This article describes the elemental requirements of a Validation Master Plan (VMP), what it should look like, what level of detail should be included, and FDA expectations.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
May/June, 2001 Vol. 21 No. 3

Reasons, Regulations, and Rules: A Guide to the Validation Master Plan (VMP)

by Brian W. Saxton

The US Food and Drug Administration (FDA) has been explicit in the need for validation, but implicit on the elements of that program. The chanting of the "thou shalt validate" mantra is heard throughout the Drug, Biologics, and Medical Devices sections of the Code of Federal Regulations (CFR), but, alas, there is no boilerplate template to follow. Organizations are thus left to interpret the regulatory requirements and craft individual programs to comply. Is there a guiding principle that can be applied here, to help companies distill reams of mind-numbing regulations into elemental validation requirements?

An adage about public speaking says there are three keys to a successful presentation:

1. Tell them what you're going to say.

2. Say it.

3. Tell them what you said.

This adage, in a slightly modified form, can be used to describe the major elements of a Validation Program:

1. Tell them what you're going to do.

2. Do it.

3. Tell them what you did.

This three-step outline is a greatly simplified model of the multitude of tasks associated with a validation program, but is an accurate summary of the goals of each step of the process. The role of the Validation Master Plan is to help an organization "get its arms around" a project-specific validation effort by setting the scope by which all subsequent documents shall be bounded.

To see how the parts of the validation program fit into this modified adage, let's briefly review the elements. "Validation Program" is an umbrella term, encompassing all of the components below - *Table A*.

Validation Master Plan (VMP)

The VMP serves as the validation roadmap, setting the course, justifying the strategy, outlining the preliminary test and acceptance criteria, and documenting the necessary programs that ensure a continuing state of validation.

Qualification

The Qualification phase provides documentation that equipment and utility systems were installed properly through an Installation Qualification (IQ), operate correctly through an Operational Qualification (OQ), and perform effectively through a Performance Qualification (PQ). Qualification assures that the criteria set forth in the Basis of Design documents generated at project inception have been met in the field installation.

Process Validation

Building on the data generated from the Qualification phase, the Process Validation (PV) phase focuses on the reproducibility of the systems used and the resulting product quality. This program challenges the ability of the systems used (methods, equipment, and operators) to meet the pre-approved design intent.

Final Reports

Final Reports (FR) compare the conclusions of data gathered to the acceptance criteria outlined in the Qualification and Validation phases. They determine the pass/fail status and address the resolution of any deviations. They also can be referred to as Summary Reports.

Compliance Programs

The Validation program must ensure policies and procedures comply with current Good Manufacturing Practices (cGMP). Systems such as calibration, preventative maintenance, change control, and revalidation contribute to a continuous state of validation.

Validation Program
Validation Master Plan (VMP) Documents Intent and Pathway
Qualification (IQ/OQ/PQ) Confirms Design Intent
Process Validation (PV) Assures Process Consistency
Final Reports (FR) Summarizes Test Results vs. Acceptance Criteria
Compliance Programs Ensures Continuing State of Validation

Table A. Validation program.

Considering the above, we can now complete the Validation Program adage:

1. Tell them what you're going to do (VMP).

2. Do it (IQ/OQ/PQ/PV).

3. Tell them what you did (FR).

This article will focus on the "Tell them what you're going to do" part of the Validation Program, otherwise know as the Validation Master Plan.

Planning Overview

The purpose of the VMP, in a prospective or concurrent validation effort, is to explain the validation rationale associated with the installation, start-up, and use of a new production line. This rationale should review manufacturing systems and assess the potential of each to affect end-product quality. The new process may be as simple as an accessory change on existing product equipment, or as complex as a new building with all new utilities and equipment. The size and scope of the project determines the size and scope of the resulting VMP. For a retrospective validation effort, the VMP documents the existing production line and outlines the anticipated test and analytical methodologies to be employed.

The VMP should be authored for its audience, including the organization's quality, engineering, and regulatory departments, the FDA, and potential outside contractors. Each group looks for different elements. Outside contractors want a Deliverables List on which to base quotes and define the scope of work; the FDA looks for the pre-approved intention to comply with Federal regulations; while in-house quality, engineering, and regulatory departments look for an accurate representation of systems and corporate policies. The VMP should address all of these concerns.

The VMP serves the purpose of documenting the intent of the validation program, and therefore needs to be pre-approved by the same departments that will ultimately be responsible for reviewing and approving the subsequent protocols. At a minimum, this includes Regulatory Affairs, Quality, and Engineering.

Opening a Dialogue with the FDA

There are a number of good reasons to create a VMP: the FDA's expectation that one be created, determining resource scheduling and loading, and defining the necessity to create or amend corporate procedures. However, one function of the VMP is often underutilized: serving as a vehicle to open up dialogue between the regional District Office of the FDA and the organization. Initiating a pre-submission meeting with the FDA to review the VMP will save time to market by addressing any concerns about the validation philosophy or methodology up front, when the correction of those issues is not on a critical path for time to market. This allows companies to work with the FDA in an advisory versus an enforcement mode, which will help take some of the anxiety out of the validation process and improves its chances of success. The FDA's Center for Biologics Evaluation and Research (CBER) has published a document through its "Manual of Standard Operating Procedures and Policies" that discusses this. It suggests that a "brief description of the validation procedures including the validation master plan"[1] be submitted for review prior to the "pre-NDA" (New Drug Application) meeting. Although this procedure was written for Biologics, the benefits of such meetings for Drug and Medical Device products is obvious, particularly if there are unique processing steps and/or equipment that the average FDA compliance officer may not be familiar with.

Regulatory References to Validation and Planning

The FDA can determine prohibited acts and penalize drug and device manufacturers who market adulterated product.[2] An adulterated product is one whose quality characteristics can not be satisfactorily assured due to nonconformity with current Good Manufacturing Practices (cGMPs)[3]. The definition of "adulterated product" is straightforward, but preventing its occurrence can be complex. In essence, a Validation Program ensures that systems, policies, and procedures exist to prevent the manufacturing of adulterated products. It's in the cGMPs for Drugs (21CFR 210 & 211), Biologics (21CFR 600) and Devices (21CFR 800) where the need for validation is specified.

Drug Products

For drug products, Parts 210 and 211 of the cGMPs refer loosely to maintaining "appropriate validation data." However, the practice of validation is implied more strongly in § 211.68 (a): "Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related

Typical VMP Contents
1. Introduction
2. Scope
3. Facility Description
4. Commissioning
5. Qualification
6. Process Validation
7. Computer System Validation
8. List of Required Protocols and Procedures
9. List of Required Standard Operating Procedures
10. Equipment and Utility System Descriptions
11. Computer System Description
12. Other cGMP Programs
13. References

Table B. Typical VMP contents.

Process Equipment/Other Systems

EQUIPMENT	Comm.	IQ	OQ	PQ	PV
Reactor System Series 100	✓	✓	✓	✓	✓
Centrifuge	✓	✓	✓	✓	✓
Catch Tank	✓				
Solvent Storage and Distribution	✓	✓	✓	✓	✓
Glass Lined Mix Tank and TCU	✓	✓	✓	✓	✓

Utility Systems

UTILITY SYSTEM	Comm.	IQ	OQ	PQ	PV
Fire Water System	✓				
Breathing Air System	✓				
Cold Glycol System	✓				
USP Water System	✓	✓	✓	✓	✓
HVAC	✓	✓	✓	✓	✓

Legend
Comm.: Commissioning
IQ: Installation Qualification
OQ: Operational Qualification
PQ: Performance Qualification
PV: Process Validation
Not Applicable

Table C. List of required protocols and procedures.

systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, and holding of a drug product." The burden of proof lies with the manufacturer to show equipment will "*perform a function satisfactorily*," and that proof should take the form of in-process testing or alternately, Process Validation.

To clarify the validation requirements implicit in this regulation, the Agency issued a Federal Register Notice proposing changes to Parts 210 and 211.[4] One change would offer this definition: "*Validation protocol* means a written plan describing the process to be validated, including production equipment, and how validation will be conducted…."[5] Another proposed section states: "The manufacturer's determination of equipment suitability shall include testing to verify that the equipment is capable of operating satisfactorily within the operating limits required by the process."[6] In both of these cases, a well-crafted VMP will show the Agency the pre-approved intent to comply with the expectations of cGMP regulations.

Biologics

For Biologics, Part 600 addresses unique considerations associated with biological products and blood components. Biological-derived drug products must adhere to Parts 210 & 211. Also, cGMP section § 601.12 requires validation for changes to an approved application. "Before distributing a product made using a change, an applicant shall demonstrate through appropriate validation… the lack of adverse effect of the change on the identity, strength, quality, purity, or potency of the product…."[7] This requirement governs changes in "…product, production process, quality controls, equipment, facilities, responsible personnel, or labeling…."[8] Whether the change is major or minor, a VMP will provide the Agency the basic components of the organizational validation philosophy and intentions to comply with applicable regulations.

Medical Devices

For Medical Devices, 21 CFR 820 serves as the cGMP requirements section. Section 820.75 deals with Process Validation and states that the "validation activities and results, … and where appropriate the major equipment validated, shall be documented."[9] This outlines the need for a validation program, and the VMP can help comply with this requirement by documenting which major equipment systems will be validated.

Part 11

All regulated industries are struggling to understand and comply with the requirements of 21CFR 11, which addresses Electronic Records and Electronic Signatures, and requires "Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records."[10] Based on the number and complexity of the computer systems utilized, a separate Computer System Validation Master Plan may need to be written and referenced in the VMP. Here again, this can serve as a vehicle for a pre-execution meeting with the FDA in order to gain guidance.

These specific instances do not explicitly detail the requirement for a Validation Master Plan; however, a properly crafted VMP will document the pathway to compliance.

VMP References

Increasingly, the FDA is showing it agrees. Recently, the Agency issued a "Guidance for Industry" document, meant to

> ***…address the selection criteria governing what equipment and utility systems need to undergo Process Validation.***

reflect the Agency's current thinking, that explicitly calls out for a VMP. In "Guidance on Quality System Regulation Information for Various Pre-Market Submissions," a requirement of the Quality System Manufacturing Dossier is "a copy of the Validation Master Plan or a description of which manufacturing processes have been or will be validated. A Validation Master Pan is a convenient method of quality planning for process validations required in the manufacturing of the device (§ 820.20(d))."[11] Clearly the expectation of the Agency is that organizations have a validation strategy as part of product and process development, and translate that strategy into a plan that will lead to an installation compliant with regulatory requirements.

The Validation Master Plan

Listed below are the headings for the major sections of a VMP followed by a description of the purpose and the suggested content - *Table B*.

1. Introduction

This section should include the company name, location, division or subsidiary name (if applicable) and business sector served. A short overview of the project provides the reader with the necessary background from a macro standpoint. A cross-reference to the relevant company Quality Assurance Policy is appropriate here.

2. Scope

This section defines the breadth and reach of the validation effort covered by the VMP. A brief description of the installation, whether single- or multi-product, and a breakdown of installed equipment as new or existing should be included here.

3. Facility Description

Whether the project is a new building, extension, or remodeling of a current building, the facility characteristics are listed here. The number of floors, the inter-connectivity of process and utility systems, isolation means, and the design product and personnel flow used to minimize cross-contamination are identified. Be sure to note any room classification (cleanroom certification levels) and specialty surfaces and finishes integral to achieving the required product quality. Process Flow Diagrams (PFDs) are useful here, depicting the anticipated personnel, raw material, process, and waste material flow. The emphasis here is on design considerations to eliminate cross-contamination of material.

4. Commissioning

Document here the selection criteria governing what equipment and utility systems will undergo Commissioning. As Commissioning is not part of the Validation Program and is not regulated by the FDA, people often wonder why they should include this section at all. The reason is the FDA is just as interested in the rationale behind why one system is not validated while another is. The VMP needs to answer that question, identifying support utilities that do not need to be validated because they do not directly affect product quality. It also demonstrates thoroughness, showing the FDA that all systems have been examined for product quality impact. To maximize the usefulness of commissioning, the system should be tested within the anticipated operating range of the respective OQ.

5. Qualification

The selection criteria governing what equipment and utility systems will undergo Qualification is discussed here. Individual definitions of IQ, OQ, and PQ, may be included. Company policies, regulatory references, and published guidelines used in this selection process should be addressed. This discussion may include considerations such as product contacting surfaces, critical/non-critical instrumentation, direct and indirect systems,[12] and downstream processing, among others. A discussion of protocol and final report formats may be included here, with either a reference to existing protocol development procedures, or a description of the format to be utilized. Final Reports may be generated as attachments to the protocols themselves, or as separate documents.

6. Process Validation

This section addresses the selection criteria governing what equipment and utility systems need to undergo Process Validation. Company policies, regulatory references, and published guidelines utilized in the selection process should be addressed. One such criteria is if the "results of a process cannot be fully verified by subsequent inspection and test, the process shall be validated…."[13] Also included is a discussion on the appropriate Cleaning Validations (CV) required to verify inter- and intra-campaign cleaning methods. *If this is to be a finished product, Packaging and Sterility validation needs to be addressed.*

7. Computer System Validation

A separate section should be devoted to the discussion of Computer Validation, whether that is in the form of a Programmable Logic Controller (PLC) or a Distributed Control System (DCS). Computer Validation criteria also should be discussed, and whether the installed control system is to be 21 CFR 11 compliant, i.e., secure audit trails, authority checks, etc.

8. List of Required Protocols and Procedures

Include here a tabular representation of the equipment and utility systems, and the required protocols and procedures associated with each - *Table C*. This is the essence of the VMP because it defines the validation requirements for the project, and can be used to determine resource loading. This table can subsequently be used as a "Deliverables List" if the validation effort is contracted outside of the organization.

9. List of Required Standard Operating Procedures (SOPs)

This should take the form of a tabular representation of the installed equipment and utility systems and the required SOP associated with each, similar to the List of Required Protocols and Procedures. This will help identify the level of SOP generation necessary to complete validation activities. These will generally take the form of Operation, Maintenance, and Cleaning SOPs.

10. Equipment and Utility System Descriptions

An overview of the particular system should be given, aligned with the Basis of Design documentation. Table D serves as an example of specific verbiage used in a typical VMP. A listing of proposed Qualification tests (IQ/OQ/PQ) should be identified with a brief description of the procedure and how the associated Acceptance Criteria will be determined. As the VMP should be developed early in the planning stage, many system specifics will be in the draft phase and subject to change. To avoid duplication of effort and unnecessary revisions, do not assign numeric-specific Acceptance Criteria in the VMP. Those details will be fully delineated in the respective Qualification and Validation protocols that will follow. Keep in mind the intent of the VMP as a scope and guidance document. System-specific acceptance criteria fall under the auspices of the individual protocols.

Section 10.0: Equipment and Utility System Descriptions

Nitrogen Distribution System

Description
Nitrogen gas is distributed throughout the facility using a network of carbon steel (from supply to inline filter) and stainless steel (from inline filter to use point) piping. Nitrogen gas is obtained from an existing 400-psig nitrogen gas system located in the facility.

A one-micron filter is utilized to filter high-pressure nitrogen to be used in the Series 100 Reactor System for pressuring, purging, and for the agitator gland seal. Nitrogen line pressure from the header is reduced prior to use-point delivery. Low-pressure header branches service the tank farm and production areas, and each branch will utilize a one-micron filter, as well as upstream and downstream pressure indicators to verify filter cartridge integrity.

Installation Qualification
Installation Qualification will be performed in accordance with the guidelines specified in SOP #95IQ001. All IQ data will be documented in an approved Installation Qualification protocol – Protocol preparation, review, and approval will be scheduled to coincide with the installation of the Nitrogen Distribution System.

Operational Qualification
Operational Qualification of the Nitrogen Distribution System will be performed in accordance with the guidelines specified in SOP #95OQ001. Proposed OQ testing and the corresponding acceptance criteria are described below.

System Capacity Testing/Flow Determination
Under maximum use conditions (system design basis), nitrogen flow rate and system header pressure must remain acceptable.

Static Pressure Testing
Nitrogen pressure at usepoints must meet system specifications and end user requirements.

Performance Qualification
Performance Qualification of the Nitrogen Distribution System will be preformed in accordance with the guidelines specified in SOP #95PQ001. Proposed PQ testing and the corresponding acceptance criteria are described below.

Moisture/Dewpoint Determination
The measured dewpoint at selected usepoints must closely correspond to the dewpoint of the supply.

Particulate
Particulate measurements will be at or below predetermined levels.

Oxygen Concentration
Oxygen concentration at predetermined usepoints must closely correspond to the oxygen concentration of the supply.

Table D. Example of an equipment and utility system description.

> ***With the inclusion of some additional information … the VMP can help serve as a resource- and task-planning tool***

11. Additional cGMP Programs

The VMP is meant to be a Validation Life Cycle document. It should cover the activities and requirements from project inception to testing completion and on through a program of continuous monitoring and evaluation. Associated with this effort are Quality Assurance/Quality Control procedures meant to support and update the validation effort. These programs include, but are not limited to:

11.1 Document/Change Control

A procedure must be in place to govern and capture documentation creation, revision, and control. This procedure will be applicable to all validation documentation, and must designate the review and approval responsibilities of various functional groups. Archival guidelines shall include duration of record retention, and means of storage and retrieval.

11.2 Standard Operating Procedures

SOPs shall exist to address such cGMP issues as facility sanitation, waste collection and disposal, the use of suitable rodenticides, insecticides, fungicides and fumigating agents, and building maintenance.

11.3 Calibration

A system shall exist detailing the methods, frequency, and documentation of the calibration program including justification for a "no calibration required" status.

11.4 Preventative Maintenance

This system will be indexed to distinct equipment identifiers, and outline the maintenance procedures required to ensure proper system functionality. This procedure will identify the appropriate documentation and frequency requirements.

11.5 Revalidation

A crucial part of the Validation program is determining when to revalidate. This determination may be periodic, or triggered by the replacement of critical instruments. Part of the Change Control program will be an assessment of the impact of any proposed change on the validated state of the affected equipment, and if revalidation is required.

11.6 Operator Training

A program must exist to ensure and document that personnel shall have the appropriate education, training, and/or experience to perform their assigned functions. Personnel shall be trained on good sanitation practices, as well as the use of protective apparel to prevent product contamination.

12. References

All company policies and procedures, as well as any applicable local, state and federal regulations, and industry standards referenced should be listed.

Input to the VMP

A certain minimum level of documentation needs to be developed in order to produce a VMP. An equipment list, which provides basic specifications such as size/capacity, instrumentation and controls, design/operating limits, and capabilities needs to be available. Additional documentation such as a "Design Basis" is important to delineate how equipment and utility systems should perform, independently and in concert, to produce the product. For Biologics and Pharmaceuticals, generally a set of preliminary Piping and Instrumentation Diagrams (P&IDs) helps define system boundaries. For Medical Devices, the Manufacturing Flow Diagrams required in the Manufacturing Dossier section of the Pre-Market Submission also may provide system boundary information.

Approval of the VMP prior to the generation of the associated protocols is as important as approval of protocols prior to data collection. Just as protocols require QA approval prior to execution, the VMP requires QA approval prior to protocol generation. The VMP should be under revision control, as it documents corporate approval of the scope and intent of the validation program, and will require QA approval. Any Basis of Design or validation philosophy changes should be pre-approved in the VMP prior to the generation of the affected protocols. The VMP needs to be updated to document major project scope changes such as the addition or deletion of equipment, and project completion (i.e., release to production). This provides a clean audit trail of pre-approved intent versus execution.

Conclusion

In its simplest form, the VMP is meant to document the major equipment and utility systems associated with the production process, assess the impact on the quality of the resulting product, and determine the validation requirements. With the inclusion of some additional information; however, the VMP can help serve as a resource- and task-planning tool. For instance, a Deliverables List can be developed from the "List of Protocols," which can be used to gauge the man-hour requirements of the job, for either internal budgeting or comparing outside contractor quotes. The "Additional cGMP Programs" section can isolate the need for policies or procedures to be created and/or updated.

The creation of a VMP at the beginning of the project serves many purposes: to identify the timing and level of anticipated resource needs, to document the corporation's validation philosophy and individual elements, and to show the FDA the pre-approved intent to bring on a new product line in full compliance. It is well worth the extra time spent to write this document at project inception, and to get early regulatory feedback via a pre-submission meeting with the FDA, than to answer Agency questions during the approval cycle and pay with a delayed product launch date.

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Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
May/June, 2001 Vol. 21 No. 3

Product Protection in the Pharmaceutical Industry – Meeting the Challenge

by Hitesh Patel

This article highlights the latest developments in metal detection for the pharmaceutical industry and addresses some of the contamination issues that pharmaceutical producers need to be aware of.

Introduction

Although the installation of metal detection systems is not specifically required by legislation, most manufacturers have adopted stringent standards and protocols which demand "best practice," usually fully recognizing the requirements and guidelines of the FDA[1]or USDA[2]. Increasingly, they are becoming aware that product protection reaches far beyond the law or regulations. Quality and integrity are fundamental requirements for the pharmaceutical, healthcare, and nutritional industries. Whether for ethical pharmaceutical formulations, generic equivalents, or over-the-counter solid dosage products, screening out contamination guarantees the safety and quality of goods, providing the manufacturer with peace of mind against potential liability claims from retailers and consumers; not to mention the loss of customer credibility that could result from a failure in the contaminant detection procedures. Most importantly, the manufacturer is able to deliver what the customer needs and wants - a safe, contaminant-free product.

Of all the possible types of product contamination, metal particles still rank among the most serious. Even with the most stringent controls possible on production techniques, metal contamination can and does occur. Every crushing, sieving, mixing, or pressing process introduces the danger that metallic particles will find their way into the product. This is where metal detectors can - if properly used and installed - minimize the risk. With enhanced sensitivity and process capability, machines can be customized to address the most difficult applications. Sophisticated software packages have been developed to assist the user, heighten the performance of machines, and ensure they can automatically facilitate controls within the manufacturer's quality systems.

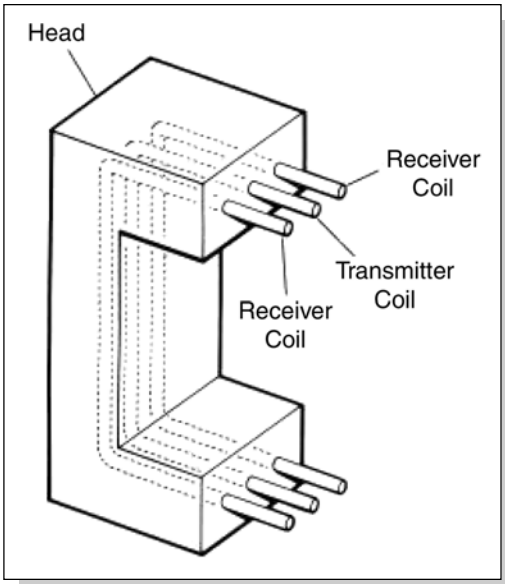

Figure 1. The search-head itself incorporates three coils: a central transmitter and two identical outer receiver coils.

Protecting the Consumer – and Your Reputation

Foreign body contamination can include unwanted materials, such as paper or plastics, but metal continues to be the most common high-risk contaminant in pharmaceutical products. Metal contamination can occur as a result of:

- contaminants entering the production line along with raw materials, ingredients, or formulations
- breakage of machinery or components such as sieves, tablet press tooling, or materials-handling systems
- inadequate cleaning of machinery after maintenance

Incorporating metal detection into the quality control processes significantly reduces the chance of costly product recalls, negative media coverage, and reputation devaluation.

For obvious reasons, process machinery in the pharmaceutical industry has to undergo regular and intensive cleaning if products are to retain the required levels of quality and integrity. For metal detectors to be fully effective, it is vital that they can withstand these aggressive conditions. When changing from one active

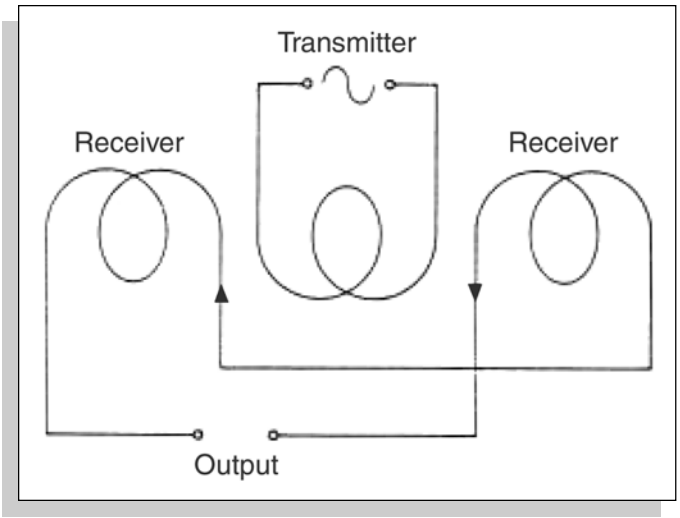

Figure 2. The two outer (receiver) coils are connected so that their induced voltages are self-canceling when the magnetic field is not being disturbed.

ingredient to another, for example, machinery must be cleaned thoroughly. The detectors themselves should be constructed from materials such as 316 or 304 (Austenitic) stainless steel, which are impervious to corrosion and to the cleaning chemicals used. The design of the detector, too, can enhance its effectiveness and resilience - for example, rounded surface edges can help prevent a build up of waste material or dust on the body of the detector itself and flat, watertight key pads, or LCD/electroluminescent screens will allow for easy cleaning.

Metal Detectors Explained

Industrial metal detection systems generally comprise two elements – the search-head (the sensor in the system) and the automatic reject device. The search-head itself incorporates three coils (Figures 1 and 2): a central transmitter and two identical outer receiver coils. These are wound around the 'aperture,' through which the product to be tested is passed. An oscillator is connected to the center coil and produces a high frequency alternating magnetic field. The two receiver coils are connected so that their induced voltages are self-canceling when the magnetic field is not being disturbed.

To achieve optimum sensitivity, the metal detector aperture should be of a size appropriate to the items or material in the product flow: too large an aperture and there is a risk of signal 'dilution' and resultant loss in sensitivity; too small and there may be insufficient allowance for product flow rates. When a contaminated product is introduced, the hidden metal element interacts with the detector's magnetic field and a disturbance is created.

Automatic Product Compensation

Conductive products, such as tablets containing iron, can create a signal when passing through the detector, even when completely free of metallic contamination. A detector with microprocessor operation is capable of memorizing the disturbance signal that may result from the standard, non-contaminated product. When a contaminated product is then introduced, the hidden metal element interacts differently with the magnetic field and the disturbance signal will alter as a consequence. The difference may be very small, but processing technology has been developed to detect the minutest particles – commonly of a dimension of a fraction of a millimeter.

Changes in temperature, mix, or moisture content of the product could traditionally cause similar variations in the product effect. With first generation, analog machines, this generated false rejections and required broader tolerances, consequently reducing sensitivity. Modern digital machines overcome these problems with automatic product tracking, ensuring that the highest levels of sensitivity and accuracy are maintained.

What Level of Performance is Possible?

This is a question commonly asked of inspection equipment to which there is no straightforward answer. Average sensitivities for one common inspection location can be seen in Figure 3.

Sensitivity is governed by two key factors: aperture size and operating frequency. The smaller the size of the aperture, the more sensitive the head. For example, an aperture height of 20mm will enable any metal contaminants as small as 0.2mm to be detected. Secondly, the higher the frequency, the greater the sensitivity. However, raising the frequency does not automatically guarantee detection as it may cause the product itself to generate a significant signal in the detector, (the 'product effect'). The aim, therefore, is to identify the optimum frequency whereby the highest achievable sensitivity is balanced against product effect. In this way, the detector rejects contaminants, avoids false readings, and product wastage. The newest digital metal detector technology does permit a very high operating frequency of 1 megahertz; however, it still provides excellent stability, as they are fast becoming the industry standard.

The Perfect Sphere?

The sensitivity of a detector is usually described in terms of the diameter of a metal sphere because a sphere does not exhibit an 'orientation effect' (discussed below). It is not appropriate to use weight as a standard because it is possible for a metal detector to detect a one-gram contaminant for example, but be unable to detect a two-gram contaminant due to its shape or orientation. In practice, contamination seldom appears in the form of a perfect sphere, but rather as metal slivers or wires.

Detector Aperture

The size of the aperture of the detector is key with a larger aperture being less sensitive than a smaller one. Both aperture width and height have some effect on sensitivity although changes in the minimum aperture dimensions will have a greater effect. The detector's capability should be given in terms of the minimum spherical particle size that can always be detected in the geometric center of the aperture. The type and grade of metal also should be specified.

The sensitivity of the detector will depend on where in the aperture it is measured. The geometric center of the aperture is the least sensitive point as it is furthest from the coils. The aperture corners have the highest sensitivity. Anywhere between the center and the corners the sensitivity will increase according to the detector's sensitivity gradient - a perfect detector would have no gradient and have equalized sensitivity throughout the aperture.

