This article describes pharmaceutical industry and regulatory perspectives, and outcomes of questionnaires and workshops, expressed during the recent, highly interactive seminar on the need for revision of Annex 13. This is the first seminar to be arranged jointly by ISPE, DIA, and EMEA.

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ISPE/DIA/EMEA Joint Seminar

Shaping EU GMPs for Investigational Medicinal Products - The Need for Revision of Annex 13

On July 5, 2000, a seminar entitled Shaping EU GMPs for Investigational Medicinal Products - The Need for Revision of Annex 13 was held at the European Agency for the Evaluation of Medicinal Products (EMEA), in London, UK.

This is the first seminar to be arranged jointly by ISPE, the Leading Global Society for Healthcare Technology Professionals, the Drug Information Association (DIA), and the European Agency for the Evaluation of Medicinal Products (EMEA). The seminar was co-chaired by Dr. Karel de Neef, of EMEA, and Mark Wakerly of ISPE/AstraZeneca, UK. The program committee was comprised of members from the three contributing organizations.

Background

Annex 13

Annex 13 provides guidance on the application of Good Manufacturing Practice (GMP) to the manufacture of Investigational Medicinal Products (IMP). It provides an interface between GMP and Good Clinical Practice (GCP). Annex 13 was first made effective in 1993. Following a review by industry at DIA, significant changes were made to the Annex during 1996 and the first revision of Annex 13 became effective in July 1997. This seminar will be integral to the consultation process leading to a new revision, which is intended for 2000/2001.

The various aspects of Annex 13 that give rise to concern and suggestions regarding its amendment have been noted by the inspectors. On July 6, 2000 immediately following this meeting, a joint subgroup of GCP and GMP inspectors (representing the Ad Hoc Meeting of GCP Inspection Services and the Ad Hoc Meeting of GMP Inspection Services), met to consider draft proposals and work on their development. This drafting continues with a further meeting in September 2000. There will be further opportunities for consultation between regulators and industry once a consolidated draft has been developed. The timescale is likely to be linked to that of the development of the Clinical Trial Directive.

Introduction

More than 100 delegates attended the seminar, with more than 70 industry representatives and 25 regulators. Delegates traveled from throughout Europe in order to attend, and several delegates also came from the United States.

The format of the seminar was highly interactive and provided both the industry representatives and European regulators with the opportunity to discuss openly the need for revision of Annex 13. All delegates were supplied with a copy of Annex 13, which was referred to frequently throughout the seminar.

Each of the three seminar originators introduced their organization, and gave a brief outline of their interest in the seminar topic. Delegates were presented the history and background of the Annex and the revision process was described. Emphasis was placed on the interactive nature of the meeting and delegates were strongly encouraged to participate in any discussions and make their views known.

Detailed presentations began with an overview of both the benefits and concerns with Annex 13. Although comprehensive in nature, and helpful to industry in understanding the critical activities required for compliance, Annex 13 raises several concerns. One such is that it has an inconsistent combination of guidance and detailed actions, often generating more questions than it actually answers. One significant area of concern, which was raised repeatedly throughout the day, was the inconsistent interpretation of Annex 13 in the different member states of the European Union (EU) and by industry (between or within companies).

Following this overview, industry and regulators presented their own perspectives on Annex 13.

Industry Perspective

The industry perspective on the need for revision of Annex 13 was given in two presentations, which centered on:

- Packaging and Labelling

Annex 13 provides guidance on the application of Good Manufacturing Practice (GMP) to the manufacture of Investigational Medicinal Products (IMP).

- Manufacturing and Control
- Regulatory and Quality Assurance

Concern was expressed that Annex 13 was not in line with technological developments. With regard to blinding, the Annex did not encompass the more sophisticated dosage forms, such as injection pens or some inhalation devices. Additionally, third party blinding or extemporaneous preparations presented specific difficulties in satisfying section 31 of the Annex.

It was felt that 'Transfer of Product', was described in too much detail, and as a result could lead to confusion. It was suggested that the Annex should address only fundamental requirements before material could be transferred. Traceability of product at the supply site was also of concern.

Section 12 of Annex 13 concerns the 'Product Specification File'. Although a simple term, its actual meaning is considered too ambiguous and this has caused many problems. It is usually interpreted as unnecessary to hold the information considered in one physical file, and industry felt it would be beneficial to clarify this point.

There was a need to trust systems and controls, which ensure that the correct material has been provided for 'Destruction'. Holding of material should act simply as a double check.

Harmonization in international clinical trials was affected by both the content and interpretation of Annex 13. Suggestions were given for changes to labelling and raised specific points of concern. The labelling instructions in the Annex are very specific and it was suggested that these instructions were replaced with general requirements. This is one of the main areas where it was suggested that the emphasis of Annex 13 should be on the 'What' rather than the 'How'.

The use of multiple languages on labels to maximize flexibility of supplies, and/or meet national requirements of some member states, complicates the content of labels, particularly on smaller pack sizes. Numerical information may become confused because so much information makes it difficult to pick out the correct numbers, and as the amount of material increases, the less 'user-friendly' the packaging becomes. Inconsistency in guidance for immediate and outer packaging and smaller versus larger packaging also raised concerns.

Re-labelling resulting from dating on labels needed to be performed under GMP and was felt to involve significant risk. Suitable alternatives exist that make removing the expiration date acceptable, especially considering that the material is under control of a sponsor. It was remarked that the FDA do not need this date and the US does not seem to have a problem.

Regulatory Perspective

Case studies were presented and the experiences of both British and French regulators were described. Regulators found several areas of difficulty with Annex 13 in relation to "real world' scenarios. Lack of documentation at both the investigator's and the sponsor's sites was cited as one area, which made it difficult for them to ascertain whether the guidelines had been followed adequately. At least some justification for any lack of validation was required, e.g., experience with a similar product.

Re-labelling is a GMP process, so it is expected that a GMP level of manufacture will be followed. However, relabelling was usually performed in a clinical environment (as permitted by article 20) but the required procedure and documentation of the activity was not always made.

The role of the 'appropriately qualified staff', which would become 'Qualified Person' (QP) with the implementation of the clinical trials directive, was described as one of the main drivers for revision of Annex 13. Surprise was expressed that this had not been raised by the industry presentations. The role of QP's in release of Investigational Medicinal Products is considered more complex than with marketed products.

Harmonization is a key issue for the regulatory authorities throughout the member states of the EU. There is no Community legislation for manufacturing Investigational Medicinal Product (IMP). The different member states of the EU have adopted different national laws or administrative positions regarding the Annex. These affect the free movement of IMP between the member states of the EU.

There is already a wish from the Commission and member states to go further regarding harmonization and the situation regarding IMP. A revision of Annex 13 would contribute to achieving a system for the free movement of medicines within the EU.

Several areas of deficiency were found in the areas of GMP/GCP. These included:

- lack of good technical agreements
- poor control of cross contamination
- lack of quality control on placebo materials
- storage/monitoring at investigator site

In addition, there were occasions where small scale aseptic processing failed to meet even basic standards. There was a question as to how information concerning third party recalls would be recorded.

Questionnaire Review

The review of questionnaires of prospective participants continued until the day preceding the seminar. This allowed as much information as possible to be captured and presented to the group. The questionnaire was designed to identify the areas which merit attention and the complicating factors when dealing with Annex 13, allowing the faculty and the attendees to tackle the fundamental issues of Annex 13 during the meeting.

This review set the scene for workshops on the topics that had been deter-

mined with assistance from the questionnaire. Delegates selected one of three workshops, which were designed to provide the opportunity to discuss specific topics affected by Annex 13. Topics discussed included:

1. Labelling, Packaging, and Expiry Dating
2. Stability, Comparators, and Shelf Life
3. Manufacture, Qualified Person Release, and Transfer of Product

Workshops

The workshop sessions proved so successful and interactive that they were twice extended to allow participants time to fully debate their individual perspectives and move toward consensus on how the Annex should be revised. At the end of the day, the findings of each workshop were presented to the entire group for final consideration and feedback.

Workshop A: Labelling, Packaging and Expiry Dating

Despite the extended time allowance, consensus could not always be achieved. The members of this workshop took a vote on whether the expiry date should be removed from the labelling instructions. The majority decided that removal would be the best option as there were alternative methods of dealing with expiry. Ultimately it is the safety of the patient, which is of prime concern and is considered the deciding factor in how this issue should be handled.

No recommendation could be given for the list of what should go on a label. Again, a full consensus could not be achieved. If a definitive list was included in the Annex and the Annex became legislation, it was felt that this would prevent the extra requirements of certain countries. Alternatively, the previous view that the Annex should state the 'What' rather than the 'How' was more acceptable.

There were found to be several reasons why re-labelling might be necessary, but they were usually exceptions. It was felt that Annex 13 is a guideline, and so does not need to detail all possible exceptions.

Clarification on 'Blinding Retention Samples', where these need to be kept, which need to be kept and the potential purpose of the sample were all brought into question.

In general, it was felt that Annex 13 is not necessarily a ruling that must be applied in all cases, and justifiable deviations and inspection by authorities should be acceptable.

Workshop B: Manufacture, Qualified Person Release, and Transfer of Product

The Product Specification File should be thought of as a concept not a single file. Thee should be a consideration of what a QP would need access to. The QP should have confidence in the quality system of the site of manufacture of the product. Annex 13 talks about a 'suitably qualified' person but it was felt that it should match the directive that says a "Qualified Person". There was a question of what would be required for a QP (IMP). Annex 13 needs clarification of where the QP's role fits in with technical and regulatory green lights.

Transfer of Product should always be an exceptional circumstance. Guidance could be changed to allow justification of the transfer, and that it is acceptable, regulatory wise, to transfer from site to site. It was suggested that the relevant section should be worded to allow transfer, but with onus on the owner for certain assurances.

It was considered that the section regarding blinding is too prescriptive and that perhaps Quality Control (QC) may not be the best people to do smelling or tasting, etc. of product. Tasting is not thought to be a good way of checking; delivery method and new technology applying to new products should be accounted for.

Overall, this workshop decided that there is a need to ensure that Annex13 does not conflict with GCP and that Annex 13 should provide more guidance.

Workshop C: Stability Comparator and Shelf Life

Specific wording of several sections concerned this workshop. Clarification of terms would be considered beneficial, such as, 'significant changes' in Section 27, which refers to comparator product.

There was a general feeling that people should have flexibility, so the Annex should not be too specific. Examples were considered as possible useful additions, for example, as a means to show stability.

The workshop was also concerned with allocation of responsibilities for different aspects of stability and shelf life.

These included:

- responsibility for the sort of information that signifies that a product is being recalled
- A sponsor company needing to ensure that sufficient data to cover any deviation from normal storage was recorded appropriately.

It was felt that stability data could be extrapolated from accelerated stability data for a company's own product, which usually had acceptable confidence limits. Contract laboratories have been used, with varying degrees of success, to find a 'Stability Indicating Assay'. This could potentially save significant time and effort, and should be accounted for in the Annex.

Conclusions

The interactive nature of the seminar proved invaluable and was helped significantly by the arrangement of the venue.

Several issues were raised throughout the day and all viewpoints were considered, even where this prevented a consensus being achieved. Labelling, particularly the inclusion of an expiration date, seemed to cause some of the greatest concerns aired during the meeting and was expressed in some form or another by all workshop groups.

Our thanks go to all those who participated in this meeting, in the organization, presentation, and discussion of Annex 13.

The seminar has been acclaimed an undoubted success by all involved, and considered a precedent for the structure of future meetings on relevant topics. The proceedings of the seminar are to be published by ISPE, EMEA, and DIA.

Organization Descriptions

EMEA

The EMEA was established in 1993. The Agency coordinates the existing scientific resources of the Member States of the European Union (EU) in order to evaluate and supervise medicinal products for both human and veterinary use throughout the whole of the EU. The EMEA is primarily involved in the centralized procedure but plays a role in mutual recognition. On the basis of the opinions of the Agency's Scientific committees, the European Commission authorizes the marketing of biotechnology and innovative products. In addition it arbitrates between Member

States for medicinal products being assessed under the mutual recognition procedure.

The Agency primarily comprises:

a) A management board which consists of two representatives per Member State, two representatives of the Commission and two representatives appointed by the European Parliament

b) EMEA staff

c) Two scientific committees, responsible for preparing the Agency's opinion on any question relating to the evaluation of human (CPMP) or veterinary (CVMP) medicinal products.

ISPE

ISPE is a worldwide, not-for-profit volunteer society of technical professionals who apply their practical knowledge in the regulated pharmaceutical and medical device manufacturing industries. ISPE is committed to advancement of the educational and technical efficiency of its members through forums for the exchange of ideas and practical experience.

Today, ISPE provides the platform to address these specific needs in health care manufacturing. Technology professionals around the world, dedicated to obtaining the highest levels of productivity and compliance, have gained their long overdue recognition as "Pharmaceutical Engineers" through their participation in ISPE.

DIA

The Drug Information Association provides a neutral global forum for the exchange and dissemination of information on the discovery, development, evaluation, and utilization of medicines and related healthcare technologies. Through these activities, the DIA provides development opportunities for its members.

The DIA, the premier organization within the healthcare arena for the exchange and dissemination of information, is a non-profit, multi-disciplinary, member-driven scientific association with a membership of more than 22,000. These members are primarily from the regulatory agencies, academia, contract service organizations, pharmaceutical, biological and device industry, and from other healthcare organizations.

This article reviews typical examples of project players, project stages, and the benefits of proper communication in each. Lines of communication must be established at the beginning of the project and carried on through to the end of the project. Failure to communicate between project players during each stage of a project and failure to communicate information from one project stage to the next will cause project failure. Only through proper communication can you assure project success.

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Communication Failure Equals Project Failure

by James A. Teigen, PE

How many projects can you think of that end up with delays, cost overruns, and retrofits because some piece of information did not get passed on or recorded at the appropriate time? How many process or utility systems did not provide the correct pressures or the necessary connections for the project equipment because someone did not take the time to provide necessary comments during a design review? How often has the Food and Drug Administration (FDA) or European Union (EU) project criteria or guidelines changed or were not applied correctly after the planning stage? How often have the shop drawings for new or modified process equipment changed and these changes were not passed on to the design team? Each of these examples causes one or more individual failures. Accumulation of sufficient individual failures will cause project failure. So, how do we prevent these kinds of failure - communication. Communication from the beginning of a project to the end of the project is essential to preventing project failures and assuring project successes.

Project Players

The start of every project in the pharmaceutical industry must begin with establishing lines of communication between the appropriate project players.[1] In each project stage, some of the players will determine the information, and other players will have this information communicated to them. Some are involved in all stages of the project and some are involved in only some of the project stages. The players for pharmaceutical projects normally include those in Table A.

Table A. Pharmaceutical project players.

IN-PLANT PLAYERS	OUTSIDE PLAYERS
Plant Engineering	Project Design Team
Process Engineering	Bids & Procurement
Production	Construction Contractor
Maintenance	Construction Manager
Validation	Equipment Vendors
Quality Assurance	
Safety	

Each of these players must be identified and included at the appropriate time in the project, and they must be kept informed throughout the project stages - *Figure 1.* The Project design team comes into the project normally after the project planning stage, unless the project is Design Build (DB) or Engineer Procure Construct (EPC), in which case, the design team comes into the project at the beginning of the project.

Project Planning

Each project goes through an initial planning or scope development stage. This stage begins with a determination of the broad base intent of the project. Is the project to be a new process line, process upgrade, or a clone of an existing line? What is the product going to be? Once these decisions have been made, the next step is selection of the design basis criteria or guidelines for the project. This can include requirements from the FDA, current Good Manufacturing Practices (cGMP), or EU, and current company standards. Next is analysis or development of the project process(es), and process equipment that will be the focus of the project. Will this be a duplication or modification of an existing process at this plant or site adapted from another plant? Will it be a new process or a scale-up from a research and development program? The next task is determination if the project will be located in an existing process area of the plant, alternative locations in the plant, or if a new building or facility is required. The analysis of the associated costs and available funding typically completes the initial planning stage.[2] If the funding is sufficient, then the project proceeds to the next stage; if not, then the planning goes through one or more iterations until the scope is within the available funding. The start of the communication effort for each typical project is shown in Figure 2, which shows the basic questions that need to be asked to develop the project criteria.

To aid in assuring that this criteria information is collected

and passed on to each succeeding project stage, all of the above information must be documented. Each meeting of the project players who develop these decisions should include detailed meeting minutes. These minutes must have assignments of tasks, responsibilities, and time tables. They must be communicated to all players, and ultimately all the criteria that comes out of this stage must be made into a written project criteria document. This documentation and the continued documentation throughout the project will not only assist in assuring project success, but also will assist in validation and in determining compliance.

Normally, this stage requires input and communication between in-plant personnel, unless the project is a DB or EPC project. The main players are plant engineering and process engineering with additional input from plant production - *Figure 3.*

If either DB or EPC methods for project development is used, then the players also will include the following:

- Design Team
- Procurement Personnel
- Construction Contractor

The following list presents additional criteria items/questions beyond those in Figure 2 that must be developed and documented in the project criteria so that the information can be communicated to the next stage of the project:

- What process or processes are required for the project?
- What will the raw materials and quantities be for the desired output?
- What types of process and utility piping systems are required?
- What are the requirements/guidelines for particle counts and air changes?
- What types of heating, cooling, air-handling, exhaust and fumigation systems are required?
- What types of air filtration systems are required (number and location of HEPA filters)?
- Which rooms will require pressurization (positive, neutral, or negative)?
- What are the desired personnel and equipment traffic flow patterns?
- What types of floors, walls, and ceilings are required?
- How much floor space and vertical space is required for the HVAC, process, systems and equipment?

Preliminary Design

This stage takes the criteria developed above and translates that information into a conceptual or preliminary design. In this stage and all those that follow, the initial criteria information is expanded with increasing details. This preliminary design stage includes development of the following preliminary drawings, which translate the criteria into the beginnings of the design:

- site and building layouts
- architectural floor plans and elevations
- structural drawings
- mechanical and process flow diagrams and/or P&IDs
- preliminary mechanical piping drawings
- HVAC drawings
- preliminary electrical power and lighting drawings
- preliminary air pressurization, process traffic drawings

It is imperative during this stage that the criteria developed in the planning stage is communicated during each design meeting, and that this criteria is used as the basis for each design review as well. Again, detailed minutes with associated tasks, responsibilities, and timetables must be developed for all meetings during this stage. Especially important during this stage is input and review by plant engineering, process engineering, and plant production personnel. This information also must be communicated to and reviewed by the design team with input from plant maintenance, safety, and QA - *Figure 4.*

All of these players must communicate all changes or updates in the following information before additional design and/or procurement can be completed.

- planned operations of the systems and equipment (if this is not communicated, there will be significant failures)
- piping systems capacity and pressures and temperatures
- process equipment size and space requirements
- equipment voltage and power requirements
- furniture and other production support equipment requirements?
- Will the process equipment fit through all door openings?
- Are all ceiling heights and room sizes adequate for process equipment (consider operation maintenance requirements)?
- Are door swings into lab rooms and in/out of airlocks correct - based upon traffic flows and air pressurization?
- Is space in personnel airlocks sufficient for clothes change (bench and gowning/storage)?

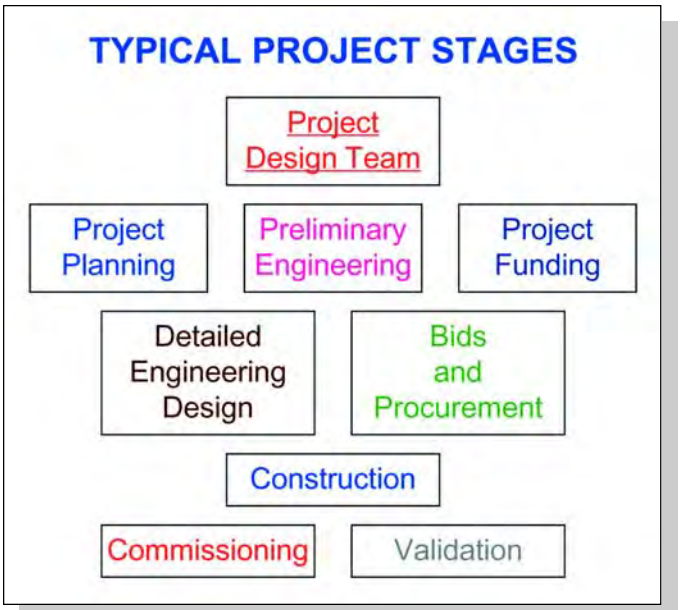

Figure 1. Typical project stages.

- Is space in equipment airlocks sufficient for passage of the largest piece of equipment with associated cart and personnel without having to move the items to close or open doors?
- Can the HVAC equipment be moved through the building into the equipment room or space?
- Can all process equipment be moved through the building into the designated process area or room without dismantling the equipment or requiring block-outs in walls or floors/ceilings?

The following discussion provides an example of problems that lack of communication can cause. Consider the impact of a vertical process tank whose height is less than that of the ceiling height in the room, but cannot be tilted up in the room, as the overall height when the tank is tilted up is too tall to clear the ceiling. This incident required removal of two layers of gyp-board ceiling and cutting out two steel ceiling joists to allow the tank to be tilted up, and then relocated out of the way until the joists were welded back in place and the gyp-board replaced and re-taped and sanded. This work was done over a weekend to minimize the impact on the already scheduled painting of the ceiling. This could have been avoided if the shop drawing data on the tank had been available earlier in the project, and the construction manager had paid more attention to the close fit of the tank in the room. This lack of communication caused construction rework, and overtime costs that could have been avoided.

Another example is allowance for sufficient ceiling height. This must be considered both for the process rooms and for equipment rooms, and pipe/HVAC spaces above the process rooms. An example is evaluation of room ceiling height during preliminary design. This includes the ergonomics of operating the process in the room, including the need for frequent access into tank or equipment hatches on top of vessels below the room ceiling, maintenance requirements to safely access these hatches with safety harnesses, and hoist equipment. This also requires evaluation of the number of times required for this access during a given process or between batches. This can have an impact on the production process cycle time if not considered sufficiently.

In the preliminary design stage, the design team also must communicate proposed design solutions back to the other players for review and confirmation.

Project Funding

Project funding is a variable that is integrated into the project development at almost any stage of the project. The main thrusts of this stage are that the limitations of funding are communicated and understood by all players, and that the project costs are reviewed (at each stage) by all project players to verify that the project remains within these funding limitations. If the funding limits are exceeded, then an iterative process must revise the preliminary design, and associated construction costs until the funding is sufficient, or additional funds can be located and approved. Only if this cannot be accomplished, should the original criteria be revised and the new criteria communicated to the plant production, process, and maintenance players. This must be communicated to the design team, and preliminary design changes made - *Figure 5*.

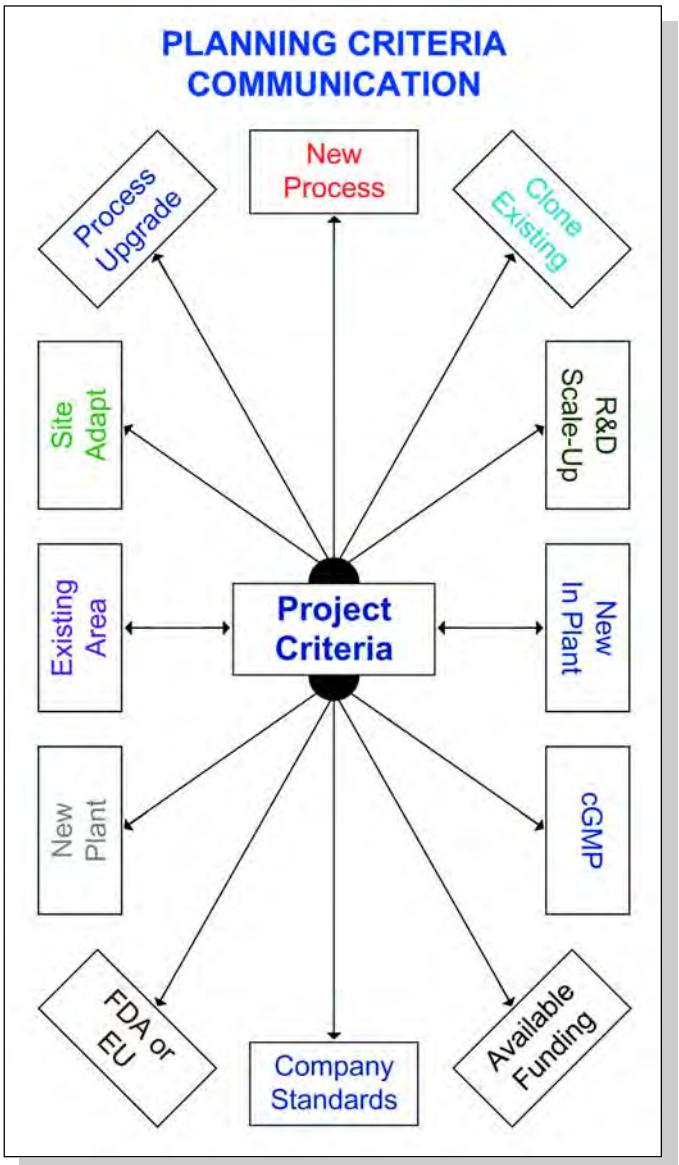

Figure 2. Planning criteria communication.

Project funding must be established according to company requirements, and must be reviewed at each stage of the project to verify that the scope is still within the original limits. At the beginning of each project, sufficient contingency must be applied to account for unforeseen changes in criteria, and changes in process or production requirements or addition of new criteria that typically occur on all projects. It is also very desirable to be able to move this contingency money from one part of the budget to another, since some parts of the project will have more significant changes and other parts only minimal changes. If this flexibility is not allowed, then you can have a cost over-run in one part of the project and a cost under-run in another part, but the overall project is still in budget.

Detailed Engineering Design

Detailed engineering or final design stage takes the preliminary design package and expands it to provide sufficient details, locations, and specifications to allow the project to be bid and equipment to be procured. By definition, the design details in this stage require more time and effort to develop. If the basis for these details was not communicated correctly in the preliminary design stage, the errors or failures will cascade to subsequent stages of the project. It is essential that the detail design drawings and specifications accurately reflect the criteria and preliminary design information. Plant maintenance, plant safety, and plant QA must communicate their respective criteria, and be included in the detailed design reviews to provide their input during this stage. Validation also must begin their tasks, and must become a part of the communication stream of information. Any and all design changes to the criteria and/or preliminary design must be documented, and the rationale for the changes specified. This documentation also will be of great assistance for all validation efforts that are begun during this stage - *Figure 6*.

In addition to the standard information in the specifications and the detailed design drawings, there are several commonly omitted specification sections which should be included to better support pharmaceutical or biotech projects. For example, parts lists for instruments and controls, and detailed descriptions of operations. These specifications, associated descriptions of operations, points lists, and details have typically not been included in the design drawing package up to this point. These sections and associated descriptions become the basis for significant parts of the commissioning, IQ, and OQ validation efforts. They include the following:

- Central or Distributed Controls and associated indication and alarms for HVAC
  - Room Pressure Control Dampers
  - Room Space and/or Duct Temperatures
  - Air Handler Fan on/off, Speed, and Pressures
  - Cooling Coil, Heating Coil, and Humidification Flows and Valve Positions
  - Pressure Differential across HEPA and other Filters
- Central or Distributed Controls and Associated Indication and Alarms for Airlocks
  - Airlock Space Pressure
  - Door Position and Door Interlocks
  - Airlock and Lab Room Pressure (Normal or out of Tolerance)
  - Emergency Overrides for Door Interlocks for Personnel Safety
- Central or Distributed Controls and Associated Indication and Alarms for Fire Protection
  - Alarms and Location of Alarms From Rooms, Hallways, Equipment Rooms and Spaces, and Fans and Ductwork
  - Controls and Locations for Shutdown of Fans and Dampers
- Central or Distributed Controls and Associated Alarms for Fumigation Systems (Fumigation, Stagnation and Exhaust Phases)
  - Position for Room Supply, Return, and Exhaust Dampers
  - Fumigation Exhaust Fan Speed Controls
  - Pressure Controls and Alarms
  - Safety Controls for System Alarms and Shutdown

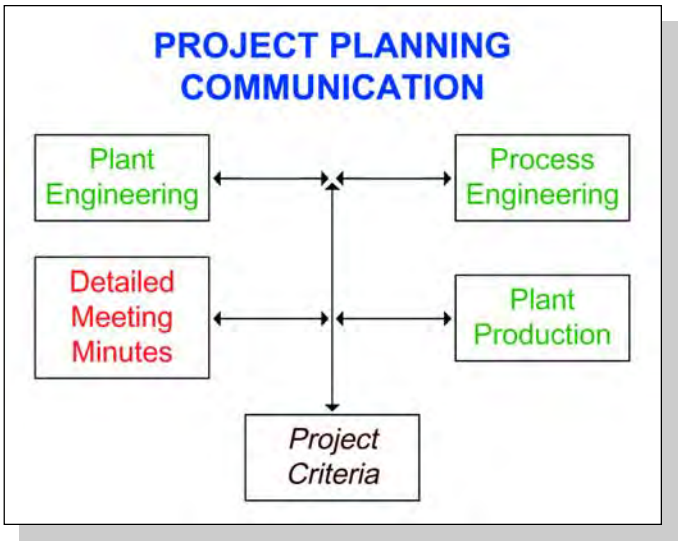

Figure 3. Project planning communication.

