall establish and maintain **procedures** to ensure that the device design is correctly translated into production specifications.

820.30(i) *Design changes*. Each manufacturer shall establish and maintain **procedures** for the identification, documentation, validation or where appropriate verification, review, and approval of design changes before their implementation.

820.30(j) *Design history file*. Each manufacturer shall establish and maintain a DHF for each type of device. The DHF shall contain or reference the **records** necessary to demonstrate that the design was developed in accordance with the approved design plan and the requirements of this part.

820.40(a) *Document approval and distribution.* Each manufacturer shall designate an individual(s) to review for adequacy and approve prior to issuance all documents established to meet the requirements of this part. The approval, including the date and signature of the individual(s) approving the document, shall be documented. **Documents** established to meet the requirements of this part shall be available at all locations for which they are designated, used, or otherwise necessary, and all obsolete **documents** shall be promptly removed from all points of use or otherwise prevented from unintended use.

820.40(b) *Document changes*. Changes to documents shall be reviewed and approved by an individual(s) in the same function or organization that performed the original review and approval, unless specifically designated otherwise. Approved changes shall be communicated to the appropriate personnel in a timely manner. Each manufacturer shall maintain **records** of changes to **documents**. Change **records** shall include a description of the change, identification of the affected documents, the signature of the approving individual(s), the approval date, and when the change becomes effective.

820.50(a) *Evaluation of suppliers, contractors, and consultants*. Each manufacturer shall **establish and maintain the requirements**, including quality requirements, that must be met by suppliers, contractors, and consultants.

820.50(a)(1) Evaluate and select potential suppliers, contractors, and consultants on the basis of their ability to meet specified requirements, including quality requirements. The evaluation shall be **documented**.

820.50(a)(3) Establish and maintain **records** of acceptable suppliers, contractors, and consultants.

820.50(b) *Purchasing data*. Each manufacturer shall **establish and maintain data** that clearly describe or reference the specified requirements, including quality requirements, for purchased or otherwise received product and services. Purchasing documents shall include, where possible, an agreement that the suppliers, contractors, and consultants agree to notify the manufacturer of changes in the product or service so that manufacturers may determine whether the changes may affect the quality of a finished device. Purchasing data shall be approved in accordance with § 820.40.

820.60 *Identification.* Each manufacturer shall establish and maintain **procedures** for identifying product during all stages of receipt, production, distribution, and installation to prevent mixups.

820.65 *Traceability.* Each manufacturer of a device that is intended for surgical implant into the body or to support or sustain life and whose failure to perform when properly used in accordance with instructions for use provided in the labeling can be reasonably expected to result in a significant injury to the user shall establish and maintain **procedures** for identifying with a control number each unit, lot, or batch of finished devices and where appropriate components. The procedures shall facilitate corrective action. Such identification shall be **documented** in the DHR.

820.70(a) *General.* Each manufacturer shall develop, conduct, control, and monitor production processes to ensure that a device conforms to its specifications. Where deviations from device specifications could occur as a result of the manufacturing process, the manufacturer shall establish and maintain process control **procedures** that describe any process controls necessary to ensure conformance to specifications.

820.70(a)(1) **Documented** instructions, standard operating procedures (SOP's), and methods that define and control the manner of production;

820.70(b) *Production and process changes.* Each manufacturer shall establish and maintain **procedures** for changes to a specification, method, process, or procedure. Such changes shall be verified or where appropriate validated according to § 820.75, before implementation and these activities shall be documented. Changes shall be approved in accordance with § 820.40.

820.70(c) *Environmental control.* Where environmental conditions could reasonably be expected to have an adverse effect on product quality, the manufacturer shall establish and maintain **procedures** to adequately control these environmental conditions. Environmental control system(s) shall be periodically inspected to verify that the system, including necessary equipment, is adequate and functioning properly. These activities shall be **documented** and reviewed.

820.70(d) *Personnel.* Each manufacturer shall **establish and maintain requirements** for the health, cleanliness, personal practices, and clothing of personnel if contact between such personnel and product or environment could reasonably be expected to have an adverse effect on product quality. The manufacturer shall ensure that maintenance and other personnel who are required to work temporarily under special environmental conditions are appropriately trained or supervised by a trained individual.

820.70(e) *Contamination control.* Each manufacturer shall establish and maintain **procedures** to prevent contamination of equipment or product by substances that could reasonably be expected to have an adverse effect on product quality.

820.70(g)(1) *Maintenance schedule.* Each manufacturer shall establish and maintain **schedules** for the adjustment, cleaning, and other maintenance of equipment to ensure that manufacturing specifications are met. Maintenance activities, including the date and individual(s) performing the maintenance activities, shall be **documented.**

820.70(g)(2) *Inspection.* Each manufacturer shall conduct periodic inspections in accordance with established procedures to ensure adherence to applicable equipment maintenance schedules. The inspections, including the date and individual(s) conducting the inspections, shall be **documented**.

820.70(h) *Manufacturing material.* Where a manufacturing material could reasonably be expected to have an adverse effect on product quality, the manufacturer shall establish and maintain **procedures** for the use and removal of such manufacturing material to ensure that it is removed or limited to an amount that does not adversely affect the device's quality. The removal or reduction of such manufacturing material shall be **documented**.

820.70(i) *Automated processes.* When computers or automated data processing systems are used as part of production or the quality system, the manufacturer shall validate computer software for its intended use according to an established protocol. All software changes shall be validated before approval and issuance. These validation activities and results shall be **documented**.

820.72(a) *Control of inspection, measuring, and test equipment.* Each manufacturer shall ensure that all inspection, measuring, and test equipment, including mechanical, automated, or electronic inspection and test equipment, is suitable for its intended purposes and is capable of producing valid results. Each manufacturer shall establish and maintain **procedures** to ensure that equipment is routinely calibrated, inspected, checked, and maintained. The procedures shall include provisions for handling, preservation, and storage of equipment, so that its accuracy and fitness for use are maintained. These activities shall be **documented**.

820.72(b) *Calibration.* Calibration **procedures** shall include specific directions and limits for accuracy and precision. When accuracy and precision limits are not met, there shall be provisions for remedial action to reestablish the limits and to evaluate whether there was any adverse effect on the device's quality. These activities shall be **documented.**

820.72(b)(1) *Calibration standards.* Calibration **standards** used for inspection, measuring, and test equipment shall be traceable to national or international standards. If national or international standards are not practical or available, the manufacturer shall use an independent reproducible standard. If no applicable standard exists, the manufacturer shall establish and maintain an **in-house standard**.

820.72(b)(2) *Calibration records.* The equipment identification, calibration dates, the individual performing each calibration, and the next calibration date shall be **documented**. These **records** shall be displayed on or near each piece of equipment or shall be readily available to the personnel using such equipment and to the individuals responsible for calibrating the equipment.

820.75(a) Where the results of a process cannot be fully verified by subsequent inspection and test, the process shall be validated with a high degree of assurance and approved according to established procedures. The validation activities and results, including the date and signature of the individual(s) approving the validation and where appropriate the major equipment validated, shall be **documented.**

820.75(b) Each manufacturer shall establish and maintain **procedures** for monitoring and control of process parameters for validated processes to ensure that the specified requirements continue to be met.

820.75(b)(2) For validated processes, the monitoring and control methods and data, the date performed, and, where appropriate, the individual(s) performing the process or the major equipment used shall be **documented**.

820.75(c) When changes or process deviations occur, the manufacturer shall review and evaluate the process and perform revalidation where appropriate. These activities shall be **documented**.

820.80(a) Each manufacturer shall establish and maintain **procedures** for acceptance activities. Acceptance activities include inspections, tests, or other verification activities.

820.80(b) *Receiving acceptance activities.* Each manufacturer shall establish and maintain **procedures** for acceptance of incoming product. Incoming product shall be inspected, tested, or otherwise verified as conforming to specified requirements. Acceptance or rejection shall be **documented**.

820.80(c) *In-process acceptance activities.* Each manufacturer shall establish and maintain acceptance **procedures**, where appropriate, to ensure that specified requirements for in-process product are met. Such procedures shall ensure that in-process product is controlled until the required inspection and tests or other verification activities have been completed, or necessary approvals are received, and are **documented**.

820.80(d) *Final acceptance activities.* Each manufacturer shall establish and maintain **procedures** for finished device acceptance to ensure that each production run, lot, or batch of finished devices meets acceptance criteria. Finished devices shall be held in quarantine or otherwise adequately controlled until released.

820.80(e) *Acceptance records.* Each manufacturer shall **document** acceptance activities required by this part. These **records** shall include:

(1) The acceptance activities performed;

(2) the dates acceptance activities are performed;

(3) the results;

(4) the signature of the individual(s) conducting the acceptance activities; and

(5) where appropriate the equipment used. These **records** shall be part of the DHR.

820.86 Each manufacturer shall identify by suitable means the acceptance status of product, to indicate the conformance or nonconformance of product with acceptance criteria. The **identification of acceptance status shall be maintained** throughout manufacturing, packaging, labeling, installation, and servicing of the product to ensure that only product which has passed the required acceptance activities is distributed, used, or installed.

820.90(a) *Control of nonconforming product.* Each manufacturer shall establish and maintain **procedures** to control product that does not conform to specified requirements. The procedures shall address the identification, documentation, evaluation, segregation, and disposition of nonconforming product. The evaluation of nonconformance shall include a determination of the need for an investigation and notification of the persons or organizations responsible for the nonconformance. The evaluation and any investigation shall be documented.

820.90(b)(1) *Nonconformity review and disposition.* (1) Each manufacturer shall establish and maintain **procedures** that define the responsibility for review and the authority for the disposition of nonconforming product. The procedures shall set forth the review and disposition process. Disposition of nonconforming product shall be **documented**. **Documentation** shall include the justification for use of nonconforming product and the signature of the individual(s) authorizing the use.

820.90(b)(2) Each manufacturer shall establish and maintain **procedures** for rework, to include retesting and reevaluation of the nonconforming product after rework, to ensure that the product meets its current approved specifications. Rework and reevaluation activities, including a determination of any adverse effect from the rework upon the product, shall be documented in the DHR.

820.100(a) Each manufacturer shall establish and maintain **procedures** for implementing corrective and preventive action. The **procedures** shall include requirements for:

(1) Analyzing processes, work operations, concessions, quality audit **reports**, quality **records**, service **records**, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems. Appropriate statistical methodology shall be employed where necessary to detect recurring quality problems;

(2) Investigating the cause of nonconformities relating to product, processes, and the quality system;

(3) Identifying the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems;

(4) Verifying or validating the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device;

(5) Implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems;

(6) Ensuring that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems; and

(7) Submitting relevant information on identified quality problems, as well as corrective and preventive actions, for management review.

820.100(b) All activities required under this section, and their results, shall be **documented**.

820.120 Each manufacturer shall establish and maintain **procedures** to control labeling activities.

820.140 Each manufacturer shall establish and maintain **procedures** to ensure that mixups, damage, deterioration, contamination, or other adverse effects to product do not occur during handling.

820.150(a) Each manufacturer shall establish and maintain **procedures** for the control of storage areas and stock rooms for product to prevent mixups, damage, deterioration, contamination, or other adverse effects pending use or distribution and to ensure that no obsolete, rejected, or deteriorated product is used or distributed. When the quality of product deteriorates over time, it shall be stored in a manner to facilitate proper stock rotation, and its condition shall be assessed as appropriate.

820.150(b) Each manufacturer shall establish and maintain **procedures** that describe the methods for authorizing receipt from and dispatch to storage areas and stock rooms.

820.160(a) Each manufacturer shall establish and maintain **procedures** for control and distribution of finished devices to ensure that only those devices approved for release are distributed and that purchase orders are reviewed to ensure that ambiguities and errors are resolved before devices are released for distribution. Where a device's fitness for use or quality deteriorates over time, the procedures shall ensure that expired devices or devices deteriorated beyond acceptable fitness for use are not distributed.

820.160(b) Each manufacturer shall maintain distribution **records** which include or refer to the location of:

(1) The name and address of the initial consignee;

(2) The identification and quantity of devices shipped;

(3) The date shipped; and

(4) Any control number(s) used.

820.170(a) Each manufacturer of a device requiring installation shall establish and maintain adequate installation and inspection **instructions**, and where appropriate test procedures. Instructions and procedures shall include directions for ensuring proper installation so that the device will perform as intended after installation. The manufacturer shall distribute the instructions and procedures with the device or otherwise make them available to the person(s) installing the device.

820.170(b) The person installing the device shall ensure that the installation, inspection, and any required testing are performed in accordance with the manufacturer's instructions and procedures and shall **document** the inspection and any test results to demonstrate proper installation.

820.180 All **records** required by this part shall be maintained at the manufacturing establishment or other location that is reasonably accessible to responsible officials of the manufacturer and to employees of FDA designated to perform inspections. Such **records**, including those not stored at the inspected establishment, shall be made readily available for review and copying by FDA employee(s). Such **records** shall be legible and shall be stored to minimize deterioration and to prevent loss. Those **records** stored in automated data processing systems shall be backed up.

820.180(a) *Confidentiality.* **Records** deemed confidential by the manufacturer may be marked to aid FDA in determining whether information may be disclosed under the public information regulation in part 20 of this chapter.

820.180(b) *Record retention period.* All **records** required by this part shall be retained for a period of time equivalent to the design and expected life of the device, but in no case less than 2 years from the date of release for commercial distribution by the manufacturer.

820.180(c) *Exceptions.* This section does not apply to the **reports** required by § 820.20(c) Management review, § 820.22 Quality audits, and supplier audit reports used to meet the requirements of § 820.50(a) Evaluation of suppliers, contractors, and consultants, but does apply to **procedures** established under these provisions. Upon request of a designated employee of FDA, an employee in management with executive responsibility shall certify in writing that the management reviews and quality audits required under this part, and supplier audits where applicable, have been performed and documented, the dates on which they were performed, and that any required corrective action has been undertaken.

820.181 Each manufacturer shall maintain **device master records (DMR's).** Each manufacturer shall ensure that each DMR is prepared and approved in accordance with § 820.40. The DMR for each type of device shall include, or refer to the location of, the following information:

(a) Device specifications including appropriate drawings, composition, formulation, component specifications, and software specifications;

(b) Production process specifications including the appropriate equipment specifications, production methods, production procedures, and production environment specifications;

(c) Quality assurance procedures and specifications including acceptance criteria and the quality assurance equipment to be used;

(d) Packaging and labeling specifications, including methods and processes used; and

(e) Installation, maintenance, and servicing procedures and methods.

820.184 Each manufacturer shall maintain **device history records (DHR's)**. Each manufacturer shall establish and maintain procedures to ensure that DHR's for each batch, lot, or unit are maintained to demonstrate that the device is manufactured in accordance with the DMR and the requirements of this part. The DHR shall include, or refer to the location of, the following information:

(a) The dates of manufacture;

(b) The quantity manufactured;

(c) The quantity released for distribution;

(d) The acceptance **records** which demonstrate the device is manufactured in accordance with the DMR;

(e) The primary identification label and labeling used for each production unit; and

(f) Any device identification(s) and control number(s) used.

820.186 Each manufacturer shall maintain a **quality system record (QSR)**. The QSR shall include, or refer to the location of, procedures and the documentation of activities required by this part that are not specific to a particular type of device(s), including, but not limited to, the records required by § 820.20. Each manufacturer shall ensure that the QSR is prepared and approved in accordance with § 820.40.

820.198(a) Each manufacturer shall maintain **complaint files**. Each manufacturer shall establish and maintain procedures for receiving, reviewing, and evaluating complaints by a formally designated unit. Such procedures shall ensure that:

(1) All complaints are processed in a uniform and timely manner;

(2) Oral complaints are **documented** upon receipt; and

(3) Complaints are evaluated to determine whether the complaint represents an event which is required to be reported to FDA under part 803 or 804 of this chapter, Medical Device Reporting.

820.198(b) Each manufacturer shall review and evaluate all complaints to determine whether an investigation is necessary. When no investigation is made, the manufacturer shall maintain a **record** that includes the reason no investigation was made and the name of the individual responsible for the decision not to investigate.

820.198(d) Any complaint that represents an event which must be reported to FDA under part 803 or 804 of this chapter shall be promptly reviewed, evaluated, and investigated by a designated individual(s) and shall be **maintained** in a separate portion of the complaint files or otherwise clearly identified. In addition to the information required by § 820.198(e), **records** of investigation under this paragraph shall include a determination of:

(1) Whether the device failed to meet specifications;

(2) Whether the device was being used for treatment or diagnosis; and

(3) The relationship, if any, of the device to the reported incident or adverse event.

820.198(e) When an investigation is made under this section, a **record** of the investigation shall be **maintained** by the formally designated unit identified in paragraph (a) of this section. The **record** of investigation shall include:

(1) The name of the device;

(2) The date the complaint was received;

(3) Any device identification(s) and control number(s) used;

(4) The name, address, and phone number of the complainant;

(5) The nature and details of the complaint;

(6) The dates and results of the investigation;

(7) Any corrective action taken; and

(8) Any reply to the complainant.

820.200(a) Where servicing is a specified requirement, each manufacturer shall establish and maintain **instructions** and **procedures** for performing and verifying that the servicing meets the specified requirements.

820.200(d) Service reports shall be **documented** and shall include:

(1) The name of the device serviced;

(2) Any device identification(s) and control number(s) used;

(3) The date of service;

(4) The individual(s) servicing the device;

(5) The service performed; and

(6) The test and inspection data.

820.250(a) Where appropriate, each manufacturer shall establish and maintain **procedures** for identifying valid statistical techniques required for establishing, controlling, and verifying the acceptability of process capability and product characteristics.

820.250(b) Sampling **plans**, when used, shall be **written** and based on a valid statistical rationale. Each manufacturer shall establish and maintain **procedures** to ensure that sampling methods are adequate for their intended use and to ensure that when changes occur the sampling plans are reviewed. These activities shall be documented.

Predicate Rule Signatures Part 820

820.30(b) Design and development planning. Each manufacturer shall establish and maintain plans that describe or reference the design and development activities and define responsibility for implementation. The plans shall identify and describe the interfaces with different groups or activities that provide, or result in, input to the design and development process. The plans shall be reviewed, updated, and **approved** as design and development evolves.

820.30(c) *Design input*. Each manufacturer shall establish and maintain procedures to ensure that the design requirements relating to a device are appropriate and address the intended use of the device, including the needs of the user and patient. The procedures shall include a mechanism for addressing incomplete, ambiguous, or conflicting requirements. The design input requirements shall be documented and shall be reviewed and **approved** by a designated individual(s). The approval, including the date and **signature** of the individual(s) approving the requirements, shall be documented.

820.30(d) *Design output*. Each manufacturer shall establish and maintain procedures for defining and documenting design output in terms that allow an adequate evaluation of conformance to design input requirements. Design output procedures shall contain or make reference to acceptance criteria and shall ensure that those design outputs that are essential for the proper functioning of the device are identified. Design output shall be documented, reviewed, and **approved** before release. The approval, including the date and **signature** of the individual(s) approving the output, shall be documented.