Operating Frequency

The operating frequency must be selected according to the application; from as low as 25KHz to as high as 1 MHz. The selection is made to optimize the unit's sensitivity for each specific application. As the operating frequency is increased,

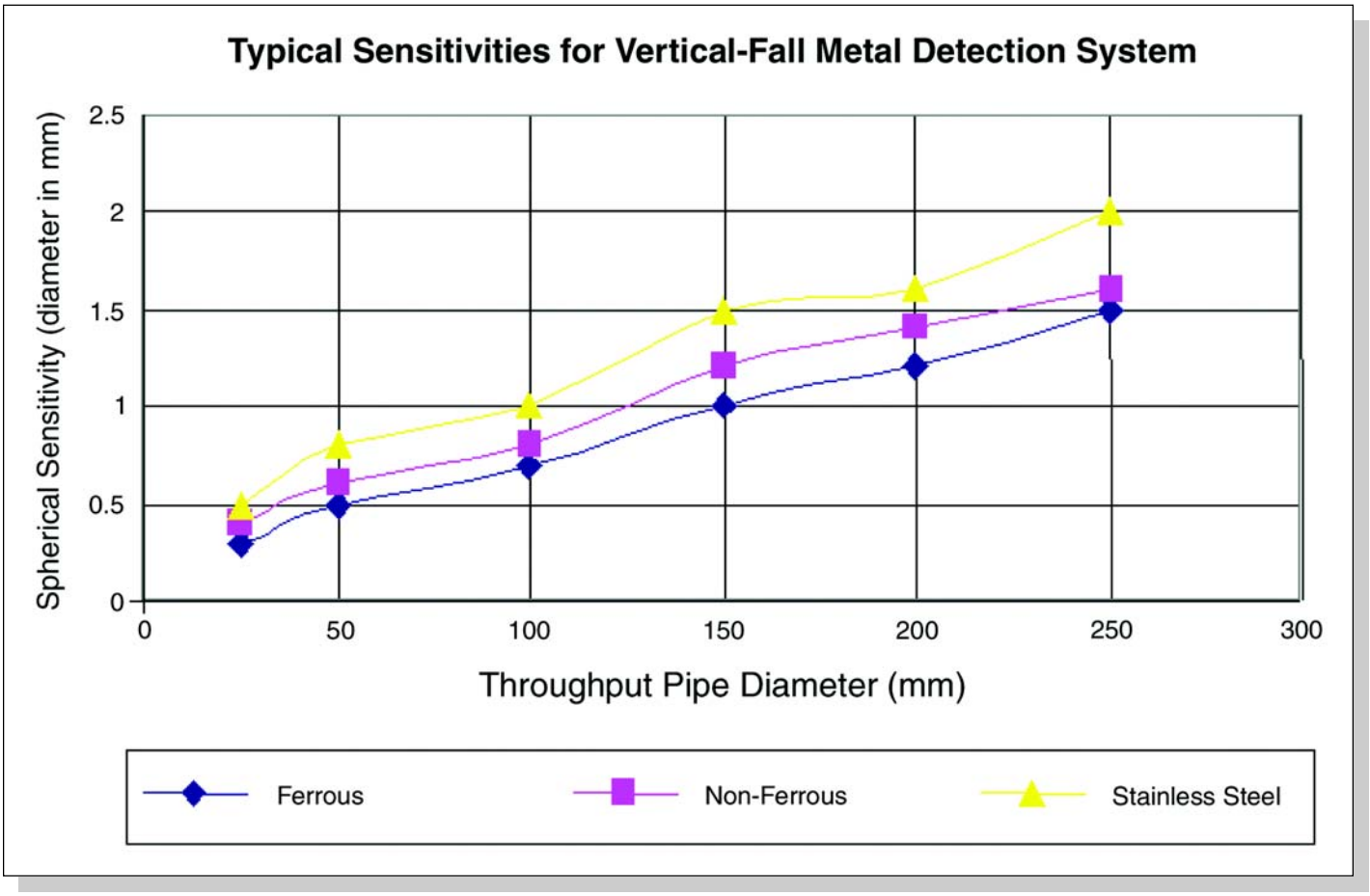

Figure 3. Average sensitivities for a typical inspection location.

sensitivity to stainless steels improves, whereas ferrous sensitivities can diminish.

Throughput Speeds

These are seldom a problem and a good metal detector usually has uniform sensitivity over a wide range of throughput speeds - *Figure 4*.

Metallic Contamination

Table A presents three types of metal that commonly affect the inspection process.

Orientation Effect

If a wire sample is passed through the aperture, it will be easily detected if the diameter of the wire is equal to or greater than the spherical sensitivity of the metal detector to the same metal. When the diameter of the wire is less than the spherical sensitivity, the 'orientation effect' will be noticed. This means that, depending on the orientation of the wire as it passes through the detector, it will be harder for the machine to detect it. The orientation effect is directly related to the spherical sensitivity of the detector. If a detector is working at a spherical sensitivity of 2.0 mm diameter for example, the orientation effect will be noticed on wires with a diameter of less than 2.0 mm. If the spherical sensitivity is increased to 1.0 mm then the orientation effect will only be noticed on wires with diameters less than 1.0 mm. A detector's ability to detect wires, slivers and other long thin pieces will depend on the spherical sensitivity it can achieve. A small deterioration in the spherical sensitivity will result in an enormous difference in the detector's ability to detect wire.

Rejection of Contaminated Product

Reliable and timely rejection of contaminated product from the production line is as crucial as detection itself. On detecting a contaminant the detector generates a reject signal, which then activates a reject mechanism usually driven by a solenoid or by a pneumatic actuator. The actual design of the reject mechanism will vary according to the specific needs of the manufacturer – different systems are required for different products and different locations in the manufacturing processes.

For inspecting free-falling ingredients or formulations, a pneumatically-operated lateral diverter should be positioned just below the detector. In the case of tablets or capsules, the detector should incorporate a fast-acting solenoid-driven lift-flap or flow diverter which will reliably separate and capture contaminated product.

For conveyor-mounted detectors in the packing line, typical reject mechanisms include pneumatic pushers, air-blast devices, retracting belts, actuated flap-gates, and conveyor sections which incline or decline. The supplier should deliver a solution customized to the needs of the packer - for example, to limit damage to rejected product if the product or packaging is to be re-used after secondary inspection.

Various levels of fail-safe protection can be incorporated in the rejection system to ensure that product protection is absolute and that human intervention and handling are minimized - as a manufacturer's quality system may often dictate.

Digital vs Analog

The first generations of metal detectors were based on analog technology. These are now becoming obsolete in favor of digital systems which incorporate microprocessors and technical improvements to facilitate ease-of-use and effectiveness, including:

- Digital processing software: digital processing software allows the user to record and collate information from a network of metal detectors - whether installed on different lines or in different plants. It provides more powerful processing and the capability to record and collate information. On-line efficiency is improved and statistical and performance data is available to enable manufacturers to optimize product protection.

- Graphic screen interfaces: Graphic interfaces provide easily interpretable views of the performance of the detectors, simplifying analysis of sources of contamination and identifying and diagnosing problems at a glance. They provide invaluable performance information, which can be transmitted directly to a PC. Process efficiency is improved, sources of contamination are more easily analyzed and problems can be identified and diagnosed at the earliest opportunity.

- Simpler operation and maintenance: Detectors used in the pharmaceutical industry must be tested or re-calibrated at regular intervals, as specified by the equipment manufacturer and the manufacturer's own quality system. With an analog system, this re-calibration and its accompanying documentation is a wholly manual process. A digital detector will automatically 'prompt' the need for re-calibration to take place and can automatically record the tests. The processor also will keep a memory of all events, such as detection of contamination, together with date and time. The record log can be used to indicate the type and size of contaminant as well as the testing frequency, providing data to help identify the cause of contamination.

Positioning

In order to achieve optimal results from a metal detector, its correct positioning in the production process is vital. To achieve optimum benefit, a metal detector needs to be seen as an essential, integrated component of the process and should, if possible, be incorporated into the line at the planning stage. If a detector is to be added to an already existing line, a detector manufacturer can often supply a variety of different-sized models and can specifically engineer a tailor-made detector according to individual specifications.

Stainless steel sieves are one of the most common causes of contamination since the fragile mesh can easily rupture and collapse, producing small fragments of stainless steel. As there are several sieves at different stages in the production line, these can be identified as hazards requiring critical control.

A popular option is to install metal detectors prior to heavy or fragile machinery as this delivers direct financial benefits by protecting downstream machinery from damage and avoiding disruption to the production line. The detector then acts as protection for delicate pumps, tablet presses, and valves, which would otherwise be damaged by metal contamination. Alternatively, it is common to install a detector at the end of the production line – in the packing hall. This provides the ultimate check for contamination in packaged goods prior to delivery to customers or retailers.

However, earlier detection of contamination can generate significant cost savings since lower-value ingredients rather than the complete product and packaging are wasted. Also, the highest degree of contaminant sensitivity can be achieved at ingredient, formulation, or tablet stages.

Historically, manufacturers of detection systems were often faced with the problem of producing machines small enough to fit into confined spaces. This challenge has been addressed by the industry and units are now available which are very compact and easy to move from one production cell to another.

Type of Metal	Easily Detected?
1. Ferrous magnetic metals; iron, magnetic stainless steel.	Easy to detect as they are both conductive and magnetic and have a significant effect on the magnetic field.
2. Non-magnetic, non-ferrous, low resistance metals; copper, aluminum, lead, and bronze.	Conductive and therefore relatively easy to detect.
3. Non-magnetic, high-resistance metals; certain grades of stainless steels such as 304 and 316.	Poor conductors which are commonly found in pharmaceutical and packaging machinery. These can be reliably identified by a good detector, tuned correctly.

Table A. The three types of metal that affect the inspection process.

Inspecting Bulk Product

The quality of the finished product can only be guaranteed if bought-in and in-process ingredients are effectively screened to remove all unwanted metallic particles. Traditionally, inspection of bulk product has been perceived as superfluous, as the product passes through several sieves before reaching the end of the production line. However, advances in inspection technology have enabled the detection of even the tiniest flakes of metal in bulk powder. This enables manufacturers to inspect in-coming raw materials in free-falling powder or granular form and to inspect formulations prior to tabletting or encapsulation.

Detecting in Confined Spaces

When a detector needs to be integrated into an existing production line, space is often limited. In this situation, a 'waferthin' unit may be appropriate. This is a detector which is compact enough to slot into confined spaces, such as above bagmaking or bottling machines. Most manufacturers will configure a system to meet the customer's specific space needs.

Inspecting at the Compression Press

High-speed tablet presses and encapsulating machines represent a critical control point for product inspection. Contamination from damaged sieves or press tooling should be detected at this stage. Generally placed before or after the de-duster for tablets and after other inspection equipment for capsules, the detector delivers the final check before packaging.

Cleaning and the Environment

Product inspection machines need to be water- and dust-

> ***Stainless steel sieves are one of the most common causes of contamination since the fragile mesh can easily rupture and collapse.***

proofed to high industry standards - at least to NEMA 4X.[3] This ensures resilience to the arduous cleaning regimes that are sometimes essential. Additionally, construction materials need to be certified to withstand attack by the cleaning chemicals used when changing from one live ingredient to another.

Finished Pack Integrity

Installed in-process, a checkweigher can help ensure the proper tablet count and compliance with label claims, as well as checking for the presence of necessary leaflets or inserts. An automatic reject system can discard underweight packs and still allow for acceptable product or packaging to be recovered and reprocessed, reducing levels of waste. The importance of maintaining line speeds means that manufacturers should ensure that a checkweigher is able to operate effectively at full line speeds.

Combination Systems – Dual Action

An integrated metal detector and checkweigher on the packaging line can additionally serve to protect against gross metal contamination from slat counters, unscramblers, cottoners, etc. The systems are capable of segregating off-weight rejected packs from those contaminated with metal. This ensures proper reconciliation of components for loss control records and satisfies regulatory requirements.

Inspecting Bottles

The inspection of tablet bottles sealed with a paper/metal foil or closed with a metal lid can present a particular challenge for a metal detector. It is advisable to inspect products prior to bottling or before the bottle enters the capping machine, thereby assuring the quality and purity of the final bottled products.

Validation

Validation procedures now represent an essential part of pharmaceutical product safety and consistency management and in order to achieve the accepted expectations of Good Manufacturing Practice, manufacturers are required to demonstrate that a validation system is in place. A lengthy process, the aim is to define everything that goes on in the manufacturing process, so that the actual equipment and materials used in the plant can be proven against that standard, now or in the future. This means that an inspector or auditor can at any time check that the plant is operating as the technical people decreed it should operate, including every piece of machinery. A vital part of the damage-limitation exercise, validation is designed to eliminate amongst other risks, the danger of contamination to drugs.

Validation documentation consists of a series of procedures and instructions for the end user. The FDA recommends certain protocols to facilitate this: IQ (Installation Qualification), OQ (Operational Qualification), PQ (Performance Qualification), and SOP (Standard Operating Procedure). Together, when completed, these comprise a complete set of validation documents.

Some equipment suppliers now supply framework validation documents with their machines - a key provision that can help alleviate the validation burden, ease the processes of installation, the subsequent operation, and the maintenance of the machines. The scope of such validation embraces not only the electrical and mechanical input of each machine's construction, but also the methodology and standards used to develop all embedded firmware and associated software.

Conclusion

Product protection is vital in today's consumer-driven market. For pharmaceutical manufacturers, the correct installation of a metal detector should constitute a fundamental part of the quality control management process. Advances in inspection technology mean that the new generations of metal detectors offer improved benefits to manufacturers - such as enhanced management data, automatic product tracking, superior rejection systems, automatic prompting for re-calibration, greater ease of use and large product memories - in addition to superior sensitivity, guaranteeing detection of even the most minute particle of metal. Although end-of-line remains a common location for inspection, manufacturers are now recognizing the significant economic and process benefits to be gained from incorporating metal detectors at earlier stages in the production process.

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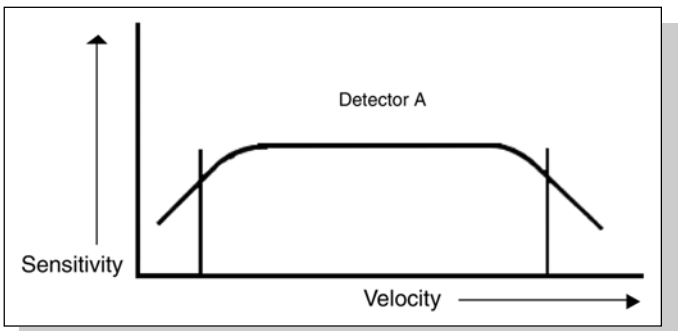

Figure 4. A good metal detector usually has uniform sensitivity over a wide range of throughput speeds.

> ***In order to achieve the accepted expectations of Good Manufacturing Practice, manufacturers are required to demonstrate that a validation system is in place.***

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Hitesh Patel is Technical Director with Lock Inspection Systems, manufacturers of metal detection and checkweighing equipment. Patel joined the company as an electrical engineer in 1990 and has held positions within various technical departments at the company. He has worked closely with suppliers and manufacturers in the pharmaceutical industry throughout his career and now specializes in developing validation documentation hardware and software for the sector. In his current role, Patel is responsible for all aspects of product management and NPD. He oversees the R&D, QA, engineering, and technical design divisions of the company.

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This article discusses the importance of introducing the concept of the COQ in the pharmaceutical industry, what is meant by the COQ, the methodology for measuring the COQ, the benefits and a summary.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
May/June, 2001 Vol. 21 No. 3

Increasing Value Through the Measurement of the Cost of Quality (COQ) – A Practical Approach

by Guy Malchi and Helen McGurk

Introduction

Ensuring quality in the pharmaceutical industry is critical both to meet stringent cGMP regulations and to guarantee safe products for customers. The trends in the pharmaceutical industry, as with most industries, are toward lower cost, higher quality, and greater added value to sustain competitive advantage and hence increase market share. In an industry where quality has become a focal point of activity, it is still rare that the most reliable measure, the Cost of Quality (COQ), is captured. The concept of the cost of quality is a powerful idea. Since profits and quality are integrally linked, it is imperative that the cost of quality is tracked, providing managers with the ability to control costs and focus on improving quality at reduced cost.

Quality is one of the most important aspects of any pharmaceutical manufacturing company. The competitive pressures of today's manufacturing environment and the strict quality regulations placed on the pharmaceutical industry mean that quality products translate into higher profit. Research has shown that companies perceived by customers to have superior quality are up to three times more profitable than those perceived to have inferior quality. This undeniable link between quality and profits combined with the need for cost reduction in a competing market mean that companies need to provide high quality products at a lower cost. Measuring COQ is the first step in achieving this success.

A product that does not meet the needs and requirements of the customer cannot be defined as a quality product since it does not provide customer satisfaction. Therefore, quality can be defined as "Conformance to Requirements," or a more traditional definition may be "Fitness for Purpose." From this, the cost of quality can be defined as: the cost of not conforming to customer requirements, and the cost of not providing customer satisfaction. COQ can be defined further as the cost of not doing activities "right first time."

Why Measure the COQ?

It is unfortunate that the most accurate measure of quality, the COQ, is still unclear in a lot of decision makers' minds and often results in a figure much higher than imagined. Practical experience has shown that the COQ can be up to 25% of gross sales, whereas it is often felt by management to be around 5%. Capturing the real COQ so that it can be managed and used as a benchmark measure is one reason alone to calculate the COQ. This can then be used to reduce costs, and is done by increased quality or "right first time," which results in reduced costs through increased efficiency and reduced nonconformance. Measuring the COQ is the first step in this cost reduction program since it provides the focus required.

What is the COQ?

Traditional COQ

The concept of the COQ did not emerge until the 1950s with many different definitions being assigned to this term.

Joseph M. Juran is one of the renowned figures in quality management. He has written many books on the subject and his theories and methods are well known. He referred not to the COQ, but rather to the cost of poor quality.

Traditionally the "cost of poor quality" was categorized by Juran under four broad categories. These four categories were:

Internal Failure Costs

Internal failure costs are those associated with defects and non-conformance that are found before the product is shipped to the customer. They are defined as costs that would disappear if there were no defects in the product prior to shipment. Examples of these costs are the cost of scrap, rework, reinspection, and reduced selling price.

External Failure Costs
External Failure Costs are costs that are associated with a product that has been shipped to the customer. These costs also would disappear if there were no defects in the product. Examples of these costs are complaint investigation, returned material, and allowances.

Appraisal Costs
Appraisal costs are costs that are incurred in determining the degree of conformance required to meet quality requirements. It is important to remember that what is classified as an appraisal cost is determined by the type of work done, not by the department it comes under. Examples of this are all inspection and testing including raw material, in process, and finished goods, audits, cost of keeping measuring equipment calibrated, whether conducted by the quality department, production, or an external laboratory.

Prevention Costs
These are the costs incurred in keeping failure and appraisal costs to a minimum. These costs include quality planning, new product review, process control, supplier evaluation, quality training, etc.

COQ System Definition
The approach taken is to design a hierarchy of indicators to each company's needs. These indicators are designed based on the needs, goals, and analysis of the current state according to the ***balanced scorecard*** philosophy. The COQ system is split into categories and elements.

The indicator hierarchy is normally made up of three tiers: 1.Target, 2. Surrogate, and 3. Explanatory.

Target Indicators
Target Indicators represent the COQ categories; they are high-level management indicators. Examples are:

- Operating Cost
- Non Conformance Cost

Most of the Target Indicators are derived from the finance section of the balanced scorecard system.

Surrogate Indicators
Surrogate Indicators are measures that have been identified to strongly correlate to performance of the Target Indicators. They represent the COQ elements and are the focal points of a COQ measurement system. Examples are:

- Cost of Preventative Labor/Output
- Cost of Appraisal Labor/Output
- Cost of Assets and Materials

Explanatory Indicators
Each Surrogate Indicator can be supported by low-level measures, called Explanatory Indicators that are used to support the investigation of high-level indicator performance. Explanatory Indicators promote understanding of the Surrogate Indicators at the local/operational level.

The hierarchical indicators system is designed to help make the COQ more explanatory and practical to all management levels, by incorporating low-level indicators into the strategic Target Indicators providing real awareness of where the costs are being consumed.

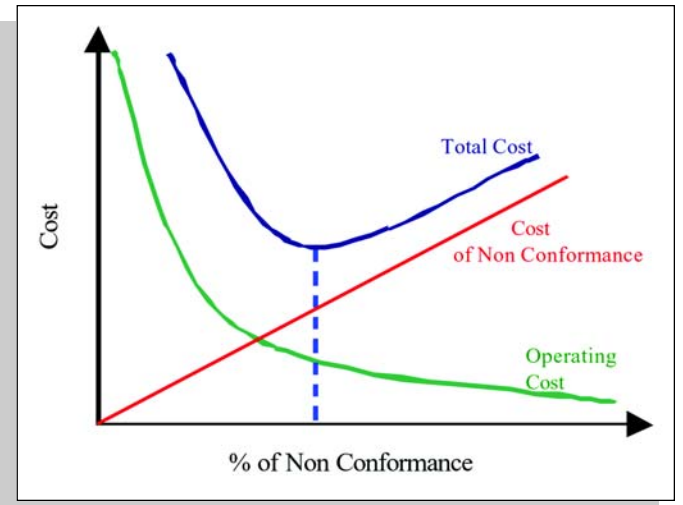

Figure 1. Optimizing the COQ.

Comparison between Traditional and Defined COQ
Table A highlights the relationships between the traditional cost of quality measures and the cost of quality as defined through the hierarchical structure.

It is clear that although the categories defined for calculating the cost of quality indicators are not the same as the traditional COQ measures, all of the costs are covered.

In addition to these categories, there is a category for hidden costs, i.e., alternative costs. It is important not to ignore hidden quality costs just because they are difficult to measure since in many companies they often have a significant impact on the bottom line. Juran also refers to these hidden costs, claiming that the obvious COQ are only the tip of the iceberg.

Some of these traditional hidden costs are:

- lost sales as a result of quality
- extra inventory
- delays
- unidentified scrap

Therefore the total cost of quality can be summarized as:

Total COQ =
Operating Cost + Non Conformance Cost + Alternative Cost

The total cost of quality can be minimized by studying the relationship between the COQ and the rate of non-conformance. Figure 1 shows that when the cost of non-conformance is high the operating cost is low, i.e., little is being spent on prevention and appraisal, and vice versa. The optimal level is where the total costs are minimized and this is recognized now as closer to zero defects.

COQ Measurement System Design – Methodology
Measurement System Design
The inputs and support of top management within a company is critical for the success of any COQ measurement program. This is one of the reasons that the first stage involves interviewing company management to understand the manage-

ment views and goals to ensure the COQ indicators support achieving these goals. What the COQ means for each company is questioned and a suitable hierarchy of indicators defined.

Current State Analysis

Data should be gathered to identify what quality costs, if any, are currently being captured and a thorough analysis of existing procedures and relevant reports should be performed to see what information is presently available. A Pareto analysis (80-20 rule) is done for the indicators designed in the previous stage to define where the costs of quality are consumed. The Pareto shows the indicators on which to focus, and if necessary, the indicators previously defined may be modified due to a low position in the Pareto. Figure 3 shows an example of a Pareto performed for the main target indicators.

Gap Analysis

Based on the analysis of the current practices and available information, the gap between the current state and the COQ system designed previously is identified. This stage also shows ease of capturing the indicators. Once again, the indicators previously designed are modified if they are low on the Pareto and difficult to calculate. This eliminates companies falling into the trap of focusing on difficult to measure or insignificant costs.

An implementation plan based on the gap analysis is developed including priorities, activities, responsibilities, schedule, and resources needed. In addition to this, a detailed plan is developed which states the data sources and procedures for calculating and reviewing the indicators.

Implementation

The final stage is full-scale implementation supporting the company in initiating the new procedures and introducing the measurement system tool for reporting the indicators. It is important not to expect the COQ measurement system to be operating perfectly in a short time, it should be treated as an evolutionary process with savings along the way. It also should be noted that the COQ might increase at first as the measurement becomes more accurate.

Normalization

In large organizations with many facilities, the COQ can be used as a benchmarking system for comparing the performance of the different facilities. However, some indicators do not easily allow for direct comparison as absolute ratios due to:

- varying constraints – different regulations between countries
- differing processes – different technologies
- dynamic factors – different customers and varying environmental factors

This can result in differences of expected levels of performance between facilities, even within the same area. To bring indicators to a common ground and allow comparison between sites, normalization is used.

To normalize an indicator, a score between 0 and 1 is applied using a step or linear function. This score represents the performance of the indicator against a set target (goal). The setting of targets and revision of them also aid a program of Continuous Improvement.

COQ Elements (Examples)	Traditional Measures (Juran)	COQ Categories
Quality Control	Appraisal Costs	Operating Cost
Calibration		
Training	Prevention Costs	
Rejects	Internal Failure Costs	Non-conformance Cost
Reworks		
Reclaims		
Recall	External Failure Costs	
External Failure		

Table A. Comparison between traditional and hierarchical structure.

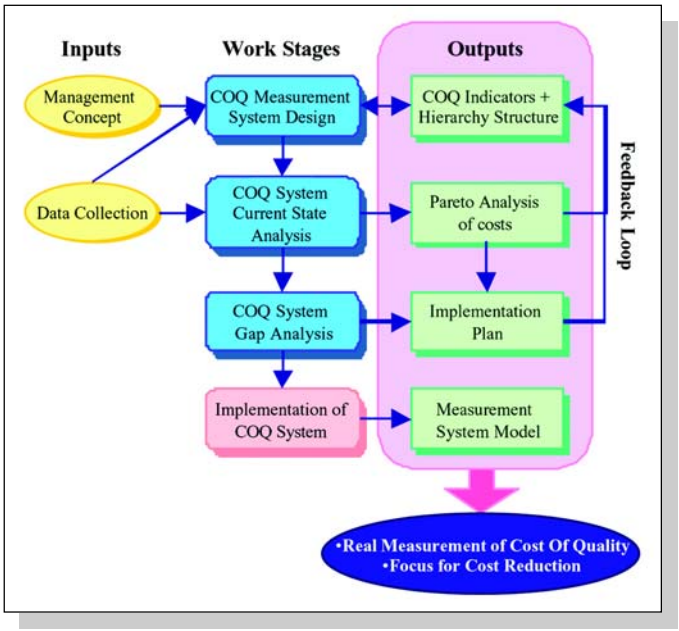

Figure 2. Methodology.

What are the Benefits of Calculating COQ?

The benefits of implementing a COQ measurement program are:

- establishment and implementation of a simple, user friendly management tool that will provide management with accurate and consistent information on the quality operations cost, especially the cost of failure
- provision of information that will lay the foundations to enable cost reductions and efficiency improvements of quality operations
- creation of a standardized scale for benchmarking between different company sites

A significant reduction in the COQ has been shown by implementing the COQ program as well as an overall increase in the level of quality.

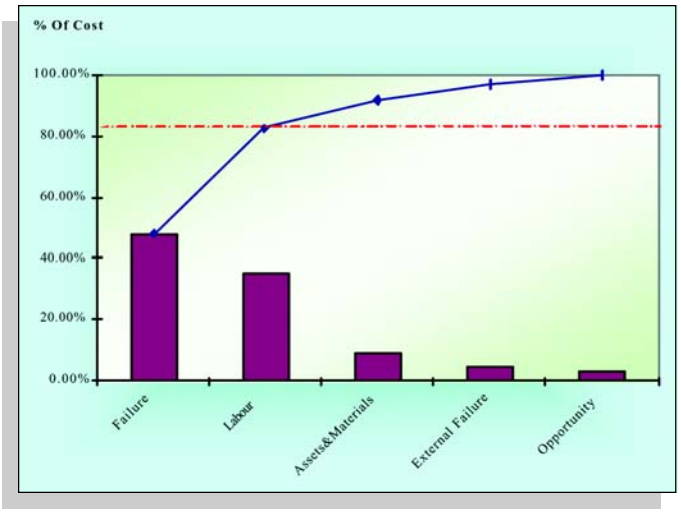

Figure 3. Pareto analysis.

This monitoring, focus, and the enforcement of the implementation plan facilitate this COQ reduction.

Case Study

The methodology described above was used in implementing a COQ program in a pharmaceutical manufacturing facility.

This first stage included performing a current state analysis on the facility. From understanding the strategic business goals and the level of data currently available, a set of indicator and a measurement system was designed to fit in with the requirements of the business, and to cover 80% + of the costs of quality.

Once the measurement system was developed, a framework was established for implementing the system. This consisted of an overall COQ owner who was responsible for the maintenance of the system. Data owners were identified for each of the indicators and were responsible for the collection and entering of data into the measurement system to enable it to calculate the indicators. The action team reviewed all indicators monthly to identify trends and generate ideas for cost reduction and ensure completion of action items. A steering committee of high-level management met monthly, reviewed the target and explanatory indicators, and prioritized the proposed cost reduction actions. To make the COQ system sustainable, a Quality Book was developed that described the indicators calculated and the procedures for entering and reviewing data.

Implementing this methodology resulted in an 11% reduction in the cost of quality. This was achieved by:

- initiating quality groups within the production department which aided in reducing the cost of non-conformance
- QC discrepancy re-engineering improved the efficiency of dealing with discrepancies and reduced the cycle time, hence man-hours involved.
- QC resource modeling defined the staffing levels required in the labs and analysis of work methods led to a reduction in non-value added activities. Subsequently, this reduced cost of labor per batch.

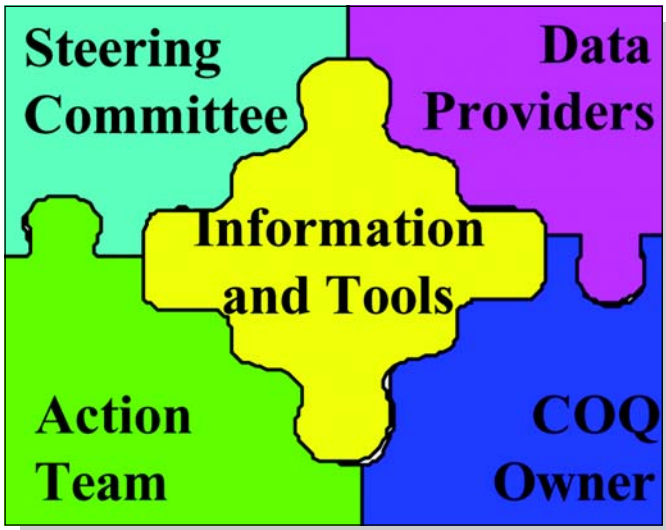

Figure 4. Reporting framework.

Summary

Since quality is critical in the pharmaceutical industry, measuring the COQ is the first step in achieving success in this area. The implementation of a COQ measurement program does not provide the awareness of the losses and action items have to be taken to reduce costs and aid continuous improvement. It is also essential to get the support of all personnel, particularly management, in order for a COQ program to work, and when it does, the benefits of the program are immense.

The COQ measurement is not a one time exercise; it should be viewed as part of the every day measurements and financial costing.

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This article reviews the regulatory requirements applicable to computer systems in the manufacturing environment based on recent regulations.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
May/June, 2001 Vol. 21 No. 3

FDA Regulations of Computer Systems in Drug Manufacturing – 13 Years Later

by Orlando López

Introduction

Since 1963, the US Food and Drug Administration (FDA) has considered validation a current Good Manufacturing Practice (cGMP) requirement. The equipment, facilities, processes, and procedures used in production and control shall be properly designed and tested to assure that the drug products have proper identity, strength, quality, and purity. This requirement also is applicable to computer systems performing functions covered by the cGMP regulations or managing electronic records known to be required by existing regulation.[1]

In Volume 8, Number 5 of the Pharmaceutical Engineering,[2] was presented the FDA point of view of the regulations applicable to process control computers. Until 1988, the attention of the Agency to computer systems was not very significant. Since then, what has happened with the cGMP regulations impacting computer systems performing functions in the manufacturing environment?

The objective of this article is to go through regulatory requirements applicable to computer systems in the manufacturing environment based on recent regulations. The discussion of the regulatory requirements before the approval of Part 11 may provide the reader the foundation to understand 21 CFR Part 11; Electronic Records, Electronic Signatures Rule (hereafter referred to as Part 11). In addition, this article proposes the relevance of Part 11 as the new computer system validation model (Figure 1) and provides examples of how this model is applicable to all computer systems.

US Regulatory Requirements for Computer Systems in cGMP Environments

Regulatory authorities hold the owner of the data[3] known to be required by existing regulation responsible for assuring the compliance of the computer systems recording and managing such data. The FDA established such responsibility in the Compliance Policy Guide (CPG) 7132a.12, "Vendor Responsibility."

The introduction by the FDA of such regulatory requirements can be traced back to the first publication of the regulations. In 1963, CFR Part 211.2(b) was incorporated as part of the regulations. It stressed on backups and documentation, including having hardcopy of master formulas, specifications, test records, master production and control records, and batch production records (batch production and control records), or calculations.