An example of lack of communication during detailed design is similar to the room ceiling height example in preliminary design. If the pipe/HVAC spaces above the room do not have sufficient height for main and branch piping, ducts and coils branches, and associated cross-over points, then there will be delays during detailed design at best, and more costly delays and rework during construction if this is not caught during

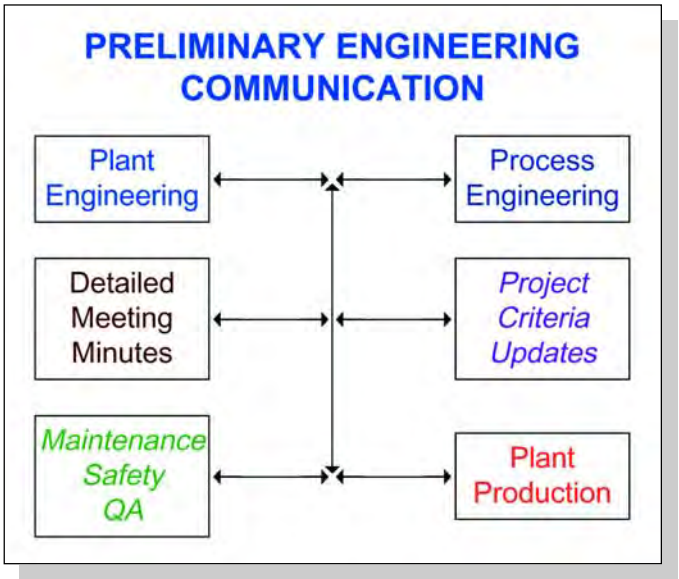

Figure 4. Preliminary engineering communication.

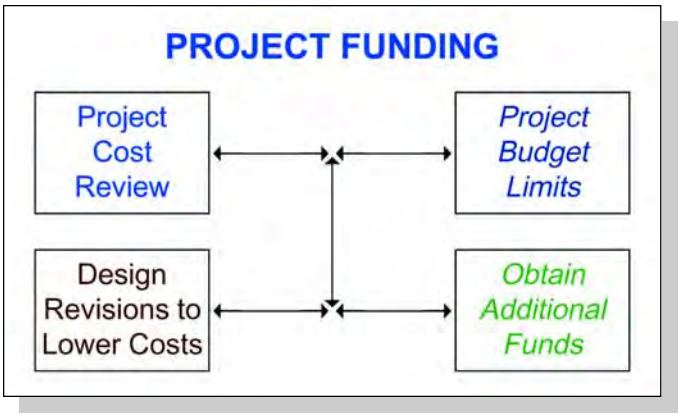

Figure 5. Project funding.

design.

Airlock spaces must have sufficient length between doors to allow both for personnel access (change benches and clothing change storage), and for passage of equipment without having to move the equipment inside the airlock to allow doors to open and close. The equipment passage length also must allow for both the equipment and the carts and personnel that typically accompany the equipment through the airlocks. If this information is not available or not communicated during design, then the impacts will range from reduction in useable room space due to increased airlock size to construction rework that can include relocation of airlock walls, replacement of airlock doors and/or door frames, and associated ductwork, wall, and ceiling rework. Another important consideration that must be communicated is the direction of the door swings for each airlock. This determination must be made based upon the personnel and equipment traffic flows, which is based upon the process design and the relative air pressure of adjacent spaces. If these items change or are not included in the original criteria, the same impacts as above also will occur.

Bids and Procurement

Bid packages are typically prepared and issued to prospective contractors for development of bid prices and schedules for construction completion. The first critical part of this stage is the level of detail in the bid package; the greater the detail, the greater the confidence that the constructed facility will communicate and incorporate the design and initial criteria, and minimize the number of price changes/adders. The second critical part of this stage is communication in the contractor's bid of any exceptions or substitutions to the bid package, and the impact of these exceptions. For this to happen, the specifications must require the contractor's bid to show this information. Any exceptions must be communicated to the appropriate project players, and they must review these exceptions to determine impacts on the project. Failure in this communication can result in construction impacts, which are very costly, and/or in a facility that does not meet the intended criteria, design, production, and product requirements.

Procurement is the purchase of owner provided process and/or other equipment that is part of the design that will not be furnished by the contractor as a part of the construction package. This can occur at this stage or earlier in the project. These items tend to have long lead times and are key pieces of equipment. The timing of these procurement activities is critical to the project. To avoid failures, procurements must be timed so the associated shop drawing information is available during the preliminary design or detailed design, so as not to significantly affect the design. For example, the change in a tank connection location or connection size is not significant, but the change in the height, weight, or width of the tank can cause changes to ceilings, doors or hallways, and can affect building layout and structural requirements. If the timing is off, the information on the equipment cannot be communicated to the design team, and there will be failures in the project - *Figure 7*.

Good communication is not limited to the design team and plant players, but also must include outside sources such as vendors or procured equipment. For example, vendor supplied shop-drawing sketches that showed electrical voltages for fan motors for the pieces of equipment. The vendor data showed single-phase 120volt requirements. This information was incorporated into several panel schedules, starter/disconnects, and associated wire and conduit home runs. After delivery of the equipment and during installation of the equipment, the contractor checked the motor nameplate information. It showed 3-phase, 460 volts. The panel breakers, starter/disconnects wiring and in some cases, the conduits all had to be replaced. Additional breaker spaces had to be located for the 3-phase 460volt power and conduit that was already embedded in concrete block walls had to be replaced. In this case, the design team and the plant players had already had meetings to review the electrical requirements for the process equipment, and the design was done accordingly. This was a mistake on the vendor's part. In this case, the shop drawings were only sketches, and were not certified by the vendor. The consequence of this was greater difficulty in getting the vendor to pay for the consequences of his mistakes.

Construction

In this stage, any items that were not communicated correctly change from a design and paper impact to a concrete, real world impact with associated higher costs and greater schedule impacts. Added players in this stage are the construction manager and the construction contractor. The construction manager must make sure that the bid package requirements are sufficient to communicate any proposed changes or substitutions so that these may be evaluated by the project players to determine all the impacts, and to verify that the contractor's construction is developed in accordance with the design documents. Communication during this stage of the project also must include weekly construction progress review meetings - *Figure 8*.

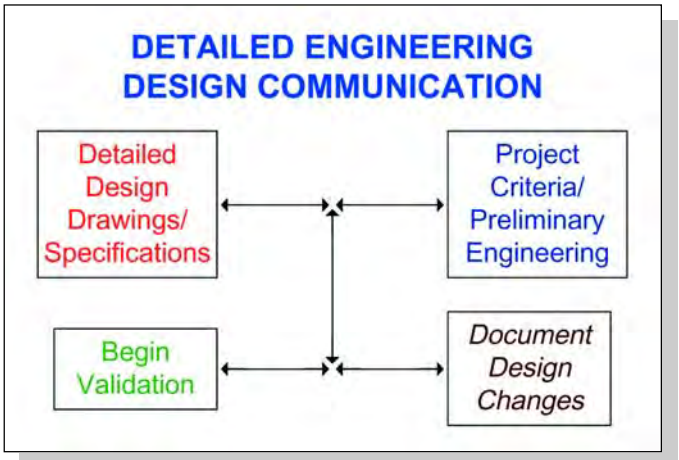

Figure 6. Detailed engineering design communication.

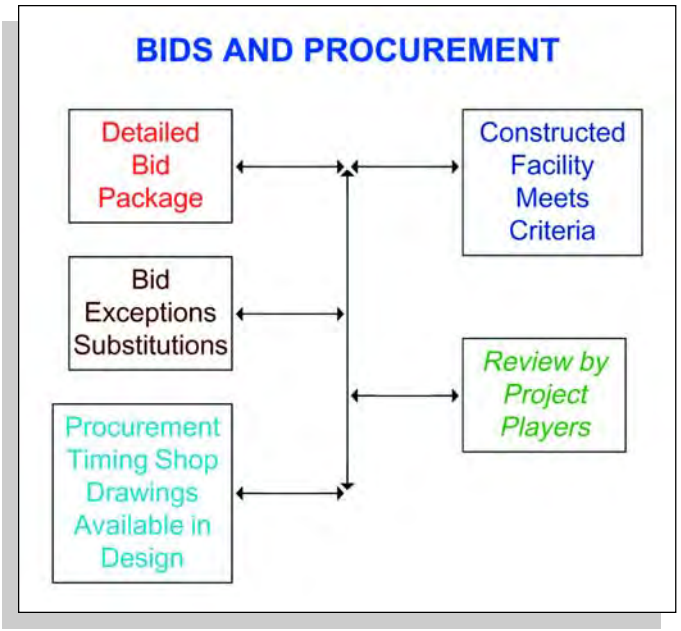

Figure 7. Bids and procurement.

Telephone conferences between the project design team, plant engineering, and the construction manager also are strongly suggested.

The construction progress review meetings should incorporate the following items:

- review of construction activities of the past week
- review of status of prior action items
- review of planned construction activities for the next week (or up to three weeks)
- current problems and assignment of action items if unresolved
- weekly schedule status reports and schedule updates as necessary
- requests for information not provided in the design package
- resolution of conflicting information in the design package
- status of shop drawings submitted, but not yet approved
- detailed minutes with action items and assignments
- updated construction schedule, at minimum every three to four weeks

In addition to the above weekly meetings, the following items also should be communicated, and the requirements enforced. If these items are not enforced, the impacts on existing, ongoing production in the area of the new project can be very significant.

- requirements for temporary construction barriers, shelters, airlocks, and dust containment (negative pressure areas)
- control of dirt and contamination from construction debris, and how it is removed from the construction area
- field change requests should be reviewed and approved by the design team, plant process, production, and plant engineering before being given to the contractor
- design deficiencies should be reviewed by the design team, plant process, production, and plant engineering before implementation
- plant access, traffic patterns, and gowning requirements for construction personnel in and around production areas

Control of dirt and contamination from the construction site, and transport of this material from the construction site to outside the plant should be given a high priority, and communicated strongly to the contractor.[3] One way to assure this communication is to place requirements and consequences in the bid package. Instructions for construction of temporary barricades, enclosures, and airlocks should be communicated to the contractor. Use of negative pressure inside the construction space can minimize contamination to the surrounding spaces and production environments. To assure that this is done, install monitoring gages in several places on the construction site, typically near airlock entrances, and require the contractor to provide written daily logs of the negative readings. The construction manager and other plant engineering personnel should monitor these gages daily also, and if there is not sufficient negative pressure, shut down construction until the situation is corrected. The written logs are also a good indication that the construction is only having minimum impact on contamination of the adjacent production spaces, and provide good documentation of this as well.

Another area that must be communicated frequently is the status of the construction schedule. The construction schedule is typically prepared at the beginning of the project, and to be effective, must be updated for each of the weekly construction progress meetings. At the beginning of most projects, there is almost always some slack in the schedule, but as the project progresses, the slack decreases and a typical result is two months of work remaining during the last month of the project. This situation almost always results in an extension of the schedule and associated cost and schedule impacts, which can include delays to production and associated delay in revenue streams from the new product. Weekly updates to the schedule can point out downstream impacts while there is still time to make changes to make up the time, develop a shorter alternative, or increase the hours worked to eliminate the schedule delay. Simply ignoring the problems or making statements such as "everything is a priority" just result in the delays and associated costs becoming worse.

Commissioning

Commissioning overlaps with the construction and validation parts of the project. Commissioning of some systems can be started and completed while other systems are still under construction. This stage of the project typically is performed to verify that each system performs as designed, and in accordance with written test/operating procedures. Commissioning challenges and documents the performance of the systems and equipment for the project. Trial production runs are made to determine if the product can be produced in accordance with

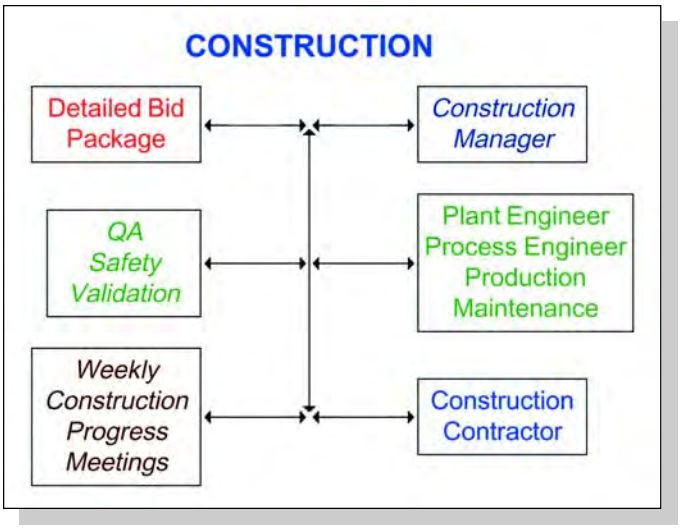

Figure 8. Construction.

the design and process specifications, and is within the normal tolerances. Commissioning should be based upon test/operating procedures developed by production and process and plant engineering. The production players have a significant role, and must communicate with the previous players to resolve all problems, and get assistance for any adjustments and minor modifications that are required - *Figure 9*.

Communication of commissioning information must be coordinated with validation. All major equipment and systems should have commissioning programs. If the equipment or systems have direct impact upon and are critical to product quality, then they must be validated. If this criteria is not communicated effectively, the consequences are a significant increase in the time, effort, and costs required for validation. The level of effort for commissioning is less than that for validation. For example, it is not necessary to validate most HVAC systems, but only commission them. This includes fans, dampers, space temperatures, and pressures. The critical item associated with this would be the product temperature alarm if it were activated due to high space temperature that is caused by a failure of the HVAC system.

Validation

Validation typically begins during the detailed design stage and continues through construction and into production. After sufficient details are known during design, the Installation Qualification (IQ) protocols can be developed. Elements that must be communicated for the IQ include the following:

- list of HVAC components including fans, filters, dampers, coils, control valves, humidifiers, room temperatures and pressures, duct temperatures and pressures
- list of critical process systems, controls, equipment, and components
- Analysis of the above items to determine which will impact product quality.[4] Only those items will require validation. Other items will require commissioning.
- Based upon the above analysis, selected protocols will be drafted, based upon the specifications for the proposed equipment and/or systems, and the selected vendor's catalog and other product data. Once the actual item is installed and actual vendor data is available, changes to the protocols must then be made and communicated to the validation team.

During construction, the Operational Qualification (OQ) protocols can be developed. Elements that must be communicated for the OQ include the following:

- list of vendor make and model information for all of the IQ elements
- proposed description of operation, set-points, and acceptable operating ranges for the IQ elements
- OQ protocols should be drafted, based upon proposed operational sequences, and receipt of vendor shop drawing and operation and maintenance data. Based upon actual vendor data, and any changes to the proposed operational sequences, the changes to the protocols must be made and communicated to the validation team

Following construction completion and commissioning of the systems and equipment, the Performance Qualification (PQ) protocols can be developed. Elements that must be communicated for the PQ include the following:

- operational requirements for systems, controls, and equipment including set-points, output or throughput, and acceptable operating tolerances
- PQ protocols can be drafted, based upon specified performance criteria, and operational sequences and other system requirements. Based upon actual performance data, the changes to the protocols must be made and communicated to the validation team - *Figure 10*.

One of the most critical items that must be communicated during validation is determination of those critical systems, which will impact product quality. This needs to be done early in the IQ validation effort. Only those systems or items that impact product quality need validation. Other items that are typically included in this evaluation will typically require commissioning, but do not require validation. Use of this

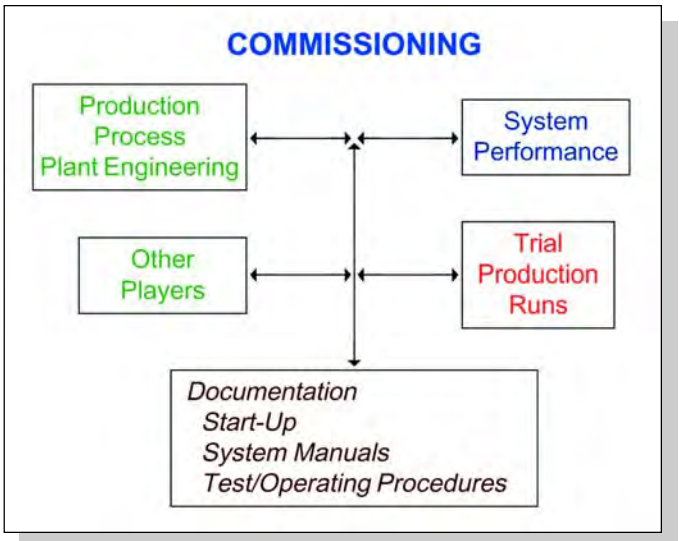

Figure 9. Commissioning.

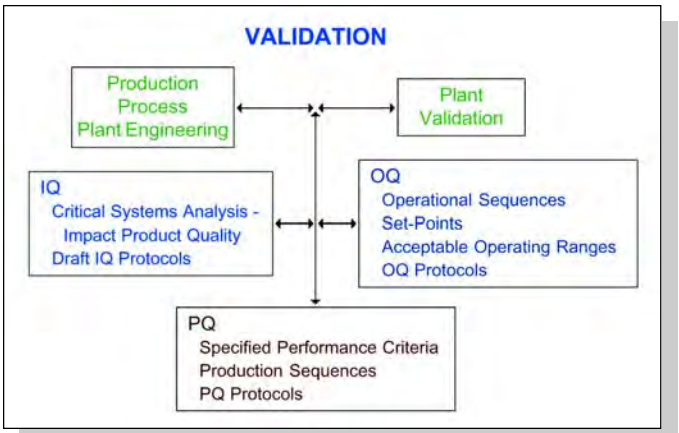

Figure 10. Validation.

criteria for determination of which systems or items need validation will result in reduced time and costs for validation of the project.

Summary

Each project begins with the development of criteria that defines the scope of the project. Each stage of the project develops additional details based upon the initial criteria. Each stage incorporates an increasingly expanded amount of information. It is essential that this information be accurately transferred to each succeeding project stage. This information must be used as the basis for each project review meeting to make certain that it is still current, and is accurately incorporated into the design. It is the role and responsibility of the various project players to communicate this information to other project players in each stage of the project to achieve a successful project. If proper communication is not maintained and documented by means of project criteria and detailed minutes of meetings; if the project players do not contribute, there will be individual failures in each stage of the project. At some level, the accumulation of these individual failures to communicate will be sufficient to cause project failure. By maintaining proper communication as well as the contributions of each project player throughout each project stage, you will avoid individual failures and assure project success.

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Meeting the Challenges of R&D Facility Design in a Dynamic Technology Business (Part 1 of 2)

by Joseph M. Phillips, AIA, and Jay Shoemaker, AIA

This two part article will identify how evolving trends and current patterns affect both the process and result. Part One deals with design strategies and specific solutions which support the emerging trends in the pharmaceutical R&D organization. Part Two will discuss facility project management with a global perspective toward building to support the changes in this highly technical industry.

Introduction

Significant changes have occurred recently in pharmaceutical R&D to influence facility design. This is not a novel event. However, current events are of a magnitude that are creating significant challenges not seen before – challenges adversely affecting companies and R&D itself if facilities are not responsive to new conditions. Understanding significant changes in R&D and their ramifications on facility design is essential to developing responsive solutions and processes. It is equally important to examine internal influences on projects. Specifically, what are the precedents, assumptions, and characteristics of project design driving the outcome of R&D facility projects? Are design solutions responding as needed? Analysis of the activities in both the evolution of R&D and design for R&D suggest new approaches for R&D facilities.

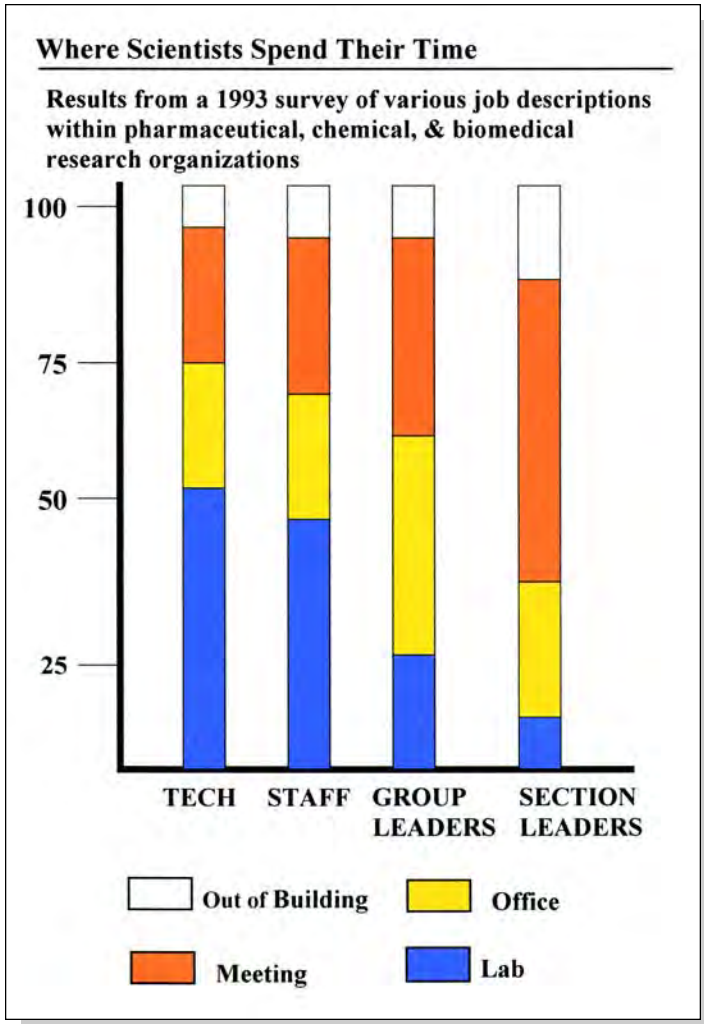

Figure 1. Results from a survey of various job descriptions within pharmaceutical, chemical, and biological research organizations. The findings validated the importance of meeting and office areas in addition to laboratories in the performance of R&D.

Conditions Driving Change in the Pharmaceutical Industry

The reputation and financial success of the pharmaceutical industry has afforded companies the ability to perform R&D at a remarkable scale and pace.[1,2] Previous investments and efforts have resulted in important products and advances, providing capital for future R&D. Though strong for some time, the level of investment in R&D continues to rise. Industry estimates show investment in pharmaceutical R&D will outpace most other industries in the near future.[3] The increased level of funding is warranted, given R&D becomes more expensive as the easier research problems have been solved. The appropriate level of funding is necessary to allow the industry to acquire and capitalize on the latest technologies. Many technologies themselves are being developed as a direct result of the interest in improving pharmaceutical research. While a significant portion of funding is in technology, the largest percentage is in salaries.[1] This helps attract bright minds and allows the industry

to retain its most valuable asset – a highly skilled technical work force.

R&D investments are made with the expectations of return. This simple assumption, combined with the magnitude of capital at risk, drives companies to scrutinize every aspect of R&D to optimize return and maintain an acceptable competitive market position in the industry. The pressure to generate value is heightened by the need to compete for investment with stellar performers in other industries such as computers and telecommunications. Explicit in calculating the financial metric of return on investment are both the generation of highest value and the reduction of cost to the minimum necessary for a desired return. R&D management's responsibility is to structure and focus the organization to use technology resources wisely and respond appropriately to market forces. Currently, efforts toward "better, faster, cheaper" are significant. Thus, discovery and development operate in ever widening spheres of science and technology searching for products of value. This effort has led to a range of process changes and innovations – from the incremental, found in continuous improvement programs, to the transformational occurring with novel discoveries and reinvention of uses for existing technologies.

Recognize Facility Projects as Investments Synchronized with the R&D Strategy

When planning an investment in an R&D facility, it is essential to recognize the principle of balance between return and investment applies in this operating arena as well. Both investment and return must be thoroughly considered before project scope and budget decisions are made. To gain a thorough perspective, working knowledge of the strategies for managing and using R&D personnel and technology assets is as valuable as understanding facility costs. Within management strategies and operational details are the leverage points where design enhances value.

It is obvious that facilities by themselves contribute nothing. Talented people, well supported by management and using the tools and technologies of R&D, generate value by their creativity.[4] **It is the degree to which the primary workplace – the R&D facility – facilitates or hinders the R&D effort that the investment in facility design should be measured.** There are, however, no specific metrics for this relationship. No formulas either, but the relationship is valid. It is reasonable to assume facilities, done in sync with R&D activities and trends, contribute to the generation of value.

Of particular interest in the process of translating needs to facilities is the practice of facility benchmarking. Benchmarking, in its theoretical form, attempts to understand relationships between past actions and intended outcomes. What works? What doesn't? Learning from past projects to understand the full ramifications of decisions is essential in most endeavors and very appropriate for facility projects. There are pitfalls in looking at data out of context. Because the R&D landscape is changing rapidly, new attitudes and techniques are constantly being implemented. It is important to understand how these new approaches force a design that differs from the previous, thereby placing typical metrics for projects outside established norms. **All too often what passes for benchmarking is a simple set of statistics about project cost and area.** What is missing is the connection to intended performance outcomes in the enhancement of R&D. This is not surprising. Project statistics are easy to gather and can be readily verified; however, enhancements to the outcome of R&D are not because of the long delay between implementation and observed result. By default, the benchmarks become cost studies. Using past performance to set future budgets and schedules could cause major problems of underfunding because change in functional performance is not recognized. Someone else's solution may be a total failure in what it was supposed to do, but have the "successful" statistics. Potentially exacerbating a bad situation, in any cost driven project model, there is always assumed pressure for reducing cost. Statistics only of cost, in isolation from analysis of R&D, need to achieve a desired outcome. It is analogous to steering a car by looking in the rear view mirror. Looking ahead is important. Different techniques and processes used by R&D to generate value will almost certainly have significantly different costs.

Begin with an Understanding of the Organization and How Work Gets Done.

"We shape our buildings; thereafter they shape us." W. Churchill

To synchronize with and facilitate R&D for the purpose of maximizing return on investment, one must understand the R&D organization, the technologies they manage, the work the technologies facilitate, and the personal activities required for

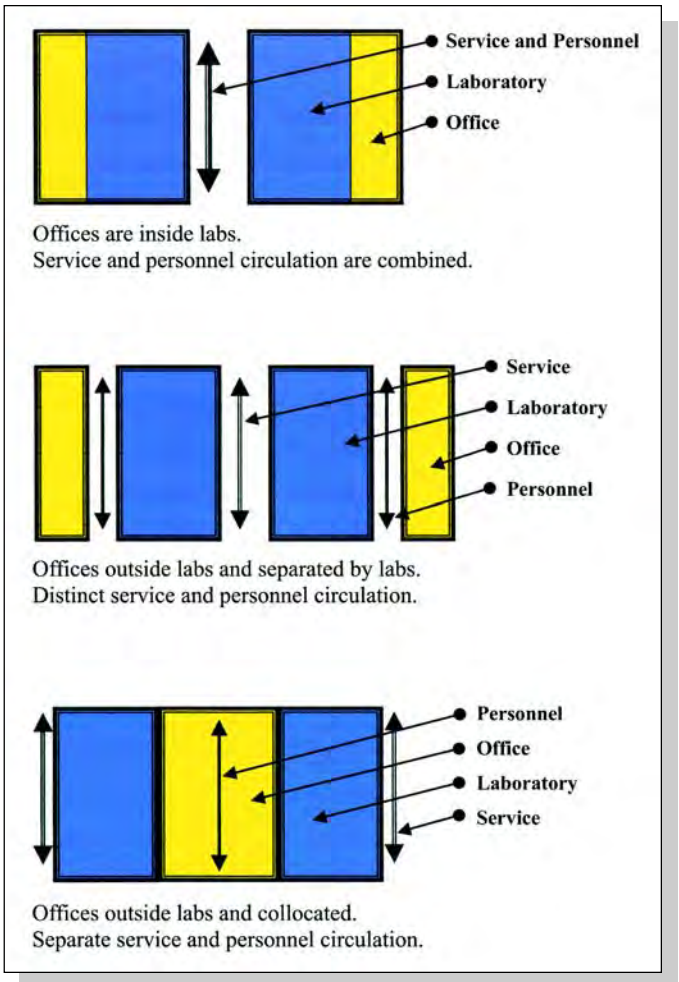

Figure 2. Once the technical offices are removed from inside the laboratories, all assumptions about their relocation must be examined. Design solutions for enhanced team performance must consider how office and meeting areas contribute to enhanced productivity and how these areas interface with laboratories. (CUH2A, Inc.)

execution. It is necessary for facility design to capitalize on opportunities to facilitate and minimize disruption in every active working relationship to play a beneficial role in market competition.