820.30(i) *Design changes*. Each manufacturer shall establish and maintain procedures for the identification, documentation, validation or where appropriate verification, review, and **approval** of design changes before their implementation.

820.40(a) *Document approval and distribution.* Each manufacturer shall designate an individual(s) to review for adequacy and **approve** prior to issuance all documents established to meet the requirements of this part. The approval, including the date and **signature** of the individual(s) approving the document, shall be documented. Documents established to meet the requirements of this part shall be available at all locations for which they are designated, used, or otherwise necessary, and all obsolete documents shall be promptly removed from all points of use or otherwise prevented from unintended use.

820.40(b) *Document changes*. Changes to documents shall be reviewed and approved by an individual(s) in the same function or organization that performed the original review and approval, unless specifically designated otherwise. Approved changes shall be communicated to the appropriate personnel in a timely manner. Each manufacturer shall maintain records of changes to documents. Change records shall include a description of the change, identification of the affected documents, the **signature** of the approving individual(s), the approval date, and when the change becomes effective.

820.50(b) *Purchasing data*. Each manufacturer shall establish and maintain data that clearly describe or reference the specified requirements, including quality requirements, for purchased or otherwise received product and services. Purchasing documents shall include, where possible, an agreement that the suppliers, contractors, and consultants agree to notify the manufacturer of changes in the product or service so that manufacturers may determine whether the changes may affect the quality of a finished device. Purchasing data shall be **approved** in accordance with § 820.40.

820.70(a)(4) [Where process controls are needed they shall include:]

The **approval** of processes and process equipment; designed, constructed, placed, and installed

820.70(b) *Production and process changes.* Each manufacturer shall establish and maintain procedures for changes to a specification, method, process, or procedure. Such changes shall be verified or where appropriate validated according to § 820.75, before implementation and these activities shall be documented. Changes shall be **approved** in accordance with § 820.40.

820.80(d) Finished devices shall not be released for distribution until:…

(3) the release is authorized by the **signature** of a designated individual(s); and

(4) the authorization is dated.

820.80(e) *Acceptance records.* Each manufacturer shall document acceptance activities required by this part. These records shall include:…

(4) the **signature** of the individual(s) conducting the acceptance activities; and

(5) where appropriate the equipment used. These records shall be part of the DHR.

820.100(a) Each manufacturer shall establish and maintain procedures for implementing corrective and preventive action. The procedures shall include requirements for:

(1) Analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems. Appropriate statistical methodology shall be employed where necessary to detect recurring quality problems;

(2) Investigating the cause of nonconformities relating to product, processes, and the quality system;

(3) Identifying the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems;

(4) Verifying or validating the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device;

(5) Implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems;

(6) Ensuring that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems; and

(7) Submitting relevant information on identified quality problems, as well as corrective and preventive actions, for management review.

820.100(b) All activities required under this section, and their results, shall be documented.

820.120(b) *Labeling inspection.* Labeling shall not be released for storage or use until a designated individual(s) has examined the labeling for accuracy including, where applicable, the correct expiration date, control number, storage instructions, handling instructions, and any additional processing instructions. The release, including the date and **signature** of the individual(s) performing the examination, shall be documented in the DHR.

2 Examples from EU Regulations

This sub-section contains examples of records, signatures and identifications required by EU Good Manufacturing Practice.

Chapter 1: Quality Management

Quality Assurance (QA)

1.2

(vi) The finished product is correctly processed and **checked**, according to the defined procedures.

(vii) Medicinal products are not sold or supplied before a QP has **certified** that each production batch has been produced and controlled in accordance with the requirements of the marketing **authorisation** and any other regulations relevant to the production, control and release of medicinal products.

Good Manufacturing Practice for medicinal products (GMP)

1.3

(vi) **Records** are made, manually and/or by recording instruments, during manufacture which demonstrate that all steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected. Any significant deviations are fully **recorded** and **investigated**.

Quality Control (QC)

1.4

(iv) **Records** are made, manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting and testing procedures were actually carried out. Any deviations are fully **recorded** and **investigated**.

(vi) **Records** are made of the results of inspection and that testing of materials, intermediate, bulk and finished products is formally **assessed** against specification. Product **assessment** includes a **review** and **evaluation** of relevant production documentation and an **assessment** of deviations from specified procedures.

(vii) No batch of product is released for sale or supply, prior to certification by a QP that it is in accordance with the requirements of the marketing **authorisation**.

Chapter 2: Personnel

Key personnel

2.4

a) ...a QP must ensure that each batch has been produced and tested**/checked** in accordance with the directives and the marketing **authorisation**.

c) A QP must **certify** in a register or equivalent document, as operations are carried out and before any release, that each production batch satisfies the provisions of Article 22.

2.5 The Head of the Production Department generally has the following responsibilities:

(ii) To **approve** the instructions relating to production operations and to ensure their strict implementation.

(iii) To ensure that the production **records** are **evaluated** and **signed** by an authorised person before they are sent to the QC Department;

(iv) To **check** the maintenance of his department, premises and equipment.

2.6 The Head of the QC Department generally has the following responsibilities:

(i) To **approve** or **reject**, as he sees fit, starting materials, packaging materials, and intermediate, bulk and finished products.

(ii) To evaluate batch **records**.

(iv) To **approve** specifications, sampling instructions, test methods and other QC procedures.

(v) To **approve** and monitor any contract analysis.

(vi) To **check** the maintenance of his department, premises and equipment.

2.7

- The **authorisation** of written procedures and other documents, including amendments;
- The **approval** and monitoring of suppliers of materials;
- The **approval** and monitoring of contract manufacturers;

Training

2.9 ....Training programmes should be available, **approved** by either the Head of Production or the Head of QC, as appropriate. Training **records** should be kept.

Chapter 4: Documentation

General

4.2 Documents should be designed, prepared, reviewed and distributed with care. They should comply with the relevant parts of the manufacturing and marketing **authorisation** dossiers.

4.3 Documents should be **approved**, **signed,** and dated by appropriate and authorised persons.

4.7 Any alteration made to the entry on a document should be **signed** and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be **recorded**.

4.8 The **records** should be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of medicinal products are traceable. They should be retained for at least one year after the expiry date of the finished product.

4.9 Data may be **recorded** by electronic data processing systems, photographic or other reliable means, but detailed procedures relating to the system in use should be available and the accuracy of the **records** should be **checked**.

Documents Required

4.10 Specifications

There should be appropriately **authorised** and dated specifications for starting and packaging materials and finished products; where appropriate, they should be also available for intermediate or bulk products.

Manufacturing Formula and Processing Instructions

Formally **authorised** manufacturing formula and processing instructions should exist for each product and batch size to be manufactured. They are often combined in one document.

Packaging instructions

4.16 There should be formally **authorised** packaging instructions for each product, pack size and type.

Batch processing records

4.17 Before any processing begins, there should be **recorded checks** that the equipment and work station are clear of previous products, documents or materials not required for the planed process, and that equipment is clean and suitable for use.

During processing, the following information should be **recorded** at the time each action is taken and, after completion, the **record** should be dated and **signed** in agreement by the person responsible for the processing operations:

d) **Initials** of the operator of different significant steps of production and, where appropriate, of the person who **checked** each of these operations (e.g., weighing).

g) A **record** of the in-process controls and the **initials** of the person(s) carrying them out, and the results obtained.

i) Notes on special problems including details, with **signed authorisation** for any deviation from the manufacturing formula and processing instructions.

Batch packaging records

4.18 Before any packaging operation begins, there should be **recorded checks** that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations, and that equipment is clean and suitable for use.

d) The **initials** of the operators of the different significant steps.

e) **Records** of **checks** for identity and conformity with the packaging instructions including the results of in-process controls.

h) Notes on any special problems or unusual events including details, with **signed authorisation** for any deviation from the manufacturing formula and processing instructions.

Other

4.28 Log books should be kept for major or critical equipment **recording**, as appropriate, any validations, calibrations, maintenance, cleaning or repair operations, including the dates and **identify** of people who carried these operations out.

Chapter 5: Production

General

5.15 Any deviation from instructions or procedures should be avoided as far as possible. If a deviation occurs, it should be **approved** in writing by a competent person, with the involvement of the QC Department when appropriate.

Starting materials

5.33 Each dispensed material and its weight or volume should be independently **checked** and the **check recorded**.

Processing operations: intermediate and bulk products

5.38 Any necessary in-process controls and environmental controls should be carried out and **recorded**.

Packaging materials

5.41 Packaging materials should be issued for use only by authorised personnel following an **approved** and documented procedure.

Packaging operations

5.55 Products which have been involved in an unusual event should only be reintroduced into the process after special inspection, **investigation** and **approval** by authorised personnel. Detailed **records** should be kept of this operation.

Rejected, recovered and returned materials

5.61 **Rejected** materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed. Whatever action is taken should be **approved** and **recorded** by authorised personnel.

5.62 The reprocessing of **rejected** products should be exceptional. It is only permitted if the quality of the final product is not affected, if the specifications are met and if it is done in accordance with a defined and authorised procedure after **evaluation** of the risks involved. **Records** should be kept of the reprocessing.

5.63 The recovery of all or part of earlier batches which conform to the required quality by incorporation into a batch of the same product at a defined stage of manufacture should be **authorised** beforehand. This recovery should be carried out in accordance with a defined procedure after **evaluation** of the risks involved, including any possible effect on shelf life. The recovery should be **recorded**.

5.65 Products returned from the market and which have left the control of the manufacturer should be destroyed unless there is no doubt that heir quality is satisfactory; they may be considered for resale, relabeling or recovery in a subsequent batch only after they have been critically **assessed** by the QC Department in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this **assessment**. Where any doubt arises over the quality of the product, it should not be considered suitable for reissue or reuse, although basic chemical reprocessing to recover active ingredient may be possible. Any action taken should be appropriately **recorded**.

Chapter 6: Quality Control

General

6.3 Finished product **assessment** should embrace all relevant factors, including production conditions, results of in-process testing, a review of manufacturing (including packaging) documentation, compliance with Finished Product Specification and examination of the final finished pack.

Testing

6.17

f) **Initials** of the persons who performed the testing.

g) **Initials** of the persons who verified the testing and the calculations, where appropriate.

h) A clear **statement of release or rejection** (or other status decision) and the dated signature of the designated Responsible Person.

3 Examples from ICH Q7A

This section provides examples of signatures and approvals required by ICH Q7A (see Appendix 13, reference 12).

ICH Q7A also contains extensive requirements for records which are not detailed in this table.

ICH Q7A § 2.2 Responsibilities of the Quality Unit

2.21 The quality unit(s) should review and **approve** all appropriate quality-related documents.

2.22 5. **Approving** all specifications and master production instructions

6. **Approving** all procedures affecting the quality of intermediates or APIs

8. **Approving** intermediate and API contract manufacturers

9. **Approving** changes that potentially affect intermediate or API quality

10. Reviewing and **approving** validation protocols and reports

ICH Q7A § 2.3 Responsibility for Production Activities

1. Preparing, reviewing, **approving**, and distributing the instructions for the production of intermediates or APIs according to written procedures.

2. Producing APIs and, when appropriate, intermediates according to **pre-approved** instructions

3. Reviewing all production batch records and ensuring that these are completed and **signed**

8. Making sure that validation protocols and reports are reviewed and **approved**

ICH Q7A § 2.4 Internal Audits (Self Inspection)

2.40 To verify compliance with the principles of GMP for APIs, regular internal audits should be performed in accordance with an **approved** schedule.

ICH Q7A § 5.3 Calibration

5.33 The current calibration status of critical equipment should be known and verifiable.

5.35 Deviations from **approved** standards of calibration on critical instruments

ICH Q7A § 6.1 Documentation System and Specifications

6.10 All documents related to the manufacture of intermediates or APIs should be prepared, reviewed, **approved,** and distributed according to written procedures. Such documents can be in paper or electronic form.

6.14 When entries are made in records, these should be made indelibly in spaces provided for such entries, directly after performing the activities, and should identify the person making the entry. Corrections to entries should be dated and **signed** and leave the original entry still legible.

6.18 If **electronic signatures** are used on documents, they should be authenticated and secure.

ICH Q7A § 6.3 Records of Raw Materials, Intermediates, API Labeling and Packaging Materials

6.30 The results of any test or examination performed and the conclusions derived from this

Documentation of the examination and review of API labeling and packaging materials for conformity with established specifications

Master (**approved**) labels should be maintained for comparison to issued labels.

ICH Q7A § 6.4 Master Production Instructions (Master Production and Control Records)

6.40 To ensure uniformity from batch to batch, master production instructions for each intermediate and API should be prepared, dated, and **signed** by one person and independently checked, dated, and **signed** by a person in the quality unit(s).

ICH Q7A § 6.5 Batch Production Records (Batch Production and Control Records)

6.51 These records should be numbered with a unique batch or identification number, dated and **signed** when issued….

6.52 **Signatures** of the persons performing and directly supervising or checking each critical step in the operation.

ICH Q7A § 6.6 Laboratory Control Records

6.60 Laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays, as follows:...

- The **signature** of the person who performed each test and the date(s) the tests were performed.
- The date and **signature** of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

ICH Q7A § 6.7 Batch Production Record Review

6.70 Written procedures should be established and followed for the review and **approval** of batch production and laboratory control records, including packaging and labeling, to determine compliance of the intermediate or API with established specifications before a batch is released or distributed.

6.71 Batch production and laboratory control records of critical process steps should be reviewed and **approved** by the quality unit(s) before an API batch is released or distributed. Production and laboratory control records of non-critical process steps can be reviewed by qualified production personnel or other units following procedures **approved** by the quality unit(s)

ICH Q7A § 7 Materials Management/General Controls

7.10 There should be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing, and **approval** or **rejection** of materials.

7.12 Materials should be purchased against an agreed specification, from a supplier, or suppliers, **approved** by the quality unit(s).

7.20 Upon receipt and before **acceptance**, each container or grouping of containers of materials should be examined visually for correct labeling...

Materials should be held under quarantine until they have been sampled, examined, or tested, as appropriate, and released for use.

7.31 Supplier **approva**l should include an evaluation that provides adequate evidence (e.g., past quality history) that the manufacturer can consistently provide material meeting specifications...

ICH Q7A § 8.3 In-process Sampling and Controls

8.32 Critical in-process controls (and critical process monitoring), including the control points and methods, should be stated in writing and **approved** by the quality unit(s)

8.33 In-process controls can be performed by qualified production department personnel and the process adjusted without prior quality unit(s) **approval** if the adjustments are made within pre-established limits **approved** by the quality unit(s)....

ICH Q7A § 9.3 Label Issuance and Control

9.31 Procedures should be established to reconcile the quantities of labels issued, used, and returned and to evaluate discrepancies found between the number of containers labeled and the number of labels issued. Such discrepancies should be investigated, and the investigation should be **approved** by the quality unit(s)

ICH Q7A § 11.1 Laboratory Controls/General Controls

11.11 There should be documented procedures describing sampling, testing, **approval**, or **rejection** of materials and recording and storage of laboratory data...

11.12 ...Specifications, sampling plans, and test procedures, including changes to them, should be drafted by the appropriate organizational unit and **reviewed** and **approved** by the quality unit(s).

11.19 Secondary reference standards should be appropriately prepared, identified, tested, **approved**, and stored....

ICH Q7A § 11.4 Certificates of Analysis

11.43 Certificates should be dated and **signed** by authorized personnel of the quality unit(s)

ICH Q7A § 19.2 APIs for Use in Clinical Trials/Quality

19.20 Appropriate GMP concepts should be applied in the production of APIs for use in clinical trials with a suitable mechanism for **approval** of each batch.

19.21 A quality unit(s) independent from production should be established for the **approval** or **rejection** of each batch of API for use in clinical trials.

Appendix 7
Case Studies

1 Introduction

The following case studies have been compiled and reviewed by GAMP Forum members worldwide to provide realistic and practical guidance on how to handle electronic records and signatures within a number of common automated systems used across the life science industries. Examples are presented of common systems used in GCP, GLP and GMP areas.

2 Topics Covered

The guidance is presented as a series of questions and answers. For each example the topics covered are:

- Type of application
- System description
- Typical user interface
- Use of networks
- Regulated data being processed
- Regulated data being recorded
- Impact of records
- Hybrid situations
- Use of electronic signatures
- Access controls
- Use of audit trails
- Change control to data
- Procedures required
- Special issues to manage

3 Common Issues

The following are common issues found across different systems and organizations:

- Changes to system configuration or environment

  Changes to system configuration or upgrades to environment or operating system should be considered as part of formal change control and a risk assessment applied to determine the extent of validation work required.

- Copies of records for regulatory inspection

  Where copies of records are required for regulatory inspection the systems described need to be able to produce the defined regulated records either as printouts from the system or exported to another system in a common portable format (see also Appendix 4 - Copies of Records).

- Use of IT Infrastructure Security Features

  The use of IT infrastructure security features, such as transaction logs, is not covered in the individual case studies below, but use of such features is good practice. Such features can assist with tracking changes to regulated electronic records and should be considered as part of the risk management approach for each system.

- Use of Document Management Systems

  Many local systems and applications, such as label printing or spreadsheets, do not have the capability to implement the controls required to enable paperless operation.

  To achieve paperless operation such systems require linking to a higher level system to manage documents that provide adequate functionality, security, and change control.