By 1976, the regulations combined Part 211.2(b) and 211.68. The outcome of this combination was the updated 21 CFR Part 211.68 (automatic, mechanical, and electronic equipment). In summary, Part 211.68 requires that:

- There must be a written program detailing the maintenance of the computer system.
- There must be a system to control changes to the computer hardware and software, including documentation.
- There must be documented checks of Inputs and Outputs (I/Os) for accuracy. In actual practice, it is implied that all computer systems under the regulations must be qualified/validated.
- There must be programs to ensure accuracy and security of computer inputs, outputs, and data.
- Computer electronic records must be controlled, including backup, security, and retention.

Validation, as established in Part 211.68, is one of the most important regulatory requirements for computer systems in the cGMP environments.

The validation of computer systems establishes conformance to the user, regulatory and safety, and intended functions that have been allocated to the computer. Computer systems validation is an element of the system development life cycle. In addition to the software and hardware testing, other verification activities include code walkthroughs, dynamic analysis,

and trace analysis.

The key elements to successfully implement the validation of computer system projects in manufacturing processes are:

- selection of a development methodology that best suits the nature of the system under development
- selection of hardware based on capacity and functionality
- identification and consideration of the operational limits to establish production procedures
- identification of operational functions associated with the users, process, regulatory, company standards, and safety requirements
- identification and testing of "worst case" production conditions
- reproducibility of the testing results based on statistics
- documentation of the validation process
- availability of written procedures to maintain the validation state of the computer system

Any modification to a component of a system must be evaluated to determine the impact to the system. If required, qualification/validation is to be re-executed totally or partially.

A clarification to CFR Part 211.68 was published in 1982 in the CPG 7132a.07, "I/O Checking." According to this CPG computer I/Os are to be tested for data accuracy as part of the computer system qualification, and after the qualification, as part of the computer system ongoing verification program.

An example of input data is the signal that a sensor feeds to the CPU via a signal converter. An output device, such as a motor, is an example of equipment that receives electrical pulses from the computer and causes an action to occur. One method to verify the accuracy of an input field device is to force a known value and compare the value displayed on the screen. If this method is chosen, I/O checks may be done during calibration since known values (standards) are applied to the instruments and the output is read on the display (actual).

CPG 7132a.07 is based on the realistic anticipation that computer I/O errors can occur on validated systems. A computer component (logic circuits, memory, microprocessor) or device (modems, displays), like mechanical parts, can fail after being tested. Another source of computer systems I/O malfunctions is electromagnetic interference (radio-frequency interference, electrostatic discharge, and power disturbance). Software errors, undetected during the validation process, also may be sources of I/O errors. To detect errors before the control system makes a decision using tainted data, a performance-monitoring program shall be established and followed to verify hardware and software I/Os during the operation of the system.

The level, frequency, and extent of the I/O checking were suggested in the Federal Register of January 20, 1995 (60 FR 4087). The level and frequency of the I/O verifications shall be guided by written procedure and based on the complexity and reliability of the computer system.

Another topic relevant to computer systems in cGMP environments is the management of application source code.[4] Before 1985, 80% of the computer systems were custom-built, making the source code a deliverable. Since then, the software developers gradually started to make available off-the-shelf applications. Today, 80% of the applications utilized to supervise manufacturing processes are configurable software. Many of the custom-built programs can be found, for example, in programmable logic controllers (PLC). On configurable applications, the source code is proprietary information of the developer, so the likelihood of acquiring the source code is very low.

The regulatory requirements applicable to source code can be found in CPG 7132a.15, "Source Code for Process Control Application Programs." These requirements include the consideration of the source code as master production and control records. Accordingly, those sections in the regulations relevant to master production and control records are to be applied to the computer application as source code. For custom-built applications, program listings are considered source code. For configurable applications, the configurable elements or scripts are considered as source code. For off-the-shelf applications, the critical algorithms, parameters, and macros listings are considered source code.

CPG 7132a.08, "Identification of 'Persons' on Batch Production and Control Records," issued in 1982, allows drug manufacturers to replace certain functions performed by operators with computer systems. Part 211.101(d) requires verification by a second person for components added to a batch. A single automated check is acceptable if it provides at least the same assurance of freedom from errors as a double check. If it does provide the same assurance, the process does not gain by applying a redundant second check, which adds nothing to

US Drugs GMP	Description
211.22	Responsibilities of QC Unit
211.25	Personnel Qualifications
211.42	Design and Construction
211.63	Equipment Design, Size, and Location
211.67	Cleaning and Maintenance
211.68	Maintenance and Calibration
211.68	Written Procedures
211.68(b)	Record Controls
211.68(b)	Validation of Computer Systems (Implicit Requirement)
211.100	Written Procedures, Deviations
211.101(d)	Double Check on Computer
211.105(b)	Equipment Identification
211.180	General (Records and Reports)
211.180(a)	Records Retention
211.180(c)	Storage and Record Access
211.180(d)	Records Medium
211.182	Use of Log(s)
211.188(a)	Reproduction Accuracy
211.188(b)	Documentation and Operational Checks
211.189(e)	Records Review
211.192	QC Record Review
211.220(a)*	Validation of Computer Systems (Explicit Requirement)
*1996 cGMP proposed regulations.	

Table A. cGMP sections applicable to computer.

assuring product quality. The equivalency of an automated single check system to a manual check must be shown; however, this might not always be possible.

In 1983, the FDA provided another important guideline applicable to computer hardware and software performing functions covered by the regulations. The "Guide to Inspection of Computerized Systems in Drug Processing" addresses the applicability of the regulations to the computer systems. According to this guideline, computer systems hardware and software are considered equipment and records, respectively, within the context of the regulations. One year later CPG 7132a.11[5] was issued confirming the applicability of the regulations to computer hardware and software. In the absence of explicit regulations addressing computer systems, the regulations provide the implicit guideline to comply with the Agency.

In accordance with CPG 7132a.11, the main sections in the regulations applicable to computer systems performing functions covered by the cGMPs are provided in Table A.

Equivalent sections can be found in the Medical Devices regulations. The introduction of Part 11 in 1997, provided the explicit regulatory requirements to computer systems performing functions in the applicable regulations.

As the reader may conclude, Subpart B in Part 11 is not essential to delineate the FDA regulatory expectations on computer systems performing functions in a cGMP framework. The elements contained in 21 CFR 11 Subpart B reconcile earliest FDA regulations and policies. Table B provides the equivalence between Subpart B 21 CFR Part 11 and, the cGMP drug regulations, applicable FDA CPGs, and the EU GMPs.

In addition to providing the operational functions required in the regulatory environment, Part 11 can be considered as the new computer systems validation model.

The New Computer Systems Validation Model

In the past, the approach to computer qualification/validation and associated configuration management in the regulated industry was based on key practices. The foundations of these key practices are contained in publications such as:

- Guideline on General Principles of Process Validation, May 1978
- Compliance Policy Guidelines, September 1982
- Guide to Inspection of Computerized Systems in Drug Processing, February 1983
- PMA Staying Current Series, (series started in May 1986)
- Application of the Medical Device GMPs to Computerized Devices and Manufacturing Processes, November 1990
- ISPE's Good Automated Manufacturing Practices (GAMP), February 1994
- PDA's Validation of Computer Related Systems, October 1994

US Drugs GMP / CPG	EU GMPs	Description	Part 11
CPG 7132a.07 CPG 7132a.08 211.68(b) 211.220(a)*	Annex 11 - 2	Validation	11.10(a)
211.180(a)	Annex 11-12 Annex 11-13	Generation of accurate and complete copies of records	11.10(b)
211.68(b)	Annex 11 - 13, 14, 15, 16	Protection of records	11.10(c)
211.68(b)**	Annex 11 - 8	Limiting access to authorized individuals	11.10(d)
Comment paragraph 186, 1978 CGMP revision	Annex 11 - 10	Use of audit trails	11.10(e)
CPG 7132a.15 CPG 7132a.08 211.100; 211.188(b)	Annex 11 - 6	Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate	11.10(f)
211.68(b)	Annex 11 - 10	Authority checks	11.10(g)
n/a	Annex 11 - 8	Use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction	11.10(h)
211.25	Annex 11 - 1	CVs and training records for those using e-records	11.10(i)
211.180	Annex 11 - 4	Controls over systems documentation	11.10(k)
n/a***	Annex 11 - 8	Controls for identification codes/passwords	11.300
Subpart D	Annex 11 - 3, 4, 6, 13, 15	Controls to computer hardware	11.10(d)
211.180(a)	Annex 11 - 14	Record Retention	Not covered

*Proposed changes to CGMP, May 1996.

**Sec. 211.68(b) requires appropriate controls over computer or related systems to ensure that only authorized personnel make changes in master production and control records or other records.

***Implicit regulations can be found in 211.68.

Table B. Equivalence US/EU GMPs and Part 11(B).

- General Principles of Software Validation, Draft Guidance, June 1997
- Best Practices for Computerized Systems in Regulated GxP Environments, PIC, Draft Rev 3.01

The constraint of key practices is that these "need to be monitored and evaluated periodically to ensure that they are suitable and to keep them current with industry and regulatory trends."[6] Across the industry, not all key practices were implemented at the same time, making related key practices divergent.

Part 11 provides the explicit and current regulatory trends applicable to computer systems performing functions in the applicable regulations. Now that the regulatory expectations are clearly established, the implementation of Part 11 is now contingent to the availability of appropriate applications compliant with the regulation. In the absence of technologies supporting Part 11, the required controls are procedural in nature.

Figure 1 depicts the new validation model introduced in this article. The elements to be verified and/or qualified during a software implementation are the type of system (open or closed), security functions, audit trails, process controlled by the computer system, and the implementation of the technology in support of the process and Part 11. These two last elements are not identical for all systems. Electronic signatures are tested when this technology is implemented. An element out of the scope of this model is the retention of electronic records, but the model shall be used to verify and validate the implementation of the system(s) that will hold these records.

For applications using electronic or digital signatures, the current validation/qualification model requires verification and/or testing to many of the following:

1. **Open/Closed Systems**

2. **Security**
   a. System Security
   b. Electronic Signature Security
   c. Codes and Passwords Maintenance
      - Codes and Passwords Security
      - Passwords Assignment
   d. Document Controls
   e. Authority, Operational, and Location Checks
   f. Records Protection

3. **Audit Trails**
   a. Audit Mechanism
   b. Metadata
   c. Display and Reporting

4. **Electronic signatures**
   a. E-Sign without Biometric/Behavioral
   b. E-Sign with Biometric/Behavioral
   c. Signature Manifestation
   d. Signature Purpose
   e. Signature Binding

5. **Certification to FDA**

A subset of the above is applicable to hybrid computer systems.[7] The implementation of these requirements was discussed in other articles.[8,9]

Figure 2 depicts the progression of the **computer systems validation** practices from current key practices to 21 CFR Part 11 Model. The transition program consists of educating the regulated industry, assessing current computer systems, and implementing the regulations using the appropriate technologies. This model is easily applicable to the new generation of computer systems by incorporating the requirements combined in Part 11 at the beginning the development process. For the current generation of systems, an assessment shall be performed to evaluate the level of conformity with the regulation.

Sample Situations

The objective of the following sample situations is to demonstrate the applicability of Part 11 as the new computer systems validation model. Each sample situation is focused on manufacturing equipment controlled by computer systems. The primary concern of these systems is that the software works correctly in the intended manufacturing process. The records required by Part 211 or Part 820, that are managed by these systems shall be reliable and authentic.

Programmable logic controllers are one of the favorite devices to control manufacturing equipment. These are capable of generating a vast amount of data stored in the PLC battery-backed read access memory.[11] At the moment the data is saved on magnetic media, these (electronic) records are used for future reference and/or archived.

In a typical automated manufacturing environment, batch production records are prepared using the data generated manually or by computer systems.

Documentation of completion to each significant step in the batch production records should include:

- dates and, when appropriate, times
- identity of major equipment (e.g., granulators, tumblers, etc.) used
- specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing
- actual results recorded for critical process parameters[12]
- any sampling performed
- signatures of the persons performing and directly supervising or checking each critical step in the operation
- any deviation noted, its evaluation, investigation conducted (if appropriate) or reference to that investigation if stored separately
- results of release testing.

First Example - Manufacturing Equipment with a Stand-Alone PLC

Figure 3 depicts this example. A V-Shell Blender may be an example of a typical oral solid dosage form manufacturing equipment that may have a stand-alone PLC or other type of controller. The objective of this equipment is the reorientation of particles relative to one another in order to achieve uniformity.

The configuration on this first example consists of a man machine interface implemented using a terminal with an operator keyboard and printer. The keyboard may be used to enter variable set points,[13] weights, batch number, menu number, and other processing information. In this case, all I/Os are

saved in the controller's transient memory. Neither the inputs (e.g., operator keyboard) nor the outputs (e.g., display) are retrieved from or saved to magnetic media. Because there are no records saved to a magnetic media, Part 11 is not applicable to this example; however, Part 11 may be used as the model to validate the software, hardware, and interfaces. In this case, the elements in Part 11 applicable to similar situations are:

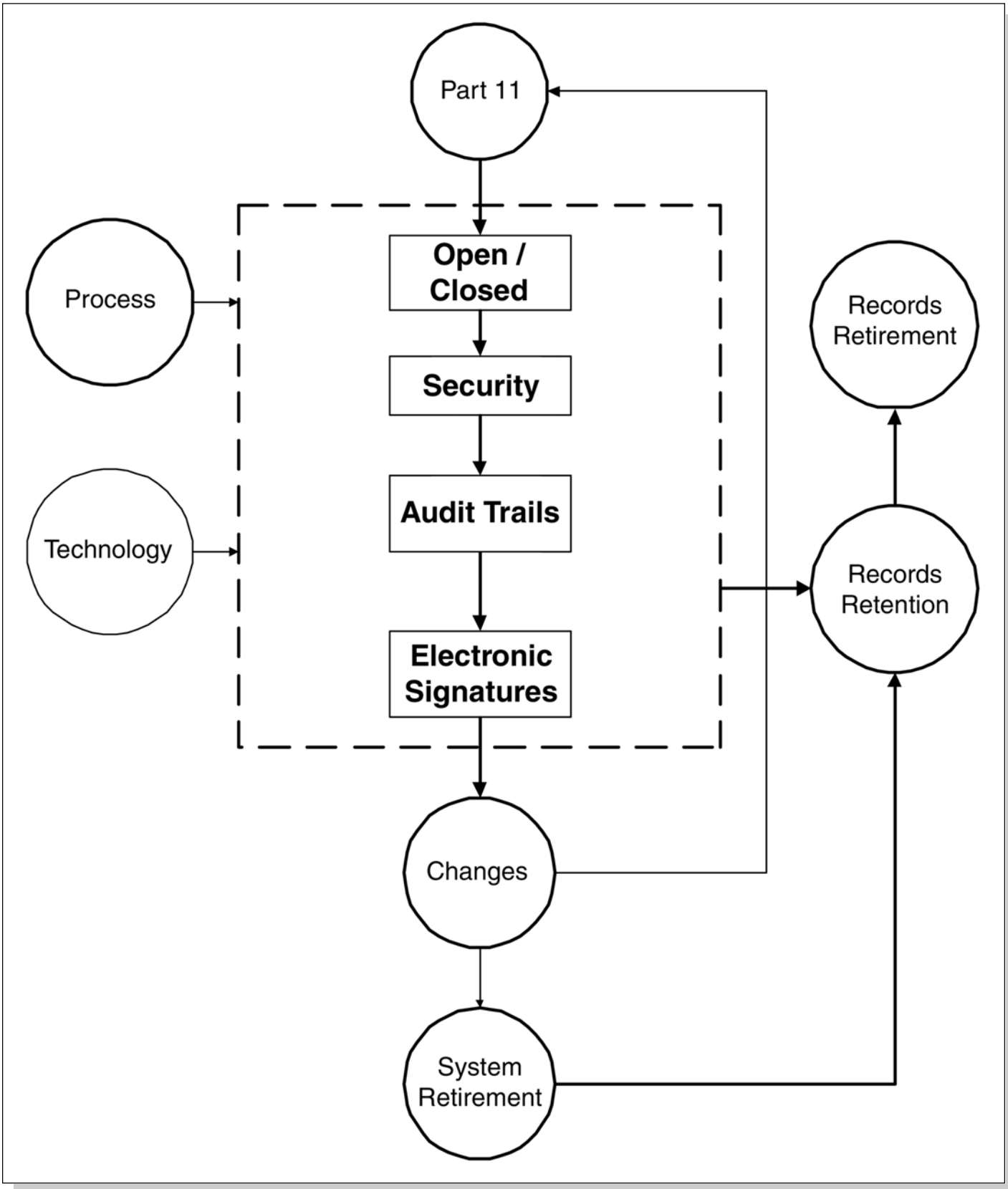

Figure 1. 21 CFR Part 11 Model.

1. Operational Checks
2. System Security
3. Codes and Passwords Security
4. Codes and Passwords Maintenance
5. Password Assignment
6. Location Checks
7. Authority Checks
8. Document Controls
9. Open/Closed Systems
10. Record Retention/Protection

Operational checks are application-dependent. Section 21 CFR 211.188(b) specifies that each significant step in the manufacture, processing, packing, or holding of the batch shall be documented. Section 21 CFR 211.188(b)(11) mandates the identification of the persons performing and directly supervising or checking each significant step in the operation.

The intent of the regulation is to secure that each step in the manufacturing, processing, packing, or holding of the batch is performed and there are records to show this, from which the history of the lot could be traced. All critical sequence of events shall be verified. In PLC based systems, operational checks may be incorporated in the software. The manufacturing procedures, control, instructions, specifications,[14] and/or process safety measures to be followed within such computer systems may be set as part of the product manufacturing process under computer control. In a blender, for example, combining the amount of blending time, blender speed, and the intensifier bar speed may be performed in a specific sequence. The Research and Development (R&D) department establishes the criticality of any of these parameters and associated sequence. In summary, computer systems are to be checked to make sure that critical operations occurred in the proper sequence.

An acceptable means of complying with the operational checks may be as follows: (1) documentation of the program, (2) verification and testing that no step or specification can be missed or poorly executed/assigned, and (3) documentation of the initial and final steps.[15] The reader may realize that the application-dependent requirements become part of the computer systems validation model through the operational verifications.

In this first example, **security** is associated with preventing accidental or intentional data manipulation, and corruption of the data that is to be displayed on the screen or used to make decisions to control the equipment. To avoid accidental, intentional, and/or lost data, the universe of data that will be collected, the procedures to collect it, and the means to verify its integrity, accuracy, reliability, and consistency must be defined. A Failure Modes and Effect Analysis (FMEA) is one of many methods to uncover and mitigate these factors. For example, to avoid data corruption, some measures shall be taken such as calibration of critical instruments[16] and implementation of an ongoing monitoring program.

Related to security is the logical access to computer systems. It includes the capability of such systems to allow the user access to the terminal and access to the parameters that are loaded in the PLC. The user interface must have the capability to have **authority checks**. The authority checks are based upon the various roles and responsibilities assigned to individuals known to the system. Computer systems shall be designed to make distinctions among control access (a) to the system, (b) to functions in the system, and (c) to input and output devices used by the system.

In this example, **location check** for the blender is not a critical element. The computer system is dedicated to the control of the equipment. Location checks enable the application software to determine whether the input being generated by a particular device is appropriate.

Passwords are one of many methods to authenticate authorized users. In view of the fact that security in cGMP systems is very critical, the expectations on activities such as assignment, security, and maintenance of passwords are clearly established by the FDA. Before Part 11, the FDA expected[17] that passwords:

- be periodically changed, not be re-assigned and re-used
- not be recognizable as reflections of their personal life
- not be shared by the users

The FDA expects written procedures or company policies, and the associated training on the subject of the use and security of passwords.

To ensure computer systems security, password files may be encrypted or otherwise secured so that passwords cannot be read by ordinary means. Password file encryption is very common in modern operating systems.

In general, the **password assignment and maintenance** are a combination of written procedures and technologies to support this requirement. Sample procedures include password aging, minimum password length, password uniqueness, default password management, and account lockout after a reasonable number of unsuccessful login attempts.

The focus of the validation program is typically the quality attributes of the system implementation, change control, and the verification and testing of the modifications to the baseline. The complete configuration management, including the **documentation,** is a key item of concern. Specifically, documentation management is very critical to the information that is contained in both the master production records and in the application.

System documentation means records that pertain to system operation and maintenance, from high-level design documents to end user manuals. Controlling system documentation includes assessing the documentation when a modification to the computer system is suggested. The high-level design documentation provides the inputs for maintenance and the user manuals provide the instructions of how to operate the system.

According to Part 11, a computer system is considered **closed** if the person responsible for the content of electronic records allows the access to authorized parties. In addition, the electronic records shall be monitored through the system's software with its required log-on, security procedures, and audit trails. In PLC based systems, it is very common to have communications to telephone connection through modems. A connection such as this is used to perform diagnostics by the system developer/integrator. This practice should be disallowed. If allowed, then the access via modem should have strict access controls and restrictions including protective software. Access restrictions on such systems should be designed to prevent unauthorized modifications.

In this example, the batch production and control records are paper based. The operator records each significant step in the manufacture of batches. The **retention and protection** to the executed batches is based on the existing regulation. The retention requirements to cGMP records can be found in

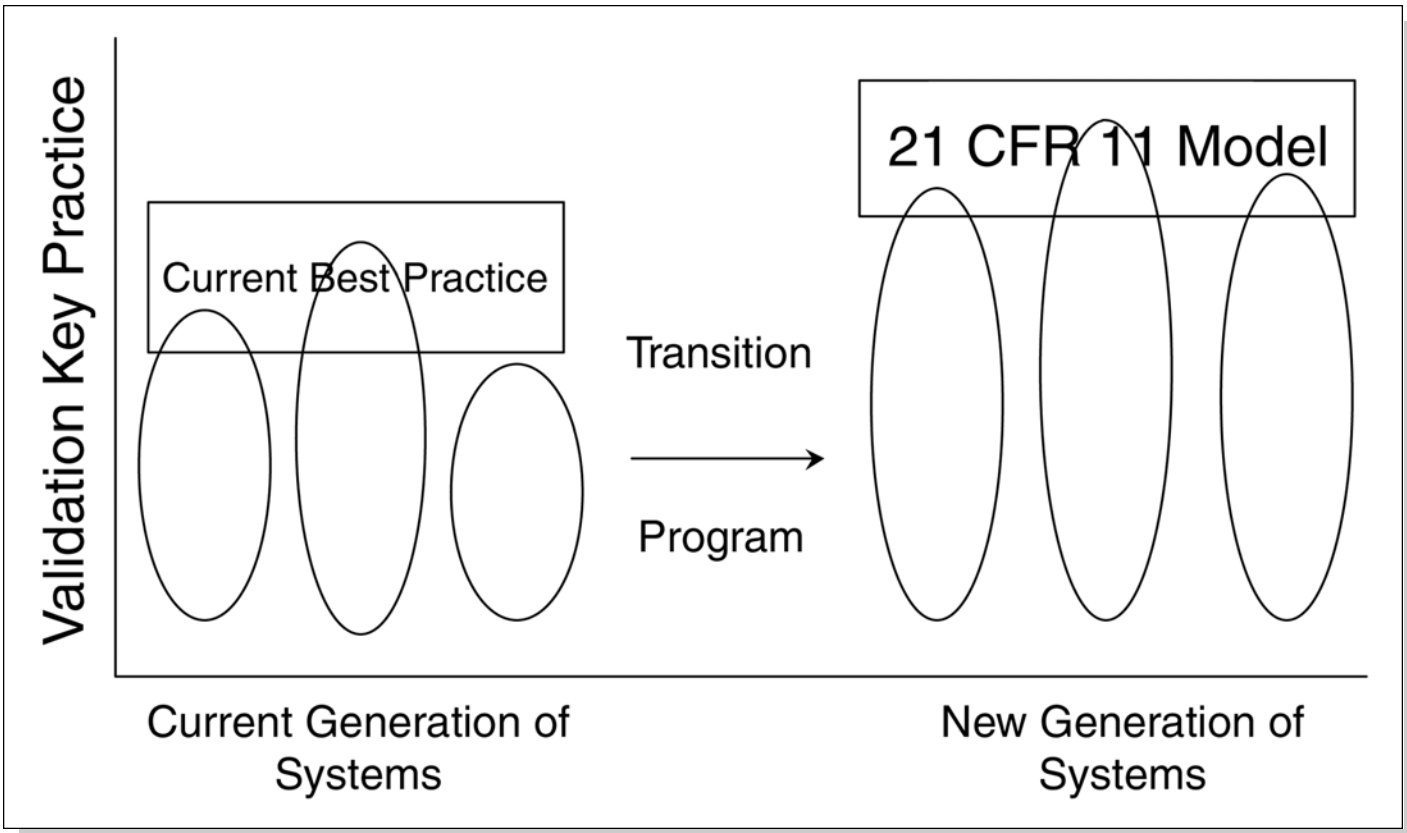

Figure 2. Progression of computer systems validation key practices.

211.180(a).

Second Example - Automated Packaging Lines Including Local Machine Controls and a Central Controller (e.g., PLC) that Stores Data in Transient Memory

As in the previous example, the main PLC is a stand-alone controller. The operator interface may be implemented using a terminal with a keyboard and a printer. Figure 4 depicts this example.

As in the previous example, there are no records saved to magnetic media and Part 11 is not applicable to this configuration. Using Part 11 as the model to validate the system software and computer hardware, the elements applicable to similar configurations are:

1. Operational Checks
2. System Security
3. Codes and Passwords Security
4. Codes and Passwords Maintenance
5. Passwords Assignment
6. Location Checks
7. Authority Checks
8. Document Controls
9. Open/Closed Systems
10. Record Retention/Protection

As noted, the only difference from the previous example is the complexity of the validation. The complexity of validation for manufacturing control systems is increased proportionally to the amount of equipment and instrumentation that the processor controls and monitors.

An example of **operational checks** applicable on automated packaging lines, is the logic of operation associated to the automation stations. These stations are employed to monitor presence of product, bottle orientation, cotton presence and height, cap presence skew, foil inner seals on caps, rates from rate monitors, labels presence and verification, and many more verifications.

Third Example - Hybrid Systems

Hybrid computer systems save data required by existing regulation on magnetic media; however, the electronic records are not electronically signed. One possible example consists of a Supervisory Control and Data Acquisition (SCADA) system in which historical data collection is archived and production batch reports may be printed directly from the SCADA station. These reports are manually signed. Figure 5 depicts a typical SCADA system. Notice the diversity sources of data.

On hybrid systems, the electronic record requirements (Sub-Part B) in Part 11 are applicable, but they cannot be submitted to the FDA. They can be maintained and retained in electronic form for the period established by the regulation requiring such records. The retention requirements of cGMP records can be found in 211.180(a).

The elements in Part 11 applicable to hybrid systems are:

1. Audit Trails and Metadata
2. System Security
3. Codes and Passwords Security
4. Codes and Passwords Maintenance
5. Passwords Assignment
6. Operational Checks
7. Authority Checks
8. Location Checks
9. Document Controls
10. Open/Closed Systems
11. Records Retention/Protection

Comparing the above list with the lists on previous examples, the audit trail is the requirement added to the above list. In addition, validation, system security, and record retention have additional complexities.

Process control systems are capable of generating accurate and detailed documentation of the manufacturing process under control. The critical issue to the electronic records within the scope of the regulations is the completeness of the recorded information. As part of **validation,** the completeness of computer generated batch production records is verified.

With the tracking purpose, **audit trails** refer to a journal that record modifications to the electronic records taken by the users or processes operating on user behalf. This mechanism provides the capability to reconstruct the data modified; therefore, not obscuring previously entered data. The tracking mechanism includes computer generated date and time stamps indicating when the record was modified, the types of modifications performed, and the identity of the person changing the record. Implicit requirements in Part 11 include the availability of tools to display and/or print audit trail records and associated metadata in human readable form. Another important use of audit trails is the protection from subsequent unauthorized alteration and destruction to permit detection and after-the-fact investigations of security violations.

The point which data becomes an electronic record should reflect its origin and intended purpose. For manufacturing systems, this may be the initial point of data acquisition. This same point also would form the basis for the recording of audit trails to all changes to a record.

To implement audit trails on SCADA systems, third parties are providing custom code to be integrated with the SCADA database. This approach provides the technological foundation for proper administration of all electronic records without replacing the application managing manufacturing and process related records. For example, audit trails may be implemented using database triggers. A trigger is a feature of Oracle™ that allows for user written code to be executed based on an event. The concept implies that the addition of a record will produce an event. The event may be defined as an insert, update, or delete from a database table.

Other alternatives are to replace the complete SCADA system with an out of the box application including audit trails.

A third alternative is to disallow modifications to the records at the data collection and acquisition domains. SCADA may be used as a temporary repository system. The permanent repository system may be located at the business logistic systems level.[18] At this level the electronic records are either maintained while in active use, or are maintained off-line

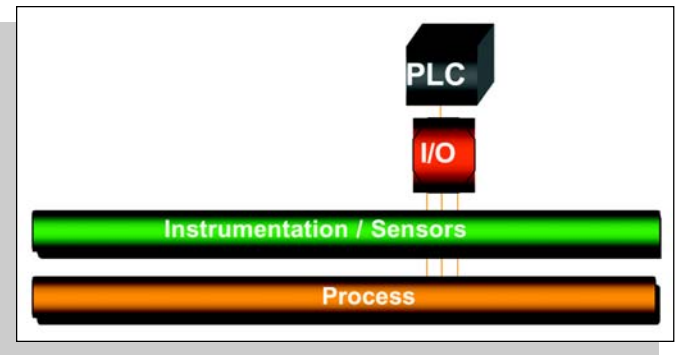

Figure 3. Sample stand-alone PLC.

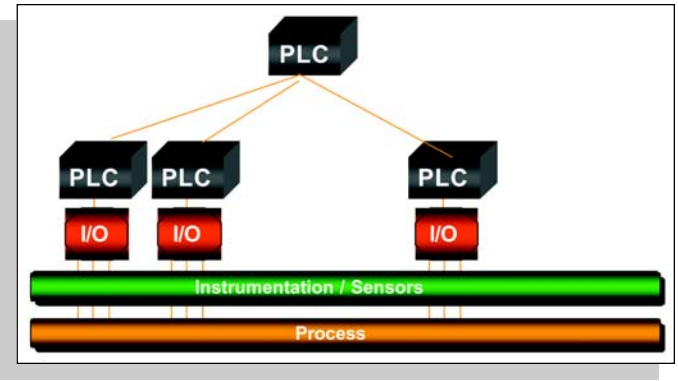

Figure 4. Sample central controller PLC.

when use is less frequent. This setting must be evaluated and, preferably, documented as part of a company wide strategy. The selected settings require procedural and technological controls.

Data is most often transferred using available drivers. The transfer/transcription process, from the secondary repository to the permanent repository, shall be completely qualified. The qualification must include all the appropriate documentation and supporting data. The objective of the qualification must be to ensure the accurate transfer of electronic records and associated content, context, and structure.