Current Management Strategies Emphasize Teamwork Among Experts

Because of the patent protected nature of products in the pharmaceutical industry, "speed to market" is a phrase describing an essential characteristic of successful pharmaceutical R&D.[5] Reduction of cycle time is pervasive, encompassing organizational dynamics and technological issues. Sharing information and generating knowledge requires organizing the work force in high performance teams.[6] Organizationally, the team approach to projects has been commonly recognized to be of value in achieving timely product launch. Today's research strategies call for a new team composition and new team environments including the following:

- R&D is extending its basic search capabilities to new sources for discovery. New sciences created by theoretical and applied advances are part of the mix. Biotechnology and genomics do not introduce techniques with radically new laboratory demands; however, when part of the R&D program, they introduce massive amounts of new raw data for scientific inquiry and discussion requiring greater Information Technology support.

- Traditional R&D operations of drug safety evaluation and drug development are being compressed into discovery. Earlier collaboration between traditionally separated departments aids earlier candidate selection provided the knowledge can be shared and managed.

There are on-going challenges within the R&D organization to create and foster high performance teams. Coordinating individuals toward a common goal, communicating better, sharing knowledge, and enhancing working relationships are human engineering factors for the organization. Technical challenges include mastering new sources of information and developing expertise with new technologies. These activities of "scientific conversation" can take place predominantly in office areas. The importance of office activities in implementing team management strategies shifts the balance of focus upon R&D facility issues from predominantly lab components to more office issues.

The new emphasis on the office environment influences the overall facility design. It is also a classic case of balancing value and cost considerations. Today in the pharmaceutical industry, office space for lab-based scientists is moving out from within the laboratory. Concerns of occupational exposures to lab hazards initiated this change. Adding force to this movement is the fact that laboratory space is significantly more expensive than office space. HVAC costs drive this issue. For that reason, building design for R&D has been traditionally driven by lab needs and cost effective solutions for lab space. **Once the decision is made to remove offices from the lab environment, the important question is "How should offices be located to best support the scientific conversation?"** This sets up a conflict between facility needs and costs. It is generally assumed, but not necessarily accurate, to be less expensive to locate laboratories central to offices to consolidate service and utility distribution. However, the desire for enhanced performance in key areas of communications and collaboration to improve speed to market suggests it is appropriate to collocate offices to enhance personnel interaction - *Figure 1*. It is crucial to successful design that alternatives be considered and new cost containment strategies emerge.

Figure 3. The proliferation of robotics has rendered useless many benchmarks based on space per person.

Within the offices, it is essential to address how individual team members actually work. It is important to understand where scientists spend their time in this new operating mode. Figure 2 illustrates that a significant percentage of time is spent out of the laboratory and in the office. For years, "interaction" dominated open office design thinking. The results were mixed at best. Interaction may have been promoted, but complaints regarding acoustic privacy and one's ability to concentrate abound. Most scientists recognize individual productivity is promoted by the ability to focus upon the tasks at hand. It is clear design solutions need to balance privacy and interaction in appropriate means to foster scientific creativity.[7] This need is amplified by the networking capabilities of computers. More reliance upon data collection and interpretation in real time at the terminal in the office demands more focus and concentration. As lab instrument control software improves to permit adjustment of experimental conditions in the lab from the office, this need will heighten.

Attention to personal needs is important for recruitment and retention. Most companies project percentage personnel growth in double digits. Combined across the industry, the demand for skilled labor is unprecedented and rapidly outstripping demand, creating intense competition. The current generation of pharmaceutical laboratories have upped the ante of personal amenities over previous facilities. Without question, most scientists are drawn to employers for compensation and professional opportunities. However, if those are equal between two companies anecdotal evidence suggests design can influence the decision. All these factors, plus the strategy to keep workers on site as much as possible combine to change the compositional patterns of R&D buildings. The result is a greater integration of laboratory, office, and amenities. This extends to the R&D campus. **The demand for multi-functional buildings or campuses creating communities by supporting more than just technical activities are more prevalent.**

Technology Remains the Engine of Pharmaceutical Innovation

Rapid improvements in technology have spawned change at all levels of the R&D organization. The technological ability to analyze and synthesize molecules continues to grow at a pace difficult for any individual to grasp. This factor alone is spawning change. Attempts to capitalize on new technologies and create the optimum multidisciplinary team for speed-to-market purposes potentially compromises both activities. Product focused R&D continues to promote the multidisciplinary interaction of specialists for varied perspectives on a single compound. Recognizing this may allow insufficient exploration of new technologies. Technology exploration is being pulled off line from product development. The new groups focus upon fully understanding the technology and its applicability to pharmaceutical R&D problems. Concentrating upon this exploratory activity promotes a more organized consideration of technology investments - an important factor when considering the potential investment options. When a promising new technology is found, its application can be refined to facilitate large-scale release and rapid implementation across the organization.

New technologies influence all of the basic sciences; therefore, fundamental facility types are changing. Utility infrastructure designed to meet either fume hood or instrument needs continues to define basic lab types as either exhaust or heat load driven. There are developing refinements that are important to the support of different activities which lessen the difference between these two archetypes. It is evident that the increase in equipment and instrumentation will continue. The sheer volume of motors and computers in labs could increase heat load so significantly that the volume of air needed to cool the lab will be comparable to the volume needed to balance exhaust driven labs. More efficient architectural and engineering approaches to managing heat gain and control costs, such as using chilled water to directly cool large instruments, are likely to become common. It also is reasonable to expect further consolidation of lab computers through the development of common software platforms. Instead of each instrument having its own computer, a single multitasking server could serve several instruments at once.

Another example of change is the need for product protection. Emerging lab types focus upon containment of hazard and/or isolation to ensure product protection. Lessons from controlling manufacturing facility costs created the use of barrier technology. Special environments were created around key process steps rather than for the entire room or facility. This approach is being applied to those processes in the R&D lab.

New technologies combined with computational power is the major force changing laboratories. As the cost of labor rises and the cost of computing drops, automation of R&D processes will continue. The goal is to increase throughput by automating as many routine tasks as possible. The philosophy is to automate what does not require special expertise or intuition. The goal is being achieved in all lab areas. Currently, most every technique is touched by some sort of automated process.[8,9] In the past, most automation served analytical instruments to provide unattended batch analysis. The most striking changes have occurred as analytical sensitivities improve. This is the true manifestation of doing more with less. More powerful instruments allow scientists to study molecules with less samples. This makes it possible to reduce the target volume of the chemistry to be performed to a scale appropriate for automation. As a result, both preparative and synthetic chemistries are becoming automated in variations of the high-throughput approach.

Automation affects the laboratory in several important ways. Most notable is space. Automation lab tasks simply translated to more space per person - *Figure 3*. **Benchmarks for labs where manual processes have dominated labs are meaningless for new automated R&D.** There is some good news in that instruments themselves are changing to respond to the laboratory space crunch. Stacked configurations to save bench space are now the norm. Improved instrument sensitivity in detection technologies allows greater micronization of processes and instruments.

Sensitivity enhancements put pressure on electrical systems. Electrical and data networks are changing character. Data network access is simply increasing; however, the need is greater than just more connections or more capacity. Robotics and automation rely more upon 220/240vac than before. Of major importance to sensitivity and robotics is the quality of the power. Computer directed automation and high resolution lab instruments need clean, uninterrupted power. The R&D organization derives no benefit from investing in automated processes for overnight or 24 hour-a-day operations if power is interrupted to a key component or contributes to background noise. Poor power forces the scientist to look for localized backup. This forces a vicious and costly sequence of benchtop redundancy for localized protection of power, increased heat loads, more space consumption, overcrowding, failure of heat labile reactions, and more.

Ventilation needs and strategies also are affected due to the nature of what is to be ventilated. Automated processes use less volume of chemicals, but venting remains important. Containment remains the preferred strategy over air intensive capture. The change is in the type and size of containment device and the manner in which it is used. Robots are generally quite large linking multiple instruments. Some provide localized containment and, thus lower air flows. Some require an enclosure with access to all sides forcing air into the center of a space. Because operations are unattended, some solutions employ different ventilation rates for set-up, clean-up, and operating modes. Operating mode evacuation rates are lower

Figure 4. Utilities need to be both accessible and out of the way to promote flexibility. Ceiling mounted utilities, which are migrating from manufacturing suites to the lab, accomplish both objectives.

than those required to provide personnel protection face velocities at openings.

Advances in instruments and their proliferation are a major design issue. Nuclear Magnetic Resonance (NMR) enhancements have improved their applicability to pharmaceutical R&D.[10] This has resulted in their proliferation. In brief, the major impact is on space for safe operations near a magnetic field and utilities to power and cool the instruments. Instruments also force design solutions to consider alternatives as to what is built into a lab. As instruments become self contained or mobile, the need for lab benches fades. Conversely, the need for utilities grows. In the past, the lab bench was the support for utility terminals. When the bench disappears, other solutions need to be considered - *Figure 4*.

Protecting Worker Safety Adds Value

Long ago, employers realized the value of protecting worker safety. First provided to fulfill legal and ethical responsibilities, a safe workplace was soon found to be more productive. Skilled workers could stay on the job longer and they could focus upon the tasks at hand knowing health and safety had been significant considerations in workplace design.

There is an inseparable relationship between health and safety issues and facility design. Nearly all health and safety guidelines are implemented by the interdependent application of appropriate protocols, equipment, and facility design to workplace hazards. Continual advances in health and safety create continual, often significant change in R&D facility design.

Several factors spur changes:

- New materials and methods are constantly introduced to the workplace, requiring health and safety action on the basis of right-to-know legislation.
- Workplace incidents receive great scrutiny and result in heightened awareness and improved practices and engineering controls.
- Routine medical surveillance and monitoring efforts toward long term worker health produce similar results.
- Medical research and allied professions identify new work related health concerns.
- When the most recent guidelines are developed and applied to the latest facility, there is a recognized need to apply them uniformly across the organization. This frequently results in the renovation or upgrade of existing facilities.

While employer awareness and legislative mandates are the primary forces focusing attention upon employee health and facility safety, architects and engineers contribute significantly. Current legislation authorizing the professional practices of engineering and architecture identifies two professional responsibilities which, when combined, encourage continuous improvement in how the workplace fosters safety. The first responsibility of licensed professionals is to safeguard the life, health, and safety of the public. The second is to protect property. The result is constant vigilance to deliver safe facilities by short and long term cost effective means.

Recent advances in environmental and occupational health and safety for two major pharmaceutical activities – animal care and chemical handling – have significant effect on the design of facilities.

Vivarium Design Benefits from Automation and Protocol Analysis

Research in the pharmaceutical industry focuses upon establishing the efficacy and safety of commercial products. Current regulations in most countries require extensive testing via experimental models which rely upon animal studies to determine the acute and long term effects of new compounds, dosage forms, and routes of administration prior to their approval for use in the general public.

Optimizing experimentation with animal models is important to limiting animal studies. Studies to improve productivity and maintain herd health are ongoing. An essential element is comprehensive consideration of hazards, work flow and practices, and risk reduction strategies. The characteristics of operations lend themselves to the systematic integration of standard protocols and equipment within a rationally designed and constructed facility to protect worker health. Occupational health studies reinforce how this approach to managing risk and consistently enforcing best practices can have a positive effect on worker health and safety.

Personnel who work in and support vivarium facilities are potentially exposed to a variety of hazards, including the physical and biohazards inherent in animal handling and the chemical hazards of processing tissues and fluids and of handling the chemical compounds being tested. Two occupational hazards have recently received special attention and significantly influence facility design: allergies and asthma and repetitive stress syndrome.

Reducing Allergies and Asthma by Integrating Protocols with Facility Design

Allergies and asthma developed from exposure to proteins pose special problems to animal care workers. Animal proteins are ubiquitous in the vivarium environment and highly prevalent in the general environment where there are animals. They are present in saliva, dander, and urine. Because proteins carry an electrostatic charge, they are spread easily, directly and via aerosol, through the air to work surfaces, on equipment and cages, and in bedding.

The special risk to humans from exposure to proteins is the development of potentially life-long sensitivities which lead to acute and chronic allergies and asthma. The development of these potentially life-threatening conditions often requires the worker to be reassigned where they will no longer be exposed to animal dander. It has been[11] that 11-44% of animal handlers develop allergies and 12-17% subsequently develop chronic asthma. When compared with the 7.6% incidence of asthma in the general population nationally, it is apparent this hazard is important to address.

Adding emphasis to the issue is the recognition that the population at risk to potential exposure from hazards is not limited to individuals working directly with animals. Protein hazards in the toxicology workplace have physical characteristics which allow them to be carried beyond the immediate point of use and beyond the workplace.

Attention to hygiene, especially hand washing, is effective when dealing with contaminated surfaces. The application of universal precautions in the workplace when handling and processing biological fluids and tissues is well documented. Aerosols carry the risk of airborne infections and can be

Figure 5. Design for unit operations requires identification of hazards created by the specialized manufacturing equipment.

created during specimen processing and from the animals themselves. For activities with airborne proteins, the procedural and facility approaches documented in *Biosafety in Microbiological and Biomedical Laboratories*[12] are useful for integrating these precautions with facility design.

To significantly reduce and potentially eliminate the incidence of acquired sensitivity from animal proteins, Fisher describes the application of additional critical practices and elements. The facility must be designed to reinforce these workplace practices. Key areas in this study were to reduce animal density and the frequency of handling, wet cleaning to reduce dust, and encouraging frequent hand washing. Engineering controls applied include filter top cages for housing, a minimum of 12 ACH general ventilation, animal rooms under negative air pressure to surrounding corridors, and equipment for all handling that includes Class I biological safety cabinets, HEPA filtered bedding exchange stations, and down-draft tables. Gowns and uniforms, gloves, hair covers, and respirators are personal protective equipment required to complete this total strategy.

Robotics Improve Throughput and Reduce Repetitive Injury

Physical hazards in the animal facility are among the most conspicuous. Animal bites and scratches, heavy cage racks, and sharp instruments used in procedures have the potential to cause physical trauma and wounds. The immediate and consequential risks are greatly reduced by the proper use of animal handling tools and appropriate personnel protective equipment. Well maintained equipment and facility hardware, good lighting, and convenient rest or break areas are also key factors in reducing physical incidents and risk.

Repetitive stress injury has evolved as an issue because of the shear number of pieces of equipment which require handling on a daily basis. Recent developments in the design of robotic systems to replace manual handling improve throughput for this work and eliminate much of the repetitive motion. The facility design issues associated with robotics in the animal facility are those similar for the integration of any essential production equipment:

- work flow and volume analysis
- integration with related and sequential manual activities
- equipment selection and specification
- utility capacity and quality
- access for utilities, controls, maintenance, and repairs
- strategies for back-up during equipment down-time

Provide Performance-Based Guidelines Where Hazard Control Is Not Fully Defined

The pharmaceutical industry has unique worker health and safety concerns in which facilities play a major role. While most industries endeavor to manufacture products that have no effect on humans, by contrast pharmaceutical R&D is directed at creating a consumer product possessing a high degree of biological activity. A basic goal of R&D in the pharmaceutical sciences is to identify and develop more selective compounds of increasing potency – provide the greatest biological effect with the least amount of drug substance. As technical success in this facet of the industry improves, there is an appropriate rise in the concern for the health and safety of the workers who create and handle these materials and for the environment. The result is higher performance demands upon the protocols, equipment, and engineering controls used to achieve increased confidence in worker safety.

The traditional industrial hygiene approach to limit workplace exposure to chemical hazards has restricted application in the pharmaceutical industry. Typically, exposure control techniques are guided by numerical exposure limits. These are developed from methods which rely upon studies of biological effect. In pharmaceutical R&D, very little dose-response relationship information is known about a compound when it is first created. The primary purpose of early research is to actually determine the physical and biological properties of a new compound. It is simply not possible to accurately establish quantitative exposure limits for new chemical entities before workers must handle them.

What has emerged in recent years as prudent practice for this conundrum is a performance-based approach to limit occupational exposure.[13] The method assigns compounds to a category of exposure control accordingly to inherent pharmacological and toxicological properties of the class of compounds being investigated. In brief, each category defines a containment level corresponding to a proven strategy of safe handling protocols, equipment, and engineering to control exposure. The options range from minimal handling precautions and few engineering controls to instances where open handling is prohibited and full robotics are required. Higher categories incorporate increasing levels of redundancy and deliver greater safety margins. The application of controls usually varies based upon the amount of material used in experimentation. Thus, criteria for the controlled operations in laboratories are different than those for unit operations where the actions of various manufacturing techniques need to be considered - *Figure 5*.

The Performance-Based Exposure Control Limits (PBECLs) work best when the risk inherent in R&D activities is well defined and when practical control measures exist. They provide a rational basis for planning, costing, and constructing facilities. Basic requirements have been identified for new construction or renovation. The PBECL approach illuminates the intent of control strategies allowing a good fit between category of compound and control. In these cases, implementing new PBECLs in R&D facilities are relatively straightforward.

Problems arise when the risk-to-control relationship is not clear and the budget and schedule targets for a

facility project remain constant relative to the previous generation of facilities. It is prudent to assume what was applicable to previous situations should not be assumed to be appropriate for future activities. Multiple factors give each new situation its own special character.

- The PBECL approach relies heavily upon professional judgement and assessments of available data.
- By the very nature of research and experimentation, the full range of activities in any R&D facility are rarely well defined.
- New technologies, instrumentation, and equipment are continually being introduced. As discussed previously, these operations frequently default to existing safety equipment designed for different operations. This one-size-fits-all approach inevitably puts upward pressure on facility budgets because of the ventilation capacity and equipment required.
- Because PBECLs are relatively new to the industry, tested guidelines may not exist. Project execution may suffer due to vague generalities or subjective terms used to describe performance expectations.
- Business mergers frequently join two sets of dissimilar guidelines, resulting in conflicting direction for a new project.
- Prevailing attitudes toward continuous improvement combine with the significance of investment for facility projects to suggest at minimum a confirmation of previous control strategies is required if not total reworking to optimize the impact of the facility investment.

The key lies in the clear definition of performance requirements for exposure control methods linked to a workplace activity. The success of any PBECL depends upon thorough multidisciplinary involvement in their development. Considerable time is required to develop and support the best practices via practical means.

The intense activity to establish PBECLs is best performed outside the schedule pressures of a new project. While the activity is extremely valuable to planning and costing facility projects, a mistimed effort can adversely affect facility projects. If schedules are inviolate and new handling activities are anticipated, unresolved conflicts over exposure control strategies threatens project implementation. If guideline development must be concurrent with design and construction, a dedicated, focused effort to identify and agree on acceptable exposure control measures for the proposed R&D activities is warranted. Should the budget and schedule remain fixed relative to benchmarks of previous facility projects, it will likely be necessary to restrict the compounds and/or handling activities in the new facility to safely match exposure control capabilities.

In both animal and chemical facilities, occupational health and safety are major concerns requiring the expertise of all the stakeholders of a facility project. For each project and for each activity, similar principles apply:

- full understanding of the hazards, their origins, and the routes of exposure
- development of multifaceted risk reduction strategy involving well developed protocols, equipment, and facility design
- constant application of education and continuous improvement attitudes.

Conclusion

The technological and management landscape of the R&D organization is changing significantly and rapidly in the face of competitive forces. Future facility projects can support this change if reasonable effort is made to understand the ramifications of change on current facilities. Careful documentation of emerging deficiencies and their effect on R&D return can be used to justify breaks with established benchmarks and assumptions.

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This article discusses the FDA ruling 21 CFR Part 11, Regulation on Electronic Records and Electronic Signatures and the status of the industry's readiness to comply. The author compares the disparity in readiness between the industry's R&D and Manufacturing segments. He further details the critical issues of adopting electronic document systems, and extensively cites the FDA official who originally developed the ruling.

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Update on Automated Paperless Documentation and Electronic Signatures

by Kevin O'Leary

Back in 1989-1990, the FDA received a citizen's petition from Burroughs Wellcome. This petition addressed the need for the FDA to allow regulated companies to work with electronic records, removing the need for paper and pen-based signatures. That was the starting point. After a long period of discussion and drafting, between the FDA and the industry, the FDA finally issued the 21 CFR Part 11, Regulation on Electronic Records and Electronic Signatures, (Federal Register, March 20, 1997, Vol. 62, No 54). This initiative has provided the foundation for a move by FDA-regulated companies toward electronic management of their records on a day-to-day basis.

When approving, disapproving, checking in, rejecting, or releasing change requests, the user is required to enter their identification ID and secondary password. This is used to validate that user's privilege to perform that function and is an alternative to the personal handwritten signature - *Figure 1.*

The FDA also has complied with the wishes of the industry in defining the method by which companies submit New Drug Applications [NDAs] for review. It is important to note that in each of these cases the FDA was responding to the needs of the industry. As a result, we are now in a situation where the introduction of 21 CFR 11 by the FDA is encouraging companies to work electronically. This seemingly slow evolution from paper records to electronic records is now driving a tidal wave of change in the way information is handled throughout the industry. The FDA has requested that all new submissions are to be made electronically by the end of 2002. Although this is not mandatory, it is clear that all companies that comply can ensure that their NDAs are reviewed as quickly as possible.

The architect of the FDA's 21 CFR Part 11 Regulation was Paul Motise. He was working with a committee that consulted closely with the industry. In a recent conversation with the author, Motise acknowledged that companies will still be able to submit NDAs on paper. He stated that, "By the end of 2002, this [issue of paper submissions] will be a moot point, because companies will have realized significant advantages associated with the use of electronic systems."

To ensure that the move from paper to an electronic world is managed properly across the industry, the FDA is now focusing upon training inspectors to audit and enforce the regulation correctly. To this end, in September of 1999, Paul Motise moved to the FDA's "Office of Enforcement" where he is currently in the process of creating the training program for those inspectors. This training is scheduled to run from the final quarter of 2000 through the first quarter of 2001.

Figure 1. Entering identification ID and secondary password.

	Before EDMS	After EDMS
Becton-Dickinson	10 days	2 hours
Cambridge Life Sciences	5 days	2-3 hours

Table A. Table showing improvement of review and approval times.

Industry Status Report

The status of automated document management within the industry to this point is varied between R&D and Manufacturing facilities.

R&D Update

Most large pharmaceutical companies have already invested in software applications that allow them to submit an NDA electronically, according to AMR Research in a report released earlier this year. There are software solutions that allow R&D centers to gather the hundreds of thousands of pages that need to be submitted to the FDA and publish them electronically.

In a report completed earlier this year, the European analyst organization Strategy Partners noted that companies have been quick to adopt this technology because of their obvious time-to-market advantages. However, even in this apparently automated environment, very few companies have realized the full advantages that can be achieved from a complete Electronic Document Management System [EDMS] solution. Many companies are placing their documents into a controlled document database and then assembling and submitting them. However, they typically are not using software to manage the authoring, reviewing, and approving of those documents prior to their use in the submission. Because of this, they are still operating in a part-paper, part-electronic world, which leads to considerable inefficiencies during the creation and approval of individual documents prior to their use in the NDA.

Manufacturing

Unfortunately, companies have historically focused more attention upon the R&D centers than on their manufacturing operations. Additionally, manufacturing facilities have been heavily restricted both logistically and economically by the recent Y2K issue, where companies have been more focused upon addressing such systems as ERP, than they were on adopting new technologies.

Between 1997 and the end of 1999, there was a major drive to upgrade or replace ERP systems, and some companies went through an explosion of systems installations during this period.

However, other systems also needed to be addressed, including everything from the desktop applications to automated shop floor equipment. For this reason, the manufacturing facilities found themselves handcuffed and only those items driven by Y2K were addressed.

In this background of Y2K activity, electronic document management vendors had to work very hard to add value to their product set to compete in a market that was not expanding at the pace originally envisaged. This has become very evident by the lack of expansion among vendors who supply Manufacturing Execution Systems [MES]. While the concept of a totally electronic batch record has been seen as something of a 'holy grail,' very few companies have actually adopted this technology. In May of 2000, Boston-based AMR Research noted that the anticipated growth of this technology has simply not materialized because it was perceived as too expensive and time-consuming to implement at a time when Y2K was taking precedent.

Where Are We Now?

As we stand here in the second half of 2000, it is still true to say that the FDA hands out more 483s related to documentation than any other issue. In his conversation with the author, Paul Motise noted, "Record management is a problem during audits almost all the time. This is caused by incomplete, contradictory or non-existent records."

The industry is now beginning to take advantage of the new EDMS technologies that are available. This is being driven by two different factors. On one side, the FDA is requesting electronic submissions and auditing for proper use of electronic records. On the other side, companies have realized a considerable financial and logistical upside to deploying such systems. It is hard to attend a conference or seminar in this sector today without a discussion-taking place regarding electronic signatures and electronic submissions. EDMS and electronic submissions appear to be the most important technology issue concerning FDA-regulated companies now.

The good news is that those companies that have not yet invested in this technology can take advantage of the years of development and experience that has been gained since the mid-1990s. Early adopters of these systems invested considerable capital and dedicated several years to building these solutions. This was due to the lack of a standard deployment approach for such systems.

According to Paul Hands, CEO of Qumas, "Today it is possible to purchase 'best-of-breed' EDMS solutions that are focused exclusively upon the FDA-regulated sector. These systems make it feasible to deploy a functionally rich, and regulatory-compliant solution within six months and at a far lower cost than earlier systems."

Companies now accept that they are not alone in addressing these problems. Organizations are finding that they share a common set of business issues and are therefore able to take industry-standard solutions with little or no modification required. After all, everybody is working under the same umbrella of FDA regulations.

This availability of standard solutions now makes it feasible for smaller and medium-sized companies to invest in the technology. Up to this point, only those companies with deep pockets could invest in and reap the benefits from an EDMS solution.

Where Does the Industry Go From Here?

We are now in the middle of a feeding frenzy in terms of the number of systems being purchased and the rate these systems are going live. Companies have emerged from the stagnation of Y2K and are racing to meet the looming deadline of the FDA. Where previously, companies were happy to concentrate on a small group of key users, they are now extending the reach of EDMS solutions to every desktop in the organization. The technology that was once reserved for critical NDA submission teams or document control departments is now critical throughout the enterprise.

Companies now realize that if they do not adopt a strategy in the near future, they will not be capable of competing with their peers or meeting the demands of the FDA. It is unreasonable for a company that has never worked with an EDMS solution to suddenly turn around in the middle of 2002 and

move to electronic submissions overnight. This type of last-minute, knee-jerk reaction will inevitably put excess strain on the company.

According to Paul Motise, "The toughest thing for companies in this sector is to keep up with emerging standards and products. For example, if you ask a company about the latest sterile technology, they are not only aware of it, but are strategically keeping up to date with developments. The same [awareness] is not true with the e-signature regulations." This indicates that there are still a significant number of companies that need to create an initiative to deploy and maintain an e-signature standard.

Advantages of Adopting EDMS

Since companies today share more common denominators than distinctions, they are positioned to take advantage of the years of development work and experience that has been gathered to this point. An off-the-shelf solution from a provider with the appropriate industry expertise provides a number of benefits.

- **Faster Deployment:** An off-the-shelf system eliminates the specification and modification cycle, along with all of its timing and cost uncertainties.
- **Cost Savings:** Off-the-shelf systems offer a significant reduction in required services.
- **Simple Validation and Training:** All validation protocols can be provided by the vendor, and the software packages typically include off-the-shelf training courses.
- **Rapid ROI:** Reduced deployment time leads to a more rapid return on investment. The long-term cost of ownership is clearly defined by a maintenance contract and eliminates the need for maintaining in-house programming resources.
- **Low Risk of Failure:** The simplicity of the installation compared with a customized solution decreases the possibility of failure.

One caveat is that late adopters will miss the opportunity to capitalize on many of the advantages that would otherwise be gained from utilizing an off-the-shelf solution.

Advantages of EDMS Solutions

The move to electronic systems has a significant upside for companies that make the investment. Tangible benefits include:

- rapid approval of changes to documents
- immediate accessibility to up-to-date documentation enterprise wide
- total compliance within the revision control process
- substantial time-savings for document retrieval
- accountability and electronic auditing of all document transactions
- reduced manpower for management in comparison to paper document management
- faster FDA review of NDAs
- facilitates adoption of global document formatting standards
- automated creation of production batch records

Companies that have adopted an EDMS solution for the creation, review, and approval of documents report reductions in review times of up to 70 percent - *Table A*. Commenting on his company's EDMS solution, Becton Dickinson Quality Assurance Manager John Mackey noted recently that *change orders that previously took seven to ten days in his company's old, paper environment can now be handled in one to two hours*. Sally Gale of Cambridge Life Sciences reported, "Qumas reduced the review cycle time from an average of five days to two to three hours."

Companies that make their documentation available online eliminate concerns associated with lost paper copies, or out-of-date documents being circulated. An electronic revision control process is simpler to audit, track, and expedite throughout the enterprise. Cross-site approvals can be carried out seamlessly. The simple ability to retrieve documentation without having to physically walk out of, or across an office or department can result in huge time-savings on a daily basis. The army of people previously dedicated to photocopying, distributing, and tracing paper documents can be usefully redeployed to carry out higher value functions for the company.