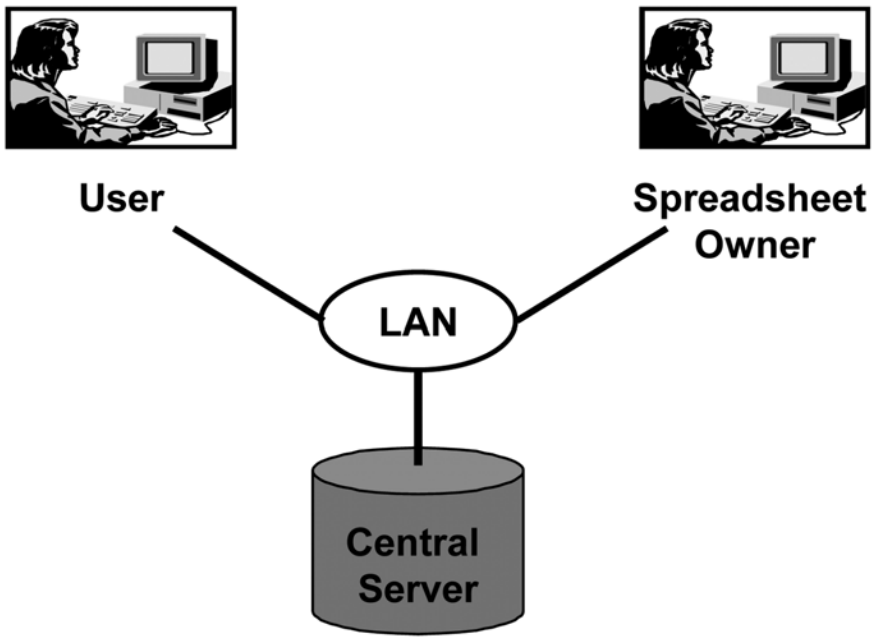
Case Study 1: Spreadsheet

Question	Answer
What is the type of application (e.g., process control, data management)?	PC application with user data.
What is the description and primary business purpose?	Wide range of uses for automation of calculations. Often used in Quality Control, Quality Assurance and in laboratory operations. For example, the calculation of test results used for releasing product, or derived data for regulatory decisions.
What is the typical user interface?	Via PC.
Is the system likely to be networked?	Can be available on standalone PC only or accessible over network. This will influence strategy for security and backup of data.
Is the system typically processing regulated data?	Can manipulate and store data related to test results, in-process controls, clinical trial results, etc.
Which regulated electronic records are typically maintained in the system (or are records passed on to another system)?	Regulated records may be retained in either electronic or paper format. There will often be template spreadsheets which are used to enter data and perform calculations and manipulations. These templates are controlled by validation and change control. Spreadsheets containing the calculation results may be retained electronically (often only the template is retained electronically and the results are retained on paper). Data is often imported from other data gathering systems and the final spreadsheet containing calculation results may be exported to another data management system.
Are the regulated electronic records high, medium, or low impact?	Spreadsheets containing calculation results, if maintained electronically and used for regulated activities, may be high impact if used for clinical trials or releasing product otherwise likely to be medium or low.
What are typical hybrid situations for records and signatures?	Very common to calculate results using a spreadsheet, to print the results, and to sign and date the printed record. Only the template is retained electronically and this is controlled by validation, change control and access controls.
Which regulated signatures are typically maintained in the system?	Difficult to electronically sign a spreadsheet, may be transferred to another system, such as an Electronic Document Management System (EDMS) for electronic approval and storage.

Case Study 1: Spreadsheet (continued)

Question	Answer
What are typical access controls? (e.g., network user-id and password, standalone user-id and password, group password, or only physical/procedural controls)	Network user-id and password, or local PC security, for access to the application. The spreadsheet application may require another level of access to protect macros, calculations, printing, creation or change of templates, etc. (e.g., Read-only for normal users, disabling the 'save as' feature and with a separate password to protect macros).
Is an audit trail normally provided?	Audit trails, if required by GxP regulation, could only be provided automatically with special software or by exporting to another system (such as an EDMS). Alternatively, paper based arrangements would be required. If audit trails are not specifically required by GxP regulation, templates can be controlled by other mechanisms such as change control and access control. The calculated results can be controlled by printing, and reviewing and approving the printed record. Appropriate procedural controls are required to manage changes to the paper record (e.g., crossed out and initialed changes).
What data or operating parameters are typically subject to formal change control?	Changes to templates, and formulae and macros within them.
Which procedures are typically required?	SOPs are required for the creation, protection, and change of templates, and for the use of templates and management of calculated results.
What special issues may need to be considered?	The security of the templates and the relatively poor security of spreadsheets in general. This makes the hybrid approach most common. Good programming practices, protection and error trapping are essential to prevent inadvertent changes by well-meaning users. Cell formulae and macros should be validated. Each spreadsheet should have an owner to ensure that the required technical and procedural controls are applied.

Schematic Diagram: Spreadsheet



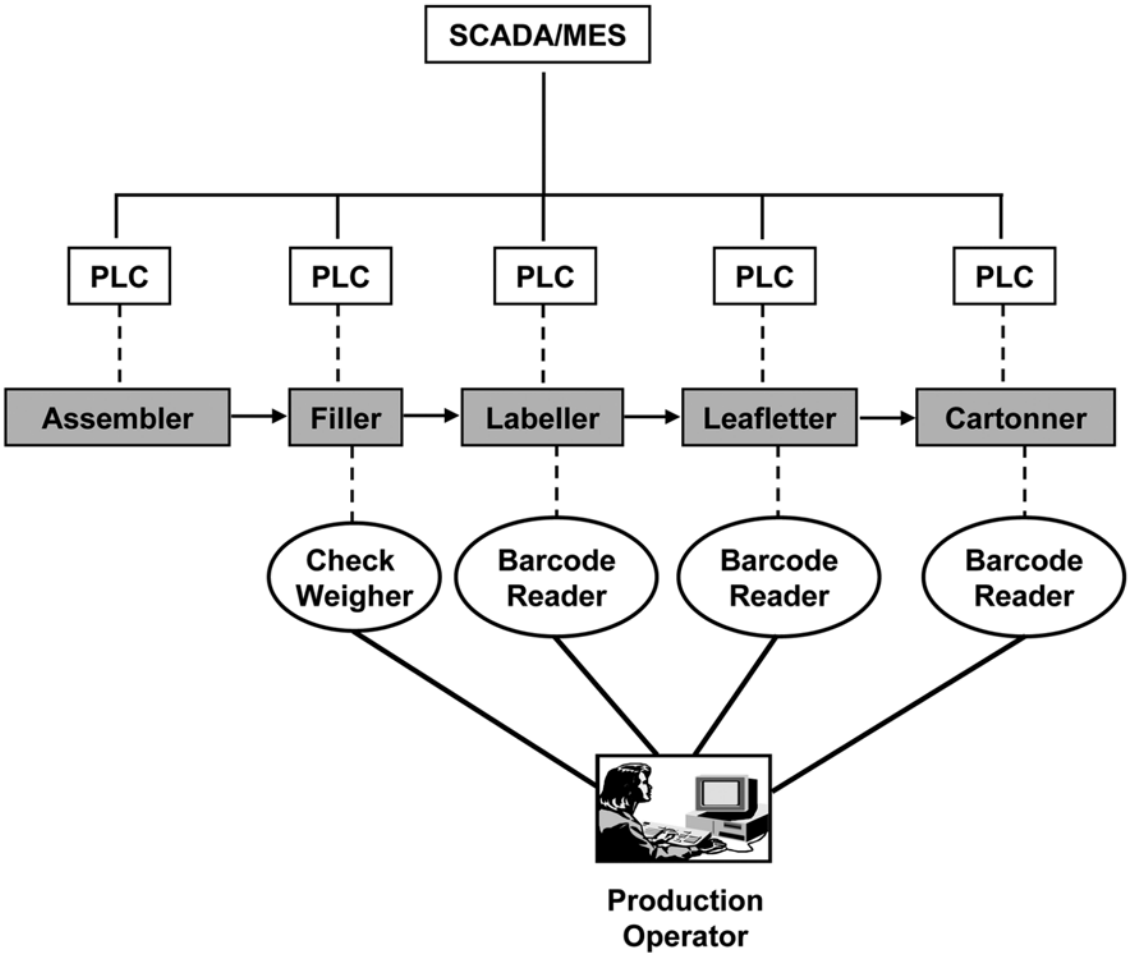
Case Study 2: PLC Controlled Packaging Equipment

Question	Answer
What is the type of application (e.g., process control, data management)?	Process Control System, which may be connected to SCADA or MES system to download batch- and component-specific data.
What is the description and primary business purpose?	Management and control of packing line. Sets parameters for packaging process, is fitted with error detection devices and instrumentation to monitor critical parameters.
What is the typical user interface?	Typically an operator panel as the interface to the PLC, but could be a PC linked to a SCADA in sophisticated applications.
Is the system likely to be networked?	May be linked to SCADA via a local area network for downloading settings or uploading data to create a record of the packaging process for printing and/or review as part of batch release. However, stand-alone devices are common.
Is the system typically processing regulated data?	These systems may have GxP impact but are unlikely to maintain regulated electronic records. Critical parameters such as sealing times, temperatures and pressures, will typically be controlled by machine settings (these are controlled by validation, change control, and access control). There may be alarms if measurements are outside limits. System may generate product labels (labels are covered in separate Case Study, so are not considered further here).
Which regulated electronic records are typically maintained in the system (or are records passed on to another system)?	Unlikely to maintain any regulated electronic records. Alarms unlikely to be retained unless connected to a SCADA or MES system. Some critical parameters may be retained for a short time to allow printing but no regulated electronic record is typically maintained. Packaging records likely to be paper but may be electronic records on a SCADA or MES system if relevant data is transferred to such a system.
Are the regulated electronic records high, medium, or low impact?	Not applicable - records not typically maintained on the system.
What are typical hybrid situations for records and signatures?	Some records may be generated by the system and would typically be printed out for subsequent review and approval.
Which regulated signatures are typically maintained in the system?	Unlikely to use electronic signatures.

Case Study 2: PLC Controlled Packaging Equipment (continued)

Question	Answer
What are typical access controls? (e.g., network user-id and password, standalone user-id and password, group password, or only physical/procedural controls)	Physical and procedural controls likely. PLC may not have electronic access controls for users. User-id and password should be required for access through another system such as SCADA.
Is an audit trail normally provided?	Electronic audit trails are not typically provided. Changes to critical parameters should be formally managed by change control procedures.
What data or operating parameters are typically subject to formal change control?	Changes to critical parameters (such as sealing temperature) are likely to be made periodically and such changes should be subject to formal change control.
Which procedures are typically required?	SOPs are required for machine set up and usage, managing access controls, and changes to critical parameters.
What special issues may need to be considered?	Any interfaces to other systems such as SCADA or MES for transferring batch record information. Some PLCs now “store and forward” data to ensure data is not lost due to temporary network problems.

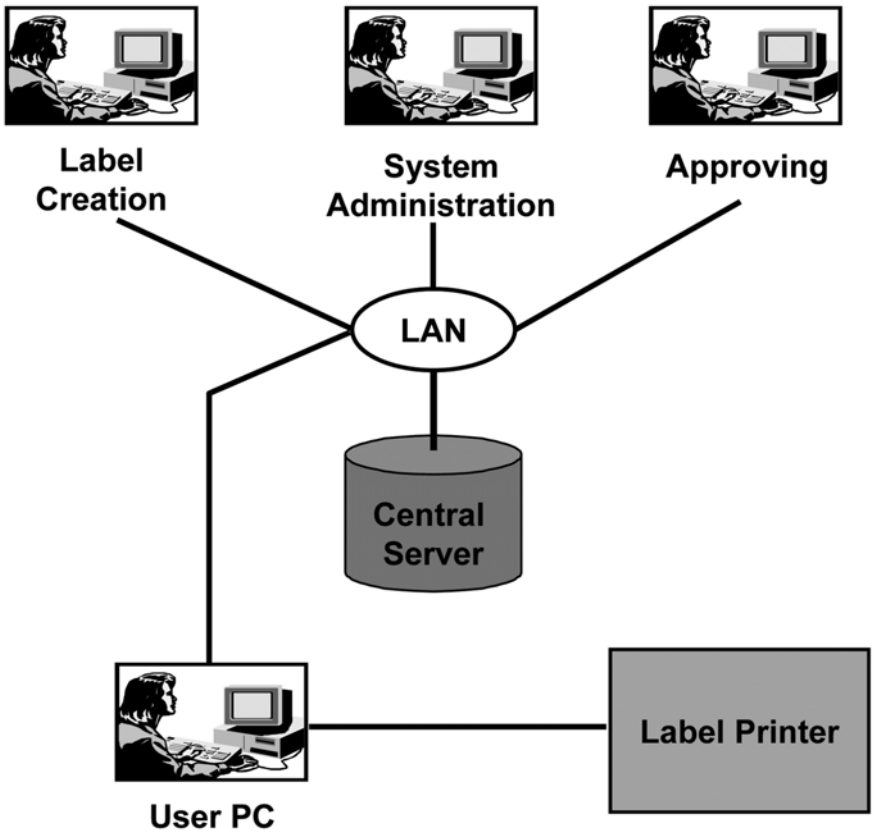
Schematic Diagram: PLC Controlled Packaging Equipment



Case Study 3: Clinical Trial Label Printing System

Question	Answer
What is the type of application (e.g., process control, data management)?	Clinical trial label printing and data management.
What is the description and primary business purpose?	Formats and prints and manages labels for clinical trial packaging materials for randomised blinded clinical trials.
What is the typical user interface?	PC standalone or in client server mode.
Is the system likely to be networked?	Networked system or stand-alone.
Is the system typically processing regulated data?	The system will process data related to trial, patient, individual presentation unit, patient safety and storage.
Which regulated electronic records are typically maintained in the system (or are records passed on to another system)?	The system will maintain data related to trial, patient, individual presentation unit, patient safety and storage. Such data may be used for investigations or recall.
Are the regulated electronic records high, medium, or low impact?	Patient data will be high impact.
What are typical hybrid situations for records and signatures?	May print and sign to approve the label master with blanked variable information.
Which regulated signatures are typically maintained in the system?	The label master may be e-signed.
What are typical access controls? (e.g., network user-id and password, standalone user-id and password, group password, or only physical/procedural controls)	User-id and password at several levels for printing, creation or change and creation of masters or macros to incorporate variable information.
Is an audit trail normally provided?	Changes to approved labels and patient data should be audit trailed.
What data or operating parameters are typically subject to formal change control?	Changes to approved labels, label data, e.g., patient information, dosage regime, etc. should be subject to formal change control.
Which procedures are typically required?	Specific procedures essential for all label creation and printing tasks and for changes to records.
What special issues may need to be considered?	The security of the random code record, which will be the only record of which patient has taken which medication.

Schematic Diagram: Clinical Trial Label Printing System



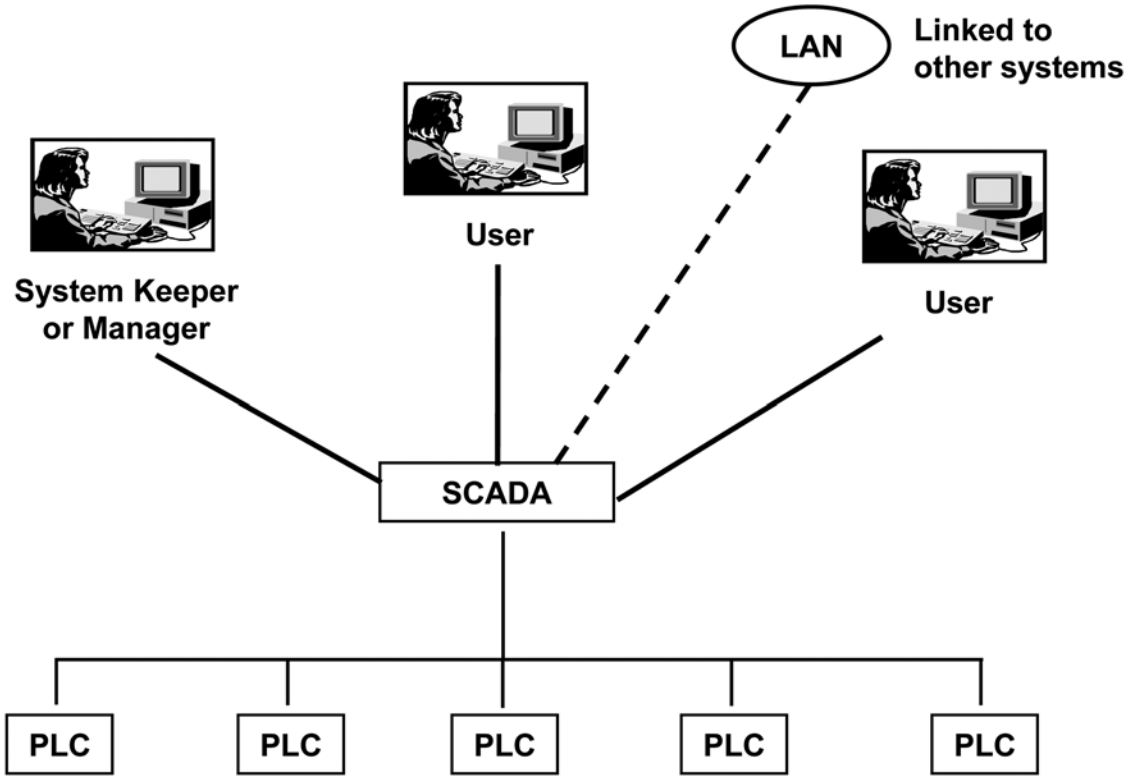
Case Study 4: Supervisory Control and Data Acquisition (SCADA)

Question	Answer
What is the type of application (e.g., process control, data management)?	Real time data acquisition, control and data processing.
What is the description and primary business purpose?	Data acquisition and control of real time processing operations, these systems are often interfaced to programmable logic controllers which control specific items of equipment, and to data storage servers. Functions include data acquisition, control, alarm generation, storage, trending, viewing and production of reports.
What is the typical user interface?	PC-based user interface and may include local operator (data entry) panels.
Is the system likely to be networked?	SCADA involves multiple devices working together on a network which is usually not the main IT network. Data can be downloaded to or uploaded from PLC controlled equipment. Summary data such as trend information may be passed to another system for incorporation into the batch record.
Is the system typically processing regulated data?	May be used for downloading, uploading or recording: critical parameter data, recipes, batch record information, trend information, calibration data.
Which regulated electronic records are typically maintained in the system (or are records passed on to another system)?	May be used to download parameters and recipes for critical processes, and to record critical parameter data, record calibration data, and produce batch record information and trend information. (NOTE: PLC records are usually temporary, often the data is either printed out after acquisition and processing or is overwritten after transfer to a SCADA system).
Are the regulated electronic records high, medium, or low impact?	Often used for engineering and management information that may be low impact. If used for downloading/uploading or recording critical parameter data, recipes, batch record information and calibration data then the records may be medium or high impact depending on the process and the product.
What are typical hybrid situations for records and signatures?	Approval signatures on printed batch records and trends.
Which regulated signatures are typically maintained in the system?	May have e-signature functionality for on screen review and approval of trends and handling alarms.
What are typical access controls? (e.g., network user-id and password, standalone user-id and password, group password, or only physical/procedural controls)	Access control may be physical/procedural as system may be permanently switched on if required for real time process control. Formal change control required for changes to settings and data related to critical parameters.

Case Study 4: Supervisory Control and Data Acquisition (SCADA) (continued)

Question	Answer
Is an audit trail normally provided?	Depends on records being maintained. Use of audit trail to document creation, modification, or deletion of regulated records would be good practice. Key processing steps such as weighing or charge in of components require signatures, other processing steps require identity checks. Changes to critical parameters controlled by change control, see below.
What data or operating parameters are typically subject to formal change control?	Formal change control required for changes to settings and data related to critical process parameters, recipes, batch record information.
Which procedures are typically required?	Formal change control for changes to critical processing parameters. Access control procedures.
What special issues may need to be considered?	Operators may enter into the system settings and actual values for critical steps of the operation. The system should record the identity, time and date of the operator making such entries. Some process entries may be recorded automatically in which case the validation should ensure that the entry is correct. Some entries are manual, e.g., which operation cycle to select and this will be entered via a keyboard. In this case the entry is subject to validation, procedural control and training. Operator interventions/holds and safety shutdown conditions should be considered as part of risk assessment. Access control may be physical as system may be permanently switched on in a manufacturing environment.