One item to be addressed during the implementation of PLC based systems is the long term archiving of an immense amount of manufacturing/quality data and associated metadata.[19] The hardware and software in support of this repository should be robust, but at the same time, flexible to stand the regulatory electronic records retention requirements.

The use of audit trails is not restricted to record modifications to the records. Audit trails may be used to record operator entries and actions during a production step, documentation that can be recorded without electronic signatures themselves. The operational checks, as delineated in 211.188(b)(11), may benefit from this feature.

In addition to security elements referenced in previous examples, additional **securities** are intended to cover electronic records. External safeguards shall be in place to ensure that access to the computer system and data is restricted to authorized personnel.

Access to batch records at the primary and secondary repositories shall be restricted and monitored through the system's software with its required log-on, security procedures, and audit trail. In case of any remote access via external software, applications must enter through the same protective security software.

As stated in this example, the batch production reports are paper-based. The operator may record each significant step during the manufacturing of batches or may only rely on the automated system. Paper records and associated electronic records are retained based on 211.180(a). In hybrid systems, one approach to associate electronic files and paper based batch reports is by referencing the file(s) as part of the report. The reference may include the name, creation date, and time of the files associated with the batch report. Modifications to any referenced electronic file invalidate the approval of the associated batch report.

In similar situations, it is very important to understand that having a signed paper-based record (e.g., report) associ-

ated with electronic records, the electronic file(s) associated with such records shall not be deleted. The regulation is very specific regarding this issue. Electronic files in hybrid systems shall be maintained electronically. The interpretation of the medical device cGMP regulations is different. Part 820 requires that "results" of acceptance activities be recorded, but not necessarily all raw data. "Results" must have audit trails. This interpretation is contained in the medical device quality system preamble (pp. 52631 and 52646).

Fourth Example - Complete Automated Facility

In this example, the total integration of the enterprise is incorporated from the plant floor all the way through to the customer, using electronic, often web-based technologies. Sensors, limit switches, and other control components on the plant floor send information to diagnostic systems and control-based monitoring systems. These in turn send information to systems that manage maintenance, modeling, scheduling, tracking, and batching operations.

In similar examples, the electronic signatures and associated requirements may be implemented as a company wide paperless strategy. This strategy will maximize resources by identifying "common" solutions to manage data, electronic records and reports (e.g., written procedures, guidelines, and databases) that may be developed once for the company for all applications to use.

This fourth example applies to the implementation of integrated enterprise and control environments. It combines the ISA SP95, S88.01,[20] and S88.02[21] standards. Figure 6 depicts sample architecture.

For applications using PINs, user identifications and passwords, digital signatures, digitized signatures, and hardware and biometric tokens, the current validation/qualification model requires verification and/or testing of many of the following:

1. Audit Trails and Metadata
2. System Security
3. Electronic Signature Security
4. Codes and Passwords Security
5. Codes and Passwords Maintenance
6. Passwords Assignment
7. E-Sig without Biometric/Behavioral
8. E-Sig with Biometric/Behavioral
9. Records Retention/Protection
10. Operational Checks
11. Authority Checks
12. Location Checks
13. Document Controls
14. Open/Closed Systems
15. Signature Manifestation
16. Signature Purpose
17. Signature Binding
18. Certification to FDA

In addition to the complexity associated with the implementation and validation of the integrated environments, such as the one depicted in Figure 6, the new requirements added to the listing are the security on electronic signatures, type of electronic signatures, signature manifestation, signatures purpose, signatures binding, and certification to the FDA.

On systems using **electronic signatures without biometrics/behavioral,** it is common to use both computer user identification (USERID) codes and passwords as authentication of users and as electronic signatures. The combination of the USERID code and password must be unique. Generally, firm's make sure the USERID codes are unique so that if by coincidence, two persons create the same password, the result is not two identical electronic signatures. Furthermore, firms generally establish unique, but not confidential, USERID codes.

Biometrics is the use of physical characteristics such as a voiceprint, fingerprint, hand geometry, and iris or retina pattern as a means of uniquely identifying an individual. When biometrics measures are applied in combination with other controls (such as access cards or passwords), the reliability of authentication controls takes a giant step forward. The use of biometrics/behavioral is less common in the FDA regulated industry. This access control technology does not change the authentication of users. It changes the implementation of how to authenticate users.

Part 11 requires a **signature manifestation** executed as part of printing and displaying signed records. The regulation requires that the name of all signers, the date and time of the executed signature, and the purpose associated with the signing be displayed/printed in human readable forms.

As part of the action of signing an electronic record, the **purpose of the signature** must be identified and becomes an element of each signed record. In the drug cGMP arena, there are relatively few purposes for a signature such as review, authorship, and approval. The execution of an action such as a production step does not require an electronic signature and can be documented via the audit trails.

Special attention must be taken to the **signature binding**. The current requirement establishes that electronic signatures shall not be replaced or removed. This requirement is an element of the integrity of signed records. In addition to the access control technologies and procedures, signature binding needs supporting tools for verification. For example, Public Key Infrastructure (PKI) technology uses hashing algorithms and keys to demonstrate the integrity of signed records. The digital signature is linked to the electronic record by incorporating that instance of the record into the signature itself. The link must be retained for as long as the record is kept, long after signer has departed the company.

On those systems using user identifications and passwords as electronic signatures, the current level of technology makes it very difficult to implement the signature-binding requirement and the trustworthiness of electronically signed records over time. In many of these cases, the electronic signatures are

based on software locks. At this moment in time, there are no automated tools available in the market to evaluate the integrity of signed records using identification codes and passwords. The combination of authentication schemes such as passwords, biometrics, physical feature authentication, behavioral actions, and token-based with cryptographic techniques, shall be used to evaluate the integrity of an electronic record.

Digital signature is a technology that fully supports integrity and trustworthiness of signed records. There are products in the market supporting integrity and signature authentication to documents written in Microsoft Word, Microsoft Excel, Microsoft Outlook, Adobe Acrobat, JetForm FormFlow, PureEdge, XML, and HTML.

The status of the **certification** to the FDA should be reviewed as part of the verifications to documentation of computer systems implementing electronic signatures. The certification is a global statement of intent, meaning a single company certification can cover all systems, all applications, all electronic signatures for all employees in a company, for all the firm's locations anywhere in the world. QA Compliance or Regulatory Affairs may submit this certification.

Conclusion

Since 1988, the attention on computer systems by the FDA has increased due to the increase in the use of computers as part of the manufacturing of drug products and the impact of the computer controlling the manufacturing process in drug quality. The records created and maintained by such computer systems are used to demonstrate the quality of the products.

The regulatory requirements applicable to electronic records in the cGMP environment contained in Part 11 are outlined in the cGMP. The cGMP contains implied regulatory requirements applicable to computer systems performing functions in the applicable regulations. With the approval of Part 11, the FDA provides, unambiguously, the regulatory requirements applicable to computer systems.

Part 11 can be used as the model to qualify/validate all computer systems. This new computer systems validation model obsoletes the "key practices" model that was used since the early '70s.

References

1. This article was created from a presentation at the IIR's Computer and Software Validation Processes Seminar, Washington, DC, July 26-28, 2000.

2. Fry, Edmond M, "FDA Regulation of Computer Systems in Drug Manufacturing," **Pharmaceutical Engineering**, September/October, 1998.

3. "**Data owner**" means a person or organization who can determine the contents and use of data collected, stored, processed, or disseminated by that party regardless of whether or not the data was acquired from another owner or collected directly from the provider.

4. **Source code** is the human readable form of the program, written in its original (source) programming language or scripting language.

5. FDA, CPG 7132a.11, "Computerized Drug Processing, CGMP Applicability to Hardware and Software," 9/4/87.

6. Grigonis, Subak, and Wyrick, "Validation Key Practices for Computer Systems Used in Regulated Operations," **Pharmaceutical Technology**, June 1997.

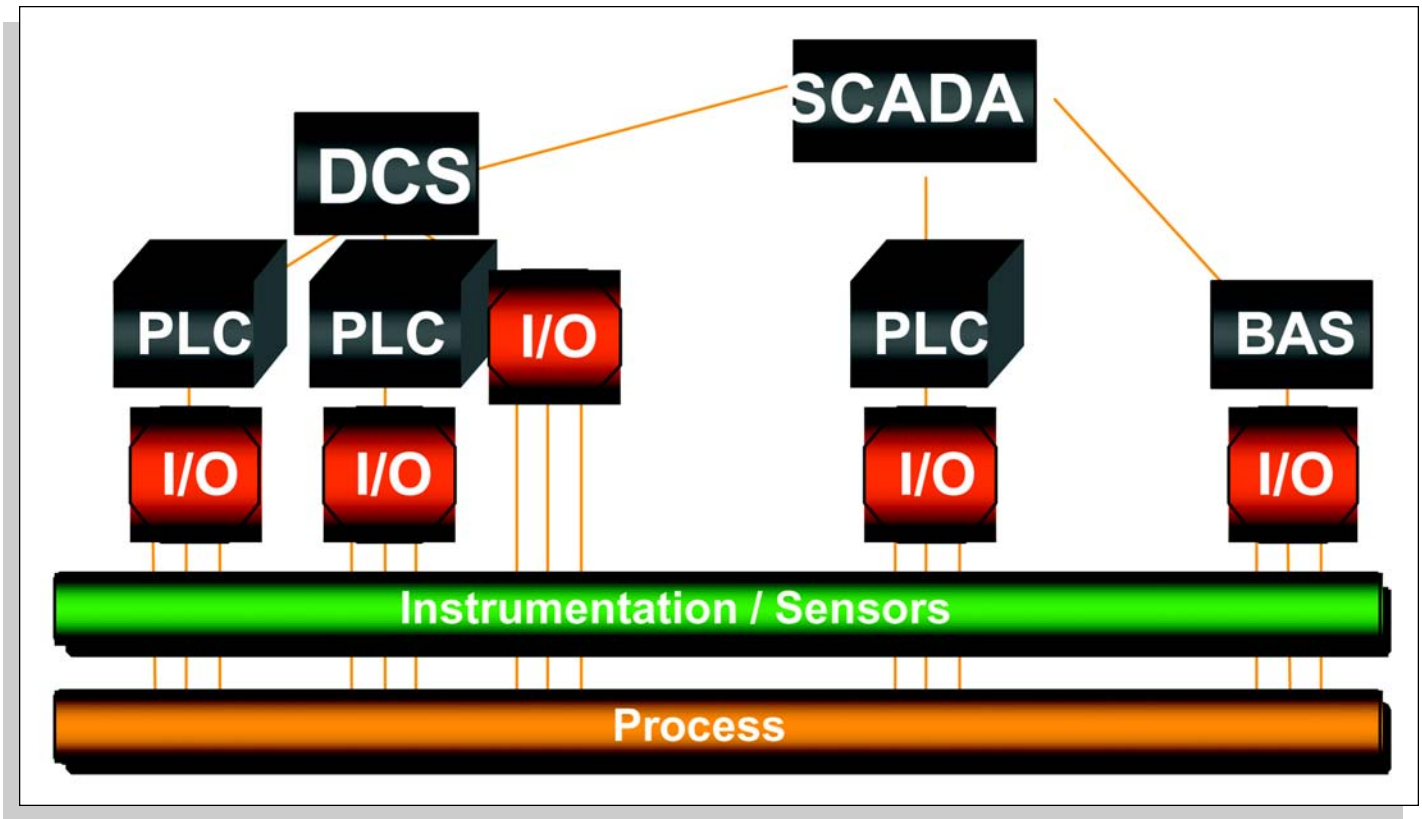

Figure 5. Sample SCADA system.

7. In hybrid systems, some portions of a record are paper and some electronic.

8. López, O, "Automated Process Control Systems Verification and Validation," **Pharmaceutical Technology**, September 1997.

9. López, O, "Implementing Software Applications Compliant with 21 CFR Part 11," **Pharmaceutical Technology**, March 2000.

10. "A Partnership Approach to Achieving Regulatory Compliance for Electronic Records and Signatures," paper presented at the October 1999 IMPACC Conference.

11. Note of the author. Current federal legislation, Electronic Signatures in Global and National Commerce Act, defines electronic records in more general terms than Part 11 does. The primary element into consideration in the current federal legislation is whether the data is accessible once put in storage, not considering the technology used. This definition will consider data in transient memory as electronic records. If this is the case, Part 11 may be considered as the computer systems validation model in all examples discussed in this article. One key element to be analyzed by the FDA and the industry is the regulatory requirements to data stored in transient memory, including audit trails.

12. **Critical parameter** is a parameter that must be properly controlled to maintain the quality, safety, identity, strength, and purity of the product. This definition is taken from "Streamlining Validation," **Pharmaceutical Engineering**, January/February 1998.

13. **Variable setpoint** is the desired value of a process variable that may change from run to run and must usually be entered by the operator.

14. An example of a specification may be **a fixed setpoint**. A fixed setpoint is the desired value of a process variable that cannot be changed by the operator during execution.

15. FDA, "Guide to Inspection of Computerized Systems in Drug Processing," February, 1983.

16. A critical instrument is an instrument that impacts the quality of the product. It may control process parameters, alert an operator to an out of control condition or be used for indication only.

17. FDA, "Draft Guideline for the Validation of Blood Establishment Computer Systems," September 28, 1993.

18. Enterprise/Control Integration standard, ISA SP95.01. The plant management level is the plan repository area

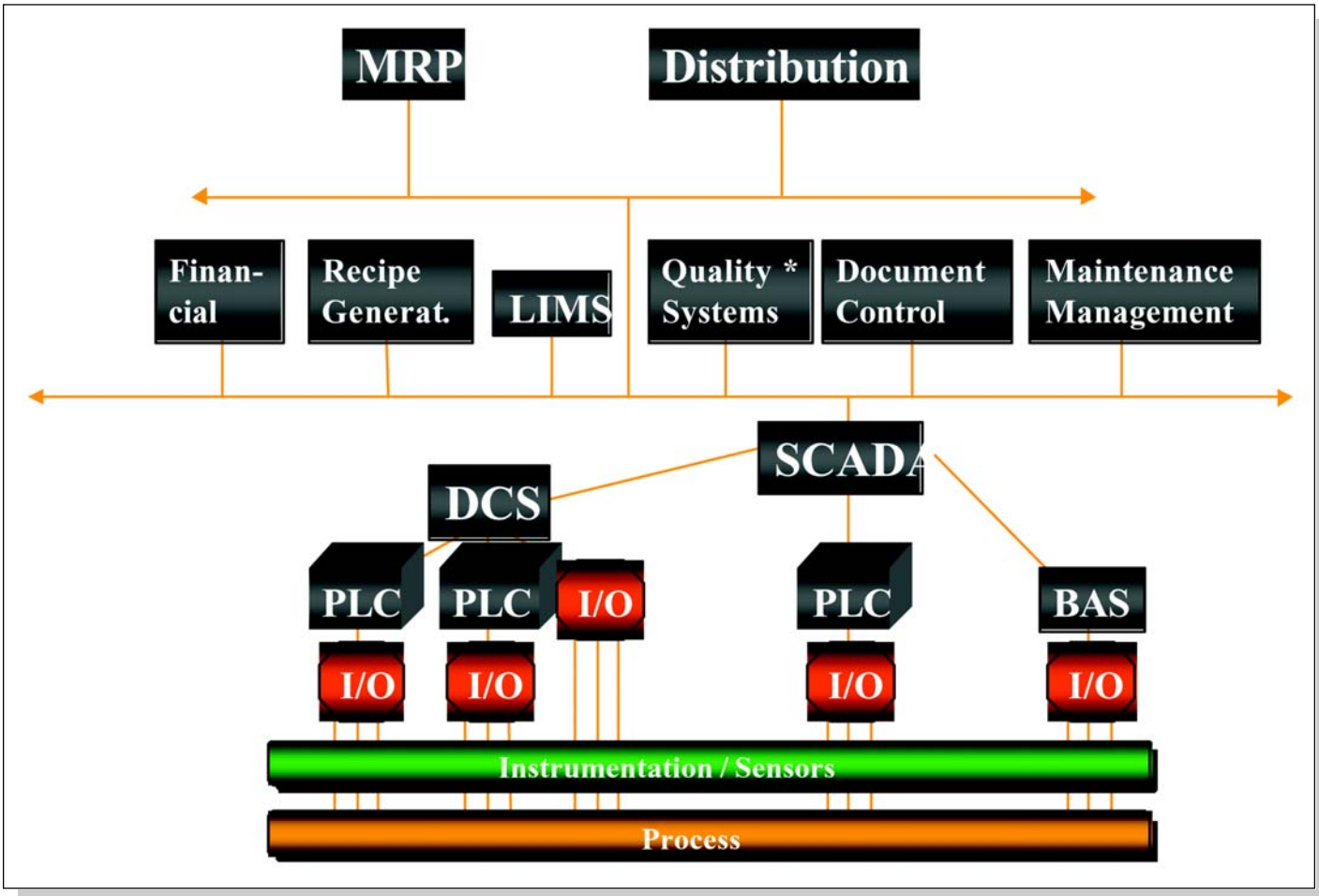

Figure 6. Sample e-manufacturing configuration.

(e.g., database server(s)) which unifies production, quality control, inventory, and warehouse data.

19. Metadata—Data describing stored data: that is, data describing the structure, data elements, interrelationships, and other characteristics of electronic records, DOD 5014.2-STD, "Design Criteria Standard for Electronic Records Management Software Applications."

20. International Society of Measurement and Control (ISA) Batch Control Standard (S88.01) defines a common set of models and terms for the design and operation of batch process control systems.

21. S88.02 standard includes a section that defines the communication requirements between the functions of recipe procedure execution and equipment control.

About the Author

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This article provides an overview of an IT tool that addresses the process documentation and recipe preparation and approval process in a multi-product, multi-purpose, bulk pharmaceutical manufacturing facility. The article concludes by forwarding a proposal outlining a road map for development of an equivalent Off-The-Shelf ISA Standard S88 compliant application.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
May/June, 2001 Vol. 21 No. 3

Automation of the Documentation Preparation Process in an Automated, Bulk Pharmaceutical Facility

by John McNulty and Dr. Rodger Edwards

Introduction

This article is based on a dissertation entitled 'Re-Engineering of the Process Documentation Preparation Business Process in an Automated Bulk Pharmaceutical Facility' submitted by John McNulty, to the University of Manchester Institute of Science and Technology for the degree of MSc in pharmaceutical engineering advanced training.

It is intended that this work, while presented in the context of a bulk pharmaceutical manufacturing facility, will be of interest to any manufacturing professional operating in a regulated environment and whose production facility/operating philosophy shares the following characteristics:

a. Multi-Product Plant
b. Multi-Purpose Plant (configurable equipment trains fixed for a given campaign)
c. Computer Controlled
d. Operated on a Campaign Basis

Table A lists five criteria which may make the Document Generation System outlined in this article applicable to the requirements of any given facility.

The automation of the preparation of process recipes and associated documentation has been considered with the specific process related objective of remedying three critical deficiencies of manual methods. These are:

1. the risk of human error and consequent risk to product integrity
2. the unnecessary duplication of effort
3. difficulties in enforcing uniformity of documentation format within a manual regime

The requirement for the DGS also is based on interpretation of the FDA requirements as applicable to multi-purpose, multi-product, bulk pharmaceutical manufacturing facilities producing drugs for human and animal consumption.[1]

Analysis of process documentation identified that its content is composed of two types of information: recipe derivable and non-recipe derivable. A software application was developed that automatically generated recipe derivable process documentation content from the associated process recipe and allowed controlled user input of non-recipe derivable information. The resultant application is known as the Document Generation System (DGS) and addresses all identified issues with the previous work system. The application was developed in conjunction with a leading software consultancy company and implemented at a production facility of a top-tier US multinational pharmaceutical company in the Republic of Ireland.

The work presented in this article is centered around the part of the overall project in which the new automated system was designed and implemented; however, it is of course the case

Table A. Criteria for evaluating the need for a DGS.

Do You Need a Documentation Generation System for your Process Batch Sheets?
1. Your plant equipment is configurable with no set equipment trains.
2. Your equipment trains for a product to be completely changed campaign from campaign.
3. Your process is computer controlled with product specific recipes.
4. You require at least one Batch Sheet to accompany the production of each batch of product.
5. Process recipes and documentation are required to be updated, reviewed, and approved each time the equipment train and/or process is modified.

1. Assign a project leader from the group primarily expert in process recipe and documentation preparation (full time for the duration of the project).
2. Form an interdepartmental team to support the project objectives (Part Time Basis).
3. Define the 'real' requirements for process documentation as defined by operational, legal, and regulatory constraints.
4. Select vendor to support the requirements and design phases.
5. IT System analyst to assist in the requirements and design phases.
6. Map the process documentation and recipe preparation process identifying: • information and efforts that are duplicated in both processes • areas of common human error
7. Define high-level logic for interpreting document content from recipe structure and content.
8. Define control mechanisms for eliminating any scope for human error and other areas of effort duplication.
9. Review and approve the Requirement Specification by all stakeholder departments.
10. Preparation of the Design Specification by the vendor's project technical lead in conjunction with the lead user representative. The design phase will iteratively define and challenge all: • recipe interpretation logic • reference data required by the system • audit trails, control mechanisms, security and archiving requirements • revised work systems to support the system • training requirements
11. High-level training on system functionality and revised work practices of the interdepartmental team members assigned to the project and targeted key users.
12. Review and approve the Design Specification by all stakeholder departments.
13. Development of the system at the customer site, in accordance with FDA validation lifecycle methodology, and in close collaboration with the primary user group via the user project lead.
14. Parallel definition of documentation standards and all reference data standards by the assigned interdepartmental team.
15. Preparation and approval of all required reference data in accordance with the defined standards.
16. All system and acceptance testing completed by joint developer-user teams using the approved reference data.
17. Standard Operating Procedures to support revised work processes were prepared based on experience of the reference data preparation process, system testing experiences and Design Specification.
18. System implementation was initially partial by maintaining both a recipe and Batch Sheet review.
19. System fully implemented and full elimination of a separate recipe review.

Table B. Project execution methodology for the documentation generation system development.

that other benefits not directly related to product would accrue from its implementation. The key business drivers for developing the 'Document Generation System' were as follows:

a. optimization of capability to respond to fluid production schedules
b. optimization of compliance
c. optimization of workforce capability by eliminating non-value added tasks
d. facilitation of staff turnover

To this end, data is presented in this article which demonstrates that substantial reductions can be achieved in both the number of personnel committed to the process of recipe and documentation preparation and the total number of staff hours required to execute the same task by manual working methods. These savings, as well as superior quality assurance of process recipes and documentation, are very attractive.

This article proposes that the functionality embodied in the DGS has potential widespread application in the pharmaceutical industry and, acknowledging that long-term maintenance of such complex customized IT systems is unsustainable, concludes by recommending that an equivalent tool be developed as an Off-The-Shelf product by existing batch software vendors. As recommendations for further work, the author proposes a road map for the evolution of such a product from customized prototype through to the production of electronic Batch Sheets.

It is hoped that this article will contribute to, and further stimulate discussion among manufacturing practitioners and vendors with the objective of influencing OTS Batch Software product development.

While the project execution is not the primary purpose of this article, Table B outlines the methodology followed in the DGS development.

Overview of Typical Process Documentation Use in an Automated Bulk Pharmaceutical Facility

Figure 1 shows a schematic overview of the interaction between operator, process documentation, and recipe. The Manual Recovery Batch Sheet contains the highest level of detail to facilitate the recipe review process and is used to direct non-automated processing on the factory floor in the event of recipe failure. This document also will include Safety Caption information and the corresponding Alarm and Interlock Report.

The Process Batch Sheet is at a level of detail to facilitate fully automated processing. Its content is restricted to instructions required for activity steps that are manually executed by an operator on the factory floor; data recording tables/other designated notes; and text that identifies required repetitive/optional conditions within a recipe.

This Next Executable Activity Table (NEAT) Network lists all the activities of the process in the order in which they are to be executed. Interdependencies between activities are indicated and activities that can be completed in parallel are also highlighted.

A master set of documentation is prepared, reviewed, and approved for processing of a specific campaign of a process step. A copy of the Master Manual Recovery Batch Sheet is taken, allocated a serial number, and issued for filing in a central location on the factory floor. This document is referenced by the operator only in the event of a recipe failure. A copy of the approved Master Process Batch Sheet and NEAT Network are

issued for processing of each batch. All required data recording and operator observations are recorded for a specific batch in its associated Process Batch Sheet. In the event of recipe failure, the operator will reference the central copy of the Manual Recovery Batch Sheet for direction, but will record all actions taken in the corresponding Process Batch Sheet for the batch in question.

During automated and non-automated processing, the operator will reference the NEAT Network for each batch to determine activities that are active simultaneously. As each activity is completed the operator will hand-mark the NEAT so that it provides a summary of the batch execution status at shift hand-over.

Regulatory requirements for process documentation were confirmed by review of subsections 211.186 and 211.188 of Part 211of the FDA's Code of Federal Regulations - Title 21 'Food and Drugs' - subsections 211.186[2] and 211.188[3] of Part 211. These requirements have been combined with the minimum requirements necessary in order to comply with Operational, Safety, and cGMP practical conventions and have been incorporated into the Document Generation System design. An overview of the resultant functional design of the system, incorporating these requirements, is included below, but the concept behind the DGS development is examined first.

Concept of the Document Generation System

Minimization of the scope for human error and duplication of effort, and facilitation of documentation standardization had been identified as the core requirements that the DGS had to address for the process documentation and recipe preparation business process. The overall objective of the DGS was to address each of the three core requirements and, in doing so, to provide a vehicle for effective and efficient work practices, and optimized compliance**.**

A recipe contains a subset of the information required to be included in the process documentation set and this information is stored according to definite rules in a defined set of database tables in a Recipe Management System (RMS). The phase actions and parameter values contained in a process recipe have a direct correspondence to the process execution actions and process conditions specified in the Manual Recovery Batch Sheet, Process Batch Sheet, and the Alarm and Interlock Report. The interactivity dependencies shown on a NEAT network should be directly reflecting dependencies within the recipe.

Business Process Task	Committed Staff	Number of Hours per Person	Total No. of Hours
Documentation Preparation	1	24	24
Documentation Review	8	6	48
Documentation Update	1	8	8
Recipe Update	1	16	16
Recipe Review	5	6	30
Recipe Update	1	4	4
Documentation Update	1	4	4
Documentation Approval	2	2	4
Recipe Approval	1	2	2
Total	---	---	140

Table C. Manual documentation preparation process.

The DGS concept was based on the manual preparation of the process recipe on a bespoke RMS application, and utilization of an information technology application to generate the documentation set from that recipe. This was accomplished by logical interpretation of the recipe data content and structure that is stored in the database tables of a RMS. Figure 2 shows the steps leading to the generation of the process documentation set. The DGS also was required to incorporate any non-recipe derivable information into the documents either by automatic inclusion or by controlled user input.

The requirement for a separate recipe review process was eliminated as the complete recipe content and structure is visible in text and graphical format in the generated documentation set.

Revised Process Documentation Preparation Business Process

Figure 3 summarizes the workflow associated with the DGS. The recipe is prepared on the RMS and its recipe content is copied from the RMS database tables to the DGS database tables via the DGS import functionality. On successful importation of a recipe to the DGS, the DGS offers Recipe Enhancement capability to the user. Recipe Enhancement is the process by which the user specifies non-recipe derivable documentation content for inclusion in the auto-generated document. The user has the option to generate documents at any stage once the recipe has been successfully imported. During document generation the DGS will automatically import the required document template as specified by the user. It also will retrieve the process sampling details required to be included in the document by a direct interface with the Sample Result Management System (SRMS), thus eliminating any scope for human error associated with the previously manual transcription process, and will select the appropriate DGS reference data for inclusion. The resultant document is automatically named and saved to a protected network drive, in accordance with agreed conventions. The document is clearly designated a status of 'Unapproved' and is not allocated a revision number. The generated documentation is circulated electronically for committee review after which the cycle is repeated to incorporate any review comments into the recipe and documentation. When the user designates the document set as 'Approved,' via the DGS, the documents are automatically moved from an 'Unapproved' subdirectory to an 'Approved' subdirectory on the protected network drive, allocated a revision number, and assigned a status of 'Complete' on the DGS and the RMS. A recipe with a status of 'Complete' on the RMS cannot be edited further, and a recipe with a status of 'Complete' on the DGS cannot be enhanced further, i.e. the content of both the recipe and the documentation is frozen.

Overview of DGS Functional Design

Figure 4 summarizes the DGS key functional modules and its external interfaces as described in the previous section. Fol-

lowing sections will provide an overview of the functionality of each key module.

DGS Reference Data

Safety Captions Reference Data

Safety captions are now managed within the DGS. They are stored in the DGS Oracle database tables and also on a read-only network-drive for site-wide access. A DGS Safety user will manage safety captions via the DGS reference data module using an integrated WORD 8 session. The DGS automatically saves safety captions both to its database and to the designated network drive. During recipe enhancement the required safety captions to be associated with the recipe are specified by selecting the required safety captions from a drop down list on the DGS. On subsequent recipe imports of the recipe or a subsequent revision of the recipe, the safety caption association is copied across from the previous import of that recipe. The most up to date version of each associated safety caption will be included on each document generation for a recipe.

User Defined Reference Data: Standard Text

Standard Text is a text representation of a phase action as parameterized in a given recipe instance. Two types of text have been identified as required to reflect a phase action, Manual Recovery Batch Sheet Standard Text and Process Batch Sheet Standard Text.

For a multi-purpose facility, the set of computer system recipe phases will be designed to operate as flexibly as possible. For example, a phase action can differ widely depending on how a phase is parameterized, different phases operate differently on different pieces of equipment, and the significance of one parameter value may be dictated by other parameter values for the same phase. Therefore, to reflect and handle this flexibility, the DGS functionality for Standard Text definition (and document generation) has been designed to be suitably versatile.

Each phase will require a library of standard text to be defined within the DGS. Sets of Standard Text are defined in pairs: one for the Manual Recovery Batch Sheet and the other for the Process Batch Sheet. Each pair of Standard Text will have a rule defined that reflects the recipe instance in which the pair is applicable for inclusion in the generated documentation. The DGS then has the capability to automatically select the most appropriate piece of Standard Text for each phase in a recipe instance for a specific document type by determining the rules that are true in that specific recipe instance. The DGS functionality associated with rule definition reflects the requirement for flexibility and is able to determine the applicable text dependent on any of the parameter values for a given phase, the equipment in use, and the type of instrumentation to be used by the phase to complete its automatic plant action.

This concept, first, facilitates one time set up of Standard Text for use in all documentation generation. It also will minimize the scope for human error since the set up and maintenance effort is now restricted to one point in the system and the document generation process for selection and insertion of the applicable Standard Text into the batch sheet is automatic. Document standardization is facilitated since there is a one point source of Standard Text. Standard Text can be defined in the DGS within an integrated WORD 8 session. This will allow the full range of WORD text formatting to be applied to Standard Text - different font types and size, underline, bold, italic, justification.