As manufacturers go paperless, the EDMS solution immediately makes their information accessible by choice to sister companies or to other business partners such as contract manufacturers. EDMS provides companies with the ability to:

1. control documentation that the contract manufacturer has access to
2. audit how the subcontractor is using the information

Another major advantage associated with using an EDMS solution is the fact that it allows multiple sites to develop a consistent format and document layout approach. This single corporate documentation format makes it very easy for manufacturing to move product manufacturing from one facility to another. Today's pharmaceutical companies require the ability to move manufacturing between locations for cost and market penetration purposes.

Options for Deployment - Buy Versus Build

It is no longer necessary for companies to install a generic document management database and then build a specific application that is unique to them. This approach was used for many years because of the lack of availability of standard solutions. This either tied up considerable internal resources or involved the contracting of a systems integrator for a long period of time.

The move to industry-focused solutions is the next natural step in the evolution of EDMS systems. As the user community becomes more educated, it will demand a total-solution approach from the vendor. Since companies today share more common denominators than distinctions, they are able to take advantage of the years of development work and experience that has been gathered to this point.

One of the more recent developments in this marketplace is the emergence of Application Service Providers [ASPs] as a vehicle for deploying applications quickly and easily. This model involves the use of an external host server upon which the application and documents are stored. Users access this server through their Web browser.

Until recently, companies that decided to go into a paperless or electronic document management environment had no choice but to purchase and manage the infrastructure associated with that system. As the functionality that is required becomes more standardized and readily available, it is now possible for ASPs to provide that functionality and make it available through a browser without requiring a large initial capital investment.

Document management vendors now have to change their pricing model to facilitate this change in delivery. The resulting solution is driven by a revenue-cost model, as opposed to an up-front capital cost. Companies are using this model as an easy way to adopt an EDMS strategy. This allows them to build their initial system at minimal cost while proving the technology, and at the same time changing the culture of the organization. Some of these companies will then make the full investment to deploy the system in-house once they are satisfied with their system choice. Other companies are finding that the ASP model provides a total solution that delivers significant long-term advantages. These advantages include minimal up-front cost, reduced cost of ownership, reduced IT involvement, and easier to upgrade.

One of the great questions surrounding the ASP model, especially within the regulated environment, is that of security. Most companies recognize that their documents represent a huge intellectual asset and are reluctant to trust that asset to a Web-based environment. As a result, the security surrounding this type of deployment needs to be bulletproof. Fortunately, this can be achieved with various layers of security, including:

- secure databases at the host location
- encrypted documents within the database
- encrypted transfer of documents
- firewall at user facilities
- password access to the application in compliance with 21 CFR Part 11
- biometric signatures on the document

In conjunction with all of these things, the end user must undertake the usual audit of the host company and is still obliged to validate the application, just as they would with any in-house application. However, it is feasible for such an architecture to meet the FDA guidelines on open systems.

Cost of Admission

From a financial point of view, it is feasible for companies to invest no more than $250,000 for a system that contains electronic document management, day-to-day revision control, and an electronic submission. A system in this range would include:

- electronic document management
- day-to-day revision control
- electronic submissions
- regulatory compliance with the FDA, EMEA, and ISO
- full validation protocol test scripts
- rapid deployment capability across the organization

Such costs assume that the company takes existing, standard applications and molds its own company to work with those systems without modification. However, the advantages of doing this far outweigh the options of redefining and reengineering a generic application. This entry cost enables companies across the industry to achieve compliance and reap great business rewards.

About the Author

Kevin O'Leary, President of Qumas, Inc., co-founded the organization in 1993 as an enterprise compliance management software company dedicated to serving regulated industries. Since then, Qumas has become the fastest growing company in the regulatory compliance sector. O'Leary began his career in the Aerospace industry, focusing upon the production and process areas, where he developed extensive knowledge of the requirements of regulated industries and the IT required to support them. Over the past decade, he has acquired extensive knowledge of pharmaceutical and medical device regulations and associated key issues. O'Leary has been a featured guest speaker at many conferences and has authored numerous articles and publications addressing the needs of regulated companies worldwide. He serves as a member and frequent guest speaker for several key regulatory organizations including DIA, AIIM, and RAPS.

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For more on Electronic Documentation, turn to page 96.

This article reviews the current status of the Baseline® Guides and includes new Guides under development.

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Baseline® Pharmaceutical Engineering Guides Update

Including Progress of Volume 6: Biotech (Draft)

Forward

The Baseline® Guides are a series of volumes produced in partnership with the FDA and industry representatives from a broad spectrum of the pharmaceutical industry. The Baseline® Guides aim to provide engineers and other professionals in the pharmaceutical industry with baseline information on the design construction and commissioning of new and renovated facilities, equipment and systems to achieve regulatory acceptance.

Three Baseline® Guides are available from ISPE. Two Baseline® Guides are due for publication this year, and a further two are under development.

It is important to understand that the Guides are not regulatory documents.

For Further Information

Executive summaries of the published Baseline® Guides, and those which are due for publication this year, are available on the ISPE Web Site at www.ispe.org.

The summaries describe both the scope and purpose of each Baseline® Guides and provide a detailed synopsis of each chapter. They are produced by the ISPE Technical Documents Steering Committee Editorial Team.

Published Baseline® Guides

The following published Guides are currently available from ISPE.

Volume 1: Bulk Pharmaceutical Chemical Facilities (BPC) Guide

The Bulk Pharmaceutical Chemical Facilities (BPC) Baseline® Guide was originally published in 1996. A full external review and revision of the BPC Baseline® Guide is now in progress and will solicit comments from those within the industry who have used this Guide. Comment on the Guide will be made available on the ISPE Web site.

Volume 2: The Oral Solid Dosage Guide

Published in 1998, The Oral Solid Dosage Guide applies to facilities producing tablets, capsules and powders.

Volume 3: The Sterile Manufacturing Facilities Guide

The Sterile Manufacturing Guide has proved popular since publication in January 1999. It applies to facilities for aseptic processing of formulated product.

Two New Baseline® Guides Soon to be Published

The following two Baseline® Guides are categorized as a **Horizontal** Baseline® Guides and, as such, provide detail of concepts that are covered briefly in the **Vertical** Baseline® Guides that apply to specific types of manufacturing operations.

Volume 4: Water and Steam Systems Guide

The Water and Steam Guide has completed review with the FDA and is intended for publication in time for the ISPE Annual Meeting in San Diego. The Water and Steam Guide applies to systems affecting all types of manufacturing facilities.

Volume 5: Commissioning and Qualification Guide

The Commissioning and Qualification Guide is intended for publication by the end of this year. This guide has already had significant input by the FDA on a chapter-by-chapter basis and is set for a final review by the FDA.

New Baseline® Guides Under Development

Volume 6: The Biotech Guide

The scope and purpose of the Biotech Guide have been established using significant feedback obtained during presentations relating to the Guide, in both Europe and the US. The content of the Guide has been outlined in detail, and writing of the draft content is now in progress. A more detailed description of the progress of this Guide is given below.

Volume 7: Packaging and Warehousing Guide

The Packaging and Warehousing Baseline® Guide will be the seventh Guide in the Baseline® series. Packaging and Warehousing will be a horizontal Baseline® Guide. It will cover, in detail, those topics related to packaging and warehousing which are touched upon by the vertical Baseline® Guides.

The scope, outline and early chapters of this Guide are currently under development, with several important issues being considered, including any correlation with the Technology Transfer Guide.

Following the success of previous guides, it is intended that the guide have a joint European and US team. Anyone wishing to become a member of the Packaging and Warehousing Baseline® Guide Team is asked to contact Gloria Hall (Director of Publications) at ghall@ispe.org.

The scope of the guide has not yet been finalized and team members joining at this early stage will be able to contribute to the definition of the final structure of the document.

Biotech Baseline® Guide Update

The Draft Biotech Baseline® Guide scope and structure have been established using feedback obtained from presentations relating to the Guide during the early part of this year. The Guide was first presented in Europe and a second presentation was given just a few weeks later in the US.

The Guide development has been lead by a Steering Committee with both chapter teams and focus groups concentrating on specific aspects of the Guide. Reviews of content will be performed on a regular basis by teams from both industry and the FDA. The detailed outline of the individual chapters of the first draft of the Biotech Baseline® Guide has been established and writing of the draft content is now in progress.

The draft contains eight chapters and several appendices, including European perspectives on issues dealt with by the Guide. The pattern of the early chapters of this Guide follows the pattern of preceding Baseline® Guides, with Chapter 1 describing the background, goals, scope, and key concepts of the Biotech Guide.

The Guide aims to clarify common industry issues and help reduce ambiguity in requirements.

To avoid repetition, operations and systems that are common to the pharmaceutical industry, such as pharmaceutical water and steam or commissioning and qualification, will be addressed by cross-referencing other Baseline® Guides. Any differences inherent to biopharmaceutical processing will be described.

The Biotech Baseline® Guide is intended to be used for the design, construction, commissioning and qualification of facilities and processes for the production of biotechnology products. For the purposes of the this Guide, biotechnology products include large molecules that are not manufactured by means of chemical synthesis, and products produced by means of fermentation and/or recovery, sourced from genetically-engineered organisms.

The Guide is intended primarily for facilities that meet regulatory requirements to supply the US market, and follows US standards and references. Issues relating to European requirements are discussed in the Appendices.

Chapter 2 deals with regulatory aspects of biotechnology and positions biotechnology in relation to bulk pharmaceutical chemicals (BPCs). Open and closed systems are discussed and international inspections are considered.

Chapter 3 focuses on the concerns and issues of production management, process operators and other plant support personnel. This chapter addresses key issues, such as the impact of open versus closed systems, multi-product operations and clinical trial versus commercial production. The operational aspects of a biopharmaceutical facility, as opposed to the physical design of the facility itself, are addressed.

Chapter 4 concerns the design and operation of processes. Process equipment that comes into contact with a product, or its components, at a stage in the process where it could influence the quality, safety, purity, strength, or identity of the ultimate product is considered.

Chapter 5 on Process Support concerns itself with the design and operation of process support systems that only "indirectly" impact the manufacture of a bulk product. Regulatory Issues include a description of how specific facility issues, such as personnel flow or room pressurization, impact (or are impacted by) process support systems.

Chapter 6 considers integrated facility design and discusses the interrelationships between the primary design disciplines that shape the modern biotech facility.

Chapter 7 on Process Control and Automation is intended to provide points to consider when developing an automation and instrumentation strategy for Biotechnology operations. Issues unique to Biotechnology are covered. Determining the optimal level of automation from both the technology and business factors is discussed.

Chapter 8 considers Commissioning and Qualification of biotechnology facilities. It also discusses process validation and the relationship between facility/equipment qualification and validation.

Along with European regulatory issues, the appendices provide cross-references to other Baseline® Guides and standards, and a glossary.

This first draft of the Biotech Baseline® Guide is intended for presentation during the ISPE Annual Meeting in San Diego, California.

For details on ordering Baseline® Guides, contact ISPE at tel 1-813/960-2105, fax 1-813/264-2816, or visit the Society's Web site at www.ispe.org.

This article outlines the structure of the international pharmaceutical industry and its chemical engineering needs.

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The Education of Chemical Engineers for Roles in the European Pharmaceutical Industry

by John E. Gillett

Statistics from a population of chemical engineers working in Europe for a large multi-national pharmaceutical company are used to explain the evolution of chemical engineering roles to meet the needs of the international pharmaceutical industry. This article identifies specific knowledge and attributes required by chemical engineers working in the industry. The evolution of chemical engineering educational courses to provide this knowledge is described in Table D. The article concludes with the author's suggestions for educating chemical engineers who plan to work in the pharmaceutical industry. In the context of this article, chemical engineering and process engineering are synonymous.

The International Pharmaceutical Industry

The international pharmaceutical industry is a high-value, low volume, research-based industry that is projected to grow at 7.8% per year over the next five years. The worldwide pharmaceutical market was valued at more than €273 billion ($260 billion) in 1998 and by 2002 is expected to be more than €364 billion ($346 billion).[1] The main markets are North America (43%), Europe (29%), Japan (15%), Latin America (8%), SE Asia and China (5%).

The global pharmaceutical market is very fragmented. For example, the largest pharmaceutical firm has more than 4% of the global market, and the top 20 companies share more

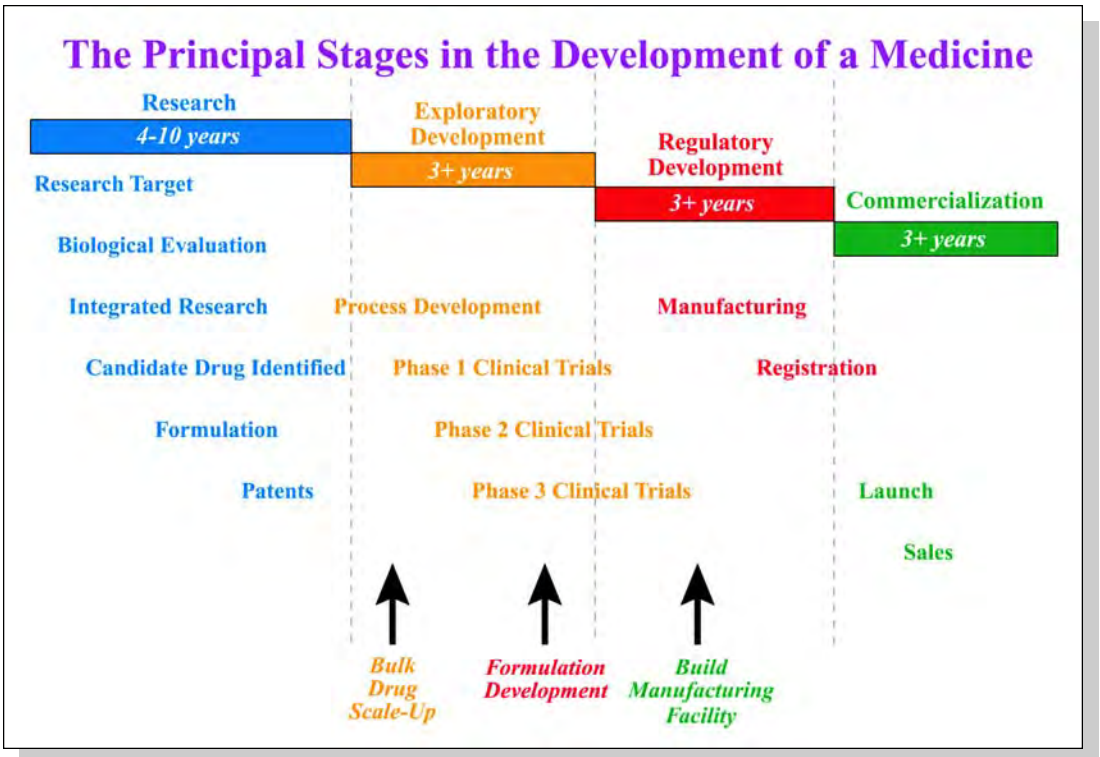

Figure 1. The principal stages in the development of a medicine.

> ***The pharmaceutical industry is expanding and provides good career opportunities for chemical engineers at all management levels.***

than half of the world market. Forecasters predict that this fragmentation will reduce over the next decade and that acquisitions and mergers will result in about 10 major multinational companies.

There is a high investment in research. The pharmaceutical industry spends more than €30 billion ($28.5 billion) on R&D resulting in the discovery of about 40-50 new chemical entities every year. The market leaders spend 15-20% of sales on research and development. Few chemical engineers are employed in pharmaceutical R&D except as specialists in biotechnology, chemical reaction or powder technology. Most chemical engineers employed by the major pharmaceutical firms work in production or capital projects.

The industry has always made effective use of contractors for manufacturing and for engineering capital projects. Some chemical engineers enter the industry by working for engineering contractors who are employed to run capital projects for manufacturing or laboratory facilities.

The industry relies upon effective quality assurance of its products, and Good Manufacturing Practice (GMP) is essential to process operations. A strong quality culture is a key factor to success in the industry. However, the industry is heavily regulated and the cost of registering new products, validating processes, and compliance with regulations is very high.

The Life-Cycle of a Pharmaceutical Product

The life cycle of a typical pharmaceutical product occurs in four stages: research, exploratory development, regulatory development, and commercialization - *Figure 1.* The time from discovery to product launch ranges from 10 to 15 years depending upon the development problems and activities to comply with regulations - *Figure 1.* The main opportunities for chemical engineering input to process development and design are during route selection and scale-up from the laboratory, during formulation

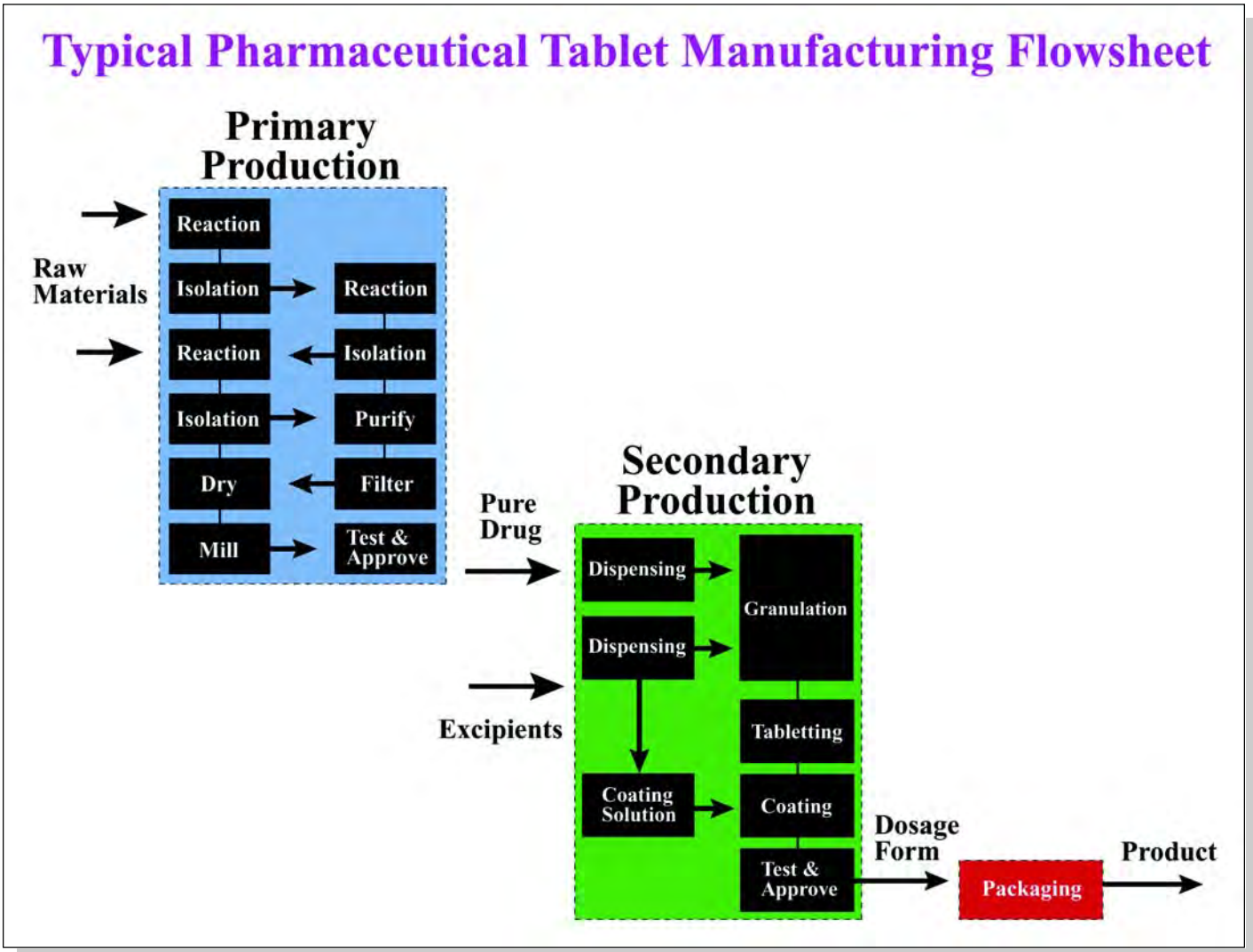

Figure 2. Typical pharmaceutical tablet manufacturing flowsheet.

DISCIPLINE	1976	1976	1998	1998
	NUMBER	%	NUMBER	%
Chemistry	360	45.8	759	32.4
Pharmacy	80	10.2	115	4.9
Biology & Pharmacology	100	12.7	430	18.4
Engineering *(Chem. Eng.)*	60 *(20)*	7.6 *(2.5)*	198 *(72)*	8.5 *(3.1)*
Biochemistry	50	6.4	194	8.3
Mathematics	25	3.2	91	3.9
Medicine	20	2.5	122	5.2
Veterinary Science	15	2.0	13	0.6
Physics	10	1.3	30	1.3
Other Sciences	15	2.0	158	6.8
Arts, Law, Languages, etc.	50	6.3	229	9.8
TOTAL	**785**	**100**	**2339**	**100**

Table A. Employment of graduates by discipline in a typical UK pharmaceuticals firm.

development, during the final capital project to provide facilities, and during commissioning.

The chance of finding a therapeutic molecule that will be a commercial success is about one in 5000.[2] This is one of the reasons for the large expenditure on research. Toxicological work and clinical trials to prove the effectiveness of products and to comply with regulations add to the basic research costs. Once a new chemical entity has been patented, the patent life, which varies worldwide, is limited to 15-20 years. Thus, pharmaceutical products must recoup the R&D costs over a short time span, before competitors can capture the market. Therefore there is a strong incentive to reduce the time from discovery to market launch. This time constraint reduces the time available for process optimization and development so pharmaceutical companies often buy equipment and processes developed elsewhere. The resultant manufacturing processes are sometimes inefficient and unreliable. There is a significant opportunity here for chemical engineers to develop and design processes ahead of demand.

Categorization of Pharmaceutical Products

There are two basic categories of pharmaceutical product: Ethical and "Over The Counter"(OTC). Ethical pharmaceutical products can only be purchased by a medical practitioner's prescription. OTC pharmaceutical products, such as aspirin, are those that can be bought without a prescription. After patent expiration, any supplier who can meet the regulatory standards can manufacture an ethical pharmaceutical product. Such products are called Generic Pharmaceuticals as they are sold by the generic name of the active constituent named in the original patent. Generic and OTC pharmaceutical products are usually manufactured to the lowest cost allowed by quality constraints. Few chemical engineers work in generic or OTC manufacture, but the opportunities are nevertheless significant.

Dosage Forms

The bioavailability of the active drug in a patient depends to a large extent upon the dosage form. A wide range of dosage forms has been developed and the selection of dosage form is a crucial step in the development cycle of a pharmaceutical product - *Figure 1*. The preferred form is the tablet as this is easy to take and has good stability. Other solid dosage forms are powders, spheroids, suppositories, and capsules. Biodegradable implants, skin patches, and other attachments are used to control drug delivery over a time period. Liquid, cream, and ointment dosage forms are used for external (topical) application. Syrups also are used for ingestion. Parenterals are injected into the blood stream. Aerosols are used to dose liquid or solid particulates. Gaseous dosage forms are used for anaesthetics. The technology used to produce dosage forms is very specialized. However, chemical engineers with a basic knowledge of pharmacy can make major contributions to the multi-disciplinary teams involved in dosage form design and development by providing a systems approach to integrate the dosage form into the manufacturing processes.

Manufacturing Processes

Primary Processes

Pharmaceutical manufacturing is performed in two basic stages: Primary and Secondary - *Figure 2*. Primary processes manufacture the crude bulk drug and purify this to provide the pure Active Pharmaceutical Ingredient (API). Primary manufacture is mostly fine chemical processing although biotechnological processes have been used widely and are becoming more effective using genetically modified organisms. Batch processing is the norm for primary manufacture. The chemical routes can be very complex and many reaction and separation stages may be required to make the crude drug. Biotechnological processes require aseptic feed systems and special cleaning and sterilization equipment, and efficient separation of the active drug is often difficult. Chemists, biochemists, and chemical engineers are usually responsible for primary process development. Chemical engineers can enter pharmaceutical primary manufacture directly after graduation and most are employed in this area. A good knowledge of organic chemistry and batch processing is essential. *(See Section on specific attributes).*

Secondary Processes

Secondary processing, often called formulation, involves the production of the final dosage form - *Figure 2*. The active ingredient is combined with excipients to optimize bioavailability and enable the dosage form to be stabilized. Formulation processes are normally operated batch-wise. Many different processes have been developed to make the wide variety of dosage forms available. Pharmacists have been responsible for formulation development for many years.

Knowledge of particle technology and materials handling is essential for the manufacture of tablets and spheroids. Granulation of active powders with poor flow properties is necessary to convert them into free-flowing granules that can be fed into high-speed tablet compressors. Many granulation processes have been developed to overcome process and dust control problems involved. Tablets are usually film-coated using equipment that poses interesting simultaneous heat and mass transfer problems. The sterile production of parenterals requires knowledge of microbiology and GMPs. Effective process control and quality assured operating procedures are crucial. The concepts of integrated systems and formulation engineering are being applied in the industry, and chemical engineers with an education in these concepts can contribute significantly in these areas.[3]

Packaging

Once the dosage form has been made, it must be packaged for distribution, ultimately to the patient. Packaging technology to protect and identify the dosage form is well developed in the pharmaceutical industry. New packs such as blister packs also can improve dosage compliance. The final packaging processes depend to a large extent upon the dosage form and package design. There is a wide variety of packaging in use and under development. Tubes, bottles, and blisters are used for tablets, spheroids, and capsules. Bottles, sachets, tubes, vials, ampoules, and pre-filled syringes are used for liquids, creams, ointments, and parenterals. Particulates are packed in specialized inhalers or aerosol cans. Specialized packs are required for pre-filled syringes, implants, and implant injectors.

Packaging technologists usually perform package development. Mechanical and production engineers who work with packaging technologists usually develop packaging equipment and processes. Chemical engineers rarely work in packaging except as line managers, but some have made significant contributions to risk assessment and integrated systems development and design.

Quality Assurance

Effective quality assurance is essential for successful pharmaceutical businesses and is firmly regulated in all countries. In Europe, pharmacists usually manage Quality Assurance (QA) and in several countries (e.g. France) this is required by law. Chemical engineers working in the pharmaceutical industry must learn and understand the principles of Good Manufacturing Practice (GMP). Chemical engineers are usually required to have post-graduate education or additional pharmacy degrees to manage QA in the European pharmaceutical industry.

Safety Health and Environment Management

Good Safety, Health, and Environment (SHE) management is essential for successful pharmaceutical operations.[4] The processes often use inflammable solvents and dusts, energetic reactions, toxic and biologically active materials, and environmental pollutants. Society also demands involvement in risk decisions and regulation, particularly those that can affect the environment. There is an increasing drive to develop a sustainable technology to protect the quality of life for future generations. It is thus not surprising that risk assessment is becoming an important decision-making tool in the pharmaceutical industry. There is significant scope for chemical engineers with suitable education in risk assessment in this important function of the pharmaceutical industry.

Employment of Chemical Engineers

International Employment Market

There are no statistics readily available for the employment of chemical engineers in the international pharmaceutical industry or for those working for contractors who design and build pharmaceutical facilities. The rapid growth of pharmaceutical markets requires increasing capital investment and, as investment in heavy chemicals declines, more process engineering contractors are moving into the pharmaceutical industry.

Rapid communications, by travel or electronics, mean that the physical location of engineers is no longer a significant constraint to their occupation. The main constraint may be language however. English is the technical language most used internationally, particularly for computer software systems. The opportunities for chemical engineers who can speak English and another language are very good in the international pharmaceutical employment market.

European Employment Market

It is estimated that more than 60,000 chemical engineers have graduated from European schools of chemical engineering over the last 20 years.[5] This figure has been increased by the flow of engineers from Eastern Europe. Using specific employment statistics from some of the major European pharmaceutical firms, less than 5% of these (3000) would be expected to be working in pharmaceuticals. In spite of consolidation, markets for pharmaceutical products are increasing in line with the rest of the world, and this is generating significant capital investment. The prospects for chemical engineers working in the European pharmaceutical industry are thus very good.

UK Employment Market

In 1996/97, there were 559 first degree graduates in chemical engineering in the UK.[6] Of these, 250 went into manufacturing industries alongside 3468 other engineers. An informal survey made in the NW region of the UK in 1976 showed that 1400 Chemical Engineers were employed in the region and that 100 (7%) worked in the pharmaceutical industry.[7] Since then the number of chemical engineers working in the region has increased to 2503 and the number in the pharmaceutical industry has more than doubled. It is estimated that in 1999 about 10% of chemical engineers working in the NW region of the UK work in pharmaceuticals. Assuming that this percentage applies throughout the UK, only about 25 first degree chemical engineering graduates would have entered pharmaceuticals manufacturing in 1996/97. It is difficult to assess the chemical engineering resource requirements of the UK pharmaceutical industry, but in the author's opinion, it would seem that there might be a significant shortfall.

The 1976 NW UK survey also showed that of the 100 chemical engineers employed in the pharmaceutical industry, 50 worked in primary production, 10 in formulation, and the rest in other roles.[7] Since that time, although the population working in pharmaceuticals has more than doubled, the distribution between primary and secondary production has remained almost the same. This indicates that there should be many opportunities in secondary production for chemical engineers with the relevant education and experience.