Schematic Diagram: Supervisory Control and Data Acquisition (SCADA)



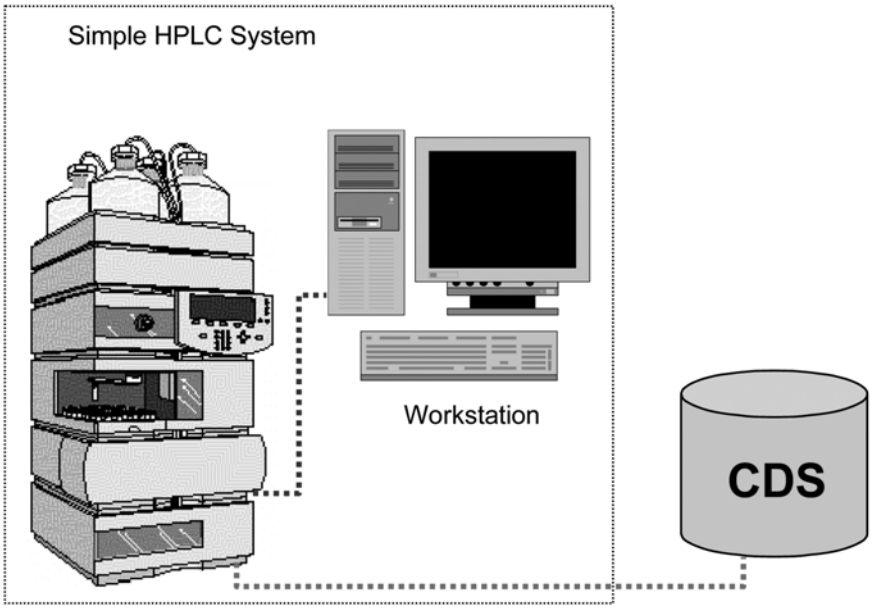
Case Study 5: High Performance Liquid Chromatography (HPLC) System

Question	Answer
What is the type of application (e.g., process control, data management)?	Chromatography analytical data acquisition and data processing system.
What is the description and primary business purpose?	To process and store raw data from chromatographic measurement. System comprises a number of firmware-based hardware modules with data analysis being performed by PC-based software for simple systems.
What is the typical user interface?	PC-based software and system-specific control pad.
Is the system likely to be networked?	Simple systems are usually not networked, but multiple systems are often networked to a Chromatography Data System (CDS).
Is the system typically processing regulated data?	The system is processing regulated data prior to printing out chromatograms or transferring the data to a CDS, see below.
Which regulated electronic records are typically maintained in the system (or are records passed on to another system)?	The HPLC retains run-time data files. Run-time data files are set-up from approved analytical methods. Typical set up data which has to be recorded includes sample/standard sequences (analytical methods), detector conditions e.g., wavelength, column temperature, solvent flow rate and composition. Chromatographic data is not maintained in the HPLC system, chromatograms are only retained prior to print out. Alternatively the chromatographic data is passed to a CDS for data analysis and data storage.
Are the regulated electronic records high, medium, or low impact?	Records are used for product quality evaluation against specifications maintained in other systems, e.g., CDS. Records are generally medium impact as final decisions are taken by management using other systems. Impact may be high for final product release depending on process and product.
What are typical hybrid situations for records and signatures?	Chromatographic results printed out as chromatograms and signed.
Which regulated signatures are typically maintained in the system?	Not typically used on simple HPLC systems.
What are typical access controls? (e.g., network user-id and password, standalone user-id and password, group password, or only physical/procedural controls)	PC-based systems have user-level access via standalone ID/password, some systems may have group passwords.

Case Study 5: High Performance Liquid Chromatography (HPLC) System (continued)

Question	Answer
Is an audit trail normally provided?	The audit trail of run-time and data analysis parameters is captured either through change control records or print out of chromatograms and results. Electronic audit trails are not required in the instrument but are required in the CDS.
What data or operating parameters are typically subject to formal change control?	Run-time parameters are typically configured at the beginning of each analysis session. Standard methods and changes to set up should be under change control.
Which procedures are typically required?	Change control procedures for changes to set up, procedures for analysis and re-analysis of data.
What special issues may need to be considered?	Unattended analysis sessions, where there may be a shift change, issues are retaining audit traceability for operating conditions, data processing, and maintaining data integrity.

Schematic Diagram: High Performance Liquid Chromatography (HPLC) System



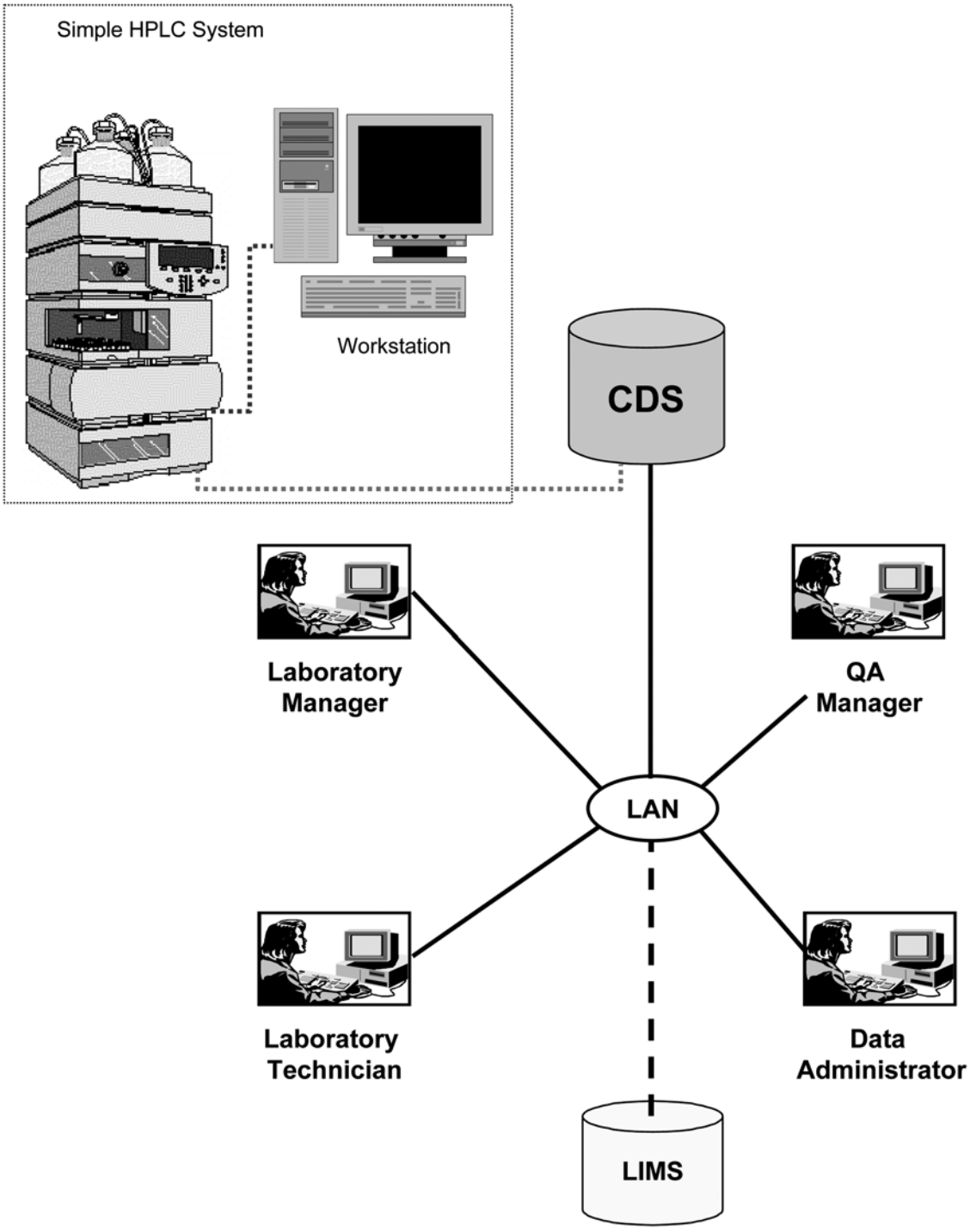
Case Study 6: Chromatography Data System (CDS)

Question	Answer
What is the type of application (e.g., process control, data management)?	Chromatography data management.
What is the description and primary business purpose?	Management & control of chromatography data including data acquisition, storage, viewing, review and approval.
What is the typical user interface?	Users interface with the data screens of the CDS client software, bar code scanning may be employed for sample label reading.
Is the system likely to be networked?	This system is usually comprised of workstations and servers operating in client server mode over a network Summary data may be passed to a LIMS. Data may be exported to Excel for recalculation, evaluation of trends,...
Is the system typically processing regulated data?	Chromatographic data is processed in the system.
Which regulated electronic records are typically maintained in the system (or are records passed on to another system)?	Approved analytical methods & chromatographic raw data and results are stored on the CDS system which may be the regulated record. Other records of run-time data files, sample/standard sequences (analytical methods), detector conditions e.g., wavelength, column temperature, solvent flow rate are maintained.
Are the regulated electronic records high, medium, or low impact?	Records are used for product quality evaluation against specifications maintained in the CDS. Records are generally medium impact as final decisions are taken by management. Impact may be high for final product release depending on process and product.
What are typical hybrid situations for records and signatures?	Review and approval of printed chromatograms and results printed from data files.
Which regulated signatures are typically maintained in the system?	May be used for on screen review and approval.
What are typical access controls? (e.g., network user-id and password, standalone user-id and password, group password, or only physical/procedural controls)	PC-based systems have user-level access using user-id and password, maybe via network.

Case Study 6: Chromatography Data System (CDS) (continued)

Question	Answer
Is an audit trail normally provided?	An audit trail is generally required for changes to regulated records. In modern systems this can be automatic. Who, what, & when is required for every action to create, modify, or delete regulated CDS records. Some GxP regulations require a reason for change to be recorded; this can be a drop down menu with choices to reduce the data storage requirements. Systems without an automatic audit trail should be controlled with a procedure to print paper records of changes which are then signed.
What data or operating parameters are typically subject to formal change control?	Formal change control required for changes to regulated records.
Which procedures are typically required?	System access control, change control and operating procedures, system suitability checks.
What special issues may need to be considered?	This critical high impact system will require 24/7 auto backup and restore functionality to maintain business continuity. These systems typically handle large volumes of data therefore adequate storage capacity should be ensured. Change control across related networked systems, e.g., CDS, LIMS and MRP.

Schematic Diagram: Chromatography Data System (CDS)



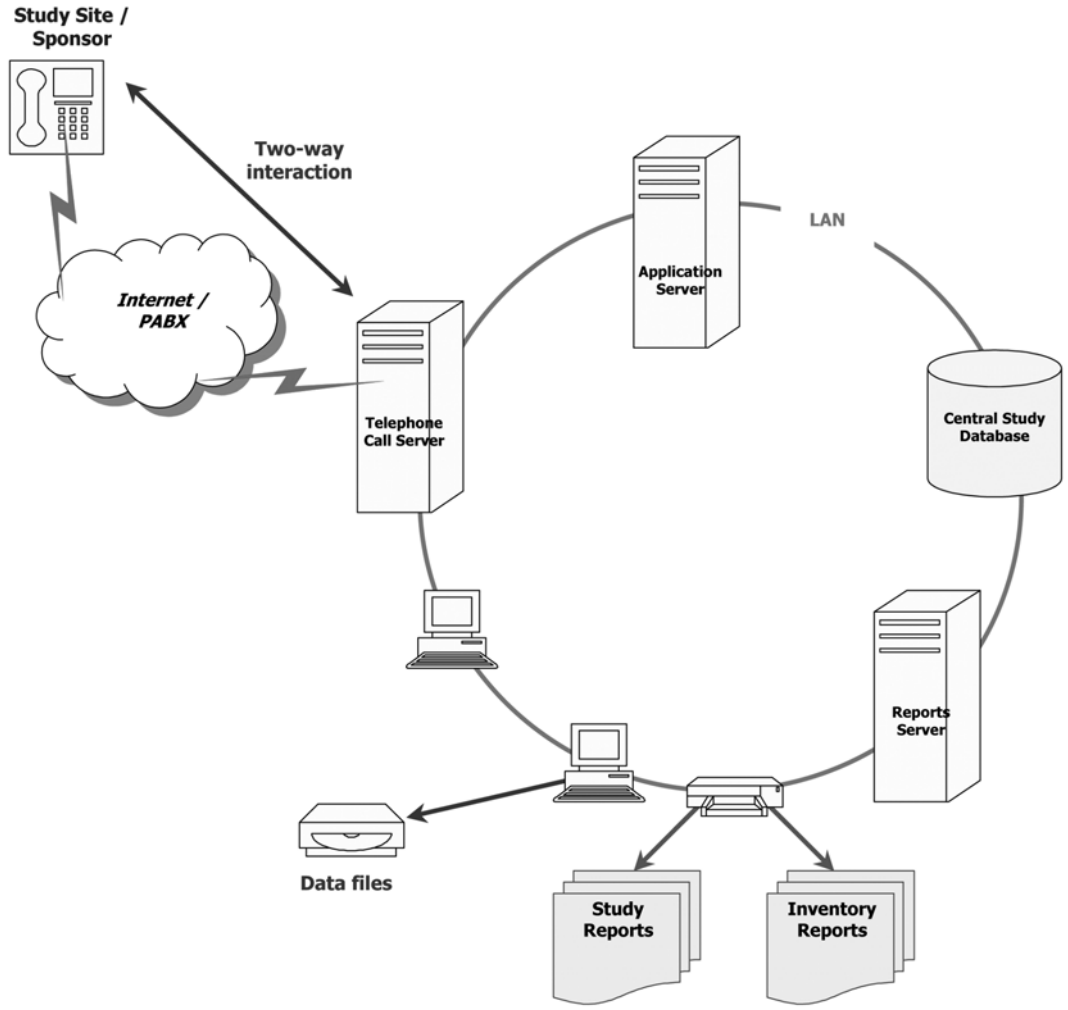
Case Study 7: Interactive Voice Response System (IVRS)

Question	Answer
What is the type of application (e.g., process control, data management)?	Data management system.
What is the description and primary business purpose?	A system designed to enable the provision of critical data to a centrally located database via the use of the telecommunication network, and increasingly used by the pharmaceutical industry for Clinical Trials. An IVRS consists of hardware and software configured and coded to allow a high degree of customization for specific client requirements with respect to clinical study protocol design. The system collects information from callers, who respond to pre-recorded prompts via the telephone keypad.
What is the typical user interface?	Typically a telephone receiver and keypad, or small hand-held tone pad adaptors.
Is the system likely to be networked?	Such systems are typically networked on a LAN with external connections via the WAN or public telephone system.
Is the system typically processing regulated data?	Information such as patient details, subject consent, dispensed packs, patient diary records.
Which regulated electronic records are typically maintained in the system (or are records passed on to another system)?	Recruitment information, patient diary records, drug inventory details, monitoring reports. Linkage to other systems is dependant upon organization and study design. Some companies may be able to integrate their own Clinical Trials Management systems (CTMS) with the real-time information contained within the IVR database via remote connection. A similar scenario may exist for Clinical Trials Supplies systems and IVR. In other cases this data transfer could be paper-based.
Are the regulated electronic records high, medium, or low impact?	This system will hold patient data information and is likely to be high impact.
What are typical hybrid situations for records and signatures?	Print out data for transfer into regulatory submissions.
Which regulated signatures are typically maintained in the system?	No e-signatures are typically applied to records within an IVRS, although printed paper records may be signed by hand.
What are typical access controls? (e.g., network user-id and password, standalone user-id and password, group password, or only physical/procedural controls)	Domain and network access controls, network user-id and password, application user-id and password. System will also require physical and procedural controls to restrict access to servers/computer room.

Case Study 7: Interactive Voice Response System (IVRS) (continued)

Question	Answer
Is an audit trail normally provided?	Yes, on the data system to record changes to critical parameters relating to each project/study protocol, or amendments to data if response was incorrect.
What data or operating parameters are typically subject to formal change control?	Changes to critical parameters relating to each project/ study protocol, or amendments to response data controlled by audit trail and standard operating procedures.
Which procedures are typically required?	Specific procedures required for system access controls, module configuration, data entry and change control.
What special issues may need to be considered?	This critical high impact system should have a tested 'hot' backup and restore process, design to maintain '24/7' global availability, and a Business Continuity Plan.