DGS functionality allows the inclusion of fields, within standard text, that are dynamically resolved, during document generation, by the system. Fields that can be included in standard text are:

- another parameter value in the phase for inclusion in the standard text
- the batch sheet activity number for inclusion in the standard text
- equipment Id on which the Phase is acting
- the requirement for a signature line

As described above, each phase will have a library of standard text pairs defined for it and each pair of standard text will have a rule that dictates the recipe instance in which it is applicable. For any recipe instance, a number of standard text pairs will be applicable. The DGS must then insert these standard text elements into the corresponding activity step of the generated document in a predetermined order. This is accomplished by allocating each standard text pair a unique sequence number as part of the phase standard text reference data. This sequence number specifies the position of its associated standard text, in the activity step of the generated document, relative to the other applicable standard text elements for the same phase instance in a given recipe. Additional phase reference data associated with standard text resolution at document generation is necessary to instigate specific DGS processing for specific phase and parameter types. A subset of phases and parameters are significant in denoting mandatory, repetitive, optional, alarm and interlock set-up, and dependency structures within the recipe. These phases and parameters will require explicit flagging as being of a specific type, in order that they may be recognized by the DGS. Utilization of phase and parameter types avoids the requirement for the DGS code to contain explicit ('hard coded') references to specific phase and parameter names, instead the code refers only to specific phase and parameter types. This is consistent with the requirement that the DGS should be designed such that, within the current scope of document generation requirements, no code amendments are required when a new phase is created or an existing phase is modified.

It also is required to allow translation of parameter values to meaningful text in the generated documents. This involves

Business Process Task	Committed Staff	Number of Hours per Person	Total No. of Hours
Recipe Update	1	16	16
Documentation Preparation	1	8	8
Document Review	8	5	40
Recipe Update	1	4	4
Documentation Update	1	2	2
Documentation Approval	2	2	4
Total	---	---	74

Table D. DGS Enabled preparation process.

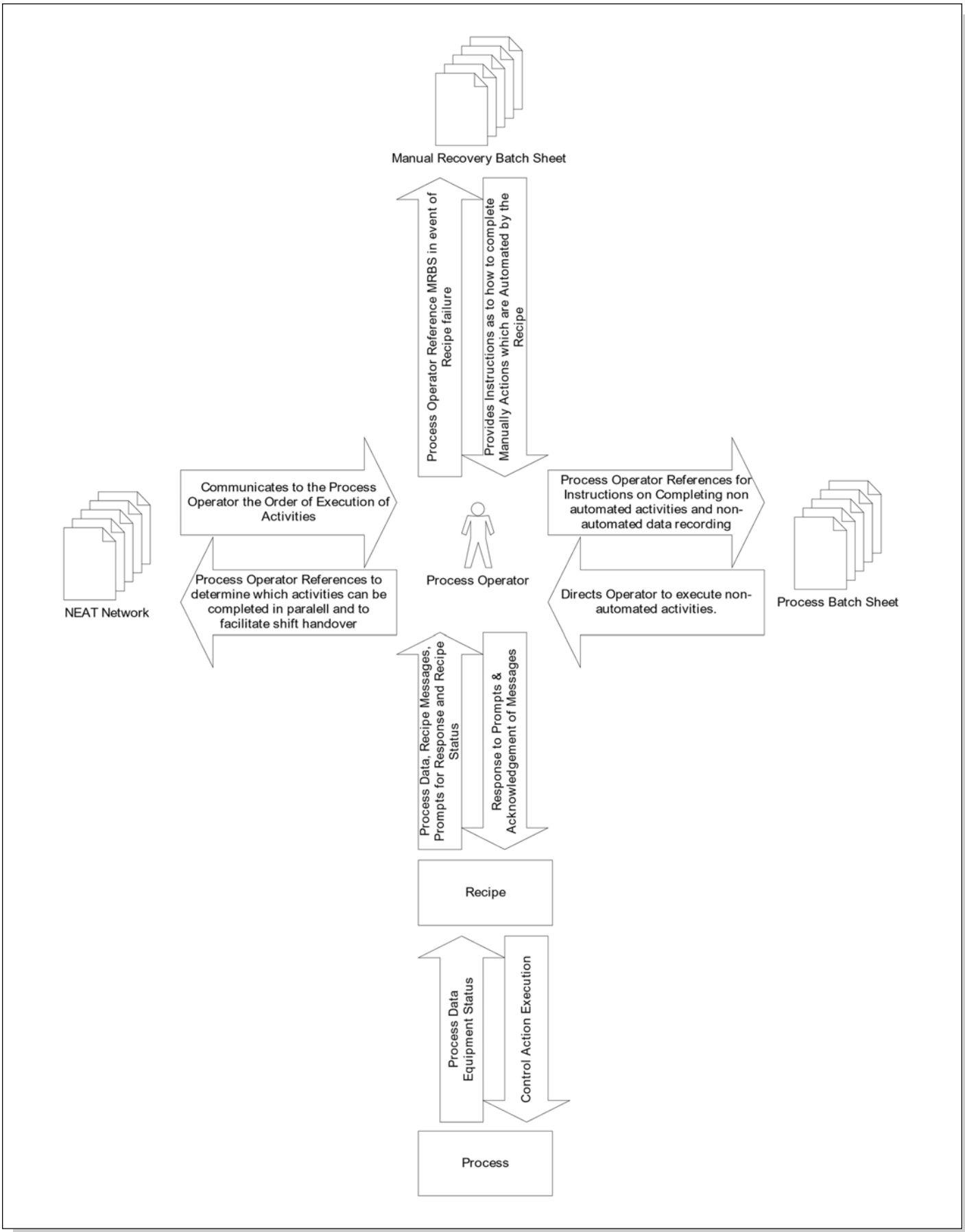

Figure 1. Overview of operator, process documentation, and recipe interaction.

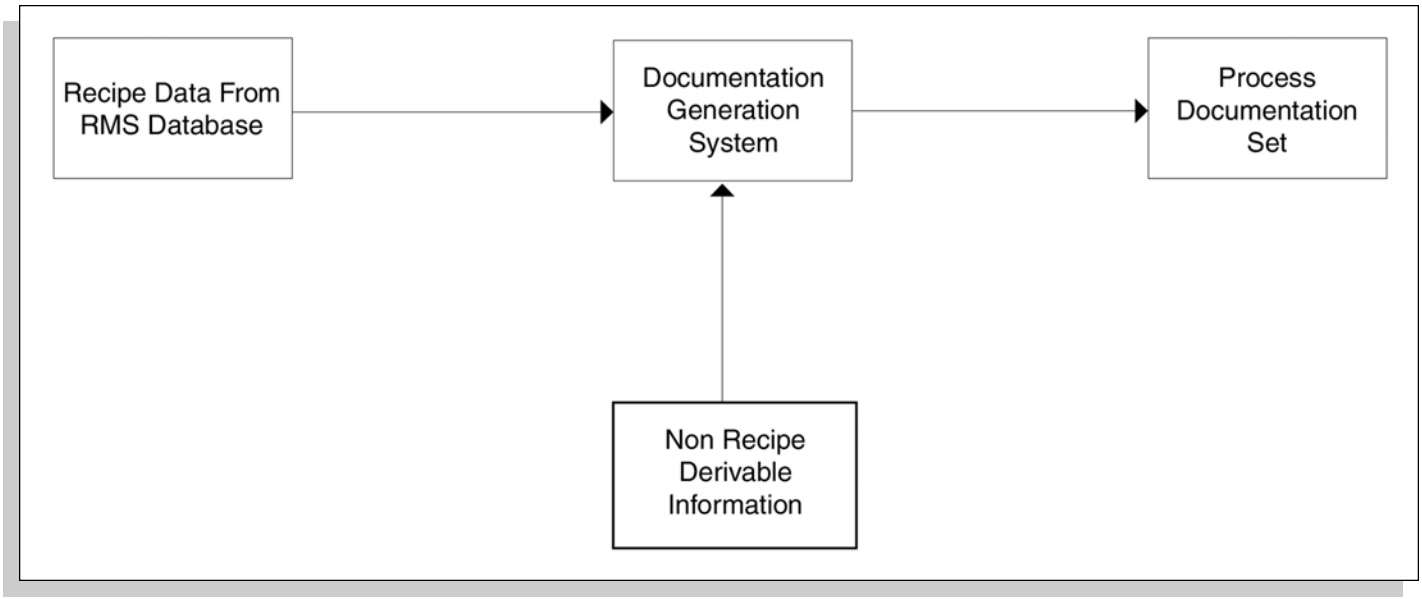

Figure 2. High level concept behind the DGS development.

associating the appropriate translated value to the allowable parameter entries for each parameter of a phase where required. This type of phase reference data is required, because not all phase parameters will be meaningful without translation. The translated parameter value will then appear in any standard text selected for that phase during document generation that contains fields referencing that specific parameter value.

In summary, to define the reference data associated with DGS Standard Text functionality for a phase the user must:

- define all possible Standard Text pairs for that phase
- allocate a sequence number to each Standard Text pair defined
- define a rule to be associated with each Standard Text pair defined
- specify if the phase or any of its parameters are specific parameter types
- define any required translation values for phase parameters

This grouping of reference data is termed the Standard Text reference data for a phase and can have a status of 'Approved' or 'Unapproved,' as specified by the user, and is subject to automatic revision control and a manual review and approval procedure. The off-line change control features and procedures associated with Standard Text facilitate the regulatory prerequisites to streamlining of the documentation review process itself, where the focus has shifted to process specific content as opposed to also incorporating generic standardization and phraseology review issues.

User Defined Reference Data: Equipment Data

To avoid human error associated with manually specifying equipment valve and instrumentation details in a document, the DGS has functionality that automatically includes the appropriate valve or instrument reference at the appropriate point in a document. The logic for this automatic document inclusion is validated and extracted from an approved master table of equipment reference data. This also will reduce document preparation and review time. Therefore, instruments or valve numbers associated with a fixed piece of equipment, where required, will be referenced in a Standard Text field requiring resolution during document generation. The DGS will extract the required data from equipment reference tables.

Activity Note Template Reference Data

A Note is defined as text that is not derivable from a recipe but is required to be defined for inclusion in a generated document. The purpose of Notes is to detail process/equipment specific instructions and to facilitate the use of the generated documents on the factory floor for processing. A Note is text that can be defined for inclusion in a generated document before document generation has taken place via recipe enhancement, or that can be automatically associated by the system with a specific phase. Defining master notes and specifying them as being of a specific type facilitates the automatic association of a note with a recipe phase. On importation of the recipe the DGS will identify the various phase types requiring automatic master note associations to be made, and will then select the appropriate master note dependent on its type.

A Master Activity Note is defined as reference data on the DGS. When the note is defined it is specified as an Activity type note and the specific phase name to which it is required to be associated with also is specified. The note's applicability to each batch sheet type, Manual Recovery Batch Sheet, or Process Batch Sheet also must be specified. On importation of a recipe the DGS will identify any phases for which a Master Activity Note has been defined and will automatically make an association between each detected phase and its defined Master Activity Note. This functionality facilitates documentation standardization by ensuring the Master Activity Note associated with a generic phase action will always be reflected in generated documentation. It also eliminates the duplication of effort associated with individual document updates encountered with the manual system and the associated human error.

All notes are defined on the DGS using an integrated WORD 8 session within the DGS. To avoid scope for human error associated with manual document updates, fields can be included in note text. Examples of fields that can be resolved and represented in the note text included in the generated docu-

ments are:

- activity numbers of the associated phase within the recipe
- parameter values of the associated phase
- equipment identifier associated with the designated phase in the recipe
- diagrams
- signature lines

Checkout Note Template Reference Data

A Master Checkout note is a note defined as reference data on the DGS. It is intended to facilitate automatic inclusion of equipment specific notes into the generated documents. When the note is defined, it is specified as Checkout type note. The

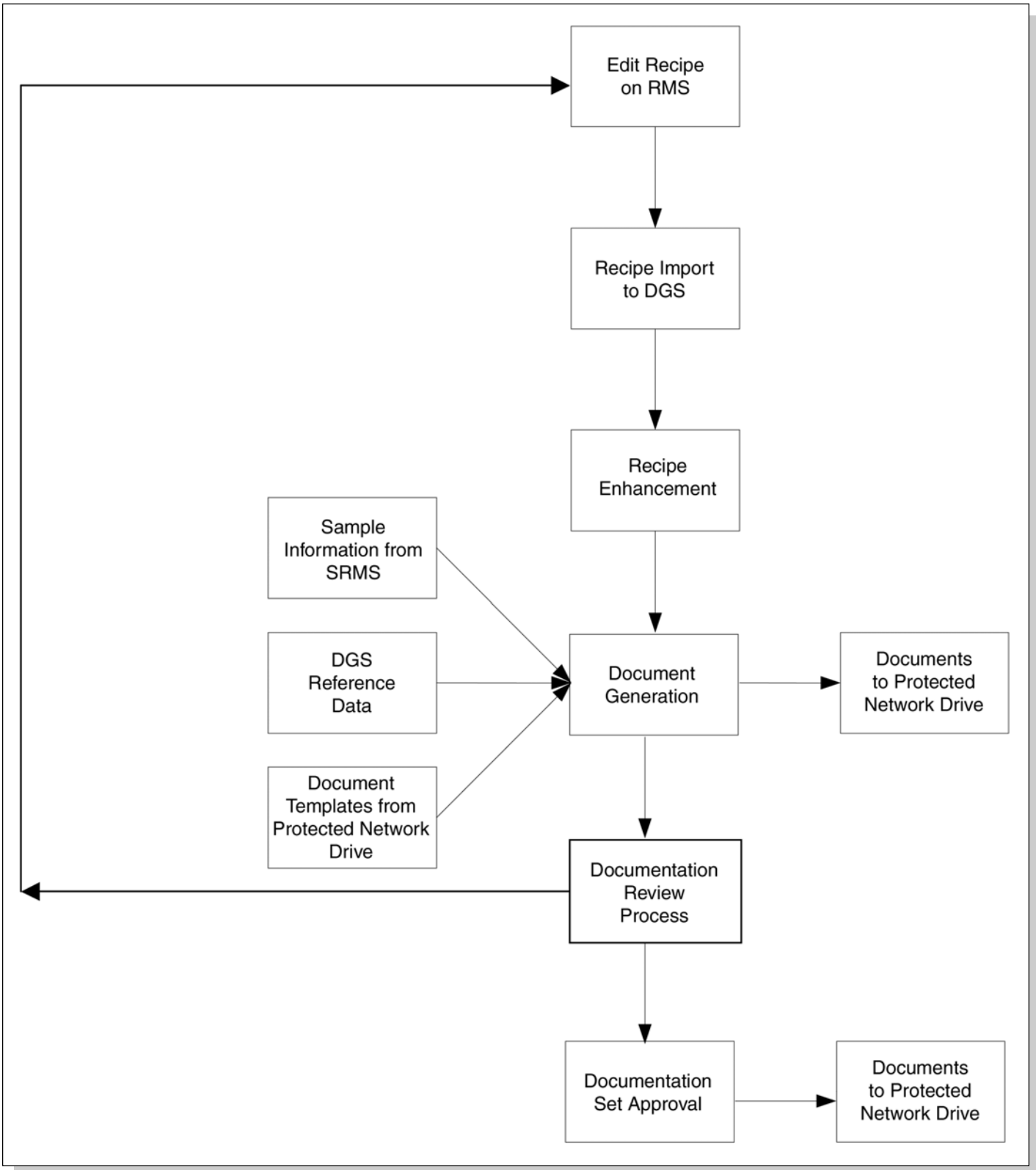

Figure 3. Revised business process utilizing the DGS.

phase type and equipment identifier for which it is required to be associated is then specified. The note's applicability to each batch sheet type, Manual Recovery Batch Sheet or Process Batch Sheet also must be specified. On recipe importation, the recipe identifies the phase type that requires a Checkout type note to be associated with it. It then identifies the equipment with which the phase is associated in the recipe and selects the appropriate checkout note from the library of checkout notes in the DGS reference data. This functionality facilitates documentation standardization by ensuring the master note associated with a generic phase action and piece of equipment will always be reflected in generated documentation. It also eliminates the duplication of effort associated with individual document updates with the manual system and the associated human error.

User Defined Reference Data: Control Text

The purpose of Control Text is to reflect the recipe structure in generated documents. The recipe structures that require representation via Control Text are:

- Repetitive Conditions
- Optional Conditions
- Dependency Conditions
- Mandatory Conditions (i.e. Regulatory Process Conditions)

The Control Text for each of the above conditions is defined as reference data in the DGS. For the Control Text to adequately describe the recipe structure, fields are inserted which allow the inclusion of the relevant activity numbers required to reflect the required recipe action. For each recipe structure listed above, an interpretation logic has been defined that enables the DGS to automatically detect specific recipe structures, select the required Control Text from the reference data, resolve the required fields, and insert the Control Text in to the generated documents at the appropriated point activity step.

Control Text is pivotal to the elimination of a separate recipe review as its inclusion in a generated document gives visibility of the recipe structure, which is a core objective of the recipe review process.

Review of DGS Import Module

The DGS user must specify the RMS recipe that is required to be imported into the DGS via a drop down list available within the DGS. The recipe must not be in use on the RMS and must have an RMS status of 'Generated' which denotes that the recipe has completed all its associated RMS error checking. The DGS user can then instigate the import. The import process will copy the recipe information from the RMS database tables to the DGS database.

The DGS will then complete pre-defined error checks on the recipe to ensure that the recipe conforms to DGS recipe conventions required for document generation. The import process fails if an error is detected and it is required that the recipe be corrected in the RMS and the import retried. The import process also completes a recipe structure analysis to detect requirements for Control Text in subsequently generated documents.

Another objective of the recipe structure analysis is to identify required recipe enhancement tasks, such as identifying phases within repetitive groups that have signatures and notes associated with them. In this instance, the user must specify, during recipe enhancement, the number of times each signature and note should be repeated in the documents.

The DGS will copy all information specified during the enhancement of the previous import of this recipe or from the last successful import of the most recent revision of the recipe being imported. The information copied in this stage of the import process is:

- the Safety Captions specified as being required to be included in generated documents
- the Notes defined for this recipe
- the number of times signature lines and notes should be repeated in repetitive activities

The import process also will identify phases whose standard text reference data has a status of 'Unapproved' and which should be approved prior to document generation. Notes whose association with the recipe being imported has been broken due to phase or stage deletions from the recipe are also identified. This information can be printed as a report during recipe enhancement to facilitate efficient work practices.

Review of DGS Enhancement Module

The Recipe Enhancement process is designed such that it does not invalidate the recipe content. A Process Note is text that can be defined for inclusion, at a specified location, in a generated document before document generation has taken place via Recipe Enhancement.

Process Notes are defined within the DGS using an integrated WORD 8 session during recipe enhancement. Similar to the Master Activity and Checkout notes discussed previously, fields can be included in Process Note text.

The user also can specify the number of repetitions required for each signature and note associated with a phase in a repetitive section of the recipe.

The Recipe Enhancement functionality associated with Safety Captions was discussed previously in the overview of the DGS reference data module.

Review of DGS Document Generation Module

The DGS user will specify the document type to be generated, as a Manual Recovery Batch Sheet, Process Batch Sheet, NEAT Network, or an Alarm and Interlock report, and the document use as wet processing, drying, dummy runs, or post campaign flush. This combination of information will enable the DGS to select the appropriate Standard Text and the correct document template to use for the document generation. The user also will specify the required approvers for the generated document from a predetermined option list. On document generation, the DGS will include the selected signature lines and descriptors on the document front page. Prior to document generation, the user also must specify the identifying information for the sample information in the SRMS that will be required to be incorporated into the generated document.

During document generation, the DGS will select the appropriate Standard Text for each phase and insert into the selected document template at the appropriate point in accordance with its activity number and step number. For each phase and stage in the recipe, the DGS will insert the associated master and process notes in the position specified at recipe enhancement time relative to the phase standard text or activity title and the other associated notes. If a phase is within a repetitive section of the recipe, the DGS will insert the required number of note and signature repetitions specified at

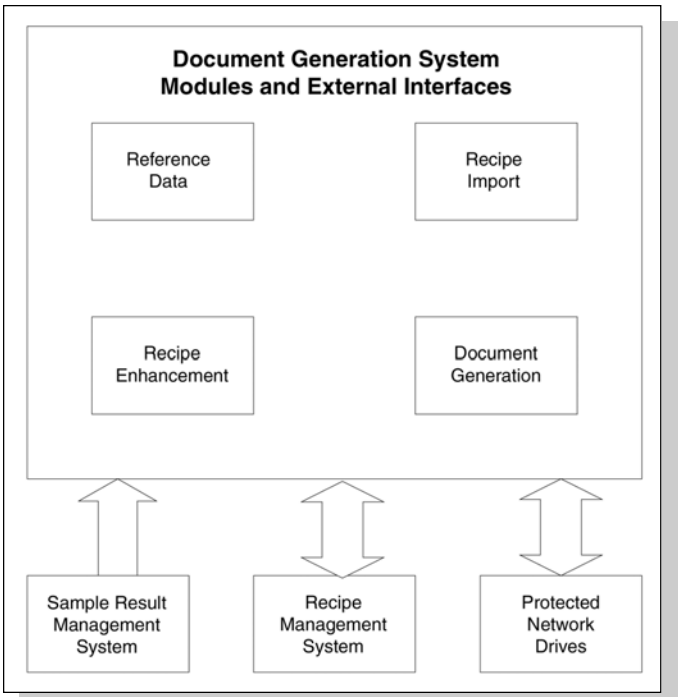

Figure 4. Overview of DGS functional design.

recipe enhancement time. All fields in applicable standard text and notes will be resolved by the DGS prior to insertion in the WORD document being generated. Resolution of fields specifying process sample information will be retrieved directly from the SRMS database and inserted into the appropriate location in the document.

The appropriate Control Text will be selected and included in the document at the appropriate location based on the data generated by the recipe import analysis. For each Safety Caption specified as being required for inclusion at recipe enhancement time, the DGS will retrieve the most recent revision from the DGS reference data database and insert in to the document.

The resultant document is automatically named and saved to a protected network drive, in accordance with agreed conventions. The document is clearly designated a status of 'Unapproved' and is not allocated a revision number. An ancillary report is automatically generated by the DGS that will identify all notes whose content has changed since the last documentation revision. This will facilitate the review and approval process. When the user designates the document set as 'Approved' via the DGS, the documents are automatically moved from an 'Unapproved' subdirectory to an 'Approved' subdirectory on the protected network drive, allocated a revision number, and designated a status of 'Approved' on the DGS.

Business Benefits

This article attempts to present the product related aspects of the development and implementation of the automated system; however, there are other obvious business benefits beyond the eradication of the three key deficiencies of the manual approach. In particular, the use of automation would be expected to have implications for the use of human resources.

Table C presents an analysis of the human resources committed to a manual documentation preparation process, based on data collected prior to the commencement of the automation project. Table D presents data for the automated preparation of the same recipe collected after the system had been commissioned. In both cases, the human resource commitments map on to the cycle of the process in question, rather than representing the total commitment to a particular type of activity, for example recipe update.

There are several striking features when the two tables are compared. First, as shown previously in this article, the number of steps in the process is seven for the automated case, compared to nine for the manual case, showing that a degree of simplification has been achieved.

Comparison of the human resource commitments for the manual and automated cases also show reduction. For the case of committed staff, reductions of 33% are achieved. Actual hours of effort are reduced by almost 50%. This is due not only to the elimination of process steps, but also because some steps, for example recipe update, take much less time. Savings of this magnitude are highly significant, and could possibly be improved by further improvements in software.

Conclusions

The introduction of the DGS has provided a successful resolution of three key issues associated with the manual system previously used. The DGS also has resulted in productivity increases in the recipe and documentation preparation and approval processes. This enhances the facility's response capability to rapid production schedule changes and new product introductions; anticipated to be an increasing trend in the pharmaceutical industry in the next decade. See Tables C and D for a comparison of the manual process versus the revised DGS enabled system.

However, a note of caution must be struck. From previous experience of bespoke applications (bespoke in this context means specific piece of software written for a given process, as opposed to generic), it has been concluded that the viability of long-term support of the system is limited, due to technological obsolescence and specific knowledge dilution, due to IT support staff turnover.

Predicted industry trends indicate a shift toward the use of multi-purpose, multi-product, bulk pharmaceutical manufacturing facilities. On this basis, it is likely that there is an industry wide opportunity for the widespread introduction of DGS type applications. The bespoke DGS described in this article could be considered as crystallizing industry requirements for an Off-The-Shelf (OTS) DGS application. The development of ISA standard S88, for application to Recipe Management Systems developed for both primary and secondary manufacturing facilities, has afforded the opportunity for the development of an OTS DGS system interfacing with an S88

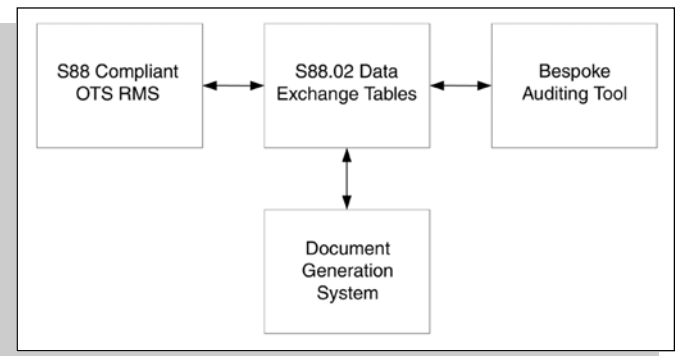

Figure 5. Interim solution in migration towards total use of OTS applications.

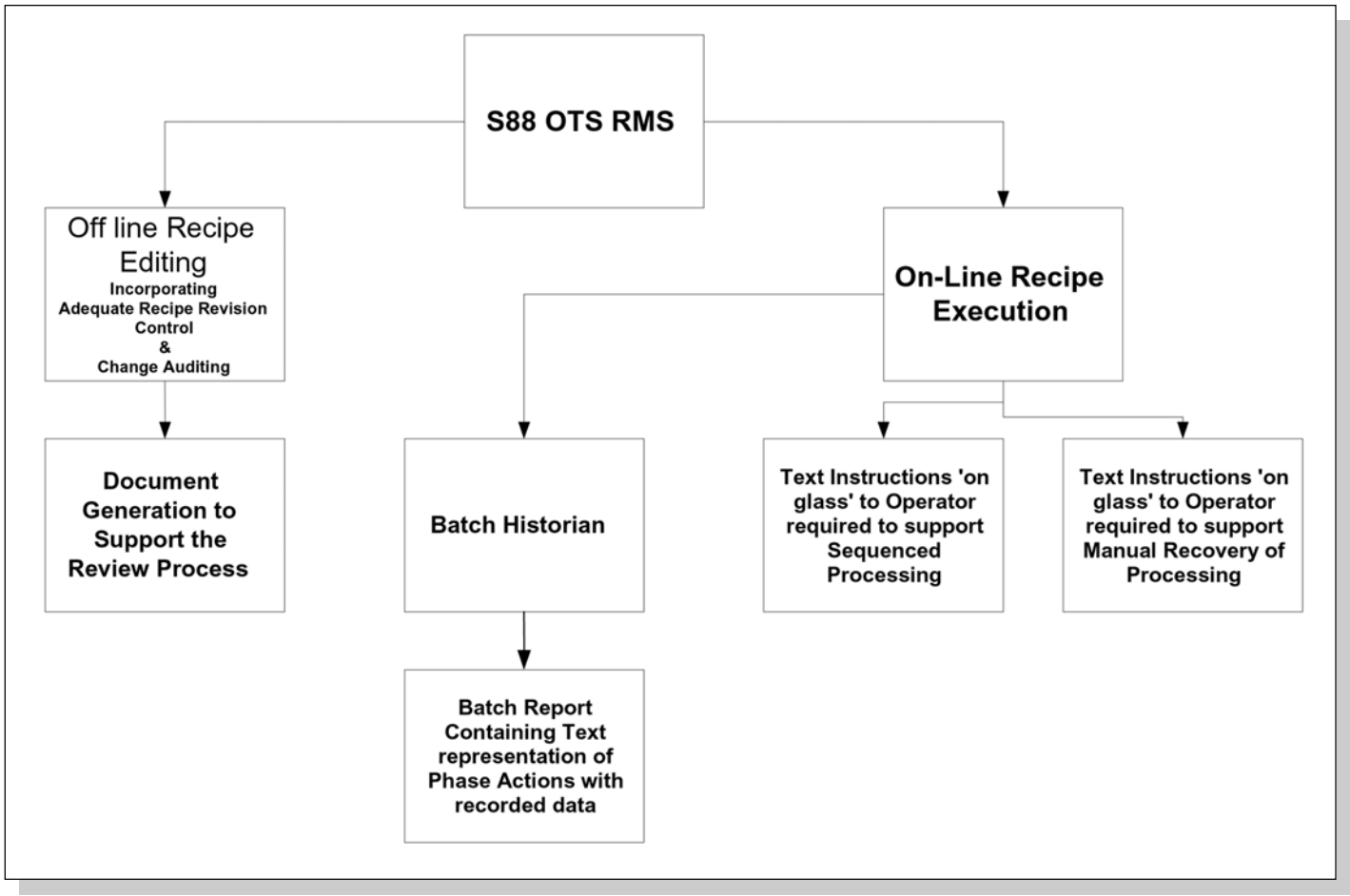

Figure 6. Proposed product model addressing Process Recipe Management and Execution in a paperless environment.

compliant RMS.

Given the industry wide applicability of a DGS type application, the technical feasibility demonstrated by the DGS and the emergence of S88 compliant recipe management products, it can be concluded that the long term solution to process recipe and documentation requirements can best be served by the development of an OTS DGS type application by a specialist batch management vendor, rather than all operating sites pressing ahead with their own bespoke solutions. Industry trends will hopefully mean that it will be economically viable for software vendors to meet the need.

Recommendations for Further Work

The ISA standard for Recipe Management systems S88.01[4] has been approved since 1995 and several S88.01 compliant OTS recipe management systems are available on the market. These applications combine the off line recipe editing capabilities and on-line recipe execution within one package. A high level assessment of the available S88 compliant OTS RMS applications is that they are extremely user friendly and powerful; however, they lack the facility to generate a document to facilitate a review process and have poor recipe revision control and change auditing capabilities.

ISA standard S88.02[5] outlines an international standard that specifies recipe database table structures to which any S88 compliant system should be capable of exporting a recipe. These tables are known as Data Exchange Tables. In considering a migration route from a work process based on wholly bespoke applications to one based solely on OTS applications, several options were considered. One option considered was the implementation of an OTS S88 compliant RMS application and the development of bespoke applications that interrogate the Data Exchange Tables and generate recipe review documentation and recipe change auditing reports. This option (Figure 5) would be expensive, as a short term solution, as the application code of the current version of the DGS is based on interpretation of the bespoke RMS database tables. To revise it to interpret the S88.02, data exchange tables would require an almost total rewrite. This migration option is not recommended, since it will result in the development and maintenance costs associated with the ancillary bespoke applications. The emphasis should be on development of a sustainable long-term solution as outlined below.