It is useful to compare the contribution of other disciplines working in the pharmaceutical industry with that of chemical engineering. Tables A and B indicate the spread of disciplines of graduates in a typical pharmaceutical firm and the changes in distribution between disciplines and functions over the last two decades.[7] The distribution between the disciplines has changed since 1976 due to market and technological forces (e.g. market growth, acquisitions, product divestments, information technology, fast-track development, etc.).

These statistics show that although chemical engineers still comprise less than 5% of the graduate population in a typical pharmaceuticals firm, the numbers employed have more than tripled over the period studied. There has been a

FUNCTION	1976	1976	1998	1998
	NUMBER	%	NUMBER	%
Senior Management	40	5.1	434	18.6
Research & Development	420	53.5	740	31.6
Medical	50	6.4	140	6.0
Production	115	14.6	390	16.7
Engineering	25	3.2	32	1.4
Marketing & Sales	85	10.8	289	12.4
Mgmt. Services (IT, HR, etc.)	30	3.8	231	9.9
Other (SHE, etc.)	20	2.6	83	3.5
TOTAL	**785**	**100**	**2339**	**100**

Table B. Employment of graduates by function in a typical UK pharmaceuticals firm.[7]

significant increase in the number of other sciences and commercial disciplines employed that is mirrored in the growth of management services such as information technology. The statistics suggest that adaptable and versatile chemical engineers could find additional opportunities outside their conventionally assigned functions.

Chemical Engineering Career Development

The author informally collected data about the careers of 100 graduate chemical engineers who worked for a single pharmaceutical company in Europe during the period 1974 - 1999. In the population studied, 81 chemical engineers entered the firm via primary production roles, 12 entered via secondary production roles, and the rest entered via general management roles - *Table E*. The entry pattern for chemical engineers in the pharmaceutical industry is very similar, but usually with fewer entries to secondary production. Most chemical engineers entered the pharmaceutical industry via primary production.

For the majority of the chemical engineers who joined as graduates, the usual career sequence was to spend the first few years in technical support to production, followed by work in either process development or process design. After gaining experience in this way, those with suitable attributes would move into technical or production management. Alternatively at this stage, some chemical engineers would make radical career changes and move into different functions or leave the firm to develop their individual careers. The most able managers would eventually be promoted to senior management roles that might be across many functions.

During the period 1974 - 1999, a total of approximately 1180 chemical engineer years were worked. Table C lists the number of chemical engineers against their years of service, and their effort input in the period studied.

Table D shows the approximate distribution of time spent in the two main areas of production and the effort distribution across the main chemical engineering occupations observed.

The effort distribution clearly shows the large chemical engineering input to primary production. However, the firm studied has developed a significant input to secondary production. Note that more than half of the chemical engineers working in the "Design/Projects" category were employed as project managers. (This would augment the effort spent in the category "Technical and Production Management"). The effort distribution above is useful to identify educational parameters, and indicates clearly the importance of education in management science and management practices.

If the population is studied on the basis of staff numbers only, the individual career moves provide several other educational pointers. Most chemical engineers entered the industry via roles in primary processing - *Table E*.

The following career statistics, based upon numbers of chemical engineers, indicate some of the key points relevant to their educational needs as undergraduates:

1. 24% of graduate chemical engineers rose to senior management level and about 50% worked in middle-management roles in production, technical functions, and project management. (In 1976, the percentage working in senior management was significantly higher than that of the average graduate - *Table B*. In 1998, it is still marginally higher although other disciplines have caught up during the expansion of graduate numbers).

2. 19% of graduate chemical engineers had PhDs or post-graduate qualifications when recruited, compared with 23% for the graduate population as a whole. 50% of the chemical engineers with PhDs attained senior management level.

3. Only 5% of graduate chemical engineers worked full-time in research departments. 10% of graduate chemical engineers worked full-time in SHE and risk assessment during the period studied although many others did similar work as part of other roles. There has been a significant increase in the amount of work to protect the environment.

4. Only one chemical engineer worked in Quality Assurance although three worked specifically in process validation. *(Process validation is a sub-set of quality assurance.)*

5. One chemical engineer moved into sales and marketing, and two others to human resources management. Several chemical engineers worked full-time in functions such as information technology, production engineering, control engineering, packaging technology, etc. as part of their career development during the period studied.

NO. YRS. SERVICE 1974-99	NO. CHEMICAL ENGINEERS	*PERCENTAGE OF POPULATION*	WORK CONTENT (C.ENG.YRS.)
1 - 4	14	*14*	38
5 - 9	33	*33*	220
10 - 14	21	*21*	227
15 - 19	8	*8*	139
20 - 24	16	*16*	356
25	8	*8*	200
TOTAL	**100**	***100***	**1180**

Table C. Service history of chemical engineers working in a typical pharmaceutical firm.

6. In 1974, no women chemical engineers worked in the firm, but by 1999, 11% of the chemical engineers employed were women.

7. 19% of graduate chemical engineers could speak at least one other language in addition to their mother tongue.

8. 4% of graduate chemical engineers were employed by contractors.

The data indicate that the pharmaceutical industry employs chemical engineers in many different functions and provides good career opportunities for chemical engineers with the relevant attributes. The data provide many useful educational points, but the most significant one, not extracted explicitly, is that holistic thinking is a crucial success factor in the complex systems of the industry. Chemical engineering first degree courses enhance this attribute by work on process optimization, process control, case study work, and the integral design project. The other relevant technical attributes can be gained by suitable university education complemented by industrial training and continuing education. The innate personal attributes also can be enhanced by suitable training and experience. A thorough description of attributes and competencies is outside the scope of this article, but specific requirements of the pharmaceutical industry are described in the next section.

Specific Attributes Required for Chemical Engineers Working in the Pharmaceuticals Industry

Chemical engineers working in the pharmaceutical industry develop their careers depending upon their personal attributes. Several basic career patterns can be observed as individuals move up through the management hierarchy from performing basic tasks to strategic decision-making - *Figure 3*. Most chemical engineers retain and use their technical knowledge and holistic approach to problem solving; however, and use this to further their careers. After many years in a general management role, some individuals, will revert to a technical role at the conclusion of their career.

Human assets are extremely important to the success of the pharmaceutical industry, and employers play a significant part in career development. Nevertheless, there have been considerable cultural and social changes over the last decades. For example, the abandonment of long-term loyalty of individuals to their firm to foster their own career objectives affects the data provided in the section on Chemical Engineering Career Development. After discussions with many chemical

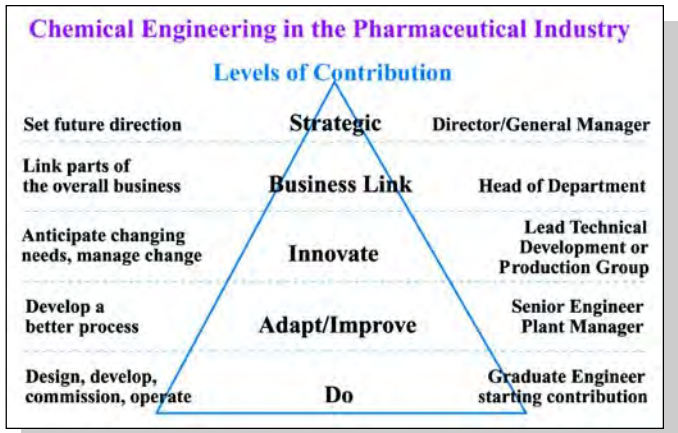

Figure 3. Chemical engineering in the pharmaceutical industry.

engineers working in the pharmaceutical industry, and from literature concerning recruitment and human resource management, the following attributes required for chemical engineers to achieve success in the industry are suggested:

Technical Knowledge: Chemical engineering, batch processing, organic chemistry, particle technology, materials handling, quality assurance knowledge, holistic/systems thinking, risk assessment, SHE management, environmental technology, biotechnology, biochemistry, microbiology, pharmacy, production engineering

Job-Related Skills: Team-working, communication, leadership

Competencies (Behavioral Attributes - How Tasks Are Done): Thinking, self-management, influencing, achievement, people management

Education of Chemical Engineers for Roles in the Pharmaceuticals Industry

In the mid '70s, there was considerable discussion and argument between academics and industrialists in the pharmaceutical industry about the discipline of "Pharmaceutical Engineering." Schools of pharmacy started to develop industrial pharmacy courses.

Several chemical engineering schools considered developing post-graduate courses in pharmaceutical engineering. In the industry, there was a general opinion that multi-disciplinary teams of specialists were better than individual polymaths.

PRODUCTION AREA	PROCESS DEVELPT.	DESIGN/ PROJECTS	TECHNICAL SUPPORT	TECH. & PROD. MGMT.	SENIOR MGMT.	SHE & RISK ASSESSMENT	QA	OTHER	TOTAL
Primary	50	210	210	103	79	34	0	0	686
Secondary	33	33	92	99	34	7	26	22	346
Both Primary, Secondary & Other Functions	0	14	7	8	71	29	4	15	148
TOTAL	83	257	309	210	184	70	30	37	1180
%	7	22	26	18	15	6	3	3	100

Table D. Chemical Engineering Effort Distribution in a typical pharmaceutical firm (The units are chemical engineer years).

However, pharmaceutical engineering began to emerge as a credible discipline.[7]

During the '80s, there were many attempts to improve the pharmaceutical education of engineers and a few distance learning and postgraduate courses were developed. Some universities developed electives in first degree courses aimed at providing engineers suitably educated for work in the pharmaceutical industry. The larger engineering institutions began to take an interest in the concept of pharmaceutical engineering.

In 1980, the International Society for Pharmaceutical Engineering (ISPE) was formed in the USA for engineers and scientists working in the industry and has since expanded globally. ISPE is non-profit-making and has more than 13,000 members worldwide, of whom 3000 work in Europe. ISPE has been very active in the education of people working in the industry and has run many seminars and conferences as well as producing several guides to best practice that are well recognized internationally.

In 1984, the Institution of Chemical Engineers (IChemE) founded the Pharmaceutical, Toiletries, and Cosmetics Subject Group (PTC) in the UK. The aim of the PTC is to organize technical meetings and conferences, and to promote the application of chemical engineering in the pharmaceutical industry. The PTC has about 350 members, mostly from the UK, and includes members from other disciplines. The PTC has done much to further the education of chemical engineers and other workers in the industry and is publishing a useful engineering guide to the industry.[3]

In the '90s, these ideas matured and courses evolved to provide a wide selection of education routes. The range of current courses known to the author (*the list is not fully comprehensive*) is shown in Table F.

INDUSTRY ENTRY POINT:	NO. CHEMICAL ENGINEERS ENTERING
Primary Processing Area	81
Secondary Processing Area	12
Both Areas	5
Other Areas	2

Table E. Chemical Engineering Entry Points to a typical UK Pharmaceutical Firm.

Conclusion

- The pharmaceutical industry is expanding and provides good career opportunities for chemical engineers at all management levels.
- Chemical engineers can provide significant benefits to the pharmaceutical industry that are not yet fully exploited.
- Chemical engineering first degree courses with a good science base provide a suitable foundation for working in primary pharmaceutical processes. The ability to think holistically is important.
- Most first degree courses need to include more education in batch processing, organic chemistry, and biotechnology to meet specific pharmaceutical industry needs.
- Conventional chemical engineering first degree courses are mostly inadequate for direct entry into secondary processing roles.

YEAR OF COURSE LAUNCH	COUNTRY	COURSE TITLE	COURSE TYPE	COURSE DURATION (YRS.)	UNIVERSITY OR SCHOOL	COURSE INTAKE REQUIREMENTS
1995	GB	Pharmaceutical Industry Advanced Training (PIAT)	Post Graduate MSc. Part Time from Industry	3 - 5	University of Manchester	Science Degree
1998	GB	Chemical Engineering with Pharmaceutical Chemistry	MEng Degree	5	Heriot Watt Edinburgh	SARTOR Requirements of the Eng'g Council
1996	GB	Fine Chemicals & Products Manufacturing	Post Graduate MSc (to become MEng 1999)	3	South Bank London	Honors Degree in Chemical Engineering or equivalent
1992	F	Pharma Plus	Double Degree	7	ENSIC Nancy	Degree in Pharmacy
1996	F	D.E.S.S. Production et Controle Pharmaceutiques	Post Graduate Diploma	1	ENSIGC Toulouse	Sixth year pharmacists, MSc., Masters in Chemical Engineering
1993	F	Final year of first degree course Elective + Industrial Work	Elective Genie Pharmaceutique	-	Ecole des Mines D'Albi	
1996	F		Double Degree	7	Ecole de Mines St. Etienne	Degree in Pharmacy
1974	B	D.E.S. Pharmaceutical Engineering & Industrial Technology	MSc equivalent	2	Louvain	Degree in Pharmacy or other degree plus industrial experience

Table F. Typical educational courses for chemical engineers in pharmaceutical industry.

- Conventionally educated chemical engineers who wish to work and succeed in secondary pharmaceutical processes need to obtain suitable education by postgraduate or industrial studies.

- The inclusion of electives in first degree courses, provision of post-graduate courses, or distance learning courses, in pharmaceutical technology are effective ways to educate chemical engineers for roles in secondary production. Several such courses are available.

- The opportunities for chemical engineers to make major contributions to SHE management in environmental technology and risk assessment in the pharmaceutical industry are considerable.

- Good communication skills are essential for working in the multi-disciplinary teams that are favored by the industry. Knowledge of English is necessary for working internationally.

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About the Author

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This article describes a simple model that was developed to identify the cost of non-conformance with quality standards and regulations, and provides the critical information needed to make the quality decisions that improve business performance. It describes how one organization adopted the model as part of a broad strategic initiative, and illustrates examples of how the process is working.

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The Cost of Non-Conformance: The Linkage Between Quality Performance and Business Results

by Terry Dwyer, Georgia Keresty, and Brian Sherry

Introduction

Customer-focused organizations in the healthcare industry have always known the important link between product quality and profits, and that excessive quality failures or non-conformances can hurt business performance. However, many of these same organizations have been unable to translate this understanding into their day-to-day business decisions due to the lack of critical information. This information includes the cost of repeated failures, how much investment is needed to improve quality performance, and how to allocate limited funds between quality and other business improvement projects. In short, these organizations need a tool to *quantify* the potential for improving overall business performance by focusing on improving product quality.

Traditionally, quality professionals have tried to support and justify quality related investment proposals with vague sounding statements such as "required to remain in compliance," or "required to avoid an adverse regulatory inspection." When these investment proposals compete with projects that have quantifiable financial returns, such as sales increases or cost reductions, management is faced with difficult choices and often has to rely upon the credibility of the quality professional to make the correct decision. Often the decision concerning the quality related investment proposal is not made prospectively and management is left responding to adverse quality events and making emergency investment decisions that have negative short-term business impacts.

Finally, many healthcare companies have embarked on total quality and operational ex-

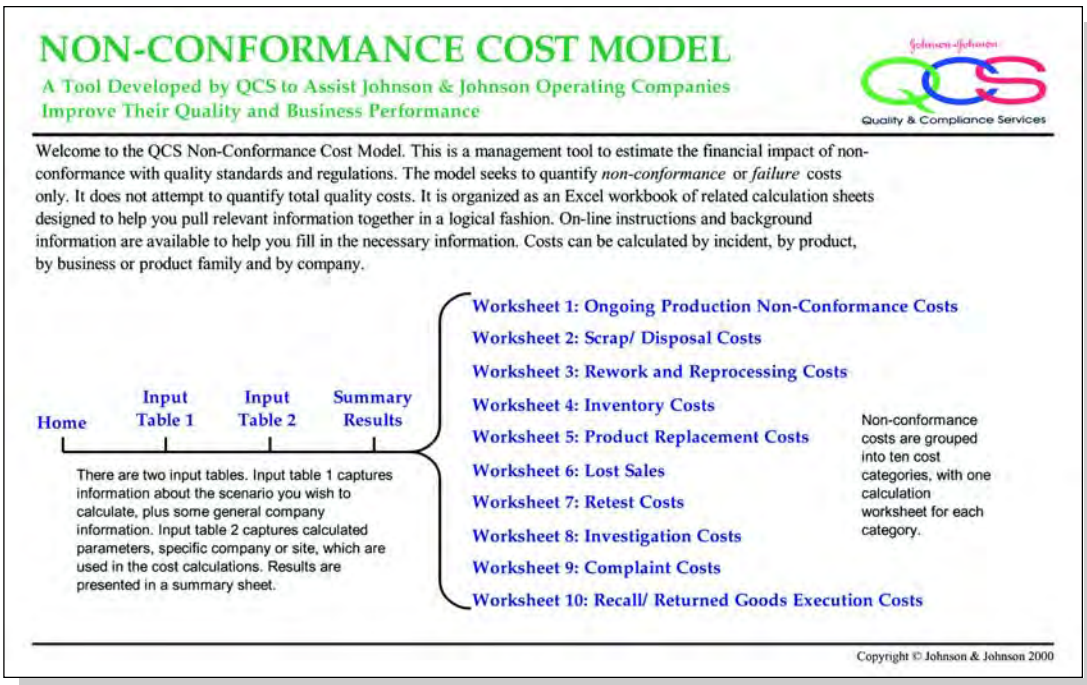


Figure 1. Cost of non-conformance design.

COST CATEGORY	CATEGORY COMPONENTS
1. Ongoing Production Failure Costs	A. Failure Costs build into Standard Costs B. Low Yield Costs C. Additional Material Costs D. Additional Labor/Overhead Costs E. Miscellaneous Costs
2. Scrap, Disposal Costs	A. Material Overhead Costs B. Disposal Costs C. Miscellaneous Costs
3. Rework and Reprocessing Costs	A. Inventory Costs due to Lower Yield of Reworked/Reprocessed Material B. Plant Capacity Costs C. Additional Materials Costs D. Additional Labor/Overtime Costs E. Rework Validation Costs F. Miscellaneous Costs
4. Inventory Costs	A. Excessive Inventory due to Quarantined Material B. Raw Material Replacement Costs C. Inventory Adjustments due to Expiry/Loss
5. Product Replacement Costs	
6. Lost Sales	A. Lost Profits B. Idle Capacity Impact
7. Retest Costs	A. Retest Costs B. OOS Investigation Costs
8. Investigation Costs	A. Minor Non-conformance Investigation Costs B. Major Non-conformance Investigation Costs C. Analytical/Laboratory Costs D. Additional Expenses
9. Complaint Costs	
10. Recall/Returned Goods Execution	A. Planning Costs B. Execution Costs

Table A. Failure cost categories.

cellence programs, using the Six-Sigma methodology, to improve their business performance and produce a competitive advantage. One common theme across all programs of this nature is that they arrive at a clear understanding of the business impact of potential projects and help to select projects that will result in the greatest potential business impact.

This article describes a simple model that was developed to provide the critical information needed to make the quality decisions to improve overall business performance. The ***Cost of Non-Conformance Model*** was developed to capture the business impact of non-conformance with quality standards and regulations. Once this information is understood, managers can determine the positive business impact of reducing non-conformances and make choices between competing projects. While the model was developed to satisfy one organization's particular needs, the concept has applicability to many organizations. Our goal is to explain the model and rationale behind it and show how it is being used to drive change by improving decision making, facilitating prioritization of projects and deployment of resources, and improving quality systems.

Model Rationale

Many authors have written on the subject of quality costs. Most texts on quality costs divide quality costs into four categories: *prevention costs, appraisal costs, internal failure costs, and external failure costs*. Discussion typically leads to accounting for these cost types using an activity-based approach. The Cost of Non-Conformance Model has a narrower and more practical focus which can be summarized in the following four points:

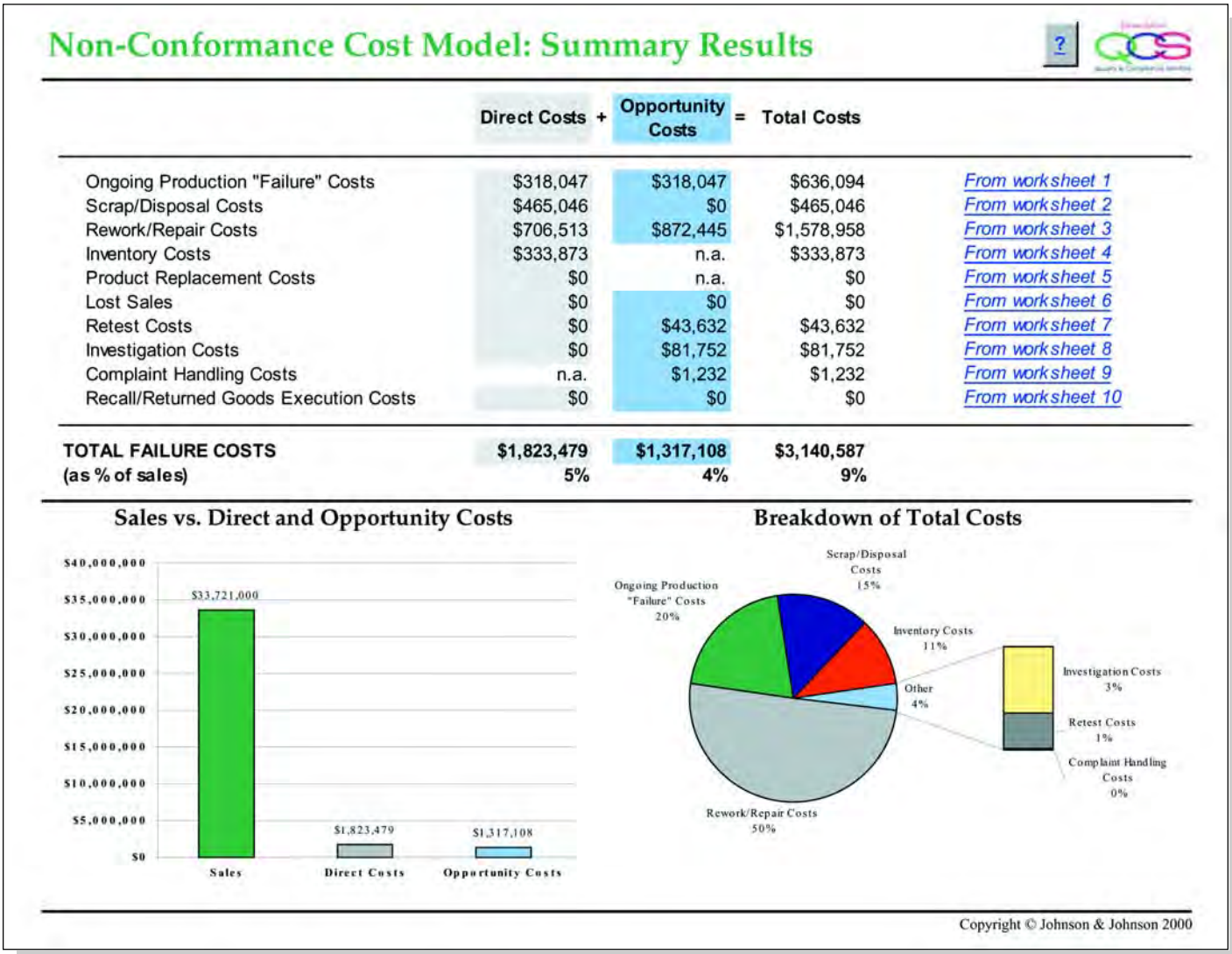
- First, the model focuses upon internal and external failure or non-conformance costs only. Focusing upon non-conformance costs alone simplifies the model. More importantly, however, once managers clearly understand non-conformance costs, they will then be better able to make the appropriate investments in prevention and appraisal activities to reduce these costs and improve overall business performance.

- Second, the model clearly differentiates between *direct* and *indirect* or opportunity costs. Direct costs are defined as additional costs incurred because of a non-conformance event or series of events that will directly impact the bottom line. There is a simple cause and effect relationship between direct costs and non-conformance events: if non-conformances occur, direct costs will be incurred; if non-conformances are reduced or eliminated, direct costs will be reduced or eliminated. Examples include scrap/disposal costs of rejected product, which are commonly measured in standard accounting reports. Indirect or opportunity costs on the other hand, are defined as costs related to a non-conformance event or series of events that typically are already included in an organization's business plan. If non-conformance events are reduced, management has the

> ***Non-conformance costs are typically related to specific events, such as product rejections, customer complaints, or manufacturing deviations.***

opportunity to reduce costs by taking appropriate action. For example, if high levels of internal resources are tied up investigating non-conformance events, reducing these events affords management the opportunity of reducing or redeploying these resources, thus producing a savings. Opportunity costs are often overlooked, and uncovering them can identify tremendous additional potential for improving business performance. Differentiating between direct and opportunity costs also is important to bridge the gap between understanding costs and understanding the potential business impact of making change, which is essential to achieving credibility with the financial community. Direct costs will always be reduced when non-conformance events are reduced, opportunity costs on the other hand, require managers to decide which items can, in fact, be reduced. This point is often overlooked in our zeal to capture all costs without regard to which costs can be reduced.

- Third, the model promotes partnerships between the Quality, Operations, and Finance groups within an organization. While most organizations have frequent interaction between these groups, this usually involves the transactional aspects of product manufacture or investigations of product failures. In most organizations, the Finance group is functionally isolated from the Operations and Quality groups, which makes interaction more difficult. This model encourages individuals from these groups to work together, in an analytical, problem-solving atmosphere, where shar-



Non-Conformance Cost Model: Summary Results

	Direct Costs +	Opportunity Costs =	Total Costs	
Ongoing Production "Failure" Costs	$318,047	$318,047	$636,094	From worksheet 1
Scrap/Disposal Costs	$465,046	$0	$465,046	From worksheet 2
Rework/Repair Costs	$706,513	$872,445	$1,578,958	From worksheet 3
Inventory Costs	$333,873	n.a.	$333,873	From worksheet 4
Product Replacement Costs	$0	n.a.	$0	From worksheet 5
Lost Sales	$0	$0	$0	From worksheet 6
Retest Costs	$0	$43,632	$43,632	From worksheet 7
Investigation Costs	$0	$81,752	$81,752	From worksheet 8
Complaint Handling Costs	n.a.	$1,232	$1,232	From worksheet 9
Recall/Returned Goods Execution Costs	$0	$0	$0	From worksheet 10
TOTAL FAILURE COSTS	**$1,823,479**	**$1,317,108**	**$3,140,587**	
(as % of sales)	**5%**	**4%**	**9%**	

Figure 2. Summary sheet for business franchise example.

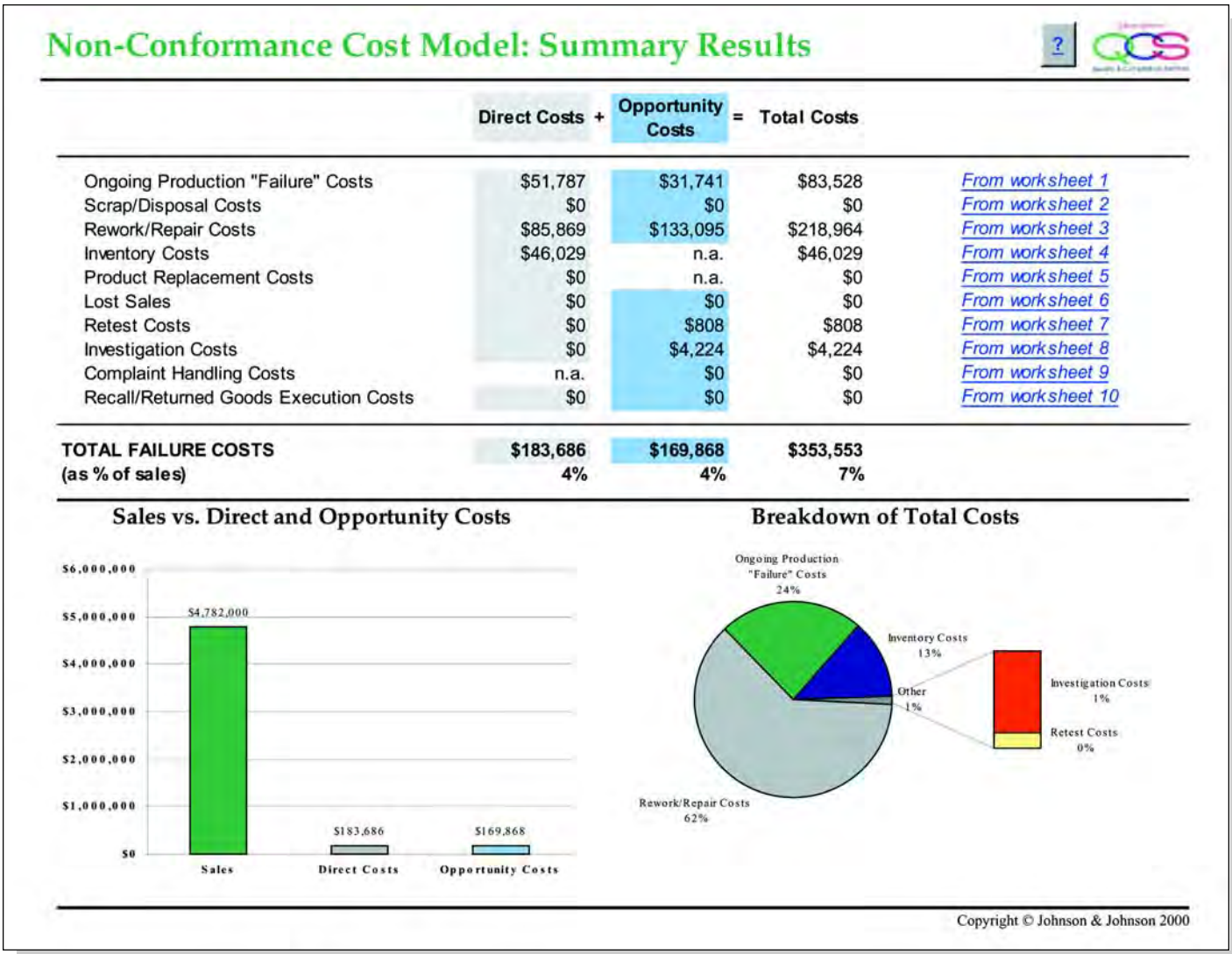


Figure 3. Summary sheet for manufacturing failure example.

ing and understanding of information is not only encouraged, but is essential to determining non-conformance costs.