Schematic Diagram: Interactive Voice Response System (IVRS)



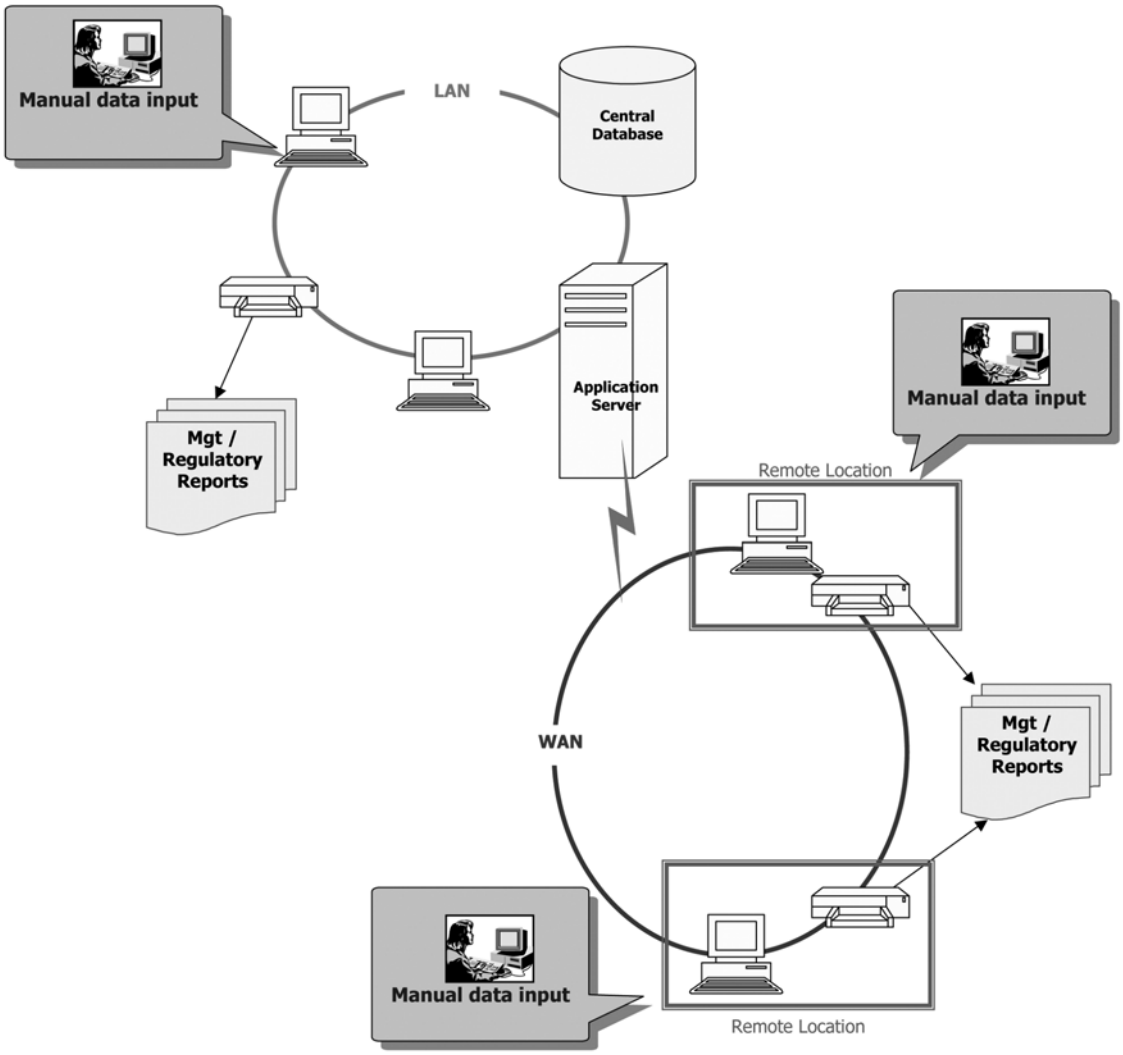
Case Study 8: Adverse Event Reporting (AER) System

Question	Answer
What is the type of application (e.g., process control, data management)?	Data management system.
What is the description and primary business purpose?	A system designed to support drug safety business processes (Pharmacovigilance) by providing various tools, which enable users to record and organize adverse event data, and use that data in the creation of submission reports required by various governmental drug agencies worldwide. Usually a global system located at one central site and accessed by several remote locations to ensure that regulatory compliance can be achieved in a timely and responsive manner on a global basis.
What is the typical user interface?	Desktop PC access to a central server via the corporate LAN/WAN and dependent upon the availability of the standard corporate desktop, the local domain and the international architecture (e.g., Citrix Program Neighbourhood Group).
Is the system likely to be networked?	Such systems are typically networked on a LAN with external connections via the WAN or public telephone system.
Is the system typically processing regulated data?	Information such as patient details, report source, adverse event, drug data.
Which regulated electronic records are typically maintained in the system (or are records passed on to another system)?	Details and status of Adverse Event, and reporting justification. Links to other systems is dependant upon organization and regulatory authority. For example, some companies utilize the ADROIT system available from the MHRA for the transfer and receipt of data. Future developments may also extend this functionality, e.g., the 'Eudravigilance' Project supported by the EMEA.
Are the regulated electronic records high, medium, or low impact?	This system will hold patient data information and is likely to be high impact.
What are typical hybrid situations for records and signatures?	Print out reports for submission to regulatory authority.
Which regulated signatures are typically maintained in the system?	No e-signatures are typically applied to records within an AER system, although printed paper records may be signed by hand.
What are typical access controls? (e.g., network user-id and password, standalone user-id and password, group password, or only physical/procedural controls)	Domain and network access controls, network user-id and password, application user-id & password.

Case Study 8: Adverse Event Reporting (AER) System (continued)

Question	Answer
Is an audit trail normally provided?	Yes, to record changes to critical parameters relating to each AE as more information becomes available.
What data or operating parameters are typically subject to formal change control?	Changes to critical parameters relating to each AE controlled by audit trail and standard operating procedures.
Which procedures are typically required?	Specific procedures required for system access controls, data entry and change control.
What special issues may need to be considered?	This critical high impact system should have a tested 'hot' backup and restore process, design to maintain '24/7' availability, and a Business Continuity Plan.

Schematic Diagram: Adverse Event Reporting (AER) System



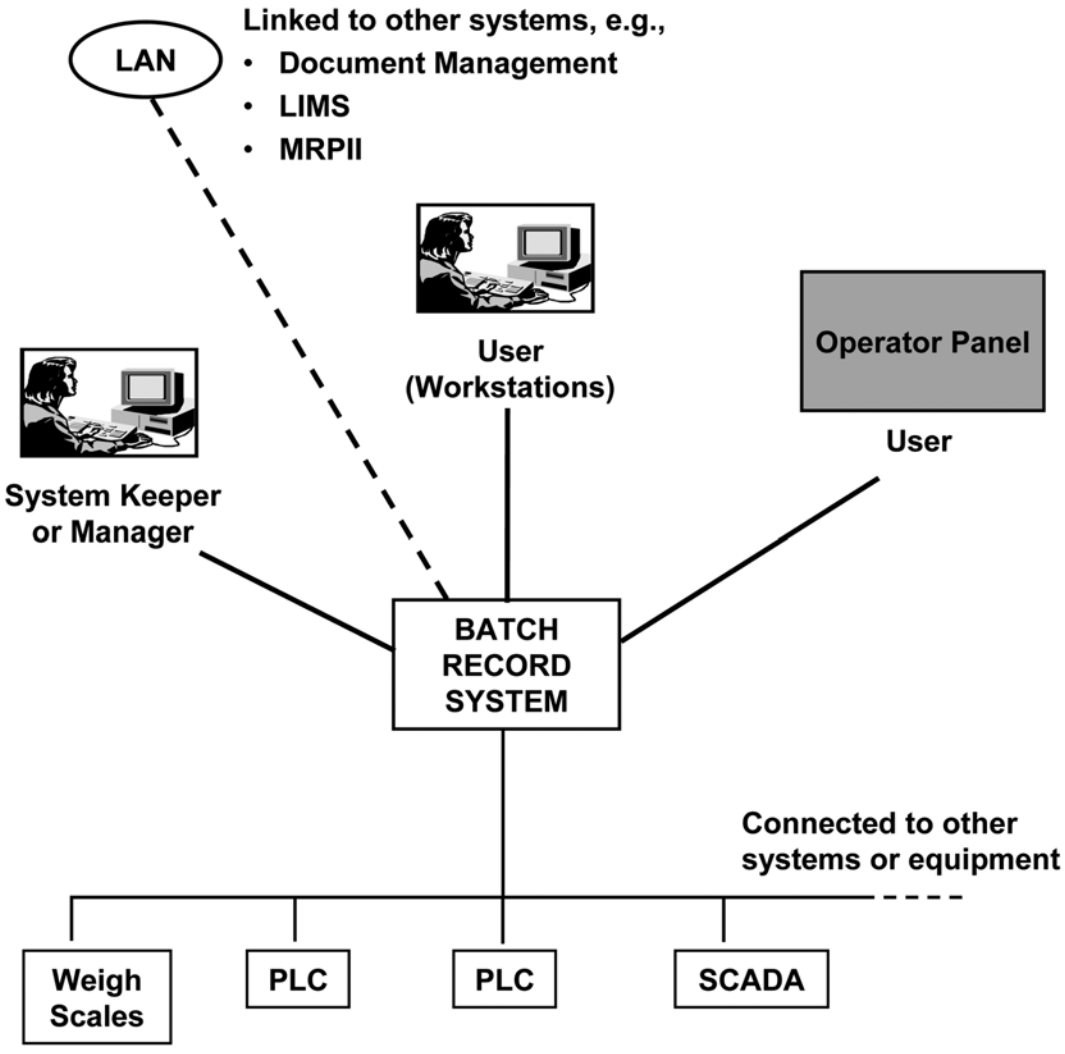
Case Study 9: Batch Record System

Question	Answer
What is the type of application (e.g., process control, data management)?	Data management system with links to a real time system which may be a separate system or part of the same system.
What is the description and primary business purpose?	Assembly, creation, modifying, storing, viewing, review and approval of batch records. This example is of a simple batch record system, not an MES containing recipes, stock details, equipment status, etc.
What is the typical user interface?	PC in manufacturing environment.
Is the system likely to be networked?	Normally networked for operator and management access, for storage of records, and for interfaces to other systems, such as LIMS, MRP. Records may either be available to system users on the network for creation, review and approval, or for view only.
Is the system typically processing regulated data?	Batch record information typically including lot number information, product/part codes, records of materials required/used, methods used, deviations, etc.
Which regulated electronic records are typically maintained in the system (or are records passed on to another system)?	Batch records may be electronic records in the system or transferred to a document management system and retained in a portable format such as PDF files.
Are the regulated electronic records high, medium, or low impact?	The records are typically high impact.
What are typical hybrid situations for records and signatures?	May print out records for subsequent review and approval.
Which regulated signatures are typically maintained in the system?	May incorporate electronic approval of records or may be by transfer to a document management system which has electronic approval.
What are typical access controls? (e.g., network user-id and password, standalone user-id and password, group password, or only physical/procedural controls)	Physical and procedural controls if the system is normally permanently switched on, or use of user-id and password for access via network applications.
Is an audit trail normally provided?	Automatic audit trail is typically provided to document creation, modification, or deletion of batch record information. Version control procedures should be applied to the electronic batch records, to record date and time of editing, identification of user making edits, and date and time of approval.
What data or operating parameters are typically subject to formal change control?	Changes to approved batch records must be made through formal change control procedures.

Case Study 9: Batch Record System (continued)

Question	Answer
Which procedures are typically required?	SOPs are required for system operation, managing access controls, and changes to batch records.
What special issues may need to be considered?	Operators may enter into the system settings and actual values for critical steps of the operation. The system should record the identity, time and date of the operator making such entries. Some process entries may be recorded automatically in which case the validation should ensure that the entry is correct. Some entries are manual, e.g., which operation cycle to select and this will be entered via a keyboard. In this case the entry is subject to validation, procedural control and training.

Schematic Diagram: Batch Record System



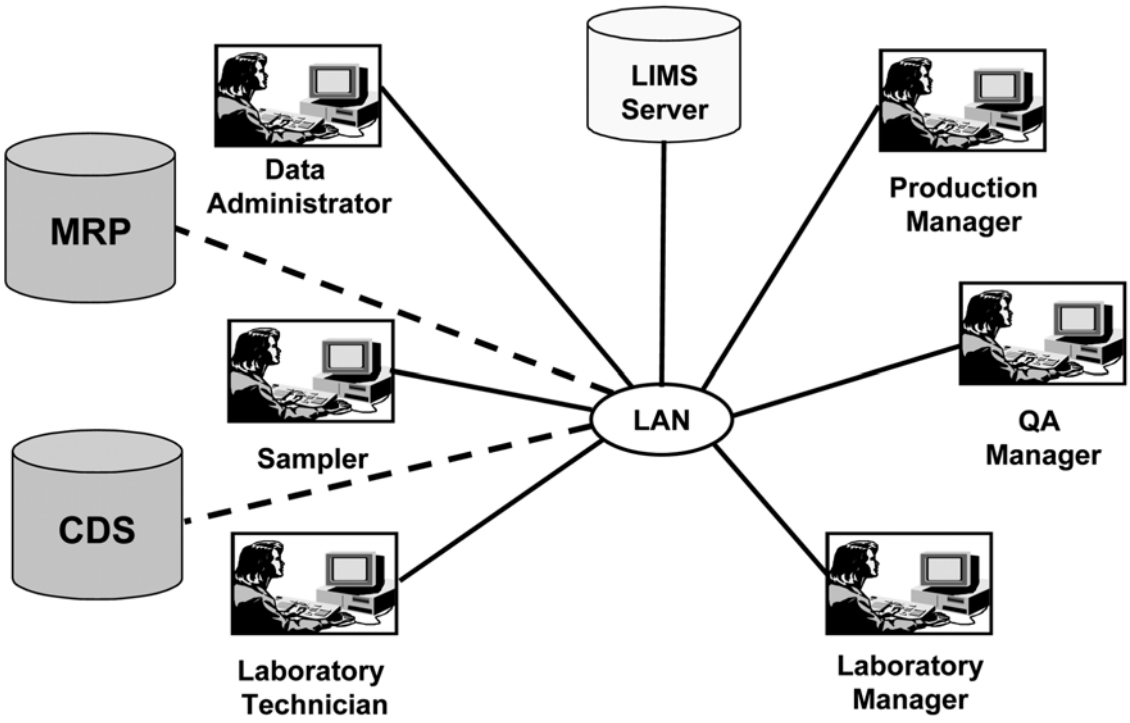
Case Study 10: Laboratory Information Management System (LIMS)

Question	Answer
What is the type of application (e.g., process control, data management)?	Laboratory data management system, may be connected to lab instruments, CDS, & MRP systems.
What is the description and primary business purpose?	Management and control of laboratory data. Used to manage workflow in the laboratory and confirm status of materials for material release and products for product release.
What is the typical user interface?	Users interface with the PC data screens of the LIMS client software. Bar code scanning may be employed for sample label reading
Is the system likely to be networked?	This system is usually comprised of workstations and servers operating in client server mode over a network Status information and potency figures for dispensing operations may be passed to an MRP system. Chromatography data may be passed from a CDS to the LIMS.
Is the system typically processing regulated data?	The system processes data and computation related to material and product specifications, methods and certificates of analysis.
Which regulated electronic records are typically maintained in the system (or are records passed on to another system)?	Material and product specifications, methods and certificates of analysis. Records are typically retained to facilitate trending, periodic reviews, and deviation investigations.
Are the regulated electronic records high, medium, or low impact?	Records are used for product quality evaluation; records are generally medium impact as final decisions are taken by management using other systems. Impact may be high for final product release depending on process and product.
What are typical hybrid situations for records and signatures?	Certificates of approval may be printed and manually signed.
Which regulated signatures are typically maintained in the system?	Certificates of analysis may be approved on screen using e-signature.
What are typical access controls? (e.g., network user-id and password, standalone user-id and password, group password, or only physical/procedural controls)	PC-based systems have user-level access using user-id & password, typically via a network. Typically there is management control of user accounts to allow appropriate levels of access.

Case Study 10: Laboratory Information Management System (LIMS) (continued)

Question	Answer
Is an audit trail normally provided?	An audit trail is required for changes to regulated records. In modern systems this can be automatic. Who, what, and when is required for every action to create, modify, or delete regulated GMP records. Some GxP regulations require a reason for change to be recorded; this can be a drop down menu with choices to reduce the data storage requirements. Older systems without an automatic audit trail may be controlled with a procedure to print paper records of changes which are then reviewed and approved.
What data or operating parameters are typically subject to formal change control?	Formal change control is required for changes to regulated records, specifications, methods, certificates of analysis, and for the addition of new specifications and methods. NOTE: there may be regulatory implications with some changes.
Which procedures are typically required?	Procedures for hybrid systems to ensure electronic records and paper records are aligned. Procedures to manage deviations or OOS (Out Of Specification) caused by instrument errors. Procedures for access controls appropriate for use of the system.
What special issues may need to be considered?	Validation of bespoke calculations and reports. This critical high impact system will require 24/7 auto backup and restore functionality to maintain business continuity. These systems typically handle large volumes of data. Change control across related networked systems, e.g., CDS, LIMS and MRP II.

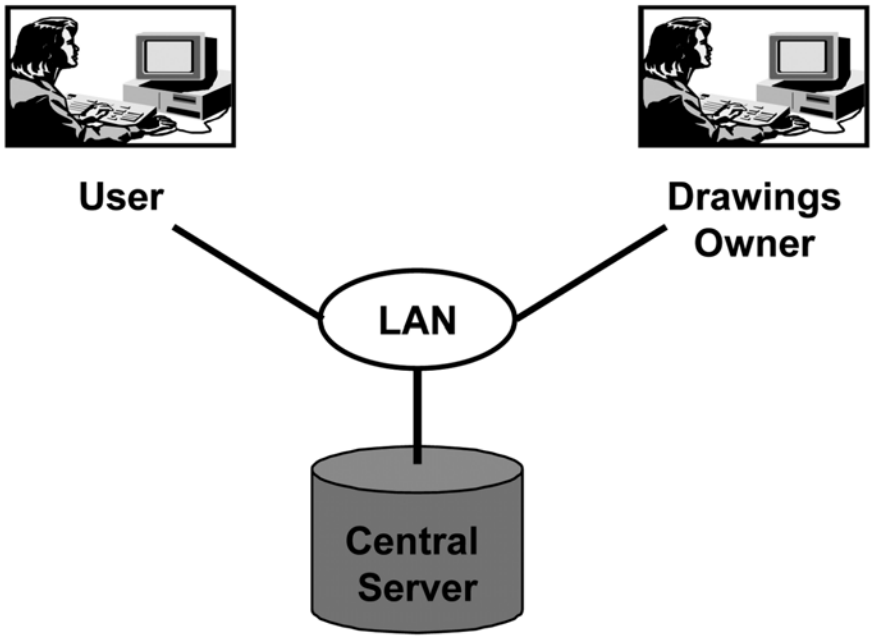
Schematic Diagram: Laboratory Information Management System (LIMS)



Case Study 11: Autocad Used For Managing Pack Drawings

Question	Answer
What is the type of application (e.g., process control, data management)?	CAD data system for creation and management of drawings.
What is the description and primary business purpose?	Creation, modifying, storing and viewing system for drawings, may be used for the digital printing of packs.
What is the typical user interface?	PC in office environment.
Is the system likely to be networked?	May be available to users for review and approval or for use on the company network or files may be transferred to a document management system Network systems and stand-alone devices are common.
Is the system typically processing regulated data?	Yes the system is used for creation, modifying, storing and viewing of primary pharmaceutical packs.
Which regulated electronic records are typically maintained in the system (or are records passed on to another system)?	Specifications of primary pharmaceutical product packs.
Are the regulated electronic records high, medium, or low impact?	This system will be high impact for drawings of primary pharmaceutical packs.
What are typical hybrid situations for records and signatures?	May print out drawings for approval by signing.
Which regulated signatures are typically maintained in the system?	Electronic signature is not possible with AutoCAD, may transfer to a document management system which has electronic approval functionality.
What are typical access controls? (e.g., network user-id and password, standalone user-id and password, group password, or only physical/procedural controls)	Physical and procedural controls if the standalone CAD system is normally permanently switched on. Will have user id and password for access via network applications and auto time out of terminals if not used for some minutes.
Is an audit trail normally provided?	The system has no audit trail capabilities. Control is by a change and version control procedure and access control. Procedure records date and time of editing, reason for change, identification of user making edits and date and time of approval.
What data or operating parameters are typically subject to formal change control?	Change control procedure required for changes to regulated records.
Which procedures are typically required?	SOPs are required for setting up access controls and changes to regulated records.
What special issues may need to be considered?	Regulated records (electronic, paper or hybrid) should be defined.