With the issuing of FDA's 21 CFR Part 11[6], detailing its ruling on electronic signatures, the industry trend in the medium term will be toward electronic batch sheets and batch records. The ideal conceptual model based on requirements crystallized by the bespoke RMS and DGS developments at a multi-purpose, multi-product, bulk pharmaceutical manufacturing site is illustrated in Figure 6. This model uses DGS capabilities to generate documentation to support a review process. The DGS functionality also could be modified to dynamically resolve text for batch sheet on glass instructions to support fully sequenced or manual recovery actions as applicable. The text presented 'on glass' to the operator would include standard text representing phase action, safety instructions, and process specific instructions. No available OTS application has the capability to represent in text form the phase action nor the required operation instruction based on

the phase action. This functionality has been developed and piloted in the DGS application development.

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About the Authors

John McNulty BEng MSc is a graduate of chemical engineering from The Queen's University of Belfast, Northern Ireland (1990). McNulty has broad operational experience in bulk pharmaceutical manufacturing having worked with a leading US multi-national pharmaceutical company at their multi-product, multi-purpose manufacturing facility in Ireland from 1990 to 2000. McNulty's experience encompasses: new product and technology introduction projects, production engineering support, participation on a team responsible for the introduction of a new DGS system, and consequent reengineering of associated business processes. Most recently, he has been responsible for leading the design and implementation of the automated Document Generation System described in this article and has participated in discussions with leading Batch Software vendors with a view to influencing their product features in the areas of recipe and documentation management. Having completed his MSc in pharmaceutical engineering advanced training by distance learning from UMIST, McNulty is currently studying full time at the London Business School for an MBA and can be contacted by e-mail at jmcnulty.mba2002@london.edu.

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This article reviews an automated material handling system at a pharmaceutical flow-down production plant. This integrated system facilitates transportation, production process service, and storage of containerized raw material and finished product.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
May/June, 2001 Vol. 21 No. 3

Automated Material Handling for Pharmaceutical Applications

by Patrick J. Conway

Introduction

Manufacturing today depends largely on just-in-time delivery of raw materials and choreographed process steps to ensure quality products in a timely fashion. Automation provides predictable product movement in the smooth flow of material from one process step to the next and provides computerized tracking of that product for purposes of validation in the tightly regulated pharmaceutical industry.

Automated material handling in the form of Self-Guided Vehicles (SGVs) has worked successfully in a variety of industries, such as automotive, textile, paper, newsprint, warehouse distribution, and hospitals. SGVs reliably carry loads, large and small, indoors and out, up and down elevators, and through automatic doors. Conveyor deck vehicles carry sheet steel in automotive stamping plants. Pallets of canned foods are pulled from house-sized pressure cookers, dripping with condensation. Coffee table sized vehicles drive underneath stainless steel cabinets, lifting them slightly off the ground, to carry linens, supplies and hot meals through multi-story hospitals. In all cases, SGVs do the job in a consistent and reliable manner, reducing manpower, increasing material tracking abilities, and improving plant safety. The SGV system solution described here is in a typical pharmaceutical flow down facility, although SGVs are used in a variety of single and multiple floor operations.

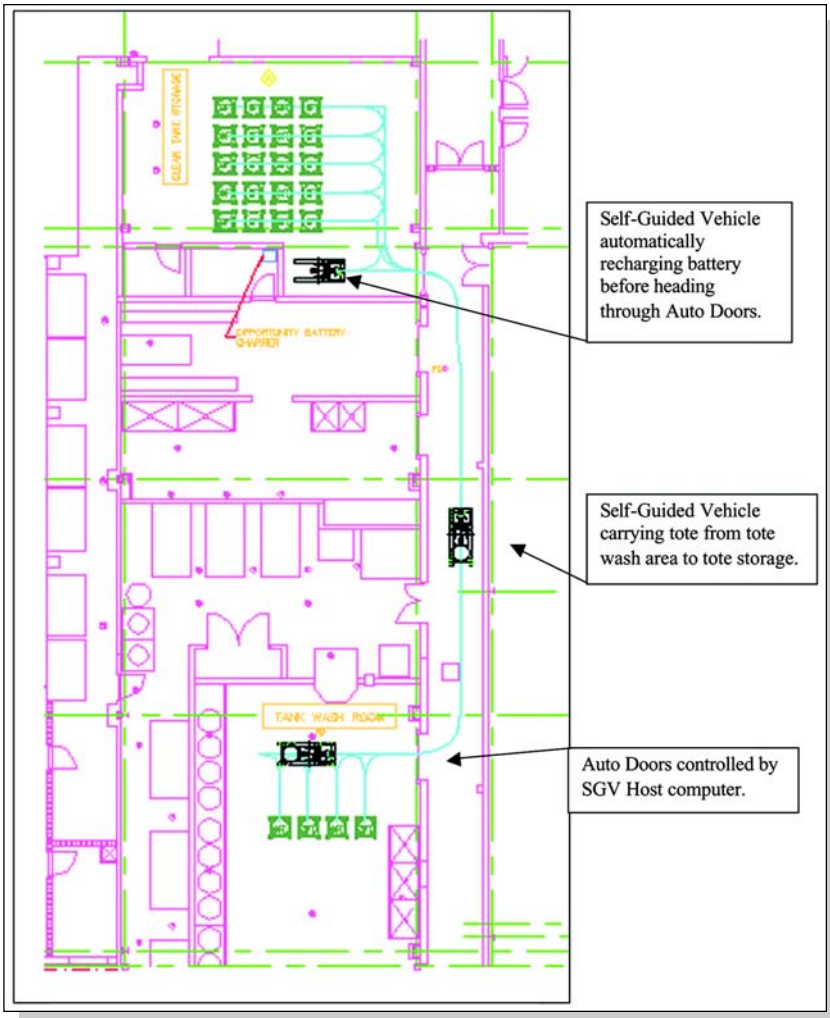

Figure 1. Typical plant layout using SGVs.

Benefits of SGV Systems

Savings for both direct (hard) and indirect (soft) cost elements should be considered when preparing a return on investment justification for a guided vehicle system. Typically the direct cost savings are easier to quantify. These direct cost savings include labor savings, elimination of the costs related to product and plant damage caused by material handling, and saving the costs associated with fork

trucks (e.g. training, OSHA compliance, maintenance, vehicle purchases/leases, etc.). The indirect cost savings are more difficult to qualify. These savings include improved safety, increased efficiency, and improved inventory accuracy.

In evaluating the utility of an SGV System, consider current material movement in the production facility. Repeated load movements from one point to another measuring 100 feet (30 m) or more are generally good applications for SGVs. Frequency of moves is typically at least 1 load movement an hour although sites requiring product tracking and increased efficiency may have fewer moves per hour. Recent advances in SGV technology allow the user to alter vehicle path as production needs change, increasing material handling flexibility.

Direct Cost Elements

The reduction in labor costs is a relatively straightforward calculation. It is simply the number of operators times the hourly rate times the number of hours worked per year. In using the hourly rate, you should use the fully burdened rate, which includes all benefits, holidays, vacations, etc.

The reduction in damage with guided vehicles vs. manual handling is usually significant. This calculation should include damage to product, racks/containers/totes, plant structure, and plant equipment (conveyors, lifts, etc.). In the pharmaceutical industry, picking and dropping a load is a delicate process. Sensors mounted on fork tips allow the vehicle to literally "see" the opening where forks need to go to pick up a load. Spring mounted sensors stop the vehicle if some form of resistance is met during the pick up process. If the tote is not squarely placed, or the pallet has a broken board, the fork tip bumper will trigger and the vehicle stops, triggering an alarm. The most important aspect in this design is the vehicle will not damage the product, particularly expensive stainless steel bins.

These fork sensors also allow the vehicle to stack pallets on top of one another, gently placing a second load on top of the first, and so on. The added benefit to this automated storage capability is the knowledge of each bin's location. If the SGV delivers the load, the SGV Host knows that load's location, and can transmit that data to the plant control network, or incorporate it into the SGV Host database.

The lift truck costs should include the purchase/lease costs, maintenance costs, operator and maintenance training costs, and costs for maintaining the OSHA records for compliance. The calculation also should take into account the fact that the average life for a guided vehicle system is much longer (20 years) than a lift truck. Vehicle battery usage is similar to manned vehicles although the SGVs charge up automatically.

Indirect Cost Elements

The increase in inventory accuracy derives from the ability of the guided vehicle system to track the movement of product. From the initial barcode scan of raw material at the receiving dock to the final scan of finished product pallets, the SGV system identifies and locates each load of material. Reports can be generated detailing the path each load has taken through the production process, all tied to the initial barcode identity. This tracking will reduce material costs, expediting charges and "redo" orders (required to replace lost product).

Automating the material handling process increases operations efficiency over manual material handling. This increase in efficiency is the result of more timely delivery of material which reduces downtime of the downstream processes (people or machinery waiting for that material). Typically, automating a manual process produces at least a 10% increase in efficiency.

Finally, the guided vehicle system will increase plant safety. The value placed on this increase in safety can vary widely depending on many factors at the specific installation (e.g. insurance rates, lost days due to accidents, OSHA fines, etc.). SGVs provide a safer working environment because they travel the same paths consistently, at exactly the same speed, allowing personnel to easily judge when and where the vehicles will move. The vehicles stay within strictly delineated areas, usually marked by yellow safety lines on the floor. Also, SGVs tend to travel at slower speeds in general, than man aboard forklifts and are fitted with a variety of long range sensors to detect personnel or objects in the vehicle path. All of these devices are fail-safe, such that if they fail on the vehicle, the SGV will shut down.

Self-Guided System Overview

SGVs, also known as Automated Guided Vehicles or AGVs, have been used in the manufacturing arena for more than 50 years. Started as crude devices to carry heavy loads over prescribed distances, SGV systems have evolved into sophisticated material handling tools designed to work in concert with state of the art production control equipment.

The backbone of SGV systems is a computer control program, known as the Host, capable of coordinating load movement requests, communicating with vehicles to fulfill these requests, and control additional equipment used to facilitate the load movement.

This additional equipment could be automatic air lock doors, fire doors, warning lights, conveyors, Automated Storage and Retrieval Systems (AS/RS), or product tracking equipment. Additional duties of the Host program are communication with plant controls, vehicle traffic control, vehicle navigation, data preservation, and disaster recovery. A Windows style operator interface allows the user to monitor the system and add load movement requests directly.

In a typical cycle of load movement, the Host computer receives the load movement request from either an operator or directly from plant control systems. Instructions are sent via RF modem to the vehicle to pick up the load, and an acknowledgement of the load movement request is sent to plant computer controls. While the vehicle is executing the load movement, the Host computer is providing a clear path by performing vehicle traffic control, and activating such devices as auto doors, elevators, and warning devices. Once the load has been delivered, the plant controls are notified and the cycle is completed.

At each stage of this load pick up and drop off sequence, the barcode on the load is scanned and tracked by the Host computer. This data can be compared to the identity of the load sent to the Host computer from the plant control system. In this way, load and batch integrity is maintained throughout the movement process. Alternatively, the SGV Host control computer can provide all of the load identity tracking, including warehouse management, without interfacing to plant controls.

SGVs

SGVs are the workhorse and most visible component of the SGV system. These battery powered, steel framed machines can perform the duties of a fork truck, a flat bed lifting device,

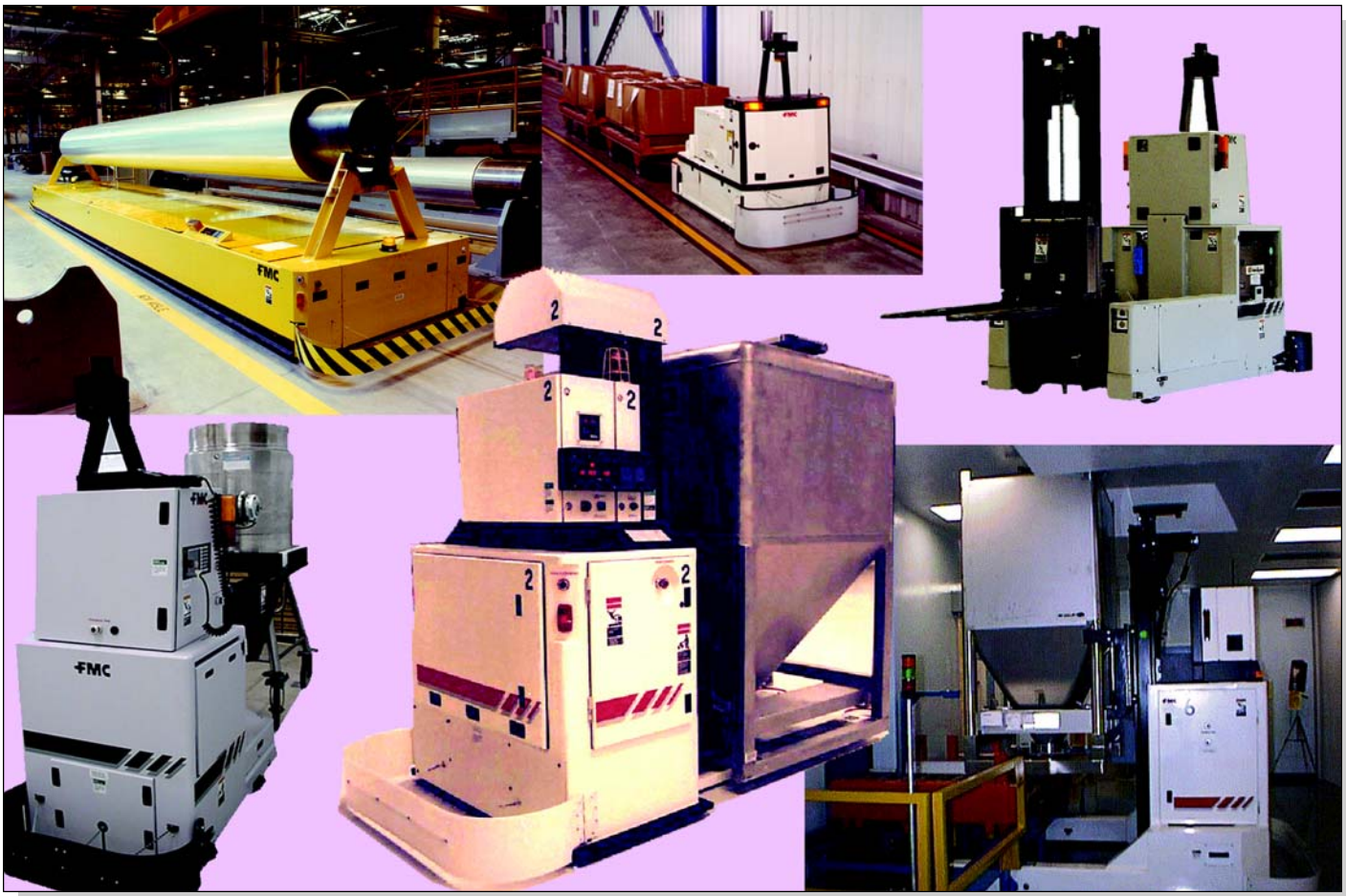

Figure 2. Front - three fork style SGVs carrying totes, rear-large load, tugger, and reach SGVs.

or a narrow aisle warehouse turret vehicle, depending on the application.

For the pharmaceutical industry, SGVs carry stainless steel totes with flat forks, transferring the load to and from the floor, a roller conveyor, or directly to dispensing stations. SGVs are mounted with hydraulic or electric lift masts sufficient to carry up to 6500 pounds (2950 kg), positioning loads accurately on delicate dispensing equipment. For movement within the warehouse, SGVs have narrow aisle fork lift attachments with a side-shifting turret carriage. These same turret vehicles carry pallets of raw material or finished product to and from the warehouse. These vehicles employ laser navigation for accuracy of load placement and automatic battery re-charging for low maintenance. Additional vehicle types are tugger, reach fork, clamp, and large unit load - *Figure 2*.

SGV System installations take from two weeks to several months, depending on customer's needs. In smaller applications, one or two vehicle systems can be installed relatively quickly, while larger facilities prefer the phased in approach, bringing several vehicles per month online, to take on more and more of production's duties. Maintenance is best performed on a consistent basis, weekly, monthly, and quarterly to maximize system uptime. A laptop vehicle maintenance application known as SGV Doctor is designed to remind users when certain vehicles need maintenance and tracks maintenance history, as well as provides troubleshooting and diagnostic capabilities.

SGV Host Computer

The SGV Host computer program is a Windows application that controls and monitors vehicle movement. It facilitates vehicle communication, traffic management and path routing, move command generation and work assignment, discreet I/O monitoring and manipulation, graphical user interfaces and links to other information and plant control systems.

The Control Terminal is the graphical user interface that is

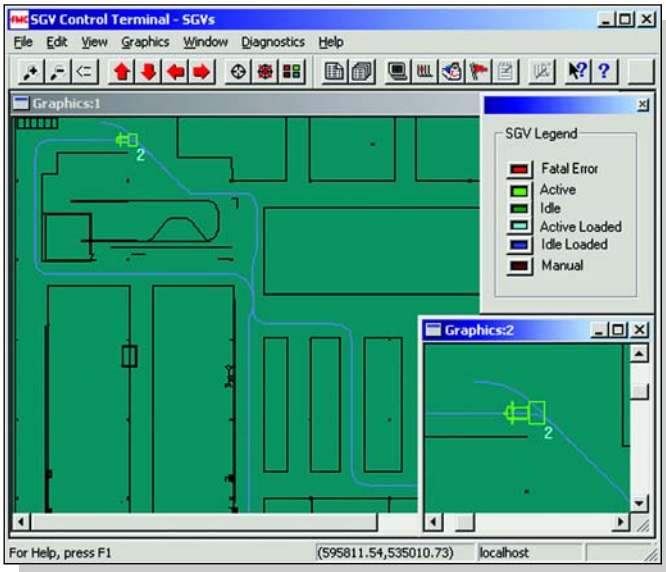

Figure 3. Host computer SGV control terminal.

the primary tool for the user to view and control the operation of the SGV Host controls. Multiple copies of the Control Terminal may be running simultaneously in a facility to allow users to monitor and control the SGV system.

Communication

The Host computer instructs the SGVs where to pick up and deliver loads using the latest industry standard Radio Frequency network. The RF network allows wireless communication from the Host Computer to a variety of remote devices, such as the SGVs hand held terminals to allow operators to access the system, or laptop PCs to diagnose problems. Panels to control the I/O Network also can communicate to the Host Computer through the same RF network, reducing installation costs by eliminating conduit runs and hard wiring. These I/O Networks control auto doors, trigger battery charging, and monitor load placement.

Host Interface to Plant Controls

The control of product movement is initiated through a network interface of the SGV Host computer and the plant network. Plant controls send load movement requests over the Local Area Network to the SGV Host controller. The Host acknowledges the request and adds an order to the order queue. When a vehicle becomes available, the order is dispatched and the load movement is accomplished.

Standard network protocols supported by the SGV host computer to communicate with plant production controls include TCP/IP, LAN, serial, discrete I/O, ODBC, and FTP server. Custom protocols have been implemented to support communications with Automated Storage and Retrieval Systems (AS/RS) for warehouse conveyor applications. An additional warehouse network interface requires the HLLAPI protocol to support IBM 3270 terminal emulation.

Process Validation

To enable the customer to meet cGMP and validation requirements, the SGV controller uses a relational database, such as Microsoft SQL server or Access, to track all product load movements performed by the SGV system. The SGV host controller ties into existing warehouse management systems and uploads load movement files to inform the WMS where and when all loads are moved throughout the facility.

Barcode scanning of individual loads by the SGVs at each pick and drop routine guarantees the integrity of load identity through the load movement process, from the receiving docks to the warehouse to the process locations and shipping of finished product.

Automated Material Handling in a Pharmaceutical Setting

The automated material handling system described below operates in a typical flow down pharmaceutical manufacturing facility. In this case, the SGVs provide product transportation, production process service, and storage of containerized raw material and finished product. Single floor systems also benefit from the use of SGVs to increase efficiency and safety.

The SGV system services the lower, main, and second floor levels of production, including the control of product movement on a material lift between the floor levels. The SGV system handles totes and plastic pallets on the main production floor level. On the second and lower floor levels, the system will handle the stainless steel bins. Bin/Tote tracking is accomplished via bar code readers located throughout the facility. These bar code readers are tied directly to the plant control computer, while the SGV system performs no direct inventory tracking.

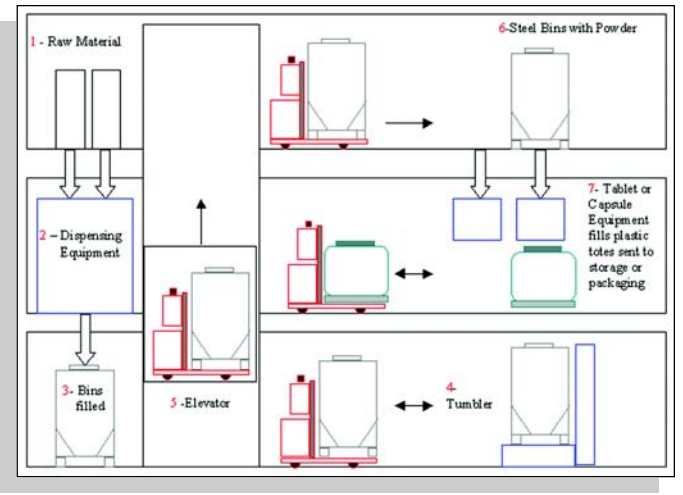

Figure 4. Flow down plant processing using SGVs.

The SGV Host interfaces to the plant network. All load movement orders are generated by the plant control network and downloaded to the SGV Host. The production process is segregated into three different levels (floors). Each level is a system within the whole. The floor levels are described separately because of the physical separation; however the same system host presides over all areas.

The lower production floor level requires only the movement of the stainless steel bins via a fork style vehicle. Raw material from the main floor is fed through one of six hoppers to the lower floor where either clean empty bins or partially filled ones are located. The bin is then transported to the tumbler, or directly to lift, scale, or holding location. Bins located at the tumbler will be transported either back to a dispensing station, for more material, or to the lift. Bins deposited on the lift are always transported to the second floor. Clean bins returning from the second floor are transported from the lift to a receiving station or holding location.

Placement of stainless steel bins by an SGV involves careful positioning on cone shaped centering dowels mounted on the receiving equipment stand. The vehicle electric lift is an accurate ballscrew and nut arrangement, monitored by encoder feedback to verify correct height for the pick and drop procedure. When a vehicle approaches a stand to drop a load, fork mounted photocells verify no other load is in this position, allowing the load to be dropped properly.

The second floor production level, like the lower level, requires only the movement of the stainless steel bins via a fork style vehicle. Full bins sent from the lower level are sent via the lift to the second floor. These full bins are transported to one of the 41 Stainless steel bin stations. At the Stainless steel bin stations, an associate will manually verify that the correct bin has been dropped at the correct location. If correct, the operator may open the hopper allowing the product to be transferred to either the main production or lower floor level. Once empty, the bin may be transported to the bin washer. Clean bins from the washer are transported to one of four inspection positions located in the inspection area. After the bins are prepped for return to the process, they are taken to the lift for delivery to the lower floor.

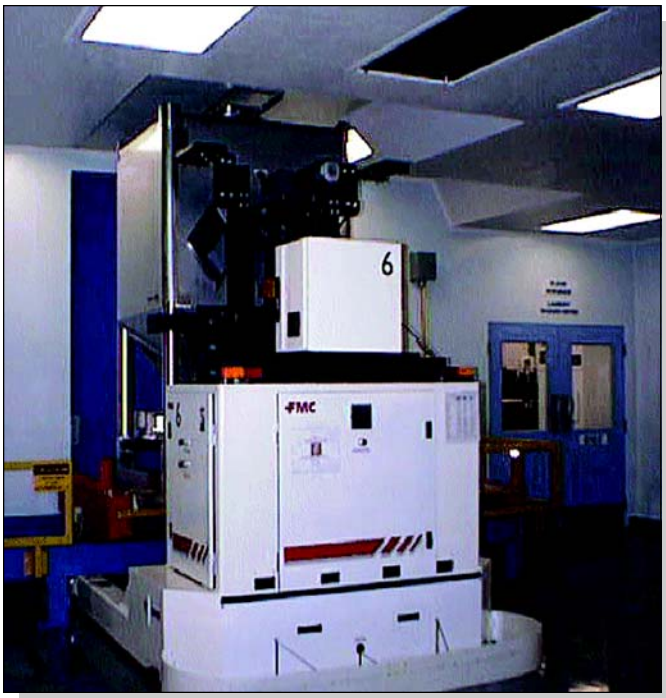

Figure 5. Fork SGV places stainless steel bin on receiving stand.

The main floor level will require the handling of the totes and plastic pallets. Turret-style vehicles handle the load movement and storage/retrieval functions. Clean empty totes are transported from the inbound tote lift to one of the tablet and encapsulation rooms.

Filled totes leaving the tablet and encapsulation rooms are transported to either the outbound tote lift or the coating rack located in the production outbound area. Totes delivered to the coating rack are manually removed for coating and/or inspection. These totes are then manually placed on the outbound tote lift after coating. At the lift, a turret-style vehicle can pick up the tote and transport it to the outbound tote lift. The plastic pallets are used to move capsules from the coating rack to encapsulation rooms and return empty or unused pallets to the coating rack.

The SGV Host interfaces with the plant's automatic door's PLC through an ethernet connection. The SGV Host writes to allocated memory in the PLC to control the door (i.e. open/close the door). The auto door's PLC will read that memory and react accordingly. When the SGV Host is interfacing with a door, the PLC locks out all other controls for that door, including manual. When the SGV Host closes the door (and the door actually closes), the SGV interface is completed. Also, the auto door's PLC performs all door interlocks that are required. When the SGV Host requests a door to open, the PLC must make sure it is permitted to open.

Conclusion

Seamless computer interfacing from production facility to automated material handling equipment allows for controlled movement of product, increased safety in the workplace, and a leg up on the increasingly time-consuming process of production validation. Turn-key automated material handling systems are a cost-effective solution for both current and future pharmaceutical processing facilities.

About the Author

Patrick Conway, Director of Sales for FMC Corporation's Automated Material Handling Systems Division, has been educating the food, pharmaceutical, newsprint, and hospital industries on the benefits of automated material handling for many years. Conway received his BS in manufacturing and mechanical engineering from Spring Garden College and his MS in organization management from LaSalle University in Philadelphia. During 25 years in the material handling industry, Conway has worked his way up through the ranks by starting at FMC in Customer Service and Order Entry. Conway found his niche in sales and was quickly promoted to regional sales manager for the Travelling Water Screen Division. Taking on more global responsibilities, Conway served as FMC's aftermarket sales manager for the Conveyor and Processing Equipment, Travelling Water Screens, Water Treatment Equipment, and AMHS divisions, all located in Chalfont, Pennsylvania. Conway is a member of ISPE, Material Handling Institute of America, and this year is Chairman of the AGV Product Section. He has made presentations on automated material handling systems at Interphex and ProMat.

FMC Corporation, 400 Highpoint Dr., Chalfont, PA 18914, tel 215/822-4300, www.fmcsgvs.com.

Figure 6. Turrent SGV moves pallets of raw material.

This article describes a cost-effective approach to flexible batch process computerized control and data reporting appropriate for implementation in a GMP compliant multi-process, multi-product API manufacturing facility.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
May/June, 2001 Vol. 21 No. 3

Flexible Batch Automation and Reporting Software Designs for Active Pharmaceutical Ingredients (APIs) Manufacturing

by Bob Carrier

Introduction

Multi-process, multi-product API batch manufacturing operations require highly flexible configurations of equipment, procedures, and automation technology. Often a single product occupies a plant area for three or fewer batches, after which the equipment is cleaned, then reconfigured for the next product. It is typical for a single product to be run only once per year, and sometimes once during the facility lifetime.

A fully developed batch sequence automation system provides functionality at the plant area level for batch scheduling, equipment resource allocation, inter-unit coordination, and material history tracking. These software capabilities are expensive to develop and time-consuming to validate, which leaves full batch sequence control best suited to dedicated manufacturing facilities. In the case of a single plant area used to produce many different drug compounds using different configurations of the same equipment with short turnaround periods between processes, it is impractical and cost prohibitive to implement full batch sequence control. However, there are some batch operations that can be conducted automatically and that are common to many API processes. These operations are candidates for batch sequence automation in that they are reusable independent of equipment scale, plus the related validation documentation package and qualification test procedures are reused in the same way.

This article is based on engineering experience gained during the 1998-2000 grassroots design and construction of a $125 million API Manufacturing Plant near Tainan, Taiwan. The drug compounds from this plant are manufactured in compliance with GMP regulations as required for drug sale in the US. This API facility is composed of different plant areas, each arranged in individual suites ranging in scale from kilo lab to pilot plant and up to large scale manufacturing. This plant was automated with a Fisher-Rosemount Systems Inc. Delta V™ DCS configured with the batch control suite of software, which was developed and validated in accordance with guidance published in the GAMP Guide 3.0.[1] For the pilot plant and manufacturing scale equipment, the manual activities that would most often be conducted by an operator during batch processing were selected for automation. These operations are reactor bulk temperature ramping, vessel nitrogen purging, vessel controlled rate depressurization, hydrogen reactor explosive vapor vent and dilution control, controlled rate chemical reactant feed based on reactor temperature requirements, single fluid heat transfer system management and, most commonly, reactor jacket utility selection and manifold valve positioning. Some additional batch sequence control software was developed for the kilo lab as required to accommodate specialized glassware configurations, custom heat transfer systems and process operations unique to that plant area.

Batch control software for the example API facility resides at the operation and phase level of the model detailed in the ISA S88.01 standard.[2] In this model, phases form the software building blocks which can be assembled in endless combinations to automate selected batch operations on each process unit. Phase logic is the workhorse of batch automation at the process unit level, and when well designed, provides great utility and flexibility.