- Finally, the model was designed to be a business decision-making tool, not an accounting tool. Where appropriate, financial assumptions are made to facilitate ease of use and to avoid excessive "number crunching." The model uses information commonly available in standard accounting reports, operating department expense reports, and quality department records to calculate business impacts of non-conformances.

Model Design

The model is an Excel® based workbook combining Input Work Sheets, Cost Category Worksheets, and a Summary Worksheet. Enhancements include web-like navigation bars, hyperlinks on-line manual, and help icons at every data entry point which add clarity and promote ease of use, but are not necessary for the model to function.

Non-conformance costs are grouped into 10 cost categories as defined below. Each category is divided into sub-categories for ease of capturing data - *Table A*.

1. *Ongoing Production Failure Costs*: This category captures costs incurred due to failure to meet validated production rates or yields or due to excessive material usage or scrap. These costs are usually less visible to quality professionals since they may not result in product failures or other quality events. In some cases, these costs may even be built in to standard product costs.

2. *Scrap Disposal Costs*: This category captures costs incurred when a decision is made to dispose of a product that has failed to meet quality parameters and cannot be reworked.

3. *Rework and Reprocessing Costs*: This category captures costs incurred when a rejected product is reworked or reprocessed to meet quality parameters and thus salable.

4. *Inventory Costs*: This category captures inventory carrying costs incurred because products are held in quarantine, beyond normal supply chain holding times, due to either ongoing investigations into quality problems or simply waiting for a production window to rework or reprocess failed material.

5. *Product Replacement Costs*: This category captures the costs associated with sending replacement product to a customer in the event that the original product was rejected.

6. *Lost Sales*: This category captures the business impact of losing sales because of an inability to supply product due to quality problems.

7. *Retest Costs*: This category captures the costs of internal resources involved in conducting retests and Out Of Specification (OOS) investigations due to test failures.

8. *Investigation Costs*: This category captures the internal and external costs incurred to conduct investigations into product failures or other non-conformance events to determine root cause and disposition of the material in question.

9. *Complaint Costs*: This category captures costs associated with processing customer complaints.

10. *Recall/Returned Goods Execution Costs*: This category captures the planning and execution costs associated with implementing a recall or returned goods event.

Non-conformance costs are typically related to specific events, such as product rejections, customer complaints, or manufacturing deviations. *However, they also can be related to ongoing failures to meet design capabilities, such as low yield or excessive scrap costs caused by poorly developed or maintained processes.*

Figure 1 is a graphical representation of the model design. One worksheet is designed to capture the necessary inputs and perform the cost calculations for each of the 10 cost categories. These worksheets are designed to capture relevant input information and perform the necessary calculations. Guidance is provided on where and how to obtain the necessary input information. In addition to the 10 cost category worksheets, two input tables are provided. Input Table 1 captures information about the company and scenario, you wish to study. Input Table 2 captures cost parameters, specific to a company or site, which can be used in repeated model scenarios. A summary worksheet also is provided to consolidate the results of the exercise and present the results graphically.

The model can be used at a high level to capture non-conformance costs associated with a business franchise or plant site, or at a more focused level to capture non-conformance costs associated with a particular product or significant quality event, such as a product recall. Even though the model breaks costs into 10 categories, some of these may or not be applicable to a particular scenario. In a plant site or business franchise scenario, all 10 cost categories may be applicable. In an internal failure scenario, on the other-hand, only three or four cost categories may be applicable. This is further illustrated by the examples below.

The key to using the model is to examine all cost categories for each scenario. In this way, the model serves as an excellent checklist to uncover all potential costs of a particular scenario.

Model Use

This model was conceived as part of a broad initiative within Johnson & Johnson to establish financial metrics in the quality, safety, and environmental areas. It was developed in 1998 and first introduced to Johnson & Johnson companies in the spring of 1999. A rollout plan was developed to maximize the use and benefits of the model. This included top-level management overviews and individual plant workshops where quality, operations, and financial professionals met to learn how to apply the model to their businesses and locations. A top-level financial professional was appointed at each company to provide guidance and consistency in using the model.

Rollout continued throughout 1999 and by the end of the year all domestic pharmaceutical and consumer companies and many international companies were using the model. Rollout continues for the device and diagnostic companies. Because of the success of the model, Johnson & Johnson decided to integrate it with the process excellence Six-Sigma initiative underway worldwide. Six Sigma is a process that allows for measurement of the quality of products and/or services. A level of Six Sigma represents the highest level of quality and the virtual elimination of defects with the rate being approximately three defects out of every million. This model is now incorporated into the process excellence "tool kit" and is included in the training of all "black belts" worldwide. Widespread use of the model has resulted in a variety of case studies that have demonstrated improved business performance.

Three examples are presented below. These highlight the versatility and flexibility of the model in different situations:

- Example 1 shows the model being used by a company to understand the impact of non-conformance costs on overall business performance.

- Example 2 shows the model being used by a manufacturing site to estimate the cost of specific product failures and provide a baseline to determine the financial benefits of eliminating the root cause of these failures.

- Example 3 is a classic example of using the model to calculate the total costs associated with a product recall.

Example 1: A Business Franchise Scenario

In this example, a company was going through restructuring and wished to understand the total impact of manufacturing failures in a particular business franchise. They used the Cost of Non-Conformance Model to estimate the total cost of non-conformance events for one year. The Model calculated the non-conformance costs to be in excess of three million dollars or nine percent of total sales - *Figure 2.* Moreover, almost two million dollars or five percent of their non-conformance costs were direct costs, providing a clear opportunity to improve business performance by reducing failures. The model also showed the breakdown of these costs between the different categories, highlighting that scrap/disposal, rework/repair, and ongoing production costs represented 85 percent of the total non-conformance costs.

This company used these results to help justify embarking on a comprehensive quality systems improvement program, and is planning to use the model to track progress on an annual basis. The company also has used the model to identify cost of non-conformance opportunities specific to selected products and manufacturing areas and has initiated projects to reduce these expenses.

This example illustrates how the model can be used to obtain an overall picture of the cost of non-conformance for a business unit and thus determine the potential for improve-

> ***Understanding the true cost of non-conformance can be a tremendous aid in driving improvement in an organization. It enables management to understand the cost impact of quality non-conformances...***

ment in business performance by reducing non-conformances. More specific uses of the model, such as described below in example 2, are then used to select and justify projects to reduce non-conformance costs.

Example 2: A Specific Manufacturing Failure Scenario

In this example, a company experienced product failures that were caused by problems in the product drying operation. They used the Cost of Non-Conformance Model to estimate the total cost of these product failures to the business. The model identified the failure costs to be $350,000, or seven percent of product sales. Sixty percent of these costs were associated with reworking the failed batches - *Figure 3*. The company subsequently invested in equipment upgrades, which corrected the problem. Using the cost savings from this model, the company calculated a payback of 2.4 years for the cost of equipment upgrades. This was based upon *direct* cost savings only; if the company also had been able to identify the *opportunity costs*, the payback would have been reduced to 1.2 years.

This example illustrates how the model can be used to provide a basis for justifying investments to reduce failures and improve manufacturing operations. It also demonstrates the synergy between improving quality and improving business performance.

Example 3: A Classic Recall Cost Scenario

In this example, a company had to withdraw two products from the marketplace due to problems with packaging. They used the cost of non-conformance model to calculate the total cost of product withdrawal and replacement and to determine the impact on overall business performance. The model calculated the total cost of the recall event to be more than seven million

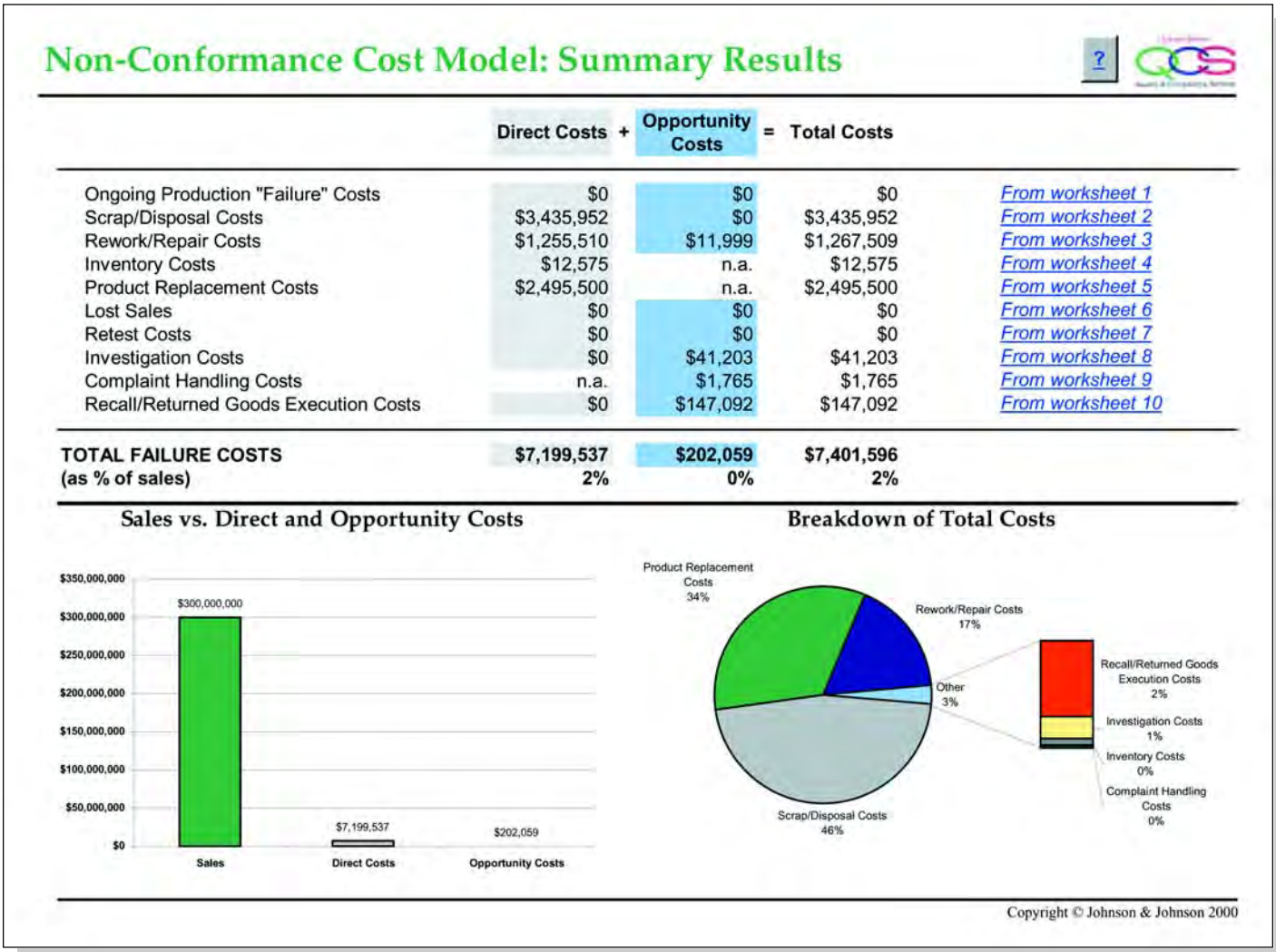


Figure 4. Summary sheet for recall example.

dollars or two percent of the annual sales for the business franchise - *Figure 3*. This example clearly illustrates the desirability of identifying and addressing non-conformance events early, before incurring the excessive costs associated with external failures.

Conclusion

Understanding the true cost of non-conformance can be a tremendous aid in driving improvement in an organization. It enables management to understand the cost impact of quality non-conformances and allows for informed decisions on quality improvements using commonly accepted business language. This promotes *timely* investments in quality improvements, when the underlying issues are still internal, thus preventing these issues from reaching an external or regulatory agency level. Finally, it encourages a partnership between quality, operations, and financial professionals in a proactive way using common terms.

This article describes how one organization developed a simple yet powerful tool, and provides examples of how the process is working. Johnson & Johnson has adopted this model as part of a broad strategic initiative to use financial models as enablers to drive home its goal of achieving beyond compliance as a competitive advantage.

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This article identifies benefits that can be derived by using a System Development Life Cycle (SDLC) approach to automation.

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Quantifying the Benefits of Automation

by Joseph F. deSpautz

Introduction

Pharmaceutical manufacturers are achieving significant benefits using automated systems. They are using process automation, Computer Integrated Manufacturing (CIM), electronic work instructions, Electronic Batch Record Systems (EBRS) as elements of operational strategies to support corporate goals and objectives. Business reengineering, organizational change management, organizational alignments and business process analysis are being used to create the information flow defining the streamlined value added tasks. Real time control (DCS, PLC, SCADA), data collection systems, batch managers, electronic work instructions, EBRS, and data historians are providing the data and transactions for this information flow.

Automation projects are introducing commercially available Enterprise Resource Planning (ERP), Manufacturing Execution Systems (MES), Quality, and Advanced Planning Systems (APS) across the plant. In many cases, benefits derived from implementing these applications are not yielding their anticipated benefits. Because these installations only serve their specific function, economic benefits are not realized to the enterprise. As most benefits are cross functional, they are maximized through the information integration of the individual point solution. Regulatory compliance adds the complexity and effort of validation to the project. Existing validated mission-critical systems must be included in the new system projects. System planning for new projects must include how to support these validated systems that may reside on different hardware platforms with different operating systems.

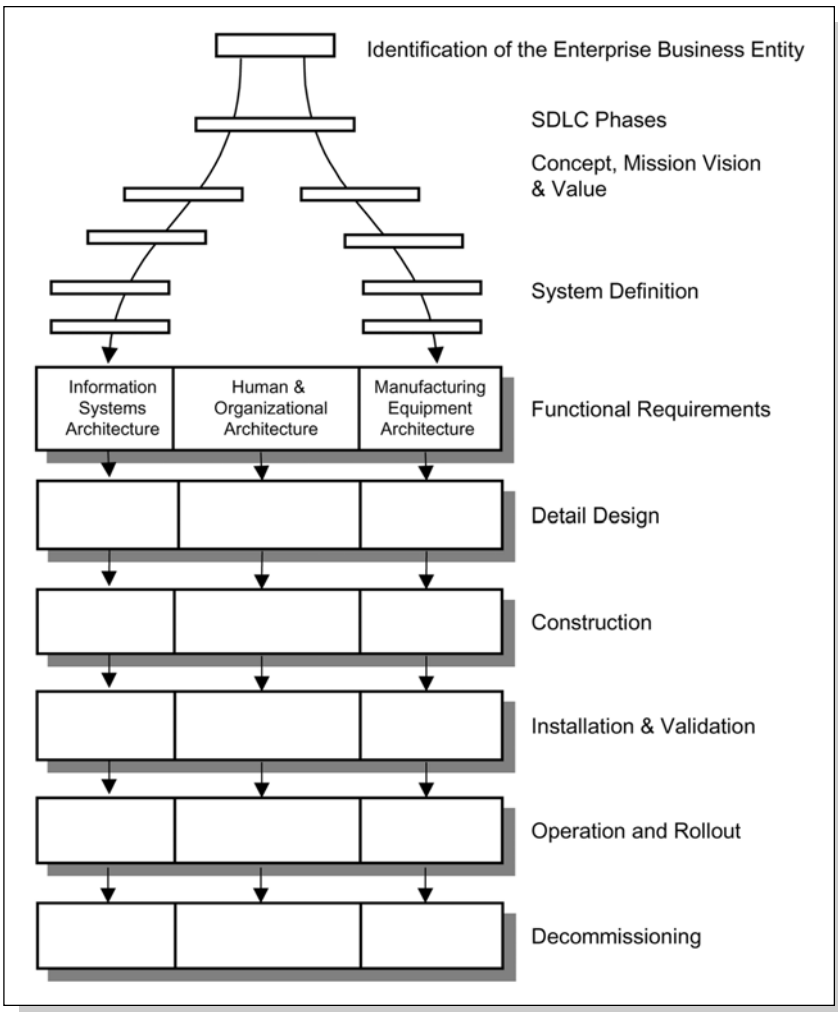

Figure 1. Purdue Enterprise Reference Architecture (PERA) SDLC.

PERA ARCHITECTURE FOR VALIDATED SYSTEMS
• Concept (mission, vision, and value)
• System Definition
• Functional Specification
• Detail Design
• Construction
• Installation and Validation
• Operation and Rollout
• Decommissioning at End of Life

Table A. PERA architecture for validated systems.

How to Quantify Benefits?

Project benefits can be classified as primary, secondary, or strategic. Primary benefits are realized when the project is executed and put into use. Not doing the project means that the benefits will not be realized. Secondary benefits occur in other organizations as a result of the project's activities. These benefits should not be ignored in determining the merits of the project because they can be substantial. An example is the savings in people and efficiency in the Documentation Department that results from implementing an EBRS for a new plant. Strategic benefits also should be factored into the cost/benefit analysis. Enhanced compliance, maintaining a market share in a specific therapeutic area or opening a plant in a new geography, may be necessary while the value may be intangible. Often secondary and strategic benefits are ignored, since they do not have an exact value. Accountants sometimes would rather be exactly wrong than be vaguely correct.

As projects involving mission critical applications will define a competitive edge for a company, specific results become company confidential and are difficult to obtain as they indicate internal financial structures, overhead rates, and product costing. Benefits from actual projects presented as percentages are available and can be applied to your own business model as they can be used to develop quantitative values once you have identified similar business issues.

A System Development Life Cycle (SDLC) methodology can be the mechanism to identify, qualify, and quantify benefits with respect to project costs and scheduling timelines as well as being the Master Validation Plan for the project implementation. By the incorporation of standards, architectural analyses, and integrating the organizational and documentation requirements, project management can create a project plan to achieve the identified benefits while controlling resources, the budget, and schedule. The focus of this article is where benefits can be identified and quantified to support the project justification, which occurs during the initial phases of the SDLC. The investigation of benefits should be based upon a system implementation framework for the project throughout its development life cycle.[1-7]

No Longer Project Management as Usual

Recent research indicated that 70% of the New Product Development (NPD) and manufacturing delays are organizational in nature and improvements would result from common processes between the business and production.[1] These issues have been at the core of automation and CIM projects for most of the 1990s and will continue into Y2K. An earlier survey[2] on business barriers to CIM concluded that system solutions must address more than information technology. Over 65% stated that people, as well as training, organizations, and changes in culture need to be included in any new business or plant floor solution. Research[3] has indicated that a number of past implementations in CIM had not achieved their intended business goals and that integration of manufacturing information was a major area for improvement.

All companies are different in business directions, manufacturing styles, and cultural perspectives. The kinds of plant automation and business process integration solutions that they will choose will be based upon their key business drivers. Management also will continue to make decisions based upon the analysis of a project's ROI and its support for enterprise business goals.

System Implementation Framework

Existing mission-critical systems must be included in the new system projects. Project planning for these systems must include how to support system validation of solutions that may span different hardware platforms with different operating systems. SDLC methodologies provide an excellent framework for these computer-based projects.[9] An SDLC is identified as a life cycle for the development of the integrated systems and includes the physical components and collection of principles, models, standards, and guidelines that are the core building blocks for the system infrastructure. The Purdue Laboratory for Applied Industrial Control has spent many years working with industry in developing reference models and reference architectures that include information, business, and technology components. The Purdue Enterprise Reference Architecture (PERA) is well known as a methodology for automation, CIM, and enterprise integration.

Figure 1 presents the PERA life cycle defining the three architectural components—information systems, human and organizational, and manufacturing equipment. Project activities at each phase of the SDLC involve the interaction of each architectural component. A phase cannot be completed until the requirements for each component are completed and documentation is prepared.

Integrating Validation with Information, Organizations, and Manufacturing

The FDA definition of process validation is contained in the General Principles of Validation Guideline[10] as:

> *"Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes."*

The FDA has no formal definition of computer system validation and expects the definition of validation to apply equally to manufacturing control processes involving computers and other types of automation equipment. The Pharmaceutical Research and Manufacturers Association (PhARMA; formerly the PMA) developed a life cycle approach to computer-related system validation[11] - *Figure 2*.

This effort defined a process for defining, developing, and testing new and existing computer systems. The Parenteral Drug Association's (PDA) Validation of Computer-Related Systems Report[12] defined a method emphasizing comprehensive computer-related system requirements (functional and design specifications), computer system construction, implementation, and qualification phases.

Computer system validation in the PDA model is defined like process validation to establish documented evidence,

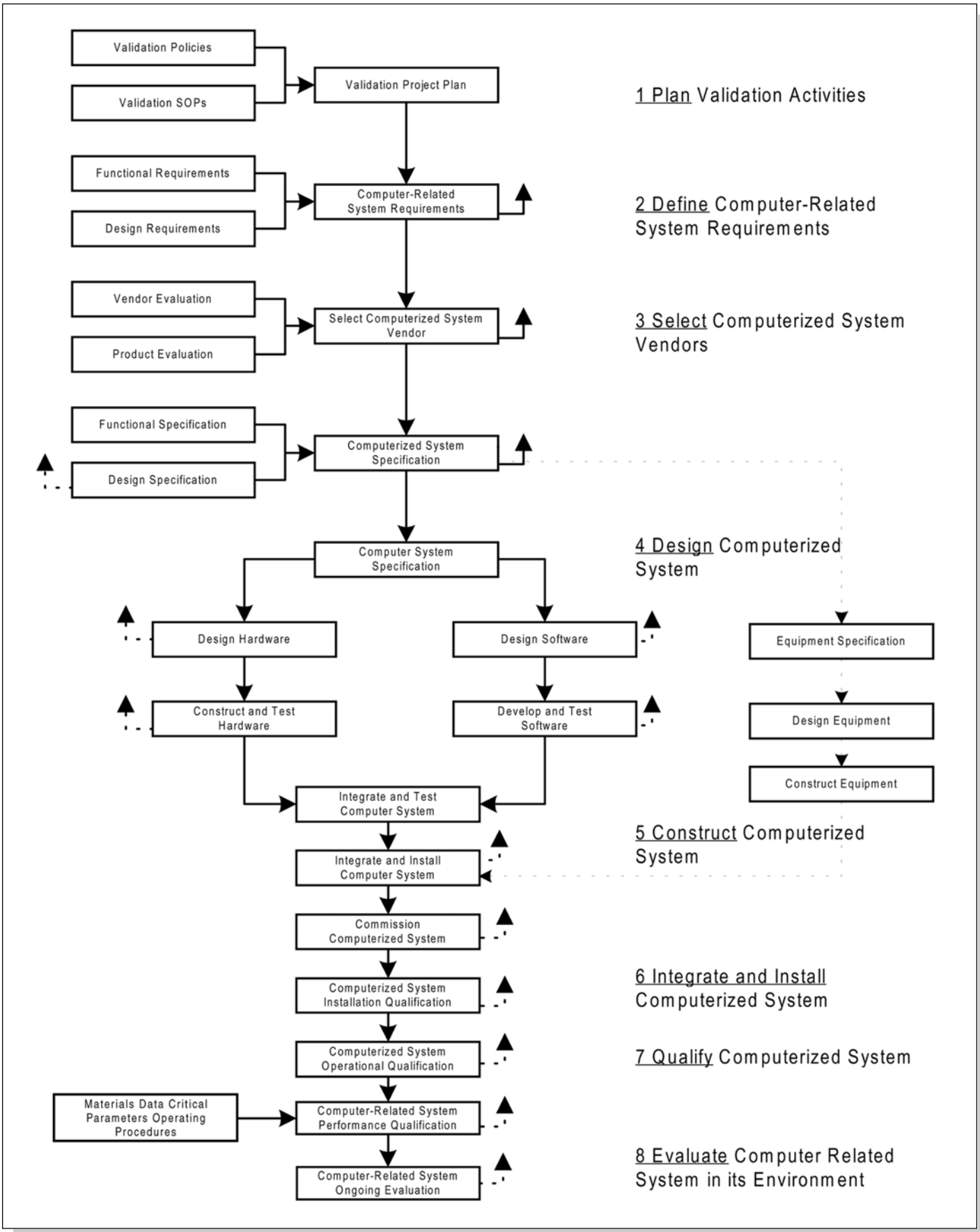

Figure 2. PDA steps in validating computer-related systems.

which provides a high degree of assurance that a specific computer-related system will consistently operate in accordance with predefined specifications. The model includes evaluating the prospective vendor's engineering environments, support and maintenance capabilities, and change control practices for meeting cGMP requirements relating to commercial system development.

PERA Architecture for Validation

Using the PERA methodology, we can represent an enhanced SDLC for pharmaceutical automation and integration projects. The methodology integrates the information, human and organizational, and manufacturing equipment architectural components into a unified validation master plan (VMP) - *Table A*.

The PERA-based SDLC is an example of an architecture that can be used for today's business focused automation projects requiring validation. The complete SDLC with phases is presented in Appendix A. Like the PhARMA and PDA methodologies, it covers all phases of system operation from conception through redesign or decommissioning. Performing analyses to derive business benefits are an integral part of the plan. These activities are established early in the project and supported throughout the development and implementation phases. This is achieved as a single plan with the integration of the following mutually independent components:

- manufacturing equipment
- human and organizational
- information including validation documentation correlated at each phase with the system information requirements

All three components are addressed in each life cycle phase. Required validation documentation is identified or developed at each phase. During the Concept phase, QA validation policies and SOPs are reviewed for applicability and the validation program plan and guidelines developed templates for the ensuing phases. Validation program planning and documentation is developed to support the functional requirement specification. Organization and team skills for how workers will be impacted are determined, and from them, certification and training program plans are developed. The detail design specification yields the factory and site acceptance plans, Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ) as well as training and educational development. Fitness for use of the resulting system is programmed into the implementation.

Because validation represents special hurdles to FDA regulated companies, the PERA-based VMP helps answer the following primary questions:

- How is the computer-based system used in manufacturing and NPD?
- What functionality is the system going to perform?
- How will the computer system record product production?
- Does the system meet its predetermined specifications and requirements?
- Do organizations have the proper education and training to use the new systems?
- Have we documented the system implementation in a manner that supports validation guidelines?

The PDA VMP fits very well within the PERA system architecture. The manufacturing component contains the physical process equipment lines, computer systems, networks, hardware controllers, operator work stations, control room functions, operator control panels, and software applications. Any infrastructure or design standards like S88.01 and S95.01 are integrated into the development process.

PERA CONCEPT AND DEFINITION PHASES
• Manufacturing, Information and Personnel Policies
• Validation Policies and SOPs
• Validation Program Plan Guidelines
• Information Technology Standards and Models
• Project Plan
• Cost vs. Benefit Analyses
• Mission, Vision, and Values
• Management Philosophy
• Organizational Plan
• Present and Proposed Production Entities including Product, cGMP and Operational Policies
• Project Identification
• Automation Strategy

Table B. PERA concept and definition phases.

The human and organizational component defines the involvement of people in the new system. The boundaries of how much automation will be implemented on both the physical and information sides of the system are fully defined and documented. Often, the changes in people skill sets needed to support the new systems are not addressed during the early life cycle phases.

The information architecture catalogues the validation documentation needed to describe each phase of the project; the information systems needed to support the process (e.g., batch record recording, SOPs, QC test results, etc.), and the system performance parameters, production batch record information, and operator instructions. Training plan, certifications, and educational development are planned, designed, and refined as the phases progress. We have all of the information for a successful and complete validation of the completed system. Nothing has been missed.

Concept and Definition Phases: Business Processes

The business planning process starts with the company's business plan. The vision for the proposed CIM project is considered in context to the corporate mission and vision objectives. The concept and definition phases define and clarify the organization's business objectives and the related elements that are critical to achieving these objectives. Taken together, these constitute the "as is" of the business or where we are today and the "to-be" environment, which represents the enhanced business state. The analyses and documents collected, catalogued, or developed during this phase are given in Table B.