Schematic Diagram: Autocad Used For Managing Pack Drawings



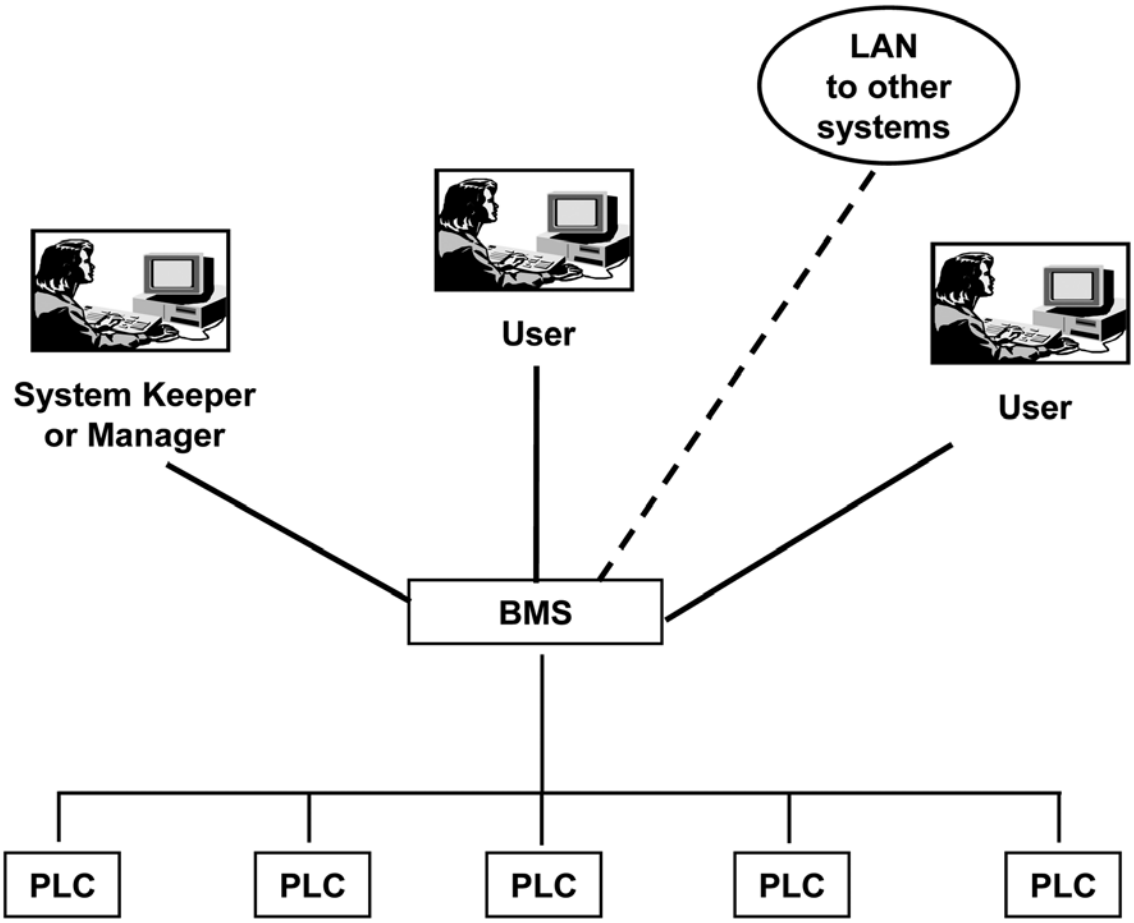
Case Study 12: Building Management Systems (BMS)

Question	Answer
What is the type of application (e.g., process control, data management)?	Process control, monitoring and data management. The process control may be through a SCADA linked to control outstations (PLCs), and data may be stored in a data historian, however there are several different BMS architectures.
What is the description and primary business purpose?	Controls and supervises a variety of facilities management and support processes, e.g., environmental control and monitoring, utility production and distribution, energy management, fire alarms, and intrusion alarms.
What is the typical user interface?	Can be PC workstations or PLC with operator pad.
Is the system likely to be networked?	Can be standalone or networked, often large networked systems evolve over a number of years.
Is the system typically processing regulated data?	The BMS may control and monitor regulated parameters depending on the process being controlled. Some companies use independent monitoring instruments with separate data collection so that the BMS does not handle regulated data. However trend data from the BMS is increasingly seen as an important control measure.
Which regulated electronic records are typically maintained in the system (or are records passed on to another system)?	May control critical parameters depending on process, e.g., environment temperature, humidity, air particulates and differential pressure.
Are the regulated electronic records high, medium, or low impact?	Often used for engineering and management information in which case impact will be low or medium. May be high impact if used for sterile manufacture without use of independent monitoring.
What are typical hybrid situations for records and signatures?	Process alarm logs and critical parameter trends printed out for review and retained with batch record.
Which regulated signatures are typically maintained in the system?	Process alarm logs and critical parameter trends retained electronically may be e-signed.
What are typical access controls? (e.g., network user-id and password, standalone user-id and password, group password, or only physical/procedural controls)	Network user-id and password for PC workstations. PLCs and outstations may have password access or physical controls.
Is an audit trail normally provided?	Not usually required by regulation, typically process parameter control changes are subject to procedural change control and access control.
What data or operating parameters are typically subject to formal change control?	Changes to critical process parameters, process control set points, control algorithms and control sequences.

Case Study 12: Building Management Systems (BMS) (continued)

Question	Answer
Which procedures are typically required?	System ownership for data ownership and backup and security administration, change control and configuration management. Maintenance and calibration.
What special issues may need to be considered?	Criticality of BMS is controlled by process being managed. Use of independent monitoring may shift criticality away from the BMS. Management of security and change control across a large and diverse number of users on big systems. Calibration of critical and non critical instruments.

Schematic Diagram: Building Management Systems (BMS)



Case Study 13: Enterprise Resource Planning (ERP) Systems

Question	Answer
What is the type of application (e.g., process control, data management)?	Management of enterprise resource planning data.
What is the description and primary business purpose?	Key foundation in integrated enterprise wide business planning, finance, manufacturing and quality management. May be linked to other systems (LIMS, MRP, WMS, Purchasing, etc.). Involved with entire supply chain processes of a company. Typically, the modules and business processes encompass: **Order to Cash** (Order Entry, Pick/Pack/Ship, Accounts Receivable). **Procure to Pay** (Purchasing, Receiving, Accounts Payable). **Manufacturing and Inventory Control** (Forecasting, Planning, Work Order Management, Inventory Management, Warehouse Management, Quality Management, Plant Maintenance, Cost Accounting). **Human Resources Information System.**
What is the typical user interface?	The system can be client server based. The system could be connected to a midrange computer such as an AS/400. The user interface could be PC based with Graphical User Interface (GUI) client software or terminal emulation, or terminals could be used. Additionally systems can have connections through bar code for inventory management and EDI (electronic data interface) for passing order information to and from customers.
Is the system likely to be networked?	Could be linked to a wide variety of systems including: • Dispensing • Transportation • Customer Relationship Management (CRM) • Laboratory/Quality Systems • Manufacturing Execution Systems (real time) Could be on a global network and the system could control multiple sites.
Is the system typically processing regulated data?	Some aspects of the system maintain and manage regulated GxP data (e.g., lot control, product release, lot tracing) and some are non GxP (e.g., finance records).

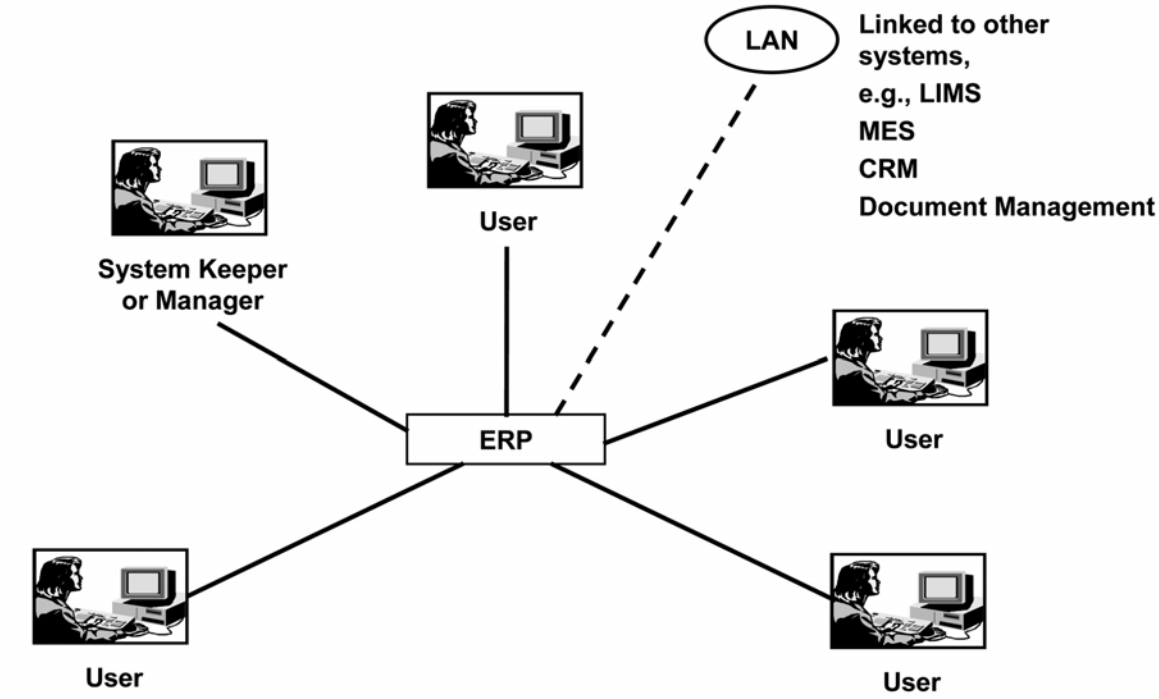
Case Study 13: Enterprise Resource Planning (ERP) Systems (continued)

Question	Answer
Which regulated electronic records are typically maintained in the system (or are records passed on to another system)?	• Lot Master (status, lot numbers, expiry date, potency, lot reconciliation) • Lot Tracing/Recall Data • Approved Vendors • Bill of Materials • Work Order information • Manufacturing Instructions and Batch Records • Training Records • Maintenance Records • Material Test Data (specifications, test data (not an all inclusive list).
Are the regulated electronic records high, medium, or low impact?	ERP systems contain a range of records of differing impact. Some electronic records are high impact, such as: • Bill of Materials • Material Status - approved/rejected • Electronic Batch Record while others have low impact such as shop order reporting.
What are typical hybrid situations for records and signatures?	Items approved online so they can be used to manufacture product or to ship to customers, but where there is no electronic signature facility available.
Which regulated signatures are typically maintained in the system?	Electronic Batch record signatures. Quality signatures for material release.
What are typical access controls? (e.g., network user-id and password, standalone user-id and password, group password, or only physical/procedural controls)	The systems typically have elaborate security control that provide users with secure access by user-ID and password that range from transaction level to field level depending on the system and criticality of the business processes. Security can also be on the local PC and the network.
Is an audit trail normally provided?	Typically audit trails are provide by all newer systems. There are further Engineering Change Control systems that can be applied for master file versioning.
What data or operating parameters are typically subject to formal change control?	Hardware, software, documentation and configuration are under change control. Changes to master files and system transactions are typically controlled through change control procedures and system security. Changes to details in specific Quality records such as Bill of Materials would follow Quality System Change Control process.

Case Study 13: Enterprise Resource Planning (ERP) Systems (continued)

Question	Answer
Which procedures are typically required?	Information Technology procedures for managing the system (such as Security Management, Change Control, Backup and Recovery, Disaster Recovery, System Operations, Incident Management, Performance Monitoring) Business procedures for the business processes that include how to perform system transactions.
What special issues may need to be considered?	• Consistent application of validation approach (may be implemented across sites, by different groups) • Size and scale of the system so risk based approach to validation is recommended • Potential global nature of system • Control of a system which may have GxP and non GxP elements • Data Conversion during project implementation • Control and compliance of supporting infrastructure • Configuration management • Data archiving and long term storage • Use of quality reports from the system

Schematic Diagram: Enterprise Resource Planning (ERP) Systems



Appendix 8
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Guideline for Risk Assessment

1 Introduction

This Guideline describes a simple Risk Assessment process that may be applied to automated systems to enable the targeting of the validation effort to those areas and functions that most require it.

Validation of new systems serves two purposes:

- To avoid any intolerable risk to patient safety or to the business
- To maximize the business benefits to be derived from the new system

User companies installing new automated systems should understand and manage the risks in conjunction with the benefits, and should be prepared to conduct several risk analyses during the implementation of a new system.

The Risk Assessment process addresses the following questions:

- Does this automated system require validation?
- How much validation is required for this system?
- What aspects of the system or process are critical to product and patient safety?
- What aspects of the system or process are critical to business?

It is impractical to completely test every aspect of an automated system; therefore the effort should be focused on critical areas. For example, Risk Assessment can support the decision on which modules in a large enterprise system require formal validation. A more detailed Risk Assessment can determine how rigorously to challenge each function that the higher level assessment has shown needs testing.

The focus of the Risk Assessment process is to assess those risks associated with the post-project operation of the automated system and not the 'in-project' risks. The Risk Assessment process allows the business to identify and minimize the impact of adverse events, while at the same time providing the necessary justification for the validation approach taken to support the system implementation. Avoiding adverse events leads to a greater likelihood of meeting the project requirements, and of providing a fit for purpose and cost effective system.

Note that while the approach outlined helps to focus validation effort, it is the responsibility of the user company to define the appropriate level of validation based on their judgment, expertise, and understanding of regulatory requirements.

2 Roles and Responsibilities

Risk Assessment is part of the overall responsibility of the project team members, however each member may take on a different role during the assessment exercise.

System Owner

The System Owner is defined as the person ultimately responsible for the operation of a system, and the data residing on that system. The System Owner is responsible for the investigation and evaluation of those risks identified as part of the GxP operational process. Approver of Risk Assessment documentation.

Business Owner

Responsible for the investigation and evaluation of those risks identified as significant to the overall business process. Approver of Risk Assessment documentation.

Software Application Personnel

Responsible for the investigation and evaluation of those risks identified as a result of the programme configuration or implementation.

Infrastructure Personnel

Responsible for the investigation and evaluation of those risks identified as a result of the infrastructure (hardware, network, peripherals, etc.) implementation.

Operations Personnel

Responsible for the investigation and evaluation of those risks identified as a result of the technical implementation.

Quality Assurance

Responsible for the investigation and evaluation of those risks associated with regulatory compliance and maintaining company quality standards and policies. Approver of Risk Assessment documentation.

3 Risk Assessment and the Validation Process

As projects are dynamic in nature, the risk priorities are likely to change throughout the life of the project. Risk Assessments should therefore be conducted at several stages of the project (see Figure 3.1). The number and timing of the assessments should be documented in the Validation Plan. As a minimum, Risk Assessments should be undertaken following:

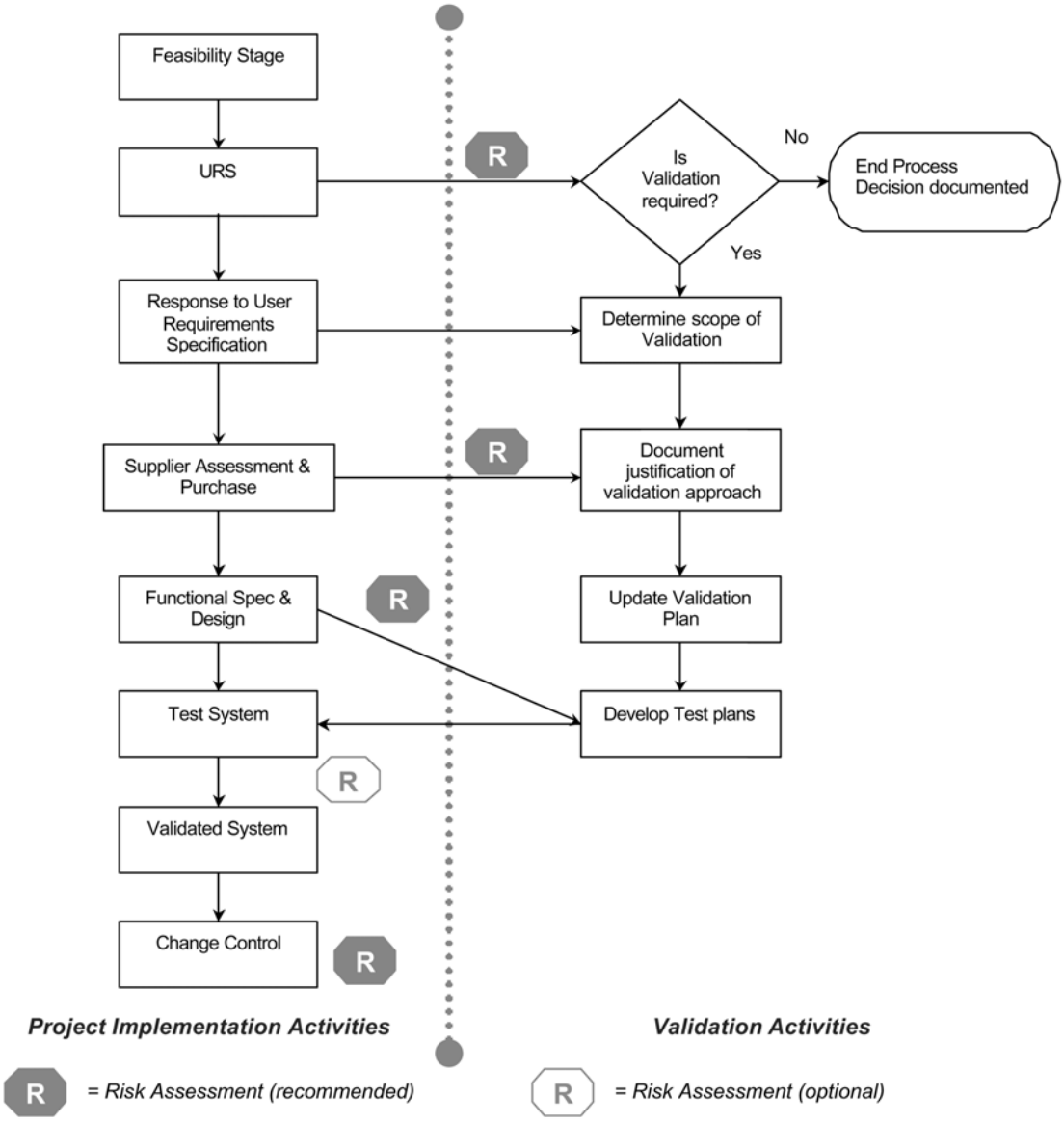
- The generation of the User Requirements Specification (URS)
- The Supplier Assessment and the development of the Functional Specification (FS)
- The completion of the Design Review prior to validation test
- Whenever any major changes are to be applied to the system

Undertaking Risk Assessments at these stages will help define the user requirements and alternatives, aid the supplier selection process, and determine any mitigation steps or additional validation requirements for the project. The findings of early Risk Assessments should be reviewed at later key points in the project, to ensure that the assumptions and circumstances upon which they were founded are still valid.

It is important to ensure that the assessments are well informed and based on verifiable evidence. The views of acknowledged experts should be called upon to ensure that the assessment of the nature and likelihood of a particular risk is as realistic as possible.