Substantial benefits are available from automation of batch operations that are reusable for many products, and that are independent of operational scale. Benefits include the ability to quickly adapt proven controls as the product schedule changes, repeatability of complex operations within a product campaign, and reduction in production errors related to use of the control system. The long-range benefit of this approach is that for products transferred to

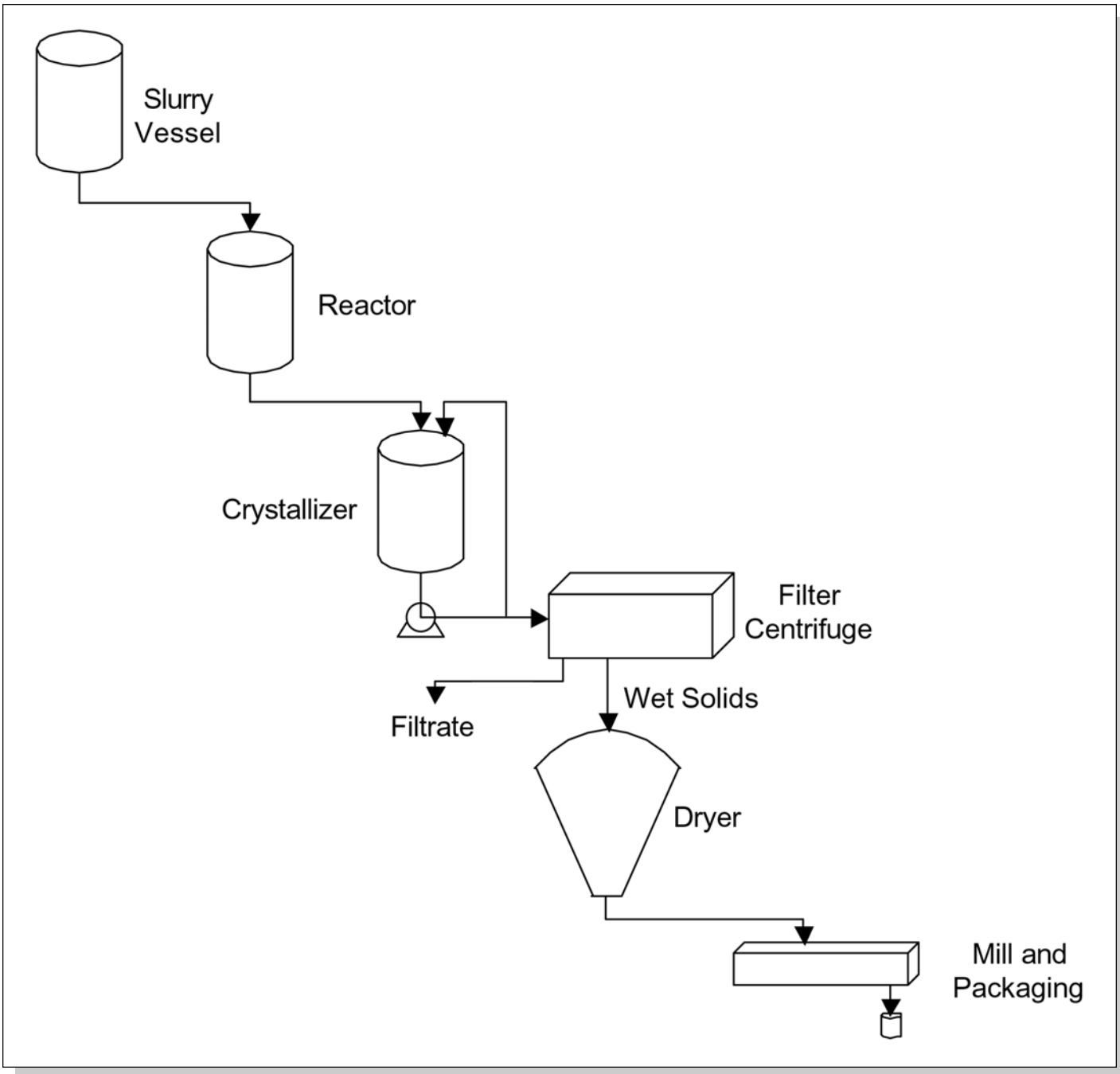

Figure 1. A typical process equipment train.

dedicated manufacturing, the phase logic and validation procedures are readily incorporated into more comprehensive plant automation strategies.

Validation Starts Early

Computerized system validation work was begun simultaneously with the facility design effort, then executed concurrently with facility construction and commissioning. The initial computer validation effort produced two key documents. One was the basis of design document describing capabilities and hierarchy of the process automation systems intended to support GMP manufacturing operations. This document was presented to the FDA at a pre-construction review meeting held at FDA offices upon the owner's request. The second document was a computer system validation plan that guided validation of the DCS and those purchased packaged equipment control systems integrated with the DCS.

It was recognized early that use of modular batch control software would provide demonstrable validation benefits by enabling reuse of fully qualified software objects, supporting specifications, and qualification test procedures. The industry standard software development lifecycle approach, as described in the GAMP Guide 3.0[1], was followed to deliver each original software module. For software this rigorous approach requires development of an approved user requirement specification, delivery of a functional requirements specification, preparation of detailed software design specifications, and creation of installation qualification and operational qualification test procedures. Fully qualified code with related specification and qualification procedure documents were released under ver-

sion control and placed under formal change control.

Project controls ensured that only released software modules were eligible for duplication or cloning to target process units. Software module qualification testing and the cloning process took place at the supplier's system development site. In the software replication process, a clone is produced from the qualified original instance of the module, then integrated with new process equipment and verified by written module test procedure.

At the job site, system software content was verified through an installation qualification procedure. Next, the operational qualification procedure was executed by running solvent batches to test all software functionality throughout anticipated equipment operating ranges under both nominal and abnormal conditions. Final performance qualification of the batch control system was done concurrently with the first three batches of a product manufactured on the unit. In the end, the entire batch process automation system validation project, including hardware and software, was summarized in a final report supported by a well organized validation documentation registry. This report addressed all discrepancies found during qualification testing and explained the way in which each was resolved.

Computerized System Description

The Distributed Control System (DCS) is capable of S88 compliant batch control, and is a good choice for batch plant automation. DCS suppliers offer batch process automation capability as an optional software license to provide a batch programming language and operator interface enhancements. Of particular interest are the phase logic blocks, which have predefined operator commands, status indications, and a fault handling framework in which the programming language is used to code owner specified functionality.

The API industry often purchases automated process equipment used for solids isolation, product packaging, environmental controls, water purification, and generation of other critical product contact utilities. A supplier of automated equipment typically employs a PLC system, which is fully integrated and designed to operate independently from other

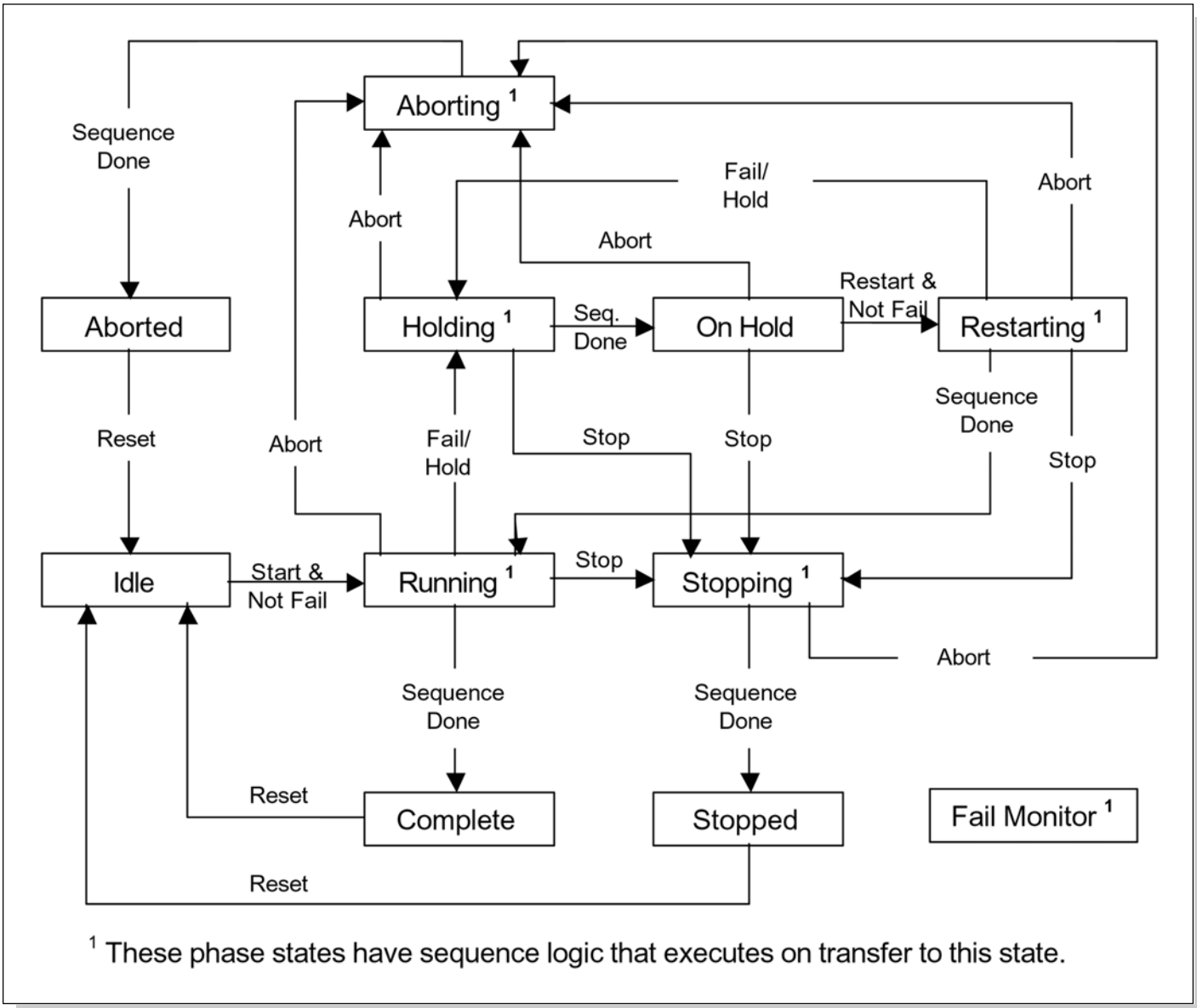

Figure 2. Phase logic module state diagram.

> ***Placing the software implementation emphasis on phase logic results in automation of batch manufacturing activities that is reusable for many products, and that is independent of operational scale.***

computer systems. Independent PLC systems offer many benefits, and should be connected in a sub-control network, preferably using Ethernet, for purposes of communication with the DCS. In this architecture, the DCS central data historian can store all critical process parameters and events documenting use of packaged process equipment.

Flexible Batch Equipment and Operations

The API facility is typically designed to provide isolated and independent plant areas or suites, each of which houses a train of process equipment. Each train of process equipment provides a different capacity, thereby providing flexibility to match the equipment size to product requirements. The API manufacturing process usually involves conducting one or more steps of organic synthesis, and isolating products as either a bulk solid drug substance or non-sterile aqueous solution.

Process Equipment

A process train is depicted in Figure 1, and is typically composed of equipment such as solids charging/containment system, slurry vessel, chemical reaction vessel, receivers, crystallizer, filtering centrifuge, conical vacuum dryer, mill, and packaging equipment.

The nature of a multi-process plant requires equipment and the related control system software to be configured for operation in unique combinations. Process equipment within a train is set-up specifically according to the needs of each product. Portable process equipment is available for temporary installation including filters, pumps, mass flowmeters, sampling valves and pH/conductivity analyzers, all of which are installed in the configurable piping system. It is in part due to these flexible equipment configurations that batch sequence control software for the example plant had to be equally flexible through a modular approach to each unit operation that was automated. A process unit is an association of equipment. The reactor unit is composed of a vessel, an agitator, a bottoms pump, overhead condenser, piping, and field instrumentation. Some processes require use of more units than do other processes. For example, not every API is dried and milled. The process unit is the smallest grouping of equipment for batch control and reporting. The DCS configuration must tag each unit with a unique identification number for use in grouping all inputs, outputs, devices, analog control loops, interlocks, and alarms associated with that unit. This relational grouping of equipment is central to flexible batch control software.

Multi-Stream Process Operations

As a product lot progresses through the equipment train, processing of a second lot of the same product can be initiated in upstream equipment. This is the multi-stream operating mode. Multi-stream operation is often done without having to perform inter-batch equipment cleaning. For instance, after the first product lot is transferred from the reactor to the crystallizer, a second lot can be using the slurry vessel and the reactor units.

It is significant to note that transfer of material from one vessel to another is typically a manual operation. Transfer piping is highly configurable via flexible hoses, manifolds, and swing-elbow piping systems. Without automated valves in the inter-vessel transfer piping, the batch control software does not have a role in product transfer.

Flexible Batch Control Software

Software Specification

The first step in specifying flexible batch control software is to group physically similar process units in classes. The instrumentation and control designs should be nearly identical for each unit assigned to a given class. Example process unit classes are reactor, reactor with distillation column, receiver, crystallizer, and filtering centrifuge.

The software development cycle begins with preparation of a user requirement specification for each process unit class. Each specification defines requirements for process measurement, device control, analog control loops, alarms, process safety interlocks, sequence controls, fault handling, the human-machine interface, and data acquisition. The user requirement specification governs software development, and defines expected results for qualification tests. Prior to developing specifications, it is recommended that a standard format be agreed upon by the development team. To ensure computer validation document traceability, each specification must uniquely identify the process units and equipment to which the document applies.

The most detailed level of batch software design provides description of each phase logic module and identification of the process unit classes that will make use of this batch sequence control software. A single phase logic module can be used by more than one unit class. For each phase module, it is necessary to produce a software design specification. Each phase logic specification needs to uniformly define the sequence logic that executes when changing states to running, holding, restarting, stopping, or aborting, and when a fault is detected - *Figure 2*. The functional specifications also define formula values used by the phase logic and the permissible operating limits for each value. To ensure computer validation requirements are met each specification must clearly state those process classes to which the software functionality applies.

Batch Start

The operator creates each batch on an individual process unit basis. The operator specifies (a) the batch identification number, (b) product name, and (c) on which process unit this batch will run. Product batches and cleaning batches are created in the same manner. The DCS should permit a batch to run only after all required information is complete, unique, and valid within predefined limits.

Determination of the batch identification number is a critical issue. The batch identification number must be unique within the DCS database of present and past batches. Since multiple process units sequentially process a single product lot number, it is necessary to assign a unique batch identification number for each batch run on a unit. The batch identification number can be a concatenation of the lot number and the unit identification number. By placing the product lot number first in the identification number, the DCS batch executive will display activity first by product lot number, followed by unit identification number.

The batch executive maintains information about batch start and end time. Start of the batch is signaled by issuance of the "acquire unit" software command, and end of batch by the "release unit" command. Equipment acquire and release software commands are standard functions in DCS batch control.

Flexibility at Runtime

To achieve greatest flexibility, the operator is the batch executive, meaning he/she is responsible for initiating and controlling execution of each automated operation. The operator inputs formula values required for the operation, and activates selected phase logic as instructed by the written batch procedure. It is often useful to program the phase logic to prompt the operator for requisite formula values.

Formula values modify phase logic behavior to fit the process or equipment. Formula value entries are compared to lower and upper range values to ensure data validity. Some formula values are equipment specific and apply to all processes, while others are process specific. Sequence code written for a phase class can accommodate minor equipment differences between units within a class by controlling program branching based on a formula value. For example, a formula value can specify the nature of jacket utilities available to a reactor in the case where one reactor has an additional utility not applied to the others in the class.

Each phase logic module available to a process unit can be activated and completed more than once during a batch. Further, more than one phase logic module can be active at any time during a batch within the unit. For example, the reactor heat-up temperature ramp can be active concurrently with the vacuum pressure decrease ramp.

Completion of a batch is signaled when the operator activates a special end of batch phase logic module. This phase is responsible for documenting batch end, closing any active phases in use on the unit, and releasing the unit for other purposes.

Unit Status Indications

The batch executive software provides indication of status for each unit. Unit status indications are (a) in-process, (b) idle, or (c) out-of-service. A secondary status indication related to the idle state indicates the clean or dirty equipment condition.

The DCS automatically manages the status change to in-process at start of a batch in a unit, and change to idle at end of a batch. The operator manages assignment of equipment statuses for dirty/clean and out-of-service. The out-of-service status is typically used in event of equipment failure or scheduled maintenance activity. When a unit has an out-of-service status, the DCS must prohibit assignment of an active batch to that unit.

Batch Report Requirements

The DCS collects and reports the real-time data record supporting GMP compliance of each batch. In batch manufacturing, there is significant process unit idle time, rendering much of the data record meaningless. Process unit idle time results from periods of process set-up, delays between lots of the same product, and from maintenance activities. Selective reporting of data from the period of actual process operations is a highly desirable software feature.

Note that for the application being described, material history, quality control test results, equipment maintenance history, investigations, and personnel qualifications are all managed by systems or procedures external to the control system.

Batch Report Structure

The batch identification number is the primary key for extraction of data from historical databases. The reporting application should assign report file names using the batch identification number. This naming convention facilitates locating all process unit reports associated with a particular lot number. Reports should contain the following data:

1. header data indicating (a) DCS unique batch identification number, (b) product name, (c) batch start date/time, (d) batch end date/time, and (e) process unit identification
2. calculated duration for batch occupation of the process unit
3. critical parameter trend history
4. transactional messages

It is most convenient to have batch reports prepared in Microsoft Office™ file format(s). This facilitates long-term record retrieval and printing as required in the future. The batch report can be prepared automatically at the end of the batch, or on operator demand. In either event, safeguards should exist to ensure the report is prepared only once without duplication.

Report Data Types

For each unit, the DCS historian stores time-series trend data for analog measurements and calculated variables, of which only some are considered critical from a GMP perspective. The group of critical parameters for an individual process unit is process independent. For example, vessel bulk temperature is always considered a critical variable without regard for the product or process being run in that unit. For compliance purposes, only critical parameters need to be included in batch reports. The DCS report application should be user configurable to select only those critical parameters for inclusion in the batch report.

Transactional messages include (a) process alarms, (b) hardware alarms, (c) operator actions, (d) batch executive messages, and (e) user configured event messages. The batch report presents the chronology of transactional messages that occurred between start and end of a batch. The report application should be capable of combining the trend data and messages in a single view of the history for a batch processed on a given unit.

Protecting Batch Report Authenticity

One should expect that DCS batch reports and related original

data files come under the auspices of the FDA electronic records rule, 21 CFR Part 11.[3] It is incumbent on the user to protect the integrity and authenticity of these electronic records that support the GMP manufacturing of a drug substance. One simple solution is to write all batch reports with related databases directly to CD-R media, which can not be changed. Other security provisions can be taken to protect the report files within the Windows™ NT file management system by setting the folder/file and file security to read only for every network account. A higher level of security can be achieved using off-the-shelf document management software providing revision control, and featuring a computer generated audit trail of changes to any report file.

It is essential to archive throughout the records retention period the software applications able to generate human readable forms of the electronic records. With software application revisions being routinely advanced, it is necessary to plan ahead to avoid the situation in which archived electronic records are no longer retrievable.

Conclusion

It is possible and practical to implement cost-effective validated batch sequence automation appropriate for the flexible batch process and multi-product demands of a GMP compliant APIs manufacturing facility. Placing the software implementation emphasis on phase logic results in automation of batch manufacturing activities that is reusable for many products, and that is independent of operational scale. This provides manufacturing with powerful automatic functions that yield reliability and consistency in producing drug substances. An additional gain is that computerized system validation efforts are reduced by reuse of fully qualified software modules and related validation documents.

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1. *GAMP Guide, Validation of Automated Systems in Pharmaceutical Manufacture,* Version 3.0 (Good Automated Manufacturing Practice Forum, March 1998).

2. ISA - S88.01 Standard, Batch Control, Part 1: Models and Terminology.

3. *Code of Federal Regulations, Food and Drugs*, Title 21, Part 11, "Electronic Records, Electronic Signatures" (U.S. Government Printing Office, Washington, D.C.).

About The Author

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This article presents a brief review of typical liquid waste decontamination system designs and highlights key design issues.

Reprinted from
PHARMACEUTICAL ENGINEERING®
The Official Journal of ISPE
May/June, 2001 Vol. 21 No. 3

Biowaste Systems

by Carl J. Carlson

Waste Sources

Biological waste can come from many sources such as hospitals, agricultural research and production facilities, biological research and production facilities, plasma fractionation facilities, etc. The treatment and requirements for treatment are based on the threat of release and propagation of biological waste that could harm or affect the public. The utilization of genetically altered plants, animals, fungi, etc. to manufacture products has challenged regulatory agencies. Our ability to alter the genetic make up has brought with it many concerns for waste management.

Regulations

The Environmental Protection Agency (EPA) regulates all effluents from a biological production plant[17] including waste disposal. Since the late 1980s, the National Institutes of Health (NIH) has provided the evaluation method for determining appropriate risk groups for containment and treatment of biological wastes in the US. The CDC/NIH have compiled a list of organisms and classified the respective hazard classification within the Biosafety in Microbiological and Biomedical Laboratories, 3rd edition, May, 1993.[1] If organisms used are not found within this list, the CDC should be consulted to classify the microorganism used. Current EPA standards dealing with pharmaceutical production plants can be found in 40 CFR Ch1. Part 439 – Pharmaceutical Manufacturing Point Source Category[12] and 40 CFR Ch1. Subpart GGG National Emission Standards for Pharmaceutical Production.[14] The Occupational Safety and Health Administration (OSHA) has developed requirements/guidelines for handling bloodborne pathogens and body fluids.[10,11] In the late 1980s, the FDA inspected facilities for "validated" waste systems as a measure of control for these new potential environmental releases. As time and experience with genetic manipulation and production vectors has evolved, many guidelines to control biological waste have followed. On July 16, 1986, the Organization for Economic Cooperation and Development (OECD) Council put forth a document that addressed the safety considerations for industrial, agricultural, and environmental applications of organisms derived from Recombinant DNA technology.[4] Within the US, the control of the biological waste releases is now completely under the EPA and OSHA jurisdiction. The "validation" of a liquid waste decontamination system falls under the EPA jurisdiction with the leadership of the NIH. The NIH Guidelines for Research involving Recombinant DNA Molecules, May 1999,[2] has been the source for determining the requirements for handling biologically active wastes within the biological and pharmaceutical industries. Canada also has biosafety guidelines that clearly delineate risk groups, treatment, and specify construction and decontamination requirements of the various levels of risk.[5,7] Classification of Biological Agents According to Risk, Physical Containment Levels and Laboratory Biosafety Guidelines 2nd edition, 1996, each support the design requirements of a waste collection system within a given risk class. Only Good Large Scale Practice (GLSP) defers to the local government requirements for large-scale operations biological waste handling. Risk Groups BL1-LS, BL2-LS, BL3-LS require containment and decon-

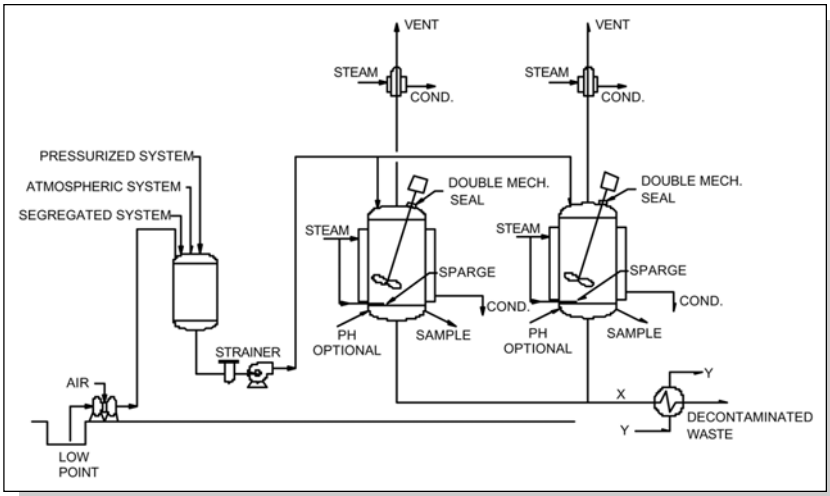

Figure 1. Dual tank batch system surge feed.

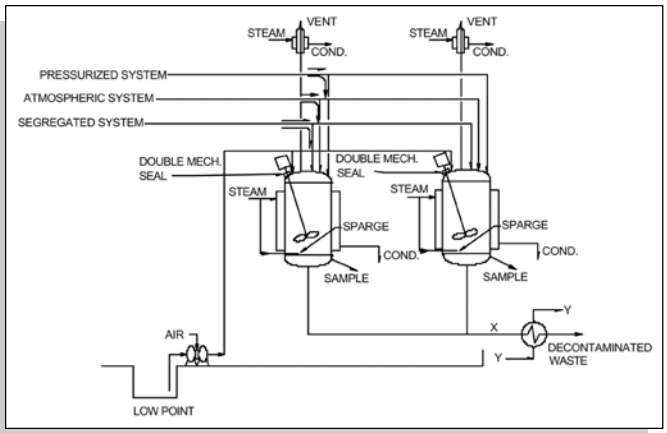

Figure 2. Dual tank batch system no surge feed.

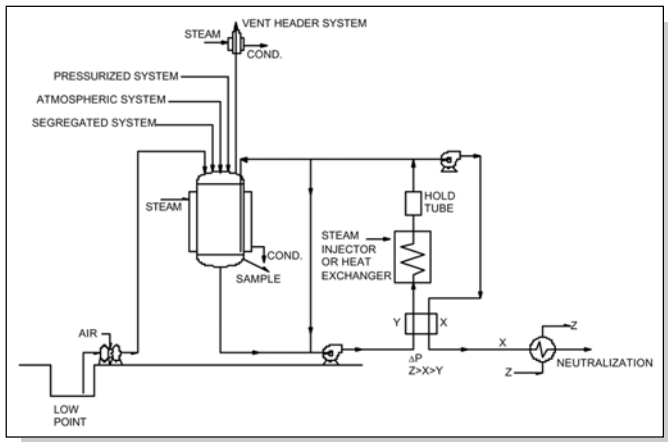

Figure 3. Single tank system continuous system.

tamination prior to release and BL4-LS require waste collection and decontamination adjacent to the containment area.[1,2,3,8,9]

Biowaste Modes of Decontamination

The method of waste collection and subsequent decontamination will vary based on the form of the waste (solid, liquid, solid-liquid) and the volume processed. A lab autoclave is the simplest form of biowaste system that employs manual means of collection and disposal of the solid or liquid waste. This is practical for small volumes of waste. The decontamination process is usually automated and documented via autoclave controller to assure reproducibility of the decontamination process. Manual chemical decontamination is often employed in hospitals, universities, and laboratories. Large volumes of medical waste (more than 500,000 lbs/year) can be processed on site via a large, continuous feed autoclave sterilization system.[15] Large scale treatment of solid regulated medical waste, infectious waste, and clinical waste to a residue that is classified as a municipal land fill waste is a practical and economical solution, and can be made in compliance with the EPA Clean Air Act standards.

Large volumes of liquid biological waste are generated from plasma fractionation facilities, antibody production facilities, and any biological or drug production facilities utilizing microorganisms to generate product. Most production facilities will fall under BSL1-LS for antibody production although organisms classified under BSL2-LS and very infrequently BSL3-LS also are utilized for some vaccine or therapeutic peptide production. The NIH guidelines list a good portion of the organisms used in order of their corresponding hazard classification. The hazard classification is determined based on the organism's potential threat to the environment and the potential for survival after release. There is a small number of organisms that are well characterized such as E. coli that have been exempt from the BL guidelines by the CDC. These organisms can be handled utilizing GLSP precautions. If the microorganism is not listed, an evaluation must be completed with the CDC/NIH. The flexibility required of the development or clinical production facility is most reasonably handled by a Batch Liquid Waste Decontamination System (LWDS). Changes to system requirements (kill times or temperatures) are easily modified in the batch system. Large production facilities with a moderate or defined range of microorganisms will best be handled by a continuous system. One must be careful to meet the conditions set forth in the permitting cycled process for either continuous or batch release waste systems. Waste effluents shall be sampled consistent with the waste throughput (continuous vs. batch) and EPA sampling requirements as well as any local or state requirements.

Liquid Waste Decontamination System (LWDS)

The following is a review of LWDSs utilized in the pharmaceutical industry today. These systems are employed to decontaminate cell culture or microbial fermentation biologically contaminated waste streams utilizing an overkill approach (see validation). In addition to biological activity, the release of hazardous material consisting of chemical or toxic nature also must be addressed. These limits are described as Hazardous Air Pollutants (HAP) and Hazardous Chemicals as defined by the EPA.[14] Biological load reduction is treated (inactivated) within a Waste Management Unit (kill tank). The owner/operator shall monitor the Total Suspended Solids (TSS), Biological Oxygen Demand (BOD), and biomass concentration.

Modes of System Operation

Thermal waste decontamination is accomplished in one of two ways. The most common method used to inactivate biological waste in small laboratories and pilot facilities is to ramp the reactor up to 121°C (250°F), hold for 20 to 30 minutes, then cool down to a maximum temperature of 60°C (140°F) prior to release. If neutralization is not performed in the LWDS, then waste must be directed to the neutralization system prior to discharge. After cool down, the material can be disposed of in the sanitary drain. Note that this process assumes that the product will be isolated from the cell mass prior to biological inactivation. If cell separation occurs within a pressurized system like a cell rupture step, then care not to affect the backpressure to the process must be provided when transferring the waste to the LWDS. For larger clinical or production facilities, the waste comes from many operations and it becomes practical to collect these wastes for automatic decontamination. The automated decontamination can occur in a batch mode or a continuous operation as described below.

Thermal batch decontamination is a straightforward collection, decontamination, cool down, and release operation. The collection can be accomplished via a surge feed where the surge tank level is used to control the feed rate to the batch kill tank – *Figure 1*. Dual kill tanks provide time for the kill operation to occur and will allow uninterrupted service in a multi-functional facility. The kill tank will be successfully

prior to release of decontaminated waste and interlocks should be provided so that accidental release is minimized. Provisions for tank sampling should be provided for system qualification. Provisions for decontaminating any portion of the system from the drain and vent system, through the sump, to the kill tank (and potentially beyond) should be provided. The surge tank can be utilized as a sump tank if the layout requires this arrangement. Note that the pump transferring from the surge or sump tank to the kill tanks is protected by a strainer. This is provided to catch the occasional pipette tip or pen cap that finds its way into the contained drain system. Although provisions will be made at sinks and tanks to prevent foreign material from entering the system, providing a strainer with the means to decontaminate it will save on system down time. Note that the ideal arrangement would be to place the LWDS system on the basement level so that sink and drain waste could be gravity drained to the system. This space will be designed to meet the requirements of the "worst case" biosafety level classification of material feeding the system. Lines should be welded and any portion of the transfer line that has a potential for leaking should be double contained if outside the containment areas (process or support space). Ideally, flange connections should only appear in the contained areas where secondary waste collection is available. Agitators should be provided with double mechanical seals to prevent accidental release of biologically active material. The surge tank is not necessary, but it reduces the number of automatic valves and simplifies the control. All systems that have the potential to fail should be provided with redundant back up if in a critical function. Switching to the back up should be possible with the closed system. Control systems should alarm when the system is not functioning or when a leak is detected from the low point depression. An air diaphragm pump can be utilized in area clean up if a spill does occur. A redundant Human Machine Interface (HMI) should be positioned outside of the contained area for operator assessment of LWDS performance. Alternatively, a panel visible from outside of the contained area with displayed alarms or a slave enunciator panel outside of the contained area could suffice. Personnel responding to an alarm ideally should have information from the control system that will alert them to the potential malfunction or conditions.