The phases define how the company's business mission, measurable business objectives, critical success factors, and

strategies impact the project and how the project will support the business goals. The specifics can be gathered by answering questions as the following:

- What and how are we doing today?
- What is our business mission?
- What business objectives will achieve this mission?
- What are the critical success factors that we have to do right in order for these objectives to be achieved?
- What business strategies will need to be deployed to ensure that we achieve these critical success factors?
- How can we measure success and when can we stop?

Measurements to Monitor Progress Toward Success

Performance measurements with numeric values or range of values are needed by the organization to monitor its progress toward success. Many different measurements can be used to monitor manufacturing and business performance. Some are primarily diagnostic tools, while others are the vital signs that allow an organization to monitor the health of operations and the success of the overall project.

Specific measurements determined during the implementation should be viewed as "dynamic" rather than "static." They define how we are operating today. They define what educational, training, and certification plans need to be developed and executed to improve performance. As performance improves, organizations may elect to change the measurements and raise the bar on performance. Corporate measurements, which senior management will review on a regular basis, will establish a hierarchy of many other measurements within each plant or manufacturing area within a plant. Accountability should be passed down throughout the organization to support meeting the new measurements. This in turn may require additional education and skill level retraining.

Validation considerations identified by the business component are incorporated into the information system that must support the deployed business strategies. By defining system purpose in the view of business processes with accompanying organizational plans, business scenarios can be constructed that show how the resulting system will document how products are being produced according to their predetermined specifications and quality attributes. As production practices

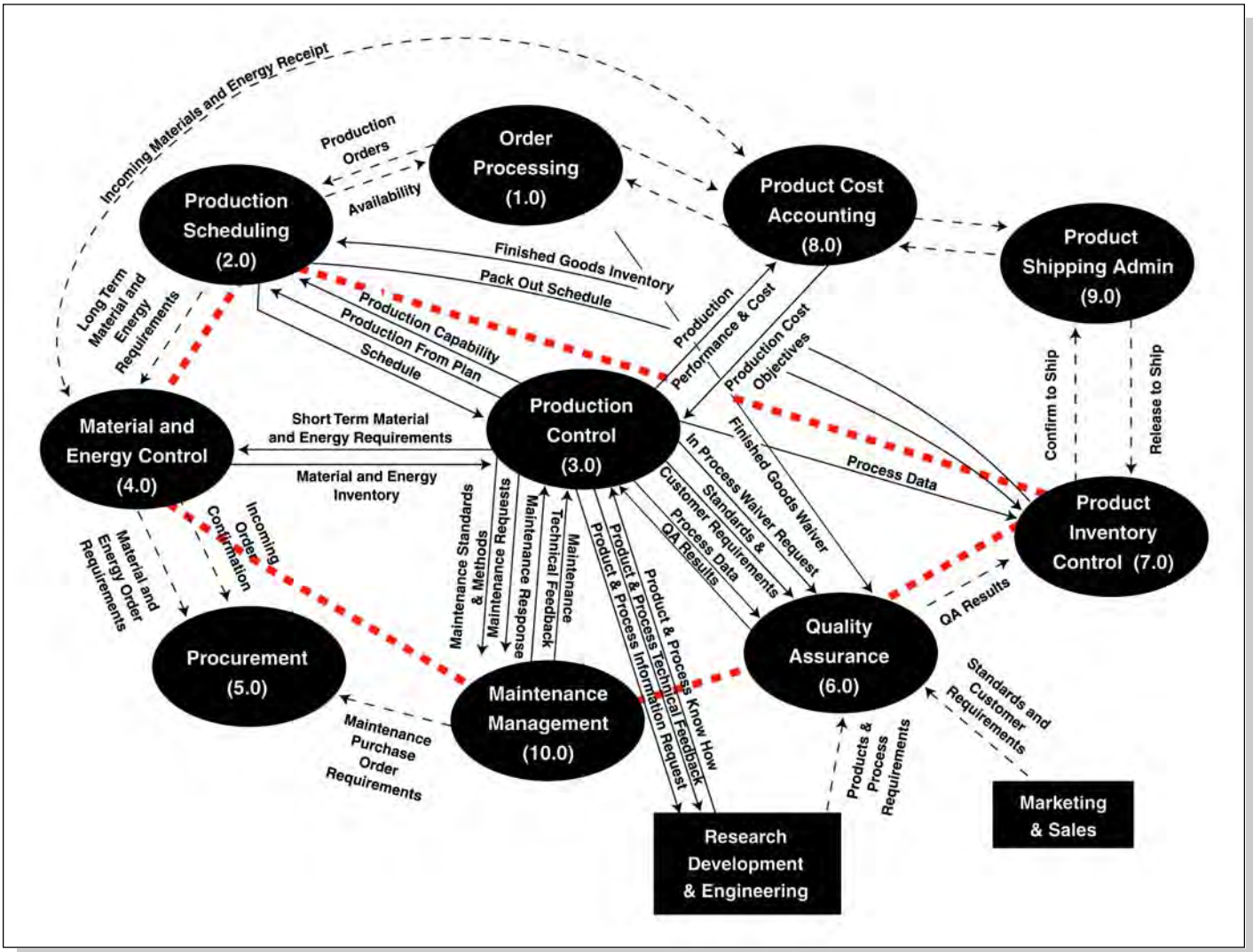

Figure 3. Manufacturing reference model for ISA S-95 Standard.

ISA S-95 BUSINESS DRIVERS

- Available to Promise
- Asset Efficiency
- Supply Chain Integration
- Supply Chain Optimization
- Regulatory Compliance
- Improved Planning based on Process Modeling
- Reduced Cycle Time
- Agile Manufacturing
- Supply Chain Management
- Quality and Traceability
- Customer Service
- Reduction of Working Capital
- Waste Minimization

Table C. ISA S-95 business drivers.

are changed by the new system, the business scenarios can be modified to reflect these changes, keeping the organizations synchronized with the new operational model.

Identifying Benefits

Key sources of potential benefits can be achieved from a number of sources like:

- using the SDLC as the tool for implementation
- using infrastructure and design standards
- integrating the organization into the project plan
- installing applications that integrate the activities between the enterprise's business processes and manufacturing's operations so that information is sharable

Life Cycle Benefits

Two studies present some interesting multi-year cost/benefit results.[18,19] They describe an automation life cycle model used at Eli Lilly to meet bulk manufacturing costs while being cost competitive. "The model forces those in charge of automation to look at both the front half of the life cycle—justify, apply, and install—as well as the back half—operate, maintain, and improve" … "Here is why! Data from 10 major facilities at Eli Lilly indicate that less than 50% of the life cycle dollars deliver a project. That's where 25% of the benefits of automation come from. An important aspect of automation is that one needs to make another 50 or 60% investment over the life cycle to get 75% of the benefits of automation."

Infrastructure standards are being used in pharmaceutical strategies because timely, accurate, and auditable information is essential in this highly regulated industry. An I/T framework has to support business objectives by being flexible, capable of growing to meet increasing demands for information and reporting, and permit the sensible inclusion of new information technology that may be required by manufacturing. As an example, using a project infrastructure technology, process automation installation costs were reduced approximately 40% with projected reduced maintenance costs over the life cycle of the installation.[20]

Use of Standards

ANSI/ISA S95.01 standard[13] defines the interface content between manufacturing control functions and other enterprise functions. The standard has been approved and is available on the ISA's Web site. S95 Part 1 contains a collection of business drivers that are critical to the success of manufacturing operations across a variety of industries - *Table C*. They include customer-driven quality requirements and operational requirements such as productivity, cycle time, deployment of new technology, strategic alliances, supplier development, and research and development.

If any of these business drivers are applicable within the manufacturing organization, it becomes the focus for determining project-related benefits that justify the automation project. A project will have little chance for success if the business drivers are not supported by its introduction.

Defining the Level of Automation

How much automation will be introduced by the planned project? The transition from manual operations to electronic practices is an important aspect of any pharmaceutical system implementation. The human and organizational architectural component of the SDLC will capture the business process rule changes for the "to-be" organization to ensure that operations will still perform properly. The key to how much automation will be implemented or conversely how much should the operator and organization do depends upon a number of independent factors such as:

- plant size and available space
- legacy systems that cannot be disturbed
- skill levels of geographic job pool
- regulatory documentation on file that cannot be changed
- union or governmental requirements

On the manufacturing side, we are involved with physical tasks that operators must perform. For example: how much can people lift, move, stir, mix? Is the operator environment safe? Is the production environment safe? The information component represents the thinking side of the organization like what data will be recorded for batch record compliance, what will the operators see on the control panels, what is required for coordinating QC results with batch release, etc. Often NPD or the introduction of new production equipment will change the degree of automation. Having the human and organizational considerations as an integral part of the development process allows the project team to address issues such as the following:

- What are the operational resources in the "to-be" environment?
- How much change can be successfully introduced within the organization within the project's time lines?
- What are the training, certification, and educational developments required supporting the "to-be" equipment processes

INFORMATION REPOSITORY BENEFITS
• Improve Customer Service
• Eliminate Duplication and Waste
• Reduce Scrap
• Enhance Data Accuracy and Response
• Reduce Labor Costs
• Enhance Consistency of Manufacturing Data
• Reduce Process Time and Order Cycle Time
• Enhance Decision Support
• Enhance Batch Record Accuracy
• Improve Record Keeping
• Minimize Product Recalls
• Reduce Work in Process (WIP) and Finished Inventories by Quicker Batch Release

Table D. Information repository benefits.

Each of these applications and its information repository is usually owned by a different organization. Benefits that can be derived from common business processes must be driven top down during the early phase of the SDLC so there can be concurrence in cross-functional processes and information sharing. This means that the project team has to develop project champions at the senior management level to have a forum for performing cross-organizational analyses. Many references state that if you do not have the support of senior management, the project will not be successful.

All areas where the future state is different from the current environment represent potential sources of benefits in the form of increased productivity, greater efficiencies, rationalization of indirect tasks, better utilization of legacy process control systems, and cost avoidance. These benefits need to be quantified without compromising regulatory compliance and manufacturing control to be useful.

Information Sharing Enables People to Work Better

The control of the plant-wide information and transaction repository is required, since it will be used by many organizations. Such features as access control, tracking and status, archiving and history of activities is required to prevent redundancies and miscommunication mistakes. During the concept and definition phases, the project team can investigate and quantify significant benefits in document management practices and the information sharing interfaces between applications - *Table D*.

Data collected in a timely manner provides workers with the tools to make better decisions which translate into secondary and strategic benefits. These benefits can be related directly to the company's business drivers. Benefits can be linked to document management on the plant floor as batch record operations, manufacturing unit operation verification, data recording, and quality test results are all required to meet US FDA current Good Manufacturing Practices (cGMP) compliance and product quality standards. Automation is one of the keys to improving productivity and efficiency, and maintaining quality.[2,3,8,21,22]

Considering that automation projects can be multiyear efforts, these benefits may yield a ROI on a per year basis or incrementally in a multi-year rollout. Document management benefits are usually recorded as secondary benefits as achieving the benefits involves cross-organizational cooperation.

Application Driven Benefits

The key applications for integrating manufacturing and enterprise activities are presented in Table E.

Using Standards to Select Applications

Process cycle times are being decreased and the number of products produced increased to match the demands for a greater number of batches and variety of products. To support these manufacturing objectives while needing improved visibility and control of the entire process, enterprise business systems are being integrated to batch managers and other plant floor systems. There are a number of design and model standards specifically created for process automation and integrating manufacturing control to business processes. Applying these standards during the implementation have yielded considerable financial benefits when applied across the plant floor.

ISA 88

The ISA 88.01 standard[25] provides standard models and terminology for the design and operation of batch process control systems. It is being used in a number of successful projects. Application of the standard has been used on projects at Kraft Jacobs Suchard and B.F. Goodrich.[26] S88 has been used as the design foundation for a production Quality Assurance process for a polymerization plant that involved enterprise business process integration.[28]

The design and model principles contained in ANSI/ISA S88.01 were used at Genentech's Vacaville, CA site.[14] The implementation was a large complicated batch process for large scale, cell fermentation, and recovery processes. Using the 88.01 concepts as the basis of the automated batch process control technology, a number of benefits were achieved by the implementation including the following:

- product and process flexibility using the detailed model design standards
- a higher degree of production success rate by implementing equipment tracking and product status reporting
- cycle time was reduced and product releases improved due to efficient data presentation and review as well as anomaly resolution

The design principles of S88.01 were applied in the implementation of a multi-product networked process cell for automating specialized equipment in a pharmaceutical site.[15] The application achieved a time saving of more than 60,000 hours

MANUFACTURING APPLICATIONS
• Enterprise Resource Planning
• Manufacturing Execution
• Electronic Batch Record
• Quality Management
• Formula Management
• Process Control
• Project Management
• Process Engineering and Design

Table E. Manufacturing applications.

($3,000,000 using a conservative effort rate of $50.00/hour) of contractor development effort for the control modules, $900,000 in unit (including phases) development and testing savings of $300,000. A total project savings of $4,200,000 was attributed to using the S88.01 model standards.

A major consulting and construction firm is applying PERA to project work across different industrial areas.[16] PERA is the framework for executing and presenting their work practices on system integration projects for clients.

ISA 95

The ISA S95.01 standard provides consistent models and terminology for defining the interfaces between an enterprise's business systems and its manufacturing control systems. The manufacturing reference model for the standard is the Purdue Reference Architecture. The activities covered by the specification are given in Figure 3.

The models and terminology defined in this standard:

- emphasize good integration practices of control systems with enterprise systems during the entire life cycle of the systems
- can be used to improve existing integration capability of manufacturing control systems with enterprise systems
- can be applied regardless of the degree of automation

Specifically, this standard provides a standard terminology and a consistent set of concepts and models for integrating control systems with enterprise systems, which will improve communications between all parties involved, and that will:

- reduce the user's time to reach full production levels for new products
- enable vendors to supply appropriate tools for implementing integration of control systems to enterprise systems
- enable users to better identify their needs
- reduce the cost of automating manufacturing processes
- reduce the life-cycle engineering efforts

Batch management and manufacturing control applications allow engineers and operators to access, analyze, summarize, and report production data. Integrating that data through batch management to the enterprise will enable quicker and more informed decisions on running the process, produce higher yields, and reduce recipe and process deviations. These types of results can be quantified into positive benefits to support the financial justification of the project.

Secondary and strategic benefits at this level are Statistical Process Control (SPC), advanced control to optimize profitability, yield and throughput, and recipe management for batch operations.

Production control provides the distribution of relevant schedules and procedural information to distributed control systems, PLCs and work-centers. Scheduling has a big impact. A number of pharmaceutical manufacturers admit to having 30 to 60 days of WIP inventory due to scheduling and other queues for products with recipes or work orders containing one day of value-added labor. A finite capacity scheduler may provide significant benefits when integrated into the enterprise solution. Scheduling of constrained resources like unique worker skills, special equipment, etc. to support cGMPs is another area that can yield significant benefits.

ERP AND MES BENEFITS

- Better Purchasing Policies
- Flexible to Respond to Special Packaging
- Improve Scheduling
- Improve Direct Labor Utilization
- Less Production Delays Due to Variance Reporting
- Reduce WIP Inventory
- Shorter Production Cycles
- Reduce Raw Material Inventories
- Enhance Decision Support
- Enhance Batch Record Accuracy
- Improve Record Keeping
- Minimize Product Recalls
- Enhance Consistency of Manufacturing Data
- Reduce Paperwork
- Improve Indirect Labor Productivity

SECONDARY AND STRATEGIC BENEFITS

- Enhance Material Tracking
- Enhance Assurance of Completed Batch Records
- Availability of Accurate Data
- Improve Order Status Visibility
- Reduce Reviews to Special Procedures
- Enhance Compliance to Work Instructions

Table F. ERP and MES benefits.

ERP and MES Applications

Integrating the Manufacturing Resource Planning (MRPII) functionality of ERP or MES into the automation program closes the loop that develops the full capabilities of the planning function. With materials costing between 40% to 50% (and as much as 80%) of the cost of manufacturing, potential benefits can be derived from reductions and productive use of raw, Work In Process (WIP), and finished goods inventory. Primary, secondary, and strategic benefits can be identified by integrating manufacturing execution with electronic work instruction systems to enhance the level of compliance while reducing costs of paper record systems.

A number of companies have installed MES and have presented experiences and perspectives on the costs and benefits of equipment integration, EBRS, and enterprise-wide integration.[22,23] Increased productivity yielding positive business benefits can be achieved through the information integration of external devices to automate manufacturing functions and process monitoring systems to the operator's workstation.[23,24]

Document Management

All production related documentation, including batch sheets, packaging specifications, material safety data sheets, equipment instructions, safety information, and labeling, require control during their life-cycle. This control includes worker access for creation and revision of documents, access and control of reference materials, review and approval cycles,

DOCUMENT MANAGEMENT BENEFITS
• Quicker Time to Create Documents
• Improve Information Flow from R&D to Manufacturing
• Less Production Delays Due to Paper Processing
• Improve Operator Productivity
• Reduce Document Cycle Time
• Reduce Paperwork Burden for Production Personnel
• Reduce Undocumented Processes and Practices
• Enhance Batch Record Accuracy
• Improve Record Keeping
• Faster Review and Approval of Process and Product Deviations
SECONDARY AND STRATEGIC BENEFITS
• Shorter Review and Approval Cycles
• Reduce Batch Record Deviations
• Improve Material Tracking
• Improve Process Visibility
• Enhance Document Quality
• Availability of Accurate Records

Table G. Manufacturing reference model for ISA S-95 Standard.

activation of the document for released work orders, archiving completed production records, and automatically generating secure audit trails of activities for regulatory compliance. Potential primary benefits of electronic work instructions, EBRS, and document management derived from investigating the aforementioned operations are shown in Table G.

The SDLC can define the document management system workflow changes and document development improvements that will continue to satisfy regulatory compliance while producing positive financial returns. EBRS is also changing workflow throughout document management, Quality Assurance, and the plant floor as information that was previously too difficult to obtain is now available across the organization. The competitive benefits of automated document management are compelling so project teams need a clear definition of how these systems function in order to identify and quantify their benefits.[8,29]

Laboratory Information Management Systems (LIMS)

The information management functions required by pharmaceutical quality operations[29] are a source of significant benefits and production improvements. Some of these functions are provided below:

- manage the inventory of samples, test results, inspection activities, and procedures
- maintain the records for traceability of procedures and results
- standardize SOPs, test procedures, and specifications.
- provide data to support process control optimizations

LIM and plant-wide quality systems can provide many benefits - *Table H*. Pfizer, Inc. has integrated its LIMS into other business applications at a plant in Ireland.[30] The plant operates on a 24 hour by seven day schedule with raw materials coming from many parts of the world. The system goals included integrating the quality system with existing MRP systems, allowing rapid transfer of information between the warehouse, laboratories, purchasing, shipping, and accounting departments.

Maintenance Management

As the organization strives to be more competitive through the implementation and utilization of advanced technologies, the importance of effective maintenance management will be increased. Maintenance initiatives can provide many benefits - *Table I*.

Summary

As pharmaceutical manufacturers move to the new millennium, they are developing different strategies to support changing business environments. The financial hurdle bar is being raised all the time for capital and operational expenditures. Automation projects being developed to support enterprise wide goals and objectives are required to demonstrate higher rates of returns on investment expenditures. At the same time, these projects are becoming more complex. Greater returns in the form of increased efficiencies, manpower rationalization, and productivity gains are being required to justify projected expenses for these new systems.

There are many areas where potential benefits can be achieved, and to identify these areas, project teams are beginning to look at the enterprise's business practices, organizations, their people, and technology. By recognizing the influence of these interrelated and interactive components, project teams are capable of defining primary, secondary, and strategic benefits that must be a part of the investment equation. They can quantify how these benefits can be achieved by defining management and employee measurements, organizational goals, and system performance objectives.

Project implementation methodologies that include the equipment, human and organizational, and information architectural components are becoming the project implementation tools of choice to assist project management. They enable an organization to achieve the difficult cross-organizational project objectives as it:

- identifies only the value-added business processes or functions
- determines the information necessary to measure the business objectives
- defines the mechanisms and controls to execute the business process function
- includes validation planning, auditing, and documentation as an integral part of the project

The PERA methodology cycle is an SDLC that makes validation activities and documentation an integral part of the implementation process. It also includes defining business benefits, changes to the company's business processes and the impact of the project on organizations. Validation planning, auditing, testing, and documentation can then assure that the new system meets its intended purposes as many issues have been resolved during the life cycle development and documented for later verification.

LABORATORY INFORMATION MANAGEMENT BENEFITS
• Reduce Test Time Queues
• Enhance Process Quality
• Optimize Process Operations by Providing Automation Parameters
• Reduce Process and Product Variability
• Shorten Production Queues
• Reduce WIP and Finished Goods Inventories
• Minimize Non-Compliant Material Usage

Table H. Laboratory information management benefits.

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MAINTENANCE MANAGEMENT BENEFITS
• Improve Maintenance Productivity
• Reduce Maintenance Inventories
• Increase Equipment Availability
• Reduce Equipment Down Time
• Improve Set-Up Time
• Enhance Problem Detection and Solving Capability
• Enhance Problem Prevention Capability
• Reduce Maintenance Budgets

Table I. Maintenance management benefits.

> ***There are many areas where potential benefits can be achieved, and to identify these areas, project teams are beginning to look at the enterprise's business practices, organizations, their people, and technology.***

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This article reviews the necessary components to successfully validate a given process designed to produce a therapeutic agent. An overview provides the possible issues associated with process validation.

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An Overview of Process Validation (PV)

by Gamal Amer, PhD

Conducting process validation is not only a regulatory requirement,[1] but also makes a great deal of sense from an engineering as well as a business point of view. It is evident that pharmaceutical companies that are well versed in conducting process validation have a competitive advantage over those who are not. Although validating a process is not a difficult matter, it requires keeping track of many issues and ensuring that they all come together at the appropriate time in order to make the process validation effort successful. In addition, keep in mind that in order to conduct a successful validation a tremendous amount of preparatory work has to be performed a-priori. This article presents a general overview, which outlines the issues to be addressed to successfully complete the validation of a given process and to ensure that the entire effort comes together properly.

The most critical requirement in process validation, a view shared by many if not all of the professionals in the field, is **common sense**. In other words, validation professionals, who are working on validating a given process, need to think logically about the issues that arise and make decisions based upon good logical deductions and sound scientific reasoning.[9] Such a competency is normally inherent in a person and may not be easy to teach. However, time and experience do enhance such capability.

In order to make the discussion easier to follow, it is important to keep in mind a typical process for manufacturing the bulk ingredient, finishing the drug, and packaging the final product. In the manufacture of Active Pharmaceutical Ingredients (APIs) one method is through chemical synthesis. First, the raw materials are weighed and the active ingredient is synthesized either through chemical reaction or fermentation process. The resulting mix is then purified and normally put into a solid form either through crystallization or if amorphous, through drying. The bulk active ingredient is then finished through mixing with excipients, sterile filtered/autoclaved if final form is an injectable or alternatively granulated and pressed into tablets or encapsulated if a solid dose product is being manufactured. Finally, the product is packaged into a suitable container.

The second component of such a manufacturing process is the facility or building that houses the entire process. The building has utilities, which service the process itself, protect the process/product, and service the building. Steam may be used to heat the reactors, Heating Ventilation and Air Conditioning (HVAC) systems are used to maintain the cleanliness of the production space and also prevent cross contamination, and electricity, besides driving the motors for the agitators, is used to light the various areas within the building. Always remember that the facility and the utilities are an integral part of the process and hence should be considered during process validation.

The Objectives of Process Validation (PV)

Process validation should be conducted with the following objectives in mind:

1. ensure drug product quality
2. ensure the consistency of the manufacturing operation and reproducibility of the process
3. demonstrate the robustness of the process
4. ensure the existence of all necessary quality assurance systems within the organization
5. ensure that personnel producing the drug product are properly trained and qualified to produce the product

These assurances should be documented and substantiated through conducting the appropriate tests and collecting the appropriate information.

What is Needed for Successful Process Validation

In addition to all the aspects required to complete the validation effort itself, an organization seeking to successfully perform process validation should make certain that the following items are in place:

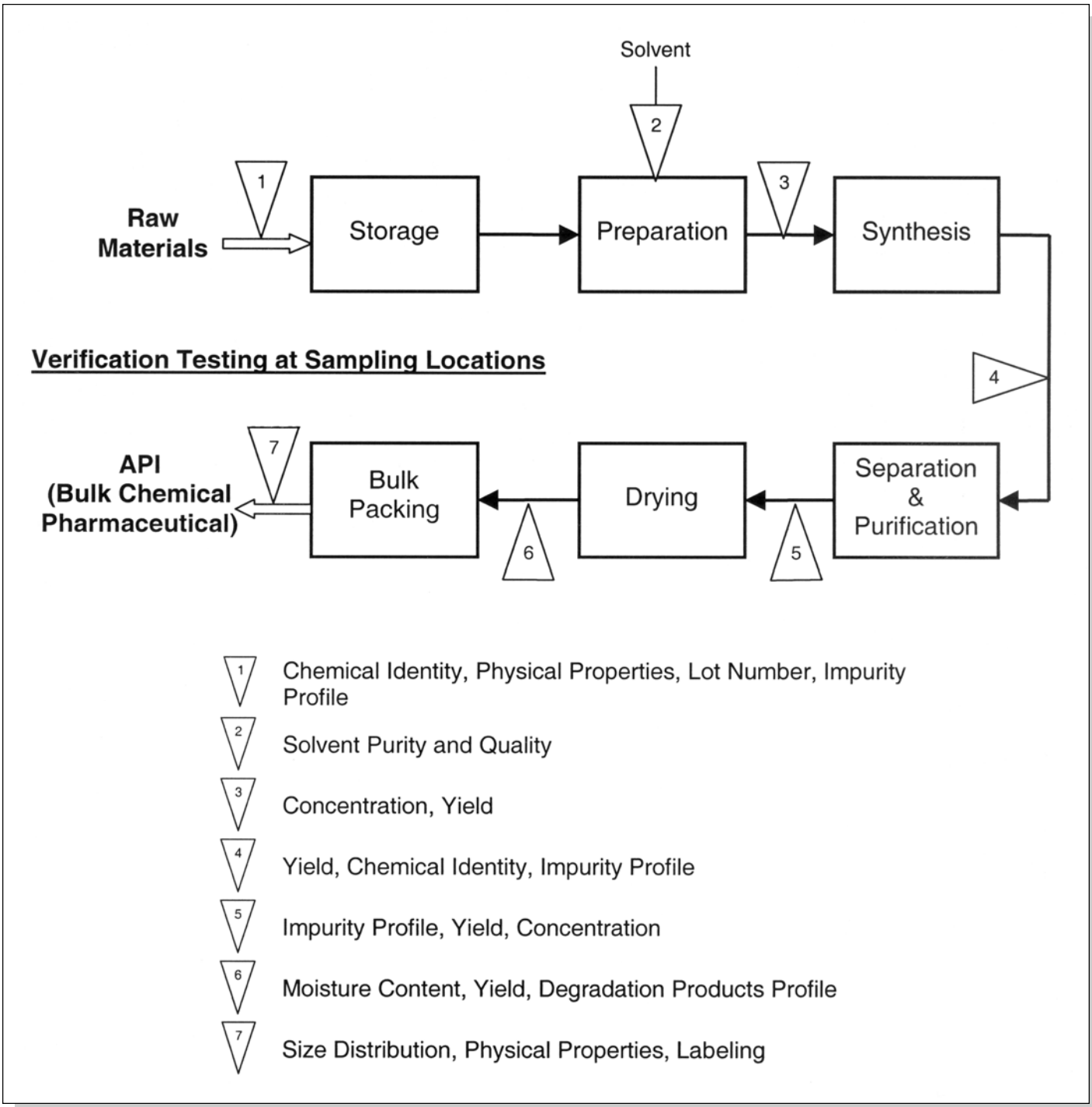

Figure 1. Active Pharmaceutical Ingredients (API) process - sampling locations and example tests.

a. a comprehensive training program for all parties involved in the manufacture of the drug - this training should not be limited to operational training, but it also should include GMP training.[3]
b. validation protocols
c. detailed operating procedures and manufacturing procedures (batch sheets)
d. the critical GMP programs
   1. a change control program[2]
   2. an Out Of Specification investigation procedure[7]
   3. process deviation reporting and investigation program
e. an instrument calibration program
f. a preventative maintenance program
g. a comprehensive cleaning program
h. a supplier audit program.
i. established process monitoring and environmental monitoring programs

Personnel Training

A very important aspect of process validation, and probably the most overlooked component in GMP compliance, is personnel training. How can personnel be expected to perform their

duties associated with the validation effort and eventually the manufacturing operation competently without proper training? The regulations require that all personnel involved in the manufacturing, processing, packaging, or holding of drug products be qualified and properly trained.

Such training, when completed, should be confirmed through appropriate measuring of training effectiveness. In other words, the organization must be satisfied that the person who was just trained has retained the important aspects of the training and is capable of remembering and applying the material when needed.

Why is a Protocol Needed?