As a minimum the System Owner, the Business Owner, and Quality Assurance should approve the Risk Assessment documentation. Additional approvers may be added as required by the team and depending upon the phase of the project.

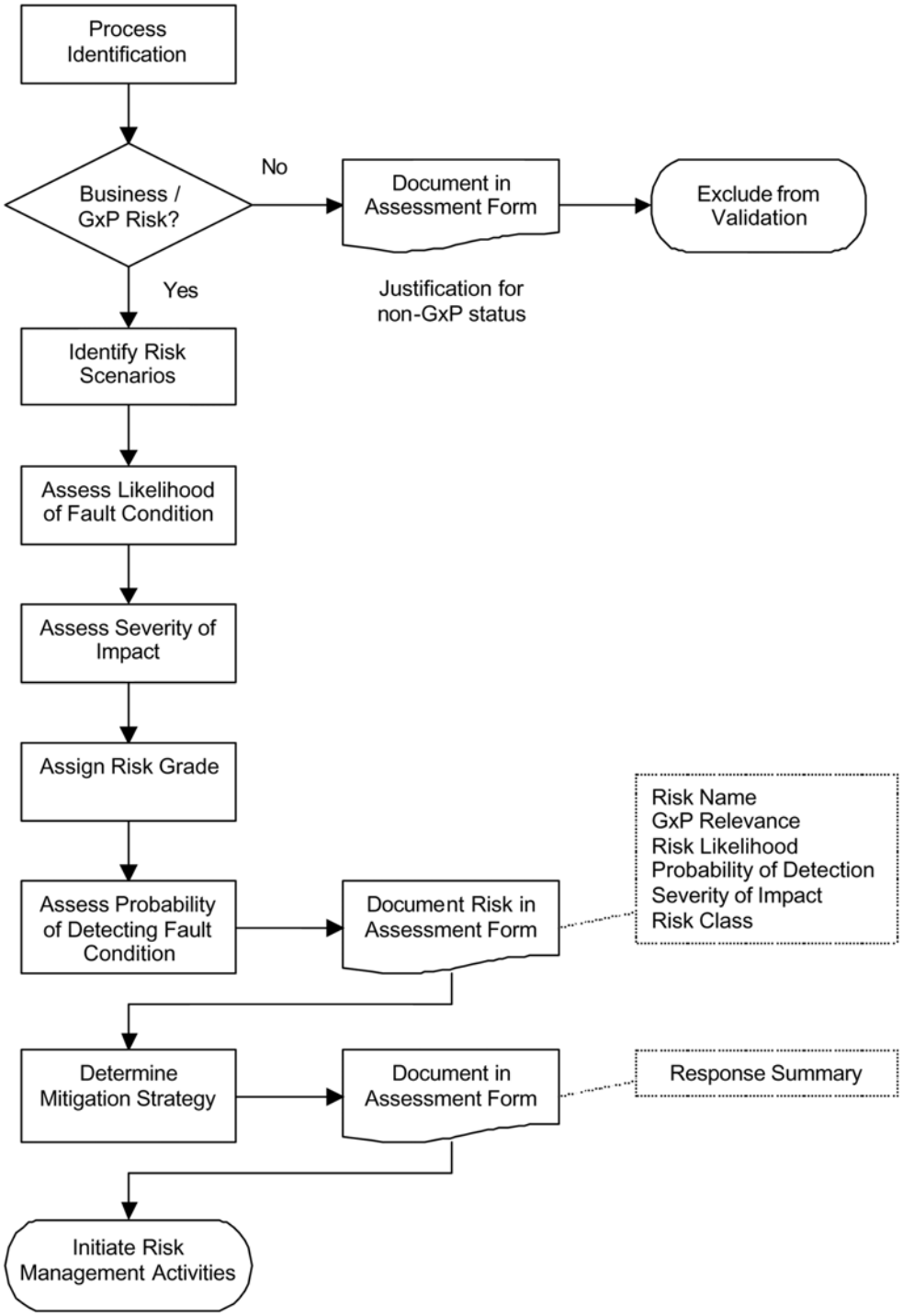
Figure 3.1: Risk Assessment and the Validation Process



4 The Risk Assessment Process

This Section provides an overview of the Risk Assessment Process and the techniques that could be adopted.

Figure 4.1: Overview of the Risk Assessment Process



4.1 Process Identification

The basis for the Risk Assessment will be the User Requirements Specification and the Functional Specification. These documents can be used to identify the system functions and their sub-functions, including the dependencies between them.

All functions and sub-functions identified during this phase should be documented and described (an example form is provided as Attachment 1 to this Appendix). Each function and sub-function should be identified clearly and meaningfully.

4.2 Risk Assessment

4.2.1 Identify GxP Risk

This step is the determination of whether the system function or sub-function represents a risk when assessed against a series of GxP criteria.

Examples of risk that may be identified include, but are not limited to:

- The pharmaceutical quality of the finished product (including clinical supplies):
  - Incorrect composition
  - Raw materials errors
  - Packaging materials errors
  - Integrity of QC laboratory results
  - Incorrect batch status
  - Failure of storage conditions
  - Batch recalls
  - Lot traceability
  - Labelling errors
- The safety of patients and consumers:
  - Adverse reactions
  - Mix-up involving samples (finished product and clinical trials)
  - Inadequate complaints handling or monitoring
- Incorrect data for the support of regulatory submissions:
  - Integrity of development laboratory results

- Statistical evaluations
- Calculation of results from test data
- Composition of the dossier

The project team should look at each function or sub-function and make an assessment of the GxP impact. The outcome of their discussions should be documented on the assessment form.

If the assessment of a particular function or sub-function determines that there is no GxP risk, the justification for taking this viewpoint should be documented on the assessment form. This is useful for future reference if required to explain a particular validation approach to a third party.

4.2.2 Identify Business Risk

A secondary element of the Risk Assessment process is to determine whether the system function or sub-function represents a risk to the business.

The types of risk to be identified include, but are not limited to:

- Corporate reputation
  - Adverse publicity
  - Shareholder responsibilities
  - Earnings impact
  - Competitive advantage
- Brand recognition
  - Customer loyalty
  - Supply chain loyalty
- Risk to manufacturing (process) equipment
  - Equipment downtime
  - Equipment damage
  - Cost of replacement equipment parts
  - Potential for injury (Health and Safety)

If the assessment of a particular function or sub-function determines that there is no business risk, the justification for taking this viewpoint should be documented on the assessment form.

4.2.3 Identify Risk Scenarios

Having determined that a particular function or sub-function may have a GxP or business risk associated with it, the assessment should proceed to identify the various Risk Scenarios (i.e., the events that identify the risks associated with use of the system). It is useful to consider for each event what the likely effect will be (note that each event may have more than one effect). An example analysis is given in Table 4.1.

Table 4.1: Example Analysis of Risk Scenarios

Function	Sub-Function	Risk Scenarios (Events)	Effect(s)
Procurement	Raising a Purchase Order	Input incorrect grade during order entry	Receive incorrect grade of material Reject material on receipt / analysis Inventory shortage
		Use non- approved supplier	Problems maintaining manufacturing process Variation in quality of finished product Rejection of product Inventory shortage
Setting up a Packing Line	Booking in printed packaging materials using bar-code reader	Bar-code read incorrectly	Material not accepted by system Packing line start delayed
		Incorrect materials delivered to the line	Material not accepted by system Packing line start delayed
		Materials not approved for use / released	Material not accepted by system Packing line start delayed
		Contents not as per the warehouse label	Material not accepted by system Packing line start delayed

4.2.4 Assess Likelihood

The next stage is to determine the likelihood (frequency or probability) of an adverse event occurring. The approach requires the team to consider the likelihood of the adverse event occurring within a given time period (day, month, year) or per a quantity of transactions, and assigning a value to that estimate. A suggested method of representing this is as follows:

Low: The frequency of the event occurring is perceived to be once per ten thousand transactions

Medium: The frequency of the event occurring is perceived to be once per thousand transactions

High: The frequency of the event occurring is perceived to be once per hundred transactions

In many instances adverse events may be as the result of systematic software faults and the team may be unable to estimate the likelihood of such an adverse event. In such instances the likelihood default value of 'High' should be assigned unless there is strong documentary evidence of a high quality development process for the software under review. When more information becomes available as the project progresses, this value can be re-assigned as required.

4.2.5 Assess the Severity of Impact

Risk Assessment requires not only the identification of the immediate effects of the risk but also the long term and widespread impact on the business of those effects. These effects must take into account a wide variety of issues, including impact on regulatory compliance, financial impact, and company reputation with customers and suppliers. For example, the immediate effect of a hard disk problem may be the corruption of some data stored on that disk, while the business impact of corrupt data relating to product distribution will eventually result in severe problems in conducting a product recall. This would result in a critical non-compliance with the regulatory requirements and could result in regulatory action such as a withdrawn manufacturing licence.

The impact of a risk occurring may be described as follows:

Low: Expected to have a minor negative impact. The damage would not be expected to have a long-term detrimental effect.

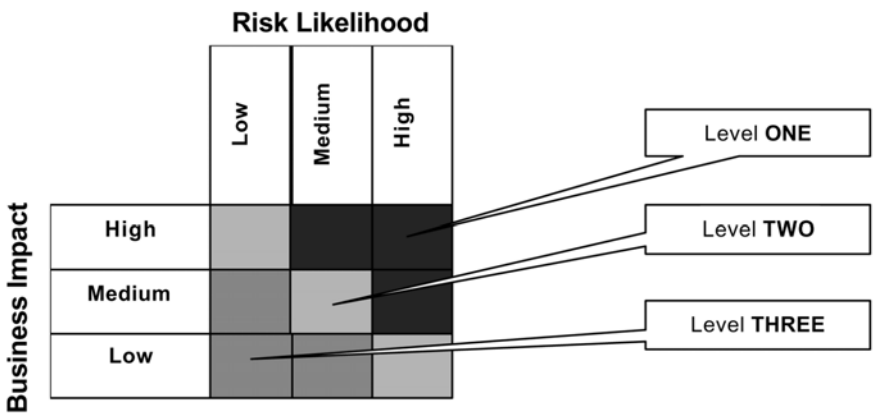
Medium: Expected to have a moderate impact. The impact could be expected to have short- to medium-term detrimental effects.

High: Expected to have a very significant negative impact. The impact could be expected to have significant long-term effects and potentially catastrophic short-term effects.

4.2.6 Assign Risk Classification

Having assigned the *Likelihood* of the risk occurring and the level of *Business Impact* that such an event may have, the risk can be classified. This is achieved by reference to the matrix shown in Figure 4.2.

Figure 4.2: Risk Classification



4.2.7 Assess Probability of Detection

The purpose of this stage in the assessment process is to identify if the risk event can be recognized or detected by other means in the system. Hence a Level One Risk, if it has a high probability of detection, may not pose such a serious threat because it can be recognized quickly and suitable corrective action taken to mitigate its impact. Conversely if the same fault condition has a low probability of detection, then the team may need to seriously consider a review of the design or the implementation of alternative procedures to avoid the event.

The probability of a risk being detected can be estimated as follows:

Low: Detection of the fault condition is perceived to be unlikely (e.g., less than 1 event in every 3 transactions or operations);

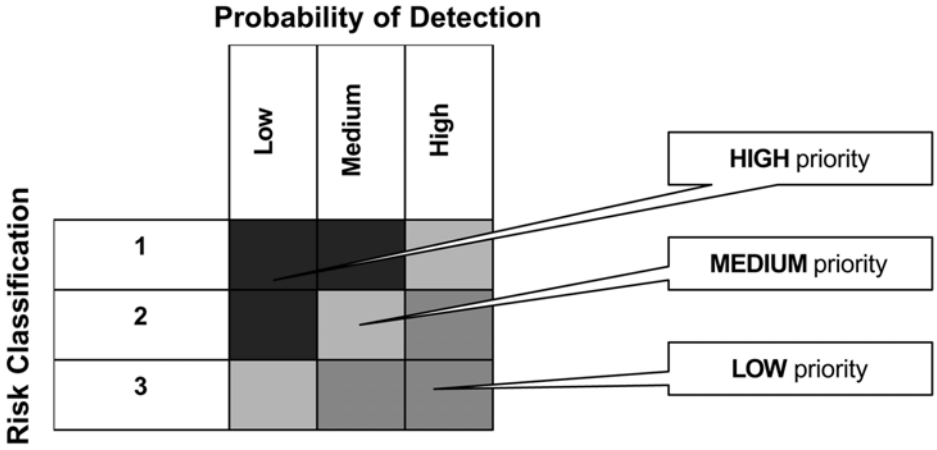
Medium: Detection of the fault condition is perceived to be reasonably likely (e.g., 1 event in every 2 transactions or operations);

High: Detection of the fault condition is perceived to be highly likely (e.g., 1 event in every 1 transaction or operation)

4.2.8 Determine Appropriate Measures for Risk Mitigation

By combining the *Risk Classification* with the *Probability of Detection*, it is possible to prioritise the fault conditions associated with each adverse event based upon those areas of greatest vulnerability. The table below (Figure 4.3) provides a model for such a process. Once these priorities have been determined the team can proceed to define and document the appropriate measure(s) to mitigate the adverse event that poses the risk (see Attachment 1 to this Appendix).

Figure 4.3: Risk Priority



The Risk Priority of the fault conditions should be used to select the appropriate risk mitigation (and focus the validation effort). For example a condition which has a risk classification of 1, but low level of detection is an area of vulnerability (= HIGH priority). By concentrating upon such an area the overall probability of failure is reduced and quality is built into the system. There are several mitigation strategies that can be used to modify risk levels, and it is possible that several of them may be appropriate for a given system. Examples of such strategies are given in the Table 4.2.

Table 4.2: Example Risk Mitigation Strategies

1. Modification of process or system design elements to mitigate risk
• **Modify Process design:** One or more independent controls are incorporated into the computer-related process e.g., additional data verification checks within the system design in order to reduce data entry errors.
• **Introduce External Procedures:** Introduction of procedures to counter possible failures, such as double checking.
• **Modify Product (or System) design:** Use is made of proven methods, tools and components; fault-tolerance may be built into the automated system (e.g., using replicated parts, system mirroring); the operating environment may be controlled.
2. Modification of project strategies to mitigate risk
• **Revisit project structure and makeup:** This refers to the people chosen for the project; their experience and qualifications; the type of project organization preferred; the amount of education and training provided.
• **Reconsider amount of (auditable) built-in quality:** Alter the amount of documentation that is approved and controlled; introduce or remove formal review points to reflect identified risk.
3. Modification of validation approach to mitigate risk
• **Increased Testing:** Increase the scope and level of testing applied during various stages of the validation process, including the development of specialized testing aimed at the testing to failure of certain functions.
• **Decreased Testing:** Decrease the scope and level of testing applied during various phases of the validation process due to the extremely low risk associated with occurrence and consequences of the fault conditions.
4. Eliminate risk
• **Avoidance:** The risks are so high that the new way of working should not be implemented.

The results of this phase of the assessment should be documented and used as justification for the validation approach. Details should include who is responsible for providing the mitigation effort and all members of the project team should approve the Risk Assessment documentation.

4.3 Risk Assessment of Change

The techniques contained within this Guideline have focussed upon the role of Risk Assessment during the development and implementation stages of a system. It is important, however, to maintain such an approach during the entire lifetime of the system. The process of Risk Assessment should be pursued at any time a change is to be applied to the system. Generally systems are at most risk of failure following initial implementation due to the application of ill-considered changes and their potential damaging impact. The application of the Risk Assessment technique as part of the Change Control process will allow the development of suitable mitigation strategies, to identify the verification and re-test activities to pursue before the change is put into operation.

5 Attachments

Attachment 1: Risk Assessment Form

Project Title / Risk Assessment Overview									**Project Number**	
Assessment Scope / Assumptions Made										
Function	Sub-Function	Assessment of Risk							Measures	
		Relevance (GxP / Business)	Risk Scenarios	Likelihood	Impact	Class	Detection	Priority		
Risk Assessment Approved by:										

Appendix 9
Example Template Form for Risk Assessment and Identification of Controls

Example Template Form for Risk Assessment and Identification of Controls

Note: In the form below, records may include electronic signatures

System Name:

Record(s):

Hazard	Consequence	Control
Physical/Environmental		
Power surge	Loss of Record(s)	*E.g., reference to backup procedure and training*
Power fail	Loss of Record(s)	*E.g., reference to backup procedure and training*
Fire and/or Smoke	Loss of Record(s)	*E.g., reference to Disaster Plan*
Environment problem	Loss of Record(s)	*E.g., reference to Disaster Plan*
Theft of hardware/software	Loss of Record(s)	*E.g., reference to Disaster Plan*
Computer-related		
Hardware undersized	Loss of Record(s)	*E.g., reference to validation testing and monitoring*
Hardware loss (e.g., disk crash)	Loss of Record(s)	*E.g., reference to backup procedure and training*
Software terminates	Loss of Record(s)	*E.g., reference to validation testing, procedures, training*
Wrong version of software	Loss of Record(s)	*E.g., reference to procedures and training*
Multiple versions of software	Loss of Record(s)	*E.g., reference to validation testing, procedures, training*
Software lost or deleted	Loss of Record(s)	*E.g., reference to backup procedure and training*
Software failure	• Invalid contents of record • Wrong record displayed • Accidental corrupted record	*E.g., Validation, technical and/or procedural controls*
Printer error or failure	Incorrect copy of record	*E.g., Validation, technical and/or procedural controls*

Hazard	Consequence	Control
Human-related (accidental or deliberate)		
Human error (includes errors of judgment and errors in carrying out required actions)	• Wrong record displayed • Accidentally corrupted record • Invalid contents of record • Incorrect copy of record	*E.g., Access controls, procedures, training*
Change error	Invalid contents of record	*E.g., Access controls, procedures, training*
Unauthorized change	Invalid contents of record	*E.g., Access controls, procedures, training*
Undetectable change	Invalid contents of record	*E.g., Access controls, procedures, training*
Wrong access rights	• Wrong record displayed • Invalid contents of record	*E.g., Access controls, procedures, training*

Completed by:	Title:	Date:
Reviewed by:	Title:	Date:
Approved by:	Title:	Date:

Appendix 10
Form for Previously Assessed 21 CFR Part 11 Systems

Example Form for Assessment of Previously Assessed 21 CFR Part 11 Systems

System(s):	
System Owner:	
Application(s):	
Location(s):	
Description of System(s):	

21 CFR 11 Applicability and Assessment Change Approvals

Signatures	Name, Title	Signature	Date
Prepared by:			
Reviewed and Approved by:			

1 Scope of 21 CFR Part 11

This section verifies that 21 CFR Part 11 still applies to the system.