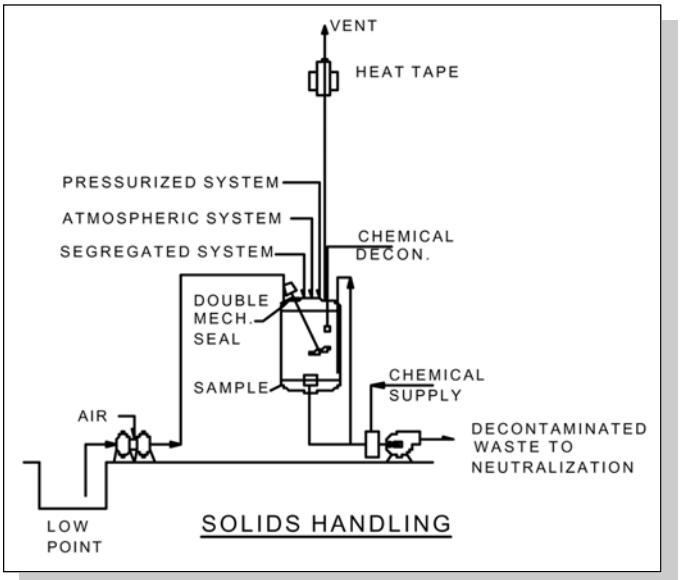

Figure 4. Chemical decontamination batch.

The removal of the surge vessel (Figure 2) could make the kill tank headspace crowded and would complicate the collection (automatic valves). The drain system would require automated switching between vessels and this could cause back up issues in the various areas. If a pumped drain system is utilized, potentially dangerous pressurized waste conditions exist when valves fail (and valves will fail). The removal of the surge vessel may not be an issue if the waste drains are gravity drains and sufficient feedback control of valves is provided.

Typical batch kill tanks will utilize plant steam jacket, or plant steam jacket and plant steam injection. Steam sparging is a preferred method because it is consistent (less fouling issues) and provides more efficiency in heat transfer. Note that the kill tank would still be jacketed in case there is a problem with the sparger. If the sparger fails, the system can still be cycled through decontamination. The tanks are sized to account for the increased volume provided by steam condensate. Attention to sound attenuation within the kill tank containment area should be provided if a sparge system is utilized. Note that the containment issues and back contamination of the plant steam system must be addressed when using a sparging system. By monitoring the pressure differential between the plant steam and the kill tank, a potential back flow can be prevented by closing isolation valves on the supply plant steam. The waste pH can be adjusted prior to decontamination with the addition of modest control. Although this makes a redundant control function (neutralization will still exist), it may improve the longevity of the kill tank.

Note that the tank waste in figures 1 and 2 is decontaminated prior to release from the tank so the outlet line "X" remains free of contamination. This will be validated so that material release can be tightly controlled. Failure of any one component will result in the re-initiation of the kill cycle once the problem is discovered and corrected. Provisions for system decontamination past the tank outlet should not be necessary. Chemical decontamination of the sump pump and transfer line could be utilized in the event of a spill. Note that the containment pit must contain 1.5 times the volume of the waste tank capacity if one of the tanks fails. If both tanks were utilized together, the pit volume would be 1.5 times the combined volume. Provisions for transfer from one tank to the other (in case of mechanical problems) could be made via the steamable sample port connections. Good design practice would assure that the pressure of the decontaminated waste cooler chilled water is of greater pressure than the waste stream "X."

Tanks should be sized to hold a minimum of one hour worth of waste (averaged within reason). In a redundant tank system, this would allow one hour for personnel to respond, slow down the waste generation, and fix the problem. Plants where operations are very forgiving can be run with one waste tank with controlled (scheduled) delivery to the tank. The addition of all autoclave condensate or sink waste is insignificant compared to the several simultaneous CIP waste collections. At least one third of the functions should be considered to occur simultaneously with other operations for tank sizing. For example, six sinks, six seed reactors, and two production reactors with one harvest tank, two recovery tanks, and one recovery operation (homogenization/centrifugation) would result in 5 GPM per two sinks, 40 GPM when cleaning two seed fermentors, 40 GPM when cleaning one harvest tank, and 20 GPM when cleaning the recovery operation in one day (eight hours). Totaling the waste (105 GPM) and understanding the duration for the operations will help to evaluate a reasonable peak load and average load per day. Time and motion analysis

of the plant operations will provide the best method for sizing the kill system tanks.

Thermal continuous decontamination is a continuum of collection, decontamination, cool down, and release operations. The collection can be accomplished via a surge feed where the surge tank level is used to control the feed rate to the batch kill tank. Dual kill tanks would provide additional time for the build up of waste, but would not be required for any reason other than redundancy. The surge tank can be utilized as a sump tank if the layout requires this arrangement. The ideal arrangement is to place the LWDS on the basement level so that sink and drain waste can be gravity drained to the system. The surge tank is not necessary in a continuous system, but if one is used, the redundant tank can prove useful in emergency situations. The surge tank also would allow for waste stream straining to prevent material from entering the kill tank. All systems that have the potential to fail should be reviewed with a cost benefit analysis and then provided with redundant back up if cost effective. For example, if the delay of waste removal would cause a loss in production, then the strainers, filters, pumps, and analytical elements/transmitters should be redundant to prevent any significant down time for routine maintenance items. Switching to the back up should be possible with the closed system. Control systems should alarm when the system is not functioning or when a leak is detected within low point sumps. As with the batch system, a redundant HMI should be positioned outside of the contained area for operator assessment of LWDS performance. Personnel responding to an alarm ideally should have information from the control system that will alert them to the potential malfunction or conditions within the LWDS contained space.

Typical continuous systems will utilize steam heat exchanger and/or plant steam injection. Plant steam injection is the preferred method. Note that with heat recovery as indicated before the steam injector, the waste feed temperature is increased by the decontaminated waste and the required plant steam for kill will be greatly reduced.

A plant steam eductor is a very clean system to use on continuous systems. This requires less routine maintenance and cleaning. Performance degradation due to waste fouling must be taken into account when sizing steam heat exchangers. The use of the eductor relieves some of the fouling issues, but care must be given to ensure that no foreign material (pipette tips, glass, paper towels, etc.) can find its way to the eductor.

When sizing the plant steam eductor, the general steam flow requirement is described by:

$$\underset{\text{Steam in}}{\Delta H_{vap}\, Q_s} + \underset{\text{Liquid In}}{c_P\, \rho\, Q_m\, T_1} = \underset{\text{Steam and Liquid Mix Out}}{c_P\, Q_s\, T_d + c_P\, \rho\, Q_m\, T_d}$$

Where

ΔH_{vap} = 1,180 $^{BTU}/_{lb}$

c_P = 1 $^{BTU}/_{lb\,°F}$

ρ = 8.34 lb/gal

Q_s = Steam flow in lbs/min

Q_m = Operating Liquid (biowaste) in GPM

ΔT = temperature rise in °F ($T_d - T_1$)

Solving for Q_s

$$Q_s = \frac{c_P\, \rho}{\Delta H_{vap} - c_P\, T_d}\; Q_m\, \Delta T$$

assume T_d = 180 to 190°F and no Heat recovery, then

$$Q_s = \frac{Q_m\, \Delta T}{120\ ^{lb}/_{gal\,°F}}$$

Specific vendor experience with available eductor sizes should be utilized when selecting the correct size eductor. The waste discharge heat exchanger is provided in cases where waste temperature is hotter than what is required to reduce the discharged decontaminated waste to 60°C (140°F).

Note that the biowaste stream "Y" in Figure 3 is a lower pressure than decontaminated waste "X" which is a lower pressure than the chilled water "Z." If heat recovery is not provided, the neutralization waste pump would not be required and the pressure of the chilled water "Z" should be greater than the biowaste stream "Y." This is important so that the mode of a single failure will not result in a release of contaminated waste. The typical operational modes for the continuous system would be as follows. Heat up mode will bring the waste feeding the heat exchanger (or eductor) to decontamination temperature while returning heated waste to the tank until kill temperature is reached. The run mode is entered once the waste reaches the required temperature over the length of the hold tube. Waste is then diverted to the neutralization feed pump (not required if no heat recovery) for discharge. A hold condition is reached if the waste decontamination goes outside of kill specification (temperature in hold tube, system pressure, etc.) and recirculation with the feed pump through the tank bypass will occur until the system is back on line or an alarm occurs (including system time out). If the system goes into alarm, it is placed in a cool down mode where the steam heating is stopped and the waste is recirculated to the tank until operator intervention places the system back in service (after fixing alarm condition). Note that some parameters could shut the system down without cool down (loss of system pressure or leak detection). Failure of the system during any of the operational modes (heat up, run, hold, cool down, and alarm) would place the unit in a safe mode until the problem is discovered, corrected, and then the system is placed back in service. Provisions for system decontamination past the tank outlet may be necessary, but sufficient controls should be in place to prevent the transfer of contaminated waste to neutralization. Plant steam decontamination of the tank, drain lines, vents, etc. should be provided for the system. The ability to manually decontaminate the tank contents prior to discharge should be provided in cases of system failure. Chemical decontamination of the sump pump and transfer line would be utilized in the event of a spill. Note that the containment pit must contain 1.5 times the volume of the waste tank capacity if the tank fails. Provisions to isolate the tank should be made to prevent the continued addition of waste to the failed system.

Tanks should be sized to hold a minimum of one hour's worth of waste as determined via time motion analysis (aver-

aged within reason). In a redundant tank system (two tanks), this would allow one hour for personnel to respond, slow down the waste generation, and fix the problem. Totaling the waste and understanding the duration for the operations will help to evaluate a reasonable load per day. Sizing the continuous system will involve sizing the hold tank based on the required discharge rate. Time and motion analysis of the plant operations will provide the best method for sizing the kill system. The tank will be sized to fill and empty the tank at slightly faster than the predicted average flow. The LWDS pumps can be provided with two speeds to provide an accelerated discharge rate if the LWDS tank is filling at a peak high rate. Note that this means that the hold tube is sized for the fastest discharge rate.

Chemical decontamination batch systems (Figure 4) are typically used in pilot plant operations where Steam-in-Place (SIP) practices are not routinely performed. All issues of containment are the same. Chemical decontamination of all components of the system must be provided in cases where the system fails to function properly. The major complications arise when system decontamination is required. Flooding the drain system with chemical decontamination solution or forcing chemical decontamination solution through a failed discharge pump may be required. Systems must be provided with total coverage so that decontaminating solutions can contact all waste. The time and concentration of chemical contact during decontamination is required, but one added concern is that the chemical is often depleted during inactivation. An overkill amount of chemical must be supplied and sufficient validation studies must be completed to support the parameters utilized in decontamination.

Chemical contact and the issues of solids within the biological waste add to the complexity of the chemical LWDS. The use of a macerator and recirculated contact with the chemical is required in some cases where solids are an issue. The amount of solid and the degree of homogeneity will determine to what level of complexity the design must go. Although not required, if release from the recirculated waste is of concern, a chemical block can be developed prior to the discharge pump. Pressurized decontamination chemical between the discharge pump and recirculation isolation valve would ensure that no contamination has leaked past the isolation valve. Some benefits of the chemical batch process are that it allows for testing (consumption of decontamination chemical) prior to discharge and it is simple to design and operate.

Chemical decontamination continuous operations (Figure 5) would add a level of instrumentation complexity. The use of a thermal continuous process allows for control via temperature control. In a chemical system, there must be some analogous handle that can be monitored to assure that the chemical supplied is of the proper concentration and that it is in contact with the microorganism for the validated kill duration. Figure 5 indicates a detection point (AE) that would ideally monitor an excess of decontamination chemical within a desired operating range. Fluctuations of the consumption of the chemical should be within the resolution of the detection method to assure the process is in a state of control. A non-homogeneous waste stream would make the continuous chemical system design a challenge and is far too complicated to be cost effective. The benefits of a simple batch chemical system do not exist with a continuous chemical system. There are no known large-scale continuous chemical LWDS.

Chemical decontamination issues all stem from the problem of contact and validatability. There is a systematic approach for the validation of thermal decontamination processes. Once the chemical decontamination process has been worked out on the bench, the implementation in the field requires a great deal of operator access and complexity from the design and layout standpoint. For example, the chemical decontamination of a sump prior to preventive maintenance will require that chemical liquid completely contact the sump tank to the isolation valves within the system – *Figure 6*. Valves must be of sanitary design (diaphragm or pinch style valves) for chemical contact with all contaminated portions of the valve. If the strainer becomes blinded by waste, there may be issues regarding sufficient contact or access of sanitizing chemical. The sequential flooding of the lines entering the sump and the manual operations required to assure coverage can be cumbersome. Due to the complexity of chemical decontamination and the material compatibility issues, the tendency in industry is to utilize thermal decontamination. The large LWDS utilized in the pharmaceutical industry use a thermal decontamination mode of operation for biological inactivation exclusively.

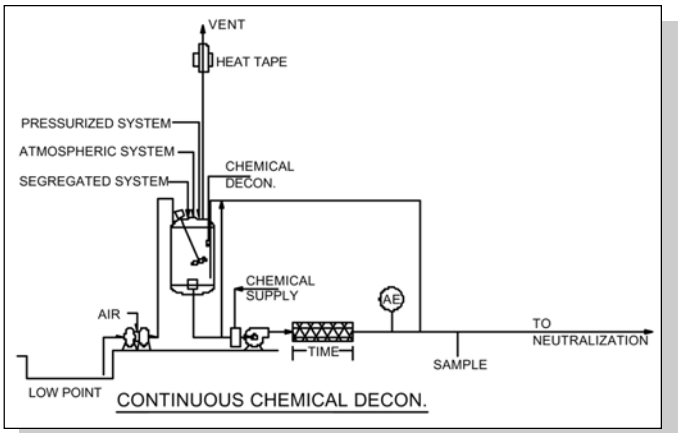

Figure 5. Chemical decontamination continuous.

Redundancy

System redundancy is important when considering the value of the product being produced and the impact of holding up operations. Many operations cannot be held up; careful consideration to the process steps affected by LWDS down time and the potential for loss of product must go into the system tank sizing and component redundancy or serviceability design approach. Instrumentation may need to be serviceable while the system is on line. The factors that greatly effect system size or throughput are the cleaning operations and volumes consumed in harvest or recovery operations. Harvest operations producing large volumes of contaminated waste such as intracellular processes harvest operations and disposal of large batches of material due to contaminated runs must be planned.

Safety

The factors affecting system safety are the potentials of:

- uncontrolled release of the system or venting system during operation
- backup of the system into operations (cross or back contamination)
- operator exposure during system servicing
- component failure during operations

During system hazardous operations review, a complete "what if" analysis must be performed to anticipate any and all modes of system failure. The use of operational descriptions and "colored" P&IDs for all phases of operation will assist in the evaluation of the design. By color coding each operational step on the P&IDs, the designer is forced to consider all conditions that affect the system components and function.

System Decontamination

The entire system, the components of the system decontamination, and the ability to reproducibly decontaminate are requirements of the EPA and OSHA. The system P&IDs should be colored to indicate the various stages of operation (heat up, run, hold, cool down, and alarm). Decontamination of the entire system and components of the system should be planned for and the operations should be "walked through."

System Maintenance

System maintenance must be considered from the beginning. Access to all serviceable components and the anticipation of how that operation would be performed "hot" must be planned. Location of serviceable components within non-contained space is not recommended. The level of component redundancy will be determined based on the system operation. Redundant components will be required if the value of the process and product dictates that uninterrupted processing is required. The system should be reviewed every six months to establish that components are performing within requirements and emissions are controlled.

System Requirements

The liquid waste decontamination system must be capable of automatic or simple reproducible operation to render the waste biologically inactive and may further treat the waste to remove chemical or toxic contaminants.

The most reproducible method of bioinactivation is to thermally inactivate the biological waste. Standard decontamination temperature and time used in industry is dependent on the organism used in production.[17] Continuous systems have control points varied from 80°C (176°F) for 90 seconds to as high as 140°C (284°F) for 50 seconds. The concentration of organisms, solution density, and the total heat imparted to the biomass is the basic driving factor to meeting the stated level of biological activity reduction (see validation). Ideally the microorganism D and Z values[16] will be determined to establish the required exposure temperature and time for kill. Some microorganisms may require higher temperatures for the same exposure time so the microbiological compliment of organisms to be utilized within the facility will help determine the required temperature and hold time to be used in decontamination. Selection of the log overkill will be based on the hardest to kill microorganism to be utilized in the facility. In contract manufacturing or development facilities, this can be difficult to anticipate so the ability to switch the system from a continuous kill to a batch kill system or modify the continuous kill hold time and temperature could be useful. This flexibility would allow for modification of the kill parameters to obtain greater temperatures or hold times. A higher degree of overkill (6 log reduction) would be expected in a BSL3-LS facility where release must be controlled compared to the BSL1-LS facility where the capture and total reduction of bioburden is not required per current guidelines. After the system validation is performed, the documentation of the kill or the successful completion of automatic decontamination cycles should then be sufficient proof that decontamination occurred. The EPA requires routine system monitoring and this approach is part of an environmental impact submission performed during the permitting process and maintained during the use of the facility.

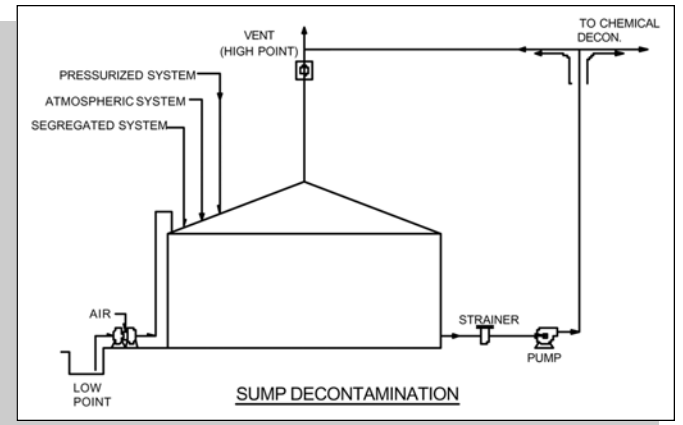

Figure 6. Chemical decontamination issues.

Vent Filtration

One of the most overlooked but critical designs in the LWDS is the vent filter integration. Filters are required to maintain a closed system. Kill tank vent filters, sump tank vent filters, and contained drain vent line filters will all require a vent filter sized for line drainage, proper tank fill, and tank evacuation. The filter housings should be heated to prevent the build up of condensation and blinding of the filters during operation. The location and means for reproducible decontamination must be provided. Thermal decontamination will require steam traps to remove condensate from both sides of the filter element. The "B" position in both the flow-through and the "tee" style filter housing (Figure 7) should be positioned to connect to the contaminated side of the system. Positioning the contaminated side toward the "A" connection will cause potential accidental exposure to operators. The use of a vent drain line may be required for automated SIP, but this may overcomplicate the system design. Standard vent and drain compression fittings would not be appropriate for these fittings. Triclamp fittings with isolation valves would be required. A bleed line could be useful to provide filter integrity test air. A drain line can be used to check for filter performance or condensed water vapor on vent lines although every added connection should be scrutinized. Note that even though these connections are on the non-contaminated side of the circuit, they should be used only after system parameters indicate that the circuit is performing properly.

The preferred configuration is a flow-through style filter although space considerations may require the use of a "tee" style filter housing (without the top vent). This can cause potential problems in sterilization if the filter top is determined to be a cold spot. Note that filters should not be placed in such precarious positions so that operators or maintenance personnel must strain in performing their work with the filters (decontamination, testing, filter element replacement, etc.).

Pressure gauges pre and post the filters are recommended so that system troubleshooting can be performed relatively quickly when investigating a decontamination system venting

problem.

Filter decontamination is typically performed via plant steam sterilization in place or the filter is bagged in place and autoclaved. The preferred method of decontamination is steam sterilization. The filter should be ergonomically positioned so that access for decontamination, preventative maintenance, and inspection is optimal. The second method (bagging) requires work to be performed in a "hot" condition where personnel and the area must be treated as a contaminated space. The personnel gowning and area segregation should be consistent with the biosafety level classification of the potential contaminating organisms for "hot" system intervention.

Redundant filters can be of benefit in several situations and can provide a level of preparedness – *Figure 8*. A contaminated vent header system, sump tank, or a continuous decontamination system kill tank could benefit from a redundant filter system. This would allow the system to stay in operation in the event of a change out of a filter (routine PM) or if a filter becomes plugged or is no longer functioning properly. Providing the filters with heat tracing (either steam or electrical) can prevent the build up of condensate and potential plugging of the filters. Provisions for filter SIP and change out independent of the other filter is required, but the controls for SIP can be made common. A temperature probe (RTD) can be used for proving that an appropriate F_O (see validation) is achieved during the decontamination process. Note that condensate from the filter SIP must be collected within the closed system because it is contaminated at the start of SIP. The arrangement indicated in Figure 8 would provide a sufficiently sized vent line to allow for condensate to run back in the vessel without affecting the venting operation of the filter in service.

Sump Collection

Sump collection is required when the facility configuration does not allow for gravity drainage to the LWDS for all biowaste streams. The sump can collect gravity waste from sinks or floor drains within several interconnected areas – *Figure 9*. Care must be provided in evaluating the cross contamination prevention approach. This approach can consist of the introduction of check valves between operational areas where interconnection is not allowed although the introduction of a mechanical device will require access and maintenance. Decontamination prior to servicing can be of concern and the failure rate of check valves makes this a dubious solution. A second approach could be to segregate the lines and collect on a single header only that waste that can be interconnected. The back flow or prevention of gas backing up into operational areas via sink or floor drain can be controlled by the use of an 8" "P" trap. These traps will need to be attended by a routine addition of decontamination solution. The decontamination solution should be compatible with the drain and LWDS materials of construction. Several segregated lines can be directed to the sump where sufficient vent capacity and level control will help to assure that cross contamination of areas is avoided. Drains and sinks should be provided with plugs for drain isolation when not in use. Water supply to "P" traps is not recommended for contained drains.

Validatability

Thermal sterilization validation in industry today is performed utilizing spore strips (dry locations) and ampoules (liquid locations) containing Bacillus stearothemophilus strategically placed at "worst case" locations within the system. Complete kill of strips and ampoules with concentrations of 10^6cells will establish a 6-log reduction of microorganisms. To pick the worst case locations (cold spots), thermal mapping may be utilized. If a given organism has a D value of two minutes at 121°C (250°F), a six-log reduction of waste would take 12 minutes at 121°C (250°F). A 12-log reduction (overkill) would therefore take 24 minutes. Kill parameters similar to overkill approach are easily obtained on batch systems and typical cycles are one to three hours including ramp up, kill, and discharge (and cool). This assures a reasonable level of confidence that there will not be a release of biologically active waste.

The system validation limits for continuous systems have been established by industry and are greatly exceeded by the overkill approach for batch systems as seen below. Use of spore strips and ampoules can provide valuable data to correlate back to the facilities specific organisms and decontamination needs.

Thermal Decontamination

The use of steam sterilization for liquid waste decontamination provides the best level of success for achieving a simple, validatable system. Steam sterilization is well understood and described in Validation of Aseptic Pharmaceutical Processes.[16] The waste produced in the facility must be fully characterized. If particular details are not known about the microorganisms utilized for production, bench testing can quickly fill in the unknowns. The information that is required of the microorganisms being introduced to the waste system is knowledge of the D value and Z value for the various biological contaminants encountered. Selecting the F_O that will provide the required level of kill assurance is then an easy task.

The D value is the amount of time that it takes to reduce a microbial population by one order of magnitude (one log base 10).

The Z value measures the rate of change for the D value at various temperatures. The Z value is the slope of the thermal death curve for a given organism.

$$Z = \frac{T_2 - T_1}{\text{Log}\,(D_2/D_1)}$$

Where T is in °C and D is the D value to the corresponding temperature T.

The F_O value for a given organism is the equivalent time in minutes (at various temperatures during the kill cycle) accumulated that equates the equivalent time that is required to produce sterilization at 121°C with a Z value of 10. The F_O in

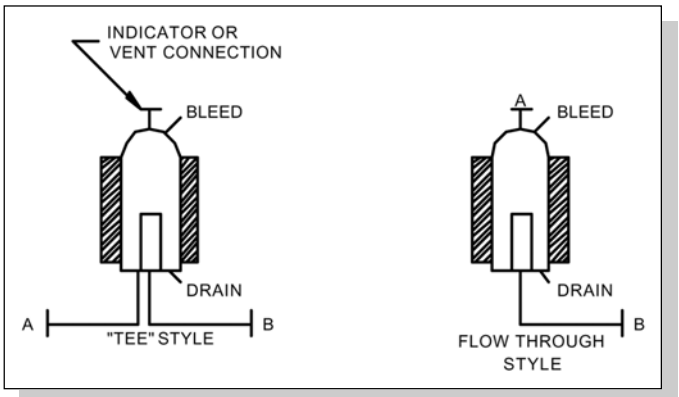

Figure 7. Typical vent filter configurations.

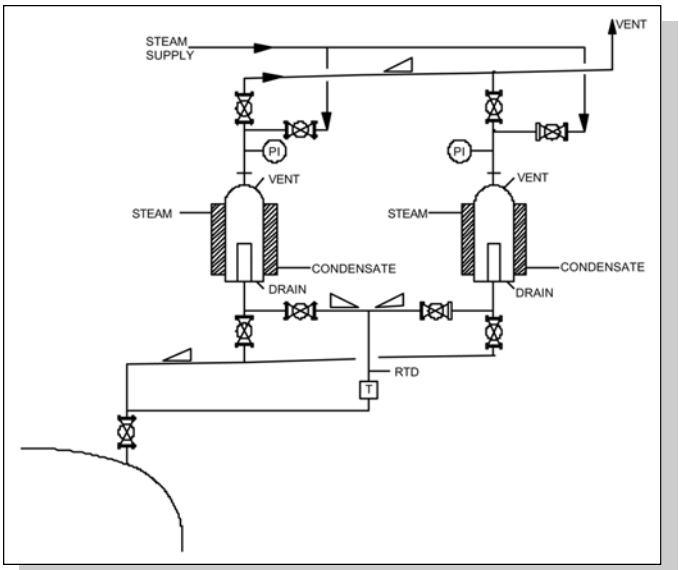

Figure 8. Redundant filter.

other words accounts for the time of effective microbial kill at all temperatures during heat up and cool down.

$$F_O = \int 10^{\left\{\frac{T-121°C}{10}\right\}} dt$$

For situations where the Z value is something other than 10°C:

$$F_O^Z = \int 10^{\left\{\frac{T-121°C}{Z}\right\}} dt$$

Once the "worst case" microorganism (highest required kill temperature for the longest time) is determined, a design can be completed and implemented. If a continuous system is employed, the required temperature to achieve the hold tube length can be selected. Planning for a system overkill approach in batch systems and planning for potential new production vectors (microorganisms) or system modifications will help to make a versatile system design. Tube length and system temperatures can always be modified so sufficient hold loop expansion room and heat exchanger modification space should be planned into the layout. These plans for versatility also must be considered when designing the control system and specifying the control components and set points (valves, sensors, flow, temperature, etc.).

Chemical Decontamination

Chemical decontamination will require that a host of issues must be addressed. Many of the systems utilized in processing or even the processes themselves may require elevated temperatures being sent to the sump or kill system. Elevated temperatures along with the chemicals utilized for inactivation must be checked for compatibility and long term exposure effects. In addition to the issues of temperature, the physical contact of all contaminated components can become an issue. Use of ball valves may raise issues with contact of biological contaminants and the crevices within the ball valve. This can be solved by the use of a diaphragm valve with suitable temperature and corrosion resistance.

The decontamination of vent systems and sump systems also will require a great deal of forethought to assure that all components can be chemically decontaminated when preventative maintenance and emergencies require access. Chemical decontamination of failed systems also will be required prior to maintenance personnel exposure. If this is not possible, the level of training for maintenance personnel to operate on "hot" systems will be required. Proper training in Universal Precautions[7,10] as prescribed by OSHA is advisable to assure operator exposure is controlled. Universal Precautions were established as the required method of treatment of all human blood or bodily fluids known to be infectious for HIV, HBV, and other bloodborne pathogens. Expansion of this concept when dealing with biological waste within a maintenance environment is good practice.

Validation of a chemical system will place more requirements on the validation efforts due to the dynamic nature of chemical systems. The need for a macerator on a chemical system will depend on the ability to control the waste stream to the system. Chemical access within a "sludge" of packed cells and exposure times must be modeled during validation studies to assure that the system achieves complete decontamination that is reproducible. This also will be of concern for thermal decontamination if a chemical form of inactivation is also required for some waste components. The identification of an analytical tool that provides a "handle" to determine the correct decontamination solution concentrations will greatly simplify the validation and control system components for continuous chemical decontamination.

Clear planning within the validation master plan can help to anticipate the issues that will be encountered within the system design, start-up, and validation. This planning will assure that the proper testing and validation studies are performed in preparation of the system design.

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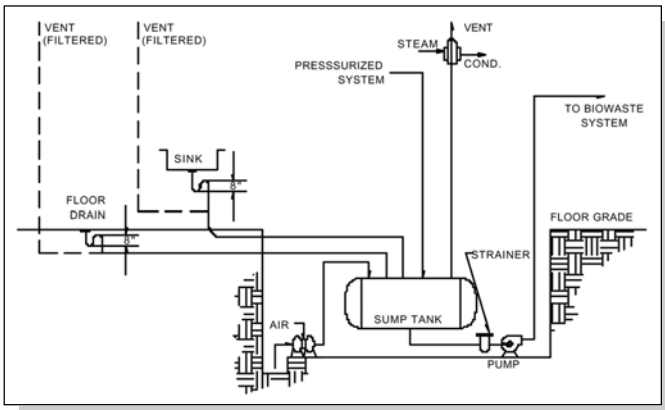

Figure 9. Typical sump.

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Carl J. Carlson is the Executive Vice President of Phoenix Imperative Inc. He has more than 15 years of industrial experience in the diagnostic and pharmaceutical industries. Experience spans from operations in development/scale-up/production to the design and integration of processes in production or pilot facilities. The integration of manufacturing expertise, process engineering, process control, current Good Manufacturing Practices (cGMPs), and compliance, provides an ideal background for quality facility and process design experience. The design and integration of critical utilities, upstream processing, and downstream processing is all focused on serving the GMP envelope where critical decisions are made. Carlson's design experience within the GMP envelope has integrated this process knowledge from bench scale pilot plants up to facilities producing kilogram quantities. Processing and design experience includes scale-up and development of conjugation, derivatization, purification, and/or extraction, of proteins, oligosaccharides, polysaccharides, sugars, glycoproteins, etc. He is a member of ISPE, American Chemical Society (ACS), American Institutes of Chemists (AIC), Instrument Society of America (ISA).

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