A validation protocol is a must have document. It is required by the regulation. It not only serves as a step-by-step set of instructions to conduct a successful validation, but it is also a place where the data obtained can be documented and analyzed. It represents the document that proves validation was conducted. It should be developed after careful thinking and while taking the technical knowledge of the organization into consideration. Prior to executing the protocol, it should be reviewed and approved by the appropriate stakeholders.

The Importance of Having Detailed Procedures

Since by definition when validation of a process represents validating the procedure by which the process is conducted/operated, you must have detailed and very focused procedures/batch sheets. These procedures must define each step to be taken by the operator and the conditions at which the step is to be performed. The industry standard for such documents is known as batch sheets and always contain a space for the operator to include all calculations performed and initials indicating that a certain step or a certain calculation was indeed performed.

It is also very critical to have an established procedure for calibrating critical instruments associated with the operation of process and utility equipment. In addition, having preventative maintenance procedures for all the critical equipment is an integral part of any process validation as well as GMP compliance program. The existence of such procedures ensures that all equipment is not only operated in a consistent manner, but that it is also well maintained and all the instruments which are used to control their operation and may be used to make processing decisions, are calibrated and present accurate readings at any given time.

Critical GMP Programs

As indicated above, an organization should have in place several GMP programs to ensure that the bounds of the validation effort are well defined and to know how it would proceed should any issue associated with the process exceed the bounds. The following are the three most critical GMP programs which should be in place prior to beginning the process validation effort:

Change Control Program

It is important to ensure that the processes to be validated are well defined. Once a given process is established and conducted in a certain manner during the validation, it is important to keep the operation in the same state as it was when it was validated. Should changes to the operation be contemplated, such changes should be studied through a change control program to ensure that whatever actions are necessary to ensure that the systems remain in a validated state and in compliance with GMP requirements, are identified and performed.[2]

Out of Specification (OOS) Investigation

When collecting data, either during the validation or once the validation effort is complete, it is important to ensure that the data fall within the expected specifications. The regulation requires the industry to carefully investigate all OOS results. The FDA issued a draft guide to the industry in 1998[7] outlining what steps need to be taken when investigating and resolving issues associated with results that did not meet specifications.

Process Deviation Reporting and Investigation System

When manufacturing therapeutic products, care must be taken to ensure that the operation/process runs in a predictable fashion at all times. It is assumed that when the validation was conducted, the predictable fashion by which the process is to run was established. Therefore, as part of the effort to validate a process, you should have a procedure that would allow you to investigate any observed deviation from the predictable way the process is expected to run and ensure that any such deviations would not result in the manufacture of an adulterated drug.

The Importance of Supplier Audits

To ensure that an operation, once validated, will remain in a validated state, an organization also should conduct audits of all their suppliers of critical materials and supplies as well as equipment. Such audits should concentrate on ensuring that these suppliers have established quality assurance systems within their operation and that they can deliver the critical supply (whether lab supplies, raw materials, process equipment, spare parts, computer software, or analytical services) at a consistently high and predictable quality.

Equipment Cleaning Procedures and Cleaning Validation

In order to successfully validate a process, you also should ensure that the appropriate cleaning procedures for the various pieces of equipment have been developed and are validated. Additionally, in many cases, cleaning of the facility as well as validation of such cleaning is critical to ensure that cross contamination is kept to a minimum. In cases where a process may be affected by biological contamination, sanitization procedures and validation of such should be developed a-priori and also validated prior to validating the entire process. Methods for cleaning and sanitizing equipment and facilities are usually developed during the research and development phase and this information should be utilized in the cleaning and sanitization effort. An excellent reference on how to develop an effective cleaning program and validate it can be found in W. Hall's article.[6]

Defining the Acceptance Criteria for Qualification/Validation Protocols

When validating/qualifying a piece of equipment, a sub-process, or the entire process, an appropriate protocol should be used. Such a protocol outlines the plan and procedure by which the validation/qualification will be conducted, lists objective test parameters, product and process characteristics, predetermined specifications, and factors which will determine acceptable results (in other words acceptance criteria for the

data to be obtained).

Defining such acceptance criteria can be based upon one or more of the following approaches:

a. the vendor's specifications for a specific piece of equipment or a combination of equipment

b. the engineering design, which presumably has been developed by competent engineers

c. product/intermediate characteristics

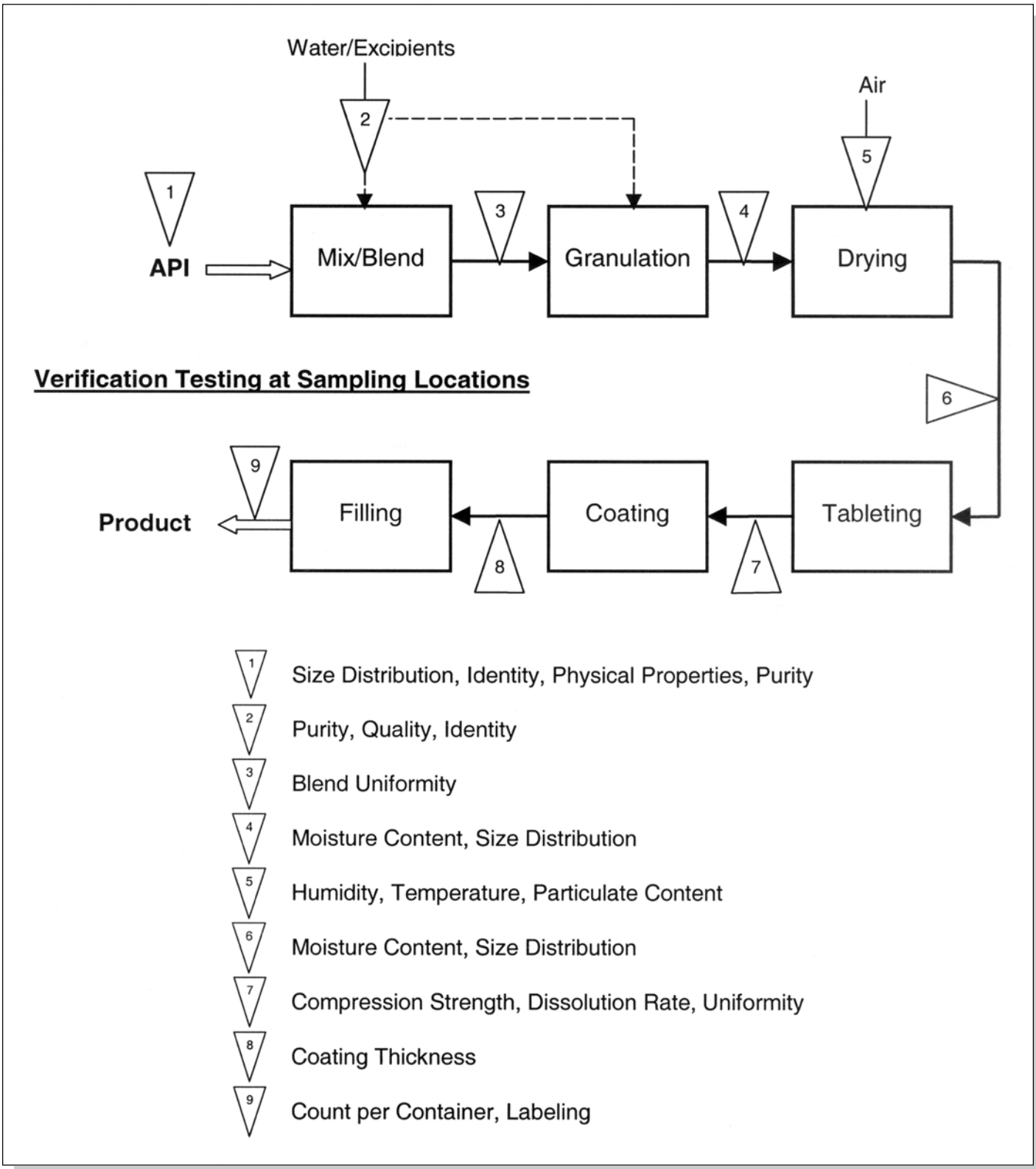

Figure 2. Solid dosage finishing process - sampling locations and example tests.

d. a specific requirement for the result obtained from the system (e.g. in mixing it could be homogeneity)

e. GMP or other regulatory requirements

f. your regulatory applications (e.g. New Drug Application or NDA)

Validating a process within the regulatory criteria is the appropriate way to ensure that the information provided to the FDA within which the process is claimed to be consistent is demonstrated. Should the process, after it has been validated, deviate from the validated range for any reason, then such a deviation should be thoroughly investigated prior to making a decision on whether or not to release the product.

Where Within the Process Does Validation Begin?

The standard approach is to validate the API process beginning at the point where the structure of the active ingredient or a significant chemical moiety of the active ingredient becomes evident. Other issues which may come into play when defining the starting point is whether or not additional synthetic steps are expected and whether or not additional purification steps are to be conducted.

In the finishing operation and packaging, this represents the final product and hence the entire process should be validated.

What are the Prerequisites?

Before the validation effort as defined in this overview is conducted, an organization has to do a tremendous amount of preparatory work. This work includes, but is not limited to, collecting all pertinent information, establishing document formats, and developing the procedures to develop and execute all the validation documents. This will ensure that all instruments, intrinsic to the equipment as well as the instruments which will be used in the validation, are properly calibrated, and establish the appropriate document storage and retrieval system.

However, an organization has to have the following items in place prior to the start of the validation effort:

a. successful equipment commissioning and troubleshooting

b. have a plan by developing a **Validation Master Plan (VMP)** which outlines how it will be done[4] - such a plan should outline the process and the facility, the systems to be addressed as part of the validation effort, and the qualification requirements for such systems. The plan also should identify how to validate the process eventually and what the acceptance criteria might be.

c. GMP systems in place (e.g. **Change Control** program, **Out Of Specification** (OOS), training programs, Standard Operating Procedures (SOPs) for performing the operation and the required maintenance, etc.)

d. all interested parties are involved in the effort (e.g. Quality Control, Quality Assurance, Operations/Manufacturing group, Engineering, Validation, and do not forget the Regulatory Affairs group if appropriate)

e. the quality unit is involved in developing and approving all aspects of the initial documentation for the process validation effort

The Seven Steps to Validating the Process

The following is an outline of seven general steps and guidelines which, when carefully followed, will assist in validating most pharmaceutical and API manufacturing and packaging processes. When implementing these steps, an organization should make sure that the process does not fall under the exceptions outlined later in this article (e.g. multi product processes, pilot plants, etc.).

Step One

Prior to beginning the validation of the process itself, make certain that the facility is suitable for manufacturing the product of interest. In addition, make sure that all the critical utilities, which may affect the quality, safety, and efficacy of the product, are capable of performing reproducibly consistently throughout validating these systems. In other words, an organization should validate the processes that produce critical utilities needed for the successful operation of the process, such as the water system, which will be used for the final wash of the purified crystalline material or the HVAC system which supplies the air in the sterile manufacturing suite.

Step Two

Once an organization has validated the utilities and confirmed the suitability of the manufacturing facility, it should qualify the processing equipment to be used in the manufacture of the pharmaceutical product. Qualifying implies that the various pieces of equipment to be used are indeed the ones which were specified by the design and are properly installed per manufacturer specifications and per the process requirements as determined by the design. In addition, qualifying a piece of equipment also entails ensuring that the piece of equipment operates as specified by the manufacturer and the user/production requirements. These two activities are known in the industry as **Installation Qualification** (IQ) and **Operation Qualification** (OQ).[2]

Both the first and second steps require the preparation of the appropriate validation protocols. The use of formalized validation/qualification protocols is also a regulatory requirement.[1] These protocols should define the operation or piece of equipment to be qualified, its function within the process, outline objective criteria to be met by the equipment and a methodology to test the piece of equipment.

Step Three

Verify the performance of critical sub-systems. For example, in a given overall process, one might encounter a set of processing steps for producing a solution. A mixing subsystem is an example which can be validated independently to confirm that it is capable of providing a product/mix of consistent homogeneity over a wide range of processing variables which covers the entire anticipated range of operation. Other examples would entail validating a chromatography system utilized to purify a component, or a viral clearing/removal system utilized in blood component processing.

Step Four

Validate the process according to a well thought out validation protocol. Make sure to run three consecutive successful batches to produce product of acceptable characteristics. This exercise

> ***The standard approach is to validate the API process beginning at the point where the structure of the active ingredient or a significant chemical moiety of the active ingredient becomes evident.***

should be conducted using the actual equipment to be used for the production of the pharmaceutical product, which has been approved by the FDA and will be marketed to the consumer. The processing conditions to be tested should reflect the conditions submitted in your NDA and should not deviate from them. If the manufacturer feels that their process is capable of performing at more stringent conditions, the manufacturer should modify its NDA to reflect the actual operating conditions.

Step Five

Invariably, when developing a process, a given organization has the opportunity to experience deviations and product failures. It is the norm in the industry to have rework procedures developed a-priori to remedy certain process failures. The organization should ensure that these rework procedures are validated to demonstrate that they do indeed remedy the product failure they have been designed for. This is only necessary if the organization intends to use these procedures.

Step Six

The organization should ensure that all the documentation generated during the qualification and the process validation, which follows, is collected and included with the process research and development information to form what one would refer to as the validation record for the specific product being manufactured.

Step Seven

As the validation proceeds, the organization would have observed what could be referred to as the **critical control points** of the process. These represent points within the process, which if they do not perform as per the process requirements, the product would suffer. For example, if the pH in the mixing tank must be in a specific range for the proper product salt to be formed and precipitated, then the pH measurement in the mixing vessel can be considered a critical control point.

Once all critical points in a process have been identified they should be monitored on a regular basis according to a predetermined frequency which ensures that the organization can identify any deviations or drifting of the data. Such an exercise is important from the process validation point of view in several ways:

a. It ensures that the process does not deviate with time from the original validated conditions, and if it does, it ensures that such a deviation will be detected and the proper investigations are conducted to correct such a problem.
b. It collects data as time progresses to demonstrate the effect of the changing seasons on the quality of the product. In essence, it completes the validation effort by studying the effect of time on the robustness of the process.

Sampling and Measurement Locations for Process Validation

When executing the process validation protocol (the equivalent to performance qualification protocol) be concerned with the sampling locations. These are usually determined by the characteristics of the process. However, some simple rules apply to define the locations for sampling and/or taking readings.

1. Take readings from instruments measuring information critical to manufacturing the product (e.g. reactor temperature).

2. Sample at critical intermediate spots within the process which would indicate the consistency of the process (e.g. for the yield out of the reactor, for purity out of a chromatography column).

Figure 1 depicts a block flow diagram representing a process for the manufacture of APIs showing some of the locations within the process where sampling should be done and the type of data which should be collected during the validation of an API process.

Figure 2 is a block flow diagram representing a process for producing solid dosage form showing some of the locations within the process where sampling should be done and the type of data which should be collected during the validation of a solid dosage form manufacturing process.

Finally, Figure 3 represents a flow diagram for a sterile product finishing process. The figure again depicts some of the locations within the process where sampling should be done and the type of data that should be collected during the validation of such a process.

Validation of Computerized Systems and Controllers

The use of computerized systems is becoming more and more prevalent in the industry. Today, computerized systems are used as databases to collect trending information from monitoring programs and store and retrieve information such as preventative maintenance as well as calibration schedules, requirements, and procedures. In addition, computerized systems are used to control process equipment in the form of Programmable Logic Controllers (PLCs) and Building Automation Systems (BAS). Material ordering and inventory systems also are becoming very common and their use is becoming an integral part of all pharmaceutical manufacturing operations.

All of these computerized systems, especially those used to make decisions which may affect the quality, purity, and efficacy of the product, should be validated as part of the overall process validation effort. In addition, be aware of the

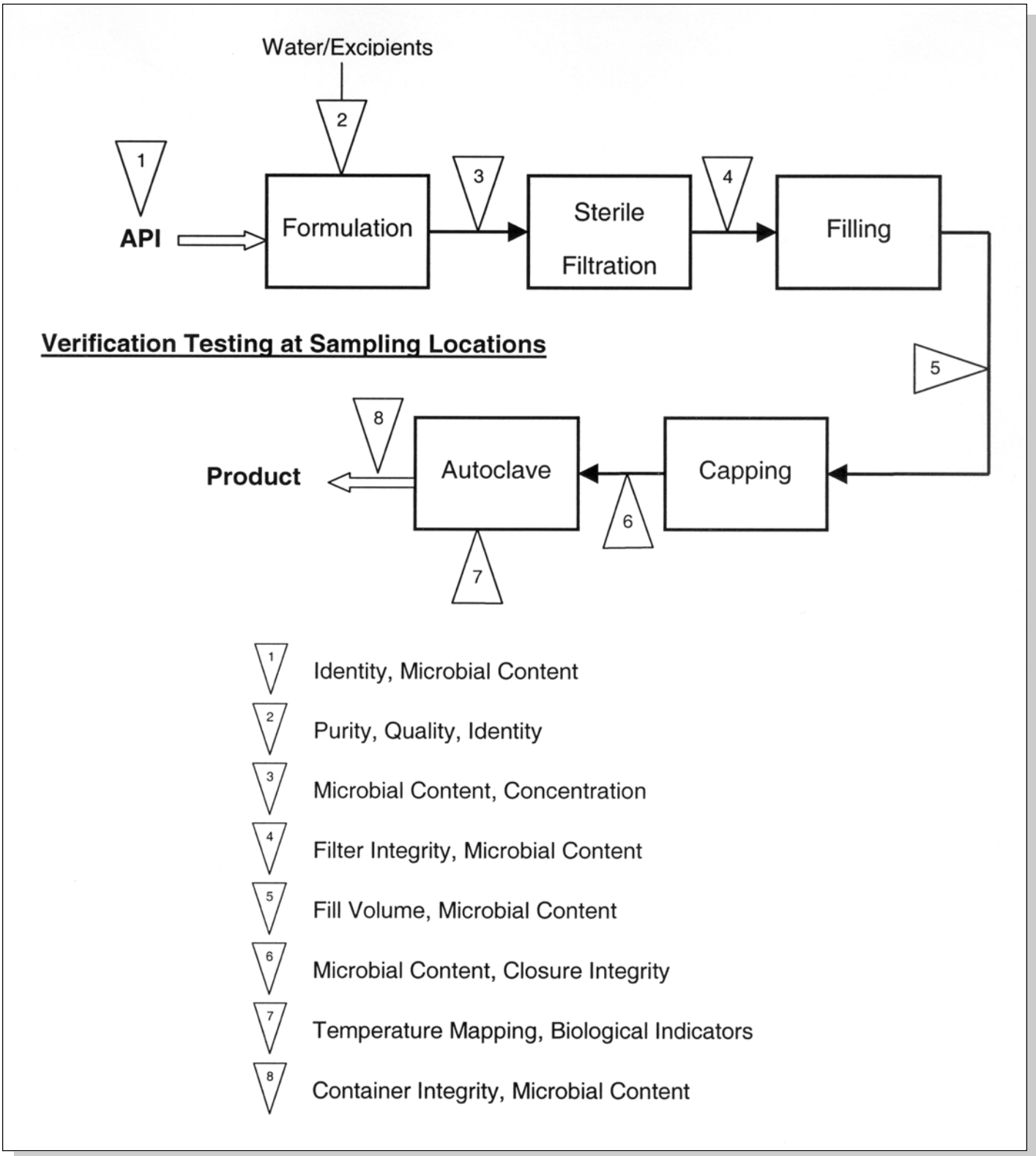

Figure 3. Sterile finishing process - sampling locations and example tests.

regulatory requirements associated with electronic records and electronic signatures[11] and be sure to follow them as appropriate. Some of the issues which should be considered are:

- recovery (including disaster recovery) and backup
- audit trails
- legacy systems are not exempt of 21 CFR 11
- reliability of the records
- structural integrity of the system
- ID authentication capabilities
- audits of software and hardware suppliers

Always keep in mind that an electronic record is created when the information is being saved not while it is being generated.

Validation of Analytical Methods

Normally, for new therapeutic compounds, the analytical methods to be used for chemical analysis are not compendial in nature. Actually in most cases, such methods are developed during the research and development phases of the process and therefore require validation to ensure that it indeed accurately and consistently predicts the quality, identity, strength, and purity of the material being tested.

The analytical method validation should address issues such as accuracy, reproducibility, ruggedness, precision, linearity, specificity, suitability, and robustness of the method. If the methods used in analyzing samples are compendial, (i.e. can be found in the US Pharmacopeia) then a separate validation study would not be required.

The Importance of Process and Environmental Monitoring

Establishing process and environmental monitoring programs is an integral part of process validation. This importance arises from the fact that the environmental monitoring program is used to complete the validation effort by identifying the effect of seasonal variations of temperature and humidity on the performance of certain systems such as the HVAC and water systems. In addition, environmental monitoring ensures that environmental conditions observed during process validation are similar to those observed during the process operation and do not vary in a significant fashion so as to affect the quality, safety, and/or efficacy of the product being produced. The process monitoring program is also an important tool used to ascertain that the process itself, and all of the subsystems utilized to support it, remain in a state of control and do not drift with time thus ensuring that the product consistency is maintained (refer to the seven step discussion above).

Moreover, monitoring ensures that the combination of prosubject was discussed in detail previously.[5] It is important to have all the important documents in a filing system, which allows for easy retrieval of such information.

Once the validation effort is complete all documentation that results should be filed in one location to allow for easy retrieval. The industry standard is to establish a validation document library which is managed by the validation group and/or the quality assurance unit. Access to these documents should be limited and controlled.

Timing and Scheduling Issues

Validation of a given manufacturing process is an elaborate project which requires careful planning and attention to the timing of the various activities to ensure that they all come together when needed to complete the effort. In planning the schedule for validating a process, the following are some of the questions to be considered:

- when to start the effort?
- when to collect necessary information and documents?
- when to bring outside contractors into the effort?[10]
- when to begin preparation of the documentation required for the validation effort?
- what to validate first and what sequence to use?
- which utility system should be validated first, and what are the priorities for validating the various process subsystems?
- when to run the three consecutive and successful batches?
- how long can a protocol stay unresolved?[10]
- how much time should be allowed to elapse between the installation and operation qualification effort and the performance qualification (or process validation) activities?

Many of the references listed in the reference section of this article contain suggestions on how to answer some of these questions. Remember that good common sense and a logical approach to the validation effort is the best way to develop a meaningful schedule and appropriately time the various activities.

Using Existing Data to Validate Existing Processes

For so called "retrospective" validation, a company could use data collected over the past for a given process to validate it. This can be done if no significant changes to the process were made during the period for which the data is considered. Such an endeavor is known as retrospective validation. Although not a favorite of the regulators, it is accepted that in cases where a process has been in use for a long time and enough data exists to demonstrate that the process is robust, consistent, and reproducible, such data could be used to conduct a validation of the process. However, there should be a protocol which has all the standard components required of a good protocol and the appropriate tables for documenting the data should be used. In addition, the protocol should outline the rationale for analyzing the data and developing the appropriate conclusions based upon data analysis.

Validation of Multiple Product Processes/Facilities

In cases where several products are manufactured using common equipment, one could devise a method to reduce the extent of the validation effort without compromising the quality of the validation. The approach would entail identifying a set of unit operations, which are common to many of the production processes. Once these operations are defined, one could validate them and demonstrate that they yield consistent results within the expected operating ranges for all the anticipated products. Once every unit operation has been validated then one could conduct a representative production run for each product to demonstrate that putting several validated unit operations in series does result in a consistent product.

Validation of Processes Being Piloted

A pilot process/plant is normally utilized in process development and to a large extent represents a process in flux. At the piloting stage, the process is not fully defined and is probably not at the expected manufacturing scale. Therefore, it makes no sense to validate it fully since it will invariably change. However, certain aspects of the piloting facility/process warrant being validated even if they will eventually change. For example:

a. If steam sterilization is being considered as part of the process, it behooves the organization to validate the steam sterilization step to confirm its importance.

b. If certain technologies are utilized to recover solvents for reuse in an API production process, it would be an excellent idea to validate the solvent recovery technology.

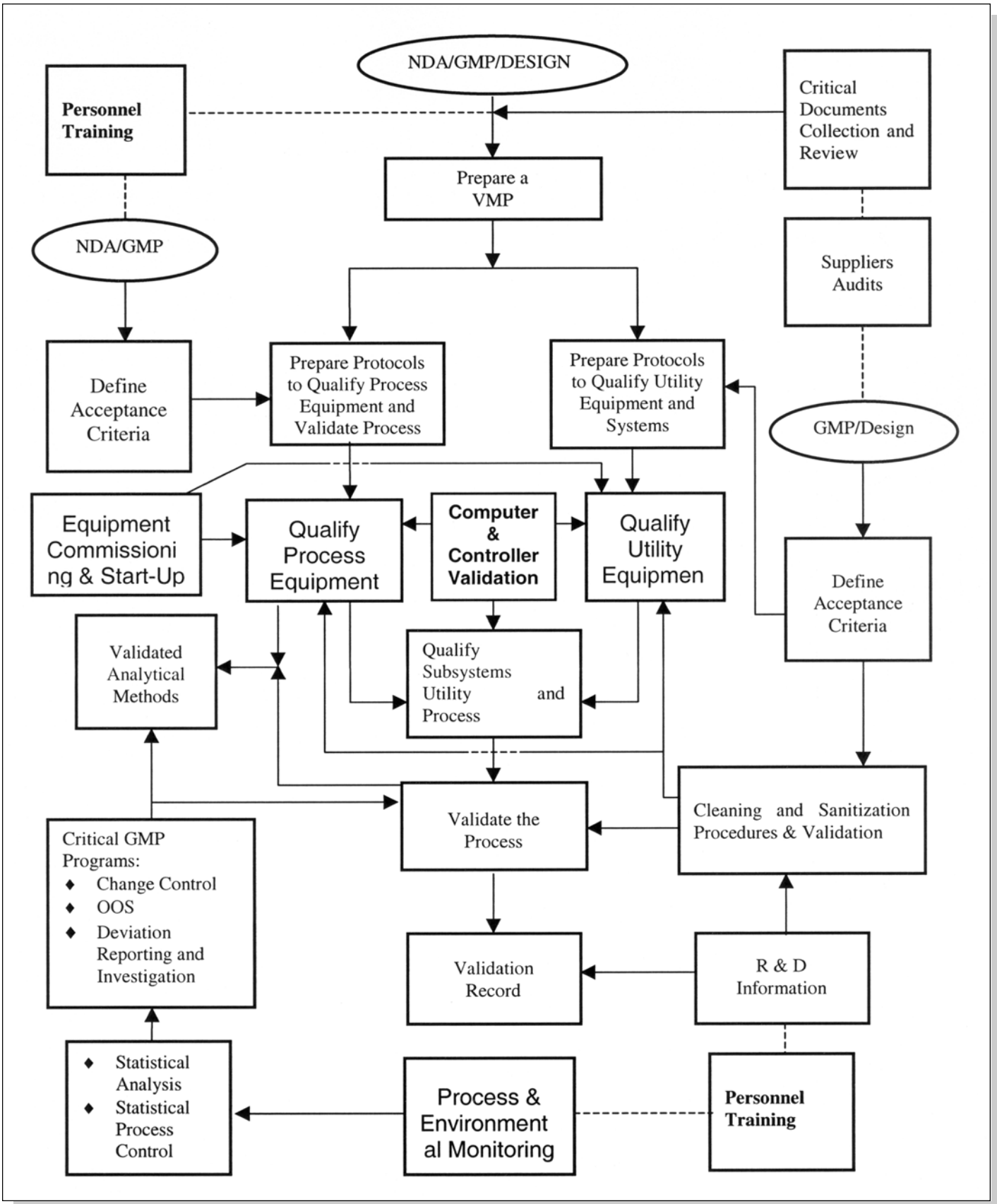

Figure 4. Overview of process validation.

Annual Revalidation Requirement

In order to ascertain that systems/equipment remain in a validated state, some practitioners believe that they should be revalidated on an annual basis. In fact, it appears that many people in the validation business believe that certain equipment such as ovens and autoclaves must be validated annually to satisfy FDA requirements. In a recent interview with Bob Coleman,[3] this issue was discussed and he concluded that if an organization has a good preventative maintenance program, a monitoring program, and a change control system in place, they may not have to validate an autoclave or an oven if a review of all the data collected through the year shows no problems with the operation of the equipment. The idea is if you have a good maintenance program and do not observe problems when monitoring the system throughout the year, and if indeed no change to the system occurred without a thorough review, all that is needed is to review the information at year's end and reach the conclusion that revalidation is or is not required.

Who Manages the Effort?

The quality unit, with the assistance of the engineering and operations organizations, normally would manage the process validation effort. In many companies, the technical services organization replaces the engineering function in managing the process validation effort. Normally, the validation/technical services group prepares the various protocols, while the engineering organization executes the IQ and parts of the OQ. The validation group usually executes the remainder of the OQ and the PQ. The operations group under the watchful eye of the validation organization executes the Process Validation (PV) protocol itself.

Conclusion

In this article, an attempt was made to outline as many of the aspects of process validation as possible. In addition, the article attempted to outline a logical approach to achieving the objective of validating a process and keeping it in a validated state. The general overview of process validation, which was discussed in this article, is presented graphically in Figure 4.

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