		Yes/No	Comment
1.1	Does the system maintain records that are required by predicate rules, in electronic format in place of paper format? For example, does the system contain electronic records which are ever used to support a batch release, audit, non-conformance or deviation investigation, or annual report?		
1.2	Does the system maintain records that are required by predicate rules, in electronic format in addition to paper format, and that are relied upon to perform regulated activities? Note: If the system generates paper records which are then the only records used to perform regulated activities, answer NO (the paper records are still subject to the appropriate controls to assure integrity, reliability, trustworthiness, and accuracy).		
1.3	Does the system maintain records submitted electronically to FDA under predicate rules?		
1.4	Does the system maintain records in electronic format, which have been used to generate a submission, where these records are themselves required by predicate rules?		
1.5	Does the system maintain electronic signatures that are intended to be the equivalent of handwritten signatures, initials, and other general signings required by predicate rules?		

If the answer to all the above questions is NO, the system is no longer within the scope of 21 CFR Part 11.

2 Legacy Systems

The FDA does not intend to take enforcement action to enforce compliance with any 21 CFR Part 11 requirements if all the following criteria are met for a specific system.

		Yes/No	Comment
2.1	Was the system operational prior to August 20, 1997?		
2.2	If yes, did the system meet all applicable predicate rules at that time?		
2.3	Does the system continue to meet all applicable predicate rule requirements?		
2.4	Is there documented evidence and justification that the system is fit for its intended purpose (including having an acceptable level of record security and integrity, if applicable)?		
2.5	If the system has been changed since August 20, 1997, is there evidence that the changes have not introduced unacceptable risk to record security and integrity, and that the changes have not adversely affected the ability to meet predicate rule requirements?		

If the answer to all the above questions is YES, no further 21 CFR Part 11 remediation work is required.

3 Approach to Specific 21 CFR Part 11 Requirements

The FDA has indicated that it intends to exercise enforcement discretion with regard to specific 21 CFR Part 11 clauses.

		Yes/No	Comment
3.1	Is there evidence that the system meets all applicable predicate rule requirements covering the following: • Validation • Audit trails, including documentation of date, time, and sequencing of events, and requirements for ensuring that changes to records do not obscure previous entries • Record retention		
3.2	Has a risk assessment of the system, taking into the account the potential of the system to affect product quality or patient safety, and record integrity, been carried out in relation to the following topics: • Validation • Audit trails • Record retention Note: Such an assessment may identify areas, based on risk, where further controls are required OR identify planned remediation that can be justified as not necessary, based on risk.		
3.3	If answer to previous question is NO, would carrying out such a risk assessment affect current remediation plans? If answer is YES go to question 3.4 If NO go to question 3.5		
3.4	If so, carry out risk assessment using guidance provided in Section 2 of this Guide. Document outcome of risk assessment and describe impact on existing remediation plans. Provide justification for the change of approach. (refer to other documentation as appropriate)		

		Yes/No	Comment
3.5	Would meeting the following objectives affect current remediation plans relating to copies of records? • ability to provide an inspector with reasonable and useful access to records during an inspection • supply copies that preserve the meaning and content of records • ability to search, sort or trend, if reasonable and technically feasible, and if that ability exists for masters		
3.6	If so, describe impact on existing remediation plans. Provide justification for the change of approach. (refer to other documentation as appropriate)		

4 Decision and Rationale

Based upon the answers above, please provide conclusions of reassessment, any required actions, and how these will be managed.

Appendix 11
Current Regulatory Situation

1 Introduction

Since the effective date of 21 CFR Part 11 in August 1997, there has been much discussion and debate among regulated life science companies, their regulators, and suppliers regarding the effective implementation of compliant electronic records and signatures.

Recent regulatory developments in Europe, Japan, and the US will fundamentally alter the way industry approaches this subject. This Appendix gives a comprehensive overview of the current regulatory situation at time of printing.

2 US Food and Drug Administration (US FDA)

On 3 September 2003, as part of the overall CGMP initiative *Pharmaceutical [C]GMPs for the 21st Century: A Risk-Based Approach*, the FDA made available the final guidance document *Part 11, Electronic Records; Electronic Signatures - Scope and Application* (See Appendix 13, reference 3). The FDA is re-examining 21 CFR Part 11 as it applies to all FDA regulated products, and anticipates initiating rulemaking to change 21 CFR Part 11 as a result of that re-examination.

The final guidance explains how FDA will narrowly interpret the scope of 21 CFR Part 11, and while the re-examination of 21 CFR Part 11 is under way, that they intend to exercise discretion with respect to certain 21 CFR Part 11 requirements. That is, FDA do not intend to take enforcement action to enforce compliance with the validation, audit trail, record retention, and record copying requirements of 21 CFR Part 11 as explained in that guidance.

In addition, the guidance explains how they do not intend to take action to enforce any 21 CFR Part 11 requirements with regard to systems that were operational before the effective date of 21 CFR Part 11, as long as certain criteria (defined in the guidance) are met.

The FDA stresses that 21 CFR Part 11 remains in effect, and that enforcement discretion applies only as identified in the guidance. They stress also that records must still be maintained or submitted in accordance with the underlying predicate rules, and that they can take regulatory action for non-compliance with such predicate rules (i.e., the underlying requirements set forth in the US FD&C Act, US PHS Act, and FDA regulations, other than 21 CFR Part 11).

Under the narrow interpretation FDA considers 21 CFR Part 11 to be applicable to records that are required to be maintained under predicate rule requirements and that are maintained in electronic format *in place of paper format*, and records that are required to be maintained under predicate rules, that are maintained in electronic format *in addition to paper format,* and that *are relied on to perform regulated activities*.

Also in scope are records submitted to FDA under the predicate rules, in electronic format, and electronic signatures that are intended to be the equivalent of handwritten signatures, initials, and other general signings required by predicate rules. The guidance states that firms should determine and document, based on the predicate rules, which records they regard as 21 CFR Part 11 records.

The guidance also describes the current FDA thinking on key topics in this area, such as validation, audit trails, record copying, and record retention, and describes the role of justified and documented risk assessment in selecting appropriate controls.

The guidance refers to existing FDA guidance documents on software and computerized systems, and the ISPE *GAMP Guide for Validation of Automated Systems, GAMP 4* (Appendix 13, reference 1).

3 EU GMP

EC Directive 2003/94 sets out the GMP principles applicable in the EU for medicinal products and investigational medicinal products. These obligations include a requirement to maintain a system of documentation. The main requirements affecting electronic records are that the data are available for the required time, that the data are made readily available in legible form, that the data are protected against loss or damage, and that audit trails are maintained.

EU GMP Chapter 4 refers to electronic data processing systems and measures that should be in place to protect the data, including:

- Access by authorized personnel only
- Use of passwords
- Creation of backup copies
- Independent checking of critical data
- Safe storage of data for the required time

Validated and secure computerized systems are required, and audit trails applied where appropriate. Records should be accurately made and protected against loss or damage or unauthorized alteration, so that there is a clear and accurate audit trail throughout the manufacturing process available to the licensing authority for the appropriate period. This documentation may be electronic, photographic, or in the form of another data processing system.

Specific requirements of Annex 11 of EU GMP include:

- Assessment of risk to product quality
- Built-in checks for correct data-entry and processing
- Data-entry and amendment by authorized personnel only
- Procedures for managing the user authorisation process
- Systems for recording attempted unauthorised access
- Accuracy checks for critical data-entry
- Recording identity of operators entering or confirming critical data

- Ability to produce printouts of electronically stored data
- Checking of data for accessibility, durability and accuracy
- Data secured against willful or accidental damage
- Procedures and arrangements to cover a systems breakdown
- A procedure to record and analyse errors, leading to correction

For further information see Section 4.2 of this Guide.

4 PIC/S Guidance

The abbreviation PIC/S describes the Pharmaceutical Inspection Convention (PIC), and the Pharmaceutical Inspection Co-operation Scheme (PIC Scheme), operating together in parallel (see www.picscheme.org for further information).

Working within PIC/S many international regulatory agencies have collaborated to produce a harmonised guidance for the implementation, management and operation of computerised systems. This document - *Good Practices for Computerised Systems in Regulated "GxP" Environment (PIC/S PI011-2),* (Appendix 13, reference 5), was published in September 2003.

The purpose of this PIC/S guidance is to provide recommendations and background information concerning computerized systems, both for training purposes and during the inspection of computerized systems. This guidance contains a section on Electronic Records and Signatures based on EU GMP, and generally equivalent to EU GMP expectations.

The guidance states that regulated companies have a choice whether to use electronic records or electronic signatures instead of paper based records and paper based signatures. When regulated users elect to use electronic records for GxP applications then it will be necessary for the companies to identify the particular regulations being applied and whether the records are to be considered legally binding and equivalent to their paper-based counterparts.

The guidance states that GMP documents (in general) should be clear, legible and up to date, and make it possible to trace the history of manufacture and testing. The records should also to be retained for the required time and protected against loss or damage.

The PIC/S guidance notes that regulations applicable to particular GxP disciplines may impose specific rules, e.g., when electronic records and electronic signatures are used as a primary source of data, records and/or evidence. It is for the regulated company to explain and justify the technologies and controls in place.

5 JAPAN MHLW

On 4 June 2003, Evaluation and Licensing Division (Shinsa-Kanri-Ka) of Pharmaceutical Bureau (Iyaku-Kyoku) at Ministry of Health, Labour and Welfare (MHLW) released a "Draft Guideline for the Use of Electromagnetic Records[9]/Electronic Signatures in Applications for Approval or Licensing of Drugs etc." [Its English translation is found below] with a request for comments (RFC) before 4 September 2003. The draft and the RFC were associated to the release of "Draft Guide for Creating Electronic Common Technical Documents" with corresponding RFC for the Draft Guide. The first version of the Draft Guideline was created by an advisory committee organized by MHLW and the released version of the Draft Guideline was prepared by MHLW regulators with some modifications. The advisory committee consisted of representatives from academia and Japanese pharmaceutical industry. Among them three members from the industry were experts in GLP, GCP and GMP areas respectively. The committee members made their efforts to make the Draft Guideline to be applicable to all GxP areas.

Disclaimer:
This translation created by GAMP Japan, GAMP 4 Translation SIG, solely for the purpose of giving general understanding of the Draft Guideline. These have been reviewed by no other organizations or regulatory bodies. GAMP Japan is not responsible for the correctness of these translations.

Draft Guideline for the Use of Electromagnetic Records/Electronic Signatures in Applications for Approval or Licensing of Drugs etc.

1 Purpose

These guidelines provide requirements to ensure reliability of electromagnetic records and electronic signatures when they are used in records relevant to applications for approval or licensing of drugs etc.

2 Definitions

The following definitions of terms apply to these guidelines.

(1) Electromagnetic record

A set of information that includes electronic data (e.g., text, numeric, graphics) that is created, modified, maintained, archived, retrieved, or transmitted by a computer system.

[9] The term "Electromagnetic Records (Denjiteki-Kiroku)" adopted in the draft is expected to be replaced with the usual term "Electronic Records (Denshi-Kiroku)" in the final guideline. (The reason why the unfamiliar term, "Electromagnetic Records" was chosen in the draft was that the term had been already adopted in another Japanese e-Commerce Law.)

(2) Electromagnetic recording media

Media on which electromagnetic records are stored, such as magnetic disks, optical disks, and magnetic tapes.

(3) Electronic signature

A signature executed to electromagnetic records as the legally binding equivalent of individual's handwritten signature is an electronic data compilation of series of symbols created, adopted, confirmed and approved by the individual.

(4) Digital signature

An electronic signature based upon, for example, a cryptographic method of signer authentication.

(5) Closed system

A system in which system access is controlled by persons who are responsible for the content of electromagnetic records that are on the system

(6) Open system

A system in which system access is not controlled by persons who are responsible for the content of electromagnetic records that are on the system

(7) Audit trail

A series of manipulation records to which accurate time stamps are added.

3 Scope

These guidelines apply to electromagnetic records defined below that pertain to approval or licensing of drugs etc., and to electronic signatures executed on these records.

(1) Records required to be submitted as a part of application and so forth

(2) Records required to be maintained

4 Requirements for the Use of Electromagnetic Records

4.1 Controls of Electromagnetic Records

The following properties listed below should be achieved in the system using electromagnetic records and in operational procedures for the system. This assumes that, for the system that uses electromagnetic records, the reliability of the system have been ensured by computer system validation.

4.1.1 Authenticity of Electromagnetic Records

Electromagnetic records should have integrity, accuracy and reliability, and clear responsibility for their creation, modification, and deletion.

In order to ensure their authenticity, the following requirements should be met.

(1) Rules and procedures for maintaining security of the system are documented and adequately implemented.

(2) A person who has created the information stored should be clearly identified. In addition, whenever the information once stored is modified, the information prior to the modification should be maintained, and the modifier should be clearly identified. For this purpose, it is recommended that audit trails are automatically recorded, and the recorded audit trail can be verified by established procedures.

(3) Backup procedures for the electromagnetic records should be documented and adequately implemented.

4.1.2 Human Readability of Electromagnetic Records

Output of the content of electromagnetic records in human readable form (e.g., displayed on a monitor, printed on paper, copied onto electromagnetic recording media) should be available.

4.1.3 Storability of Electromagnetic Records

Electromagnetic records should be stored in a condition in which their authenticity and readability have been preserved throughout their retention period.

In order to ensure their storability, the following requirements should be met.

(1) Procedures for ensuring their storability, such as management of electromagnetic recording media, should be documented and adequately implemented.

(2) If electromagnetic records that have been stored are transferred to other electromagnetic recording media or formats, the authenticity, human readability, and storability of the converted electromagnetic records should be preserved.

4.2 The Use of Closed Systems

When persons use closed systems to create, modify, maintain, archive, retrieve, or transmit electromagnetic records, the requirements set forth in section 4.1 should be met in order to ensure the authenticity, readability, and storability of the electromagnetic records. Whenever electronic signatures are used, the requirements set forth in 5. should be met.

4.3 The Use of Open Systems

When persons use open systems to create, modify, maintain, archive, retrieve, or transmit electromagnetic records, in addition to the requirements set forth in section 4.1, additional measures necessary for ensuring the authenticity and confidentiality of the records from the point of their creation to the point of their receipt should be adequately implemented. These additional measures may include adoption of such technologies as electromagnetic record encryption and/or digital signature. Whenever electronic signatures are used, the requirements set forth in section 5. should be met.

5 Requirements for the Use of Electronic Signatures

If electronic signatures are used, the following requirements should be met in order to ensure the reliability of the electronic signatures.

(1) Procedures for management and operation for electronic signatures should be documented and adequately implemented in accordance with the laws pertaining to electronic signatures and authentication activities (Law No. 102, dated 31 May 2000).

(2) Each electronic signature should be unique to identify each individual, and not be reused by or reassigned to any others.

(3) If electronic signatures are executed on electromagnetic records, the signed electromagnetic records should include information that indicates all of the following:

- The name of the signer
- The date and time when the signature was executed
- The meaning of the signature (such as, creation, review, approval)

(4) Electronic signatures executed to electronic records should be linked to their respective electromagnetic records to ensure that the signatures cannot be deleted or copied to falsify the electromagnetic records by ordinary means.

6 Measures to be taken By Applicants

Persons intending to use electromagnetic records and electronic signatures in records for their applications for approval or licensing of pharmaceuticals and medical devices should identify managers, administrators, organization, facilities, and education/training that are required for the use of electromagnetic records and electronic signatures.

Appendix 12
Glossary

Glossary

1 Definitions

Automated System

A broad range of systems including, but not limited to, automated manufacturing equipment, automated laboratory equipment, process control, manufacturing execution, laboratory information management, manufacturing resource planning, clinical trials data management, and document management systems.

The automated system consists of the hardware, software, and network components, together with the controlled functions and associated documentation. Automated systems are sometimes referred to as computerized systems.

Company

Is used in this Guide to refer to the regulated entity (such as company, partnership, corporation, or association). It is synonymous with the term "firm", as used by the FDA, and "User Company" as used in *GAMP 4*.

GxP Regulation

Refers to the underlying international life science requirements such as those set forth in the US FD&C Act, US PHS Act, FDA regulations, EU Directives, Japanese MHLW regulations, or other applicable national legislation or regulations under which a company operates.

Harm

Physical injury or damage to the health of people, or damage to property or the environment.

Hazard

Potential source of harm.

Hybrid situation

Co-existence of paper and electronic record and signature components. Examples include combinations of paper (or other nonelectronic media) and electronic records, paper records and electronic signatures, or handwritten signatures executed to electronic records.

Impact

Is a measure of the possible consequences of loss or corruption of a record.

Predicate Rules

The underlying requirements set forth in the US Federal Food, Drug, and Cosmetic Act, in the US Public Health Service Act, and in FDA regulations (other than 21 CFR Part 11).

One-off program

A program used with a specific set of data from a single study, (e.g., Clinical trial).

Regulated Record

Is one required to be maintained or submitted by GxP regulations. A regulated record may be held in different formats, for example, electronic, paper, or both.

Regulated Signature

Is one required by a GxP regulation. The term s*ignature* and s*igned* are defined as "*The record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature."* (Guidance for Industry Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, ICH).

Risk

Combination of the probability of occurrence of harm and the severity of that harm.

Risk Assessment

Overall process comprising a risk analysis and a risk evaluation:

- Risk analysis: systematic use of available information to identify hazards and to estimate the risk
- Risk Evaluation: judgment, on the basis of risk analysis, of whether a risk which is acceptable has been achieved in a given context

Risk Control

Process through which decisions are reached and protective measures are implemented for reducing risks to, or maintaining risks within, specified levels.

Risk Management

Systematic application of management policies, procedures and practices to the tasks of analyzing, evaluating, and controlling risk.

Severity

Measure of the possible consequences of a hazard.

2 Acronyms

ADRs	Adverse Drug Reactions
AEs	Adverse Events
CDS	Chromatography data system
COTS	Commercial Off The Shelf
CT	Clinical Trial
CTA	Clinical Trial Application (for Authorization)
GCP	Good Clinical Practice
ER&S	Electronic Records and Signatures
GDP	Good Distribution Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GPvP	Good Pharmacovigilance Practice
GVP	Good Vigilance Practice
GxP	One or a combination of GCP, GLP, GMP, GDP, GVP, medical device quality systems regulations
HPLC	High Performance Liquid Chromatography
IMP	Investigational Medicinal Product
ISMS	Information Security Management System
INDs	Investigational New Drug Applications
IRB	Institutional Review Board
IT	Information Technology
IVRS	Interactive Voice Response System
LAN	Local Area Network
LIMS	Laboratory Information Management System
NDAs	New Drug Applications

PLC	Programmable Logic Controller
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
SCADA	Supervisory Control and Data Acquisition
SOP	Standard Operating Procedure
WAN	Wide Area Network

3 Abbreviations

CDRH	Center for Devices and Radiological Health
FDA	US Food and Drug Administration
ICH	International Conference on Harmonisation
IEEE	Institute of Electrical and Electronics Engineers
ISO	International Organization for Standardization
MHLW	Ministry of Health Labour and Welfare in Japan
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
NIST	National Institute of Standards and Technology
PIC/S	Pharmaceutical Inspection Co-operation Scheme

Appendix 13
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