

# NewsLetter

Biotech/Pharmaceutical

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## PRO-ACTIVE VALIDATION

BHAWANI MUKHERJEE, P.E.

The pharmaceutical industry recognizes the need to demonstrate cGMP compliance for the manufacture of drugs. cGMP is also mandatory for the clinical trial materials for the Phase II and III programs according to a recent declaration of the EU regulatory agency. Regulatory enforcement is on the rise for facilities where non-compliance is most likely to yield adverse public health consequences. Lack of documented validation of the manufacturing facility is one of the major causes of regulatory action. The industry is well aware of the consequences and has taken considerable measures to ensure that documented validation programs are in place.

Unfortunately, increased regulatory attention seems to have a panic effect on validation on the manufacturing floor. The cost of validation has escalated and the validation timeline has been extended unnecessarily. A disconnect in the logical interface between engineering and validation has emerged and has caused major disruptions to the beneficial occupancy of facilities. Enormous amounts have been spent on legacy validation without an overall review of systems and equipment of a validation master plan.

Validation of facilities, systems and equipment when planned, organized and executed with a cross functional team can significantly accelerate the cGMP production schedule.

There are some misconceptions in the industry that engineering and validation activities are independent of each other and should be separated by design. The concern is that checks and balances may be diminished if the validation task is delegated to the same organization responsible for the engineering and design. In reality, the engineering and validation are interdependent activities and can be made complementary to each other.

Checks and balances in any organized effort should be built into the process so that value is enhanced, not eroded. The objectives of the engineering, construction and the validation by design should be convergent and lead to early availability of a cGMP compliant facility for beneficial occupancy.

### Early Start in the Planning Process

Validation input should be started during the preliminary engineering stage to take advantage of synergistic interfaces with the engineering function. Contribution of a lead validation member in the project design team can significantly improve the validation time line. The block logic diagram shown in Figure 1 illustrates the validation interface in a facility project.

Documentation necessary for validation protocol preparation should be an organized handout package at the end of detail

engineering and factory acceptance testing of equipment. The validation involvement in the design phase of the project can specify document requirements from the equipment and systems vendor. A protocol for the transfer of engineering documents called a "turn over package" should be developed jointly by the engineering and validation team members during the project design stage. This package can essentially deliver all documentation necessary for the installation qualification.

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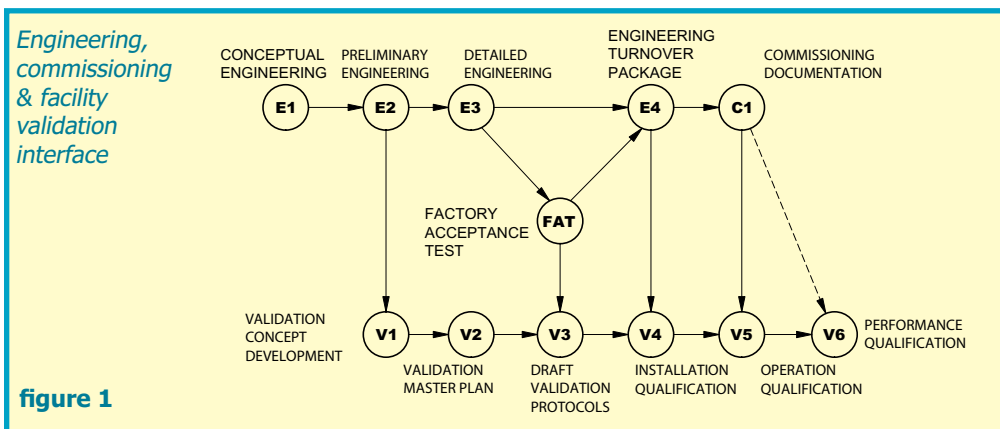
### New Research Facility for Cadbury Adams

PS&S provided full design\* and engineering services for this 150,000 sq. ft. R&D facility. PS&S has been involved in the initial site selection, through Basis of Design, Programming and Final Design Phases for this facility, which will consume half of this 31-acre location.

One third of the building will be comprised of office space, while the other portions of the facility will consist of laboratory space and a pilot plant, in order for small-scale product research to occur. The new facility was specifically designed to be flexible and to support the client's universal candy and gum development endeavors.

Commissioning assistance will also be provided by PS&S as part of its comprehensive service for the client.

"PS&S maintained an exceptional balance between creating a state of the art facility with the necessary functionality, while staying within an extremely tight budget. In addition, in all my years I have never seen such team players on a project that truly meshed with all parties of the owner, constructor and contractors", said Steven Wehner, Director, Facilities Operations at Cadbury Adams.



\*Architectural services provided by Paulus, Sokolowski & Sartor Architecture, P.C.

Simply stated, the active approach between engineering and validation minimizes (if not eliminates), the duplication of efforts and results in cost and time savings.

### Validation Timeline

The execution of validation protocols should be organized such that minimal field efforts achieve maximum effectiveness. The interface with documented commissioning is essential to avoid deviations in operational qualifications. Execution protocols before the system and equipment are fully commissioned leads to numerous deviation reports and delays in the overall schedule.

### Master Plan

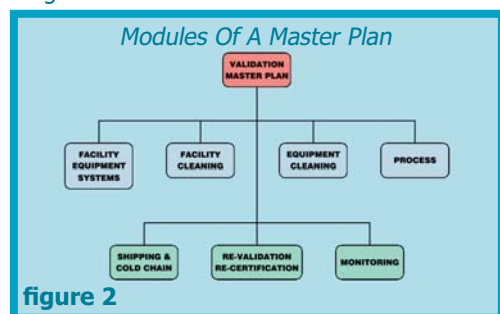
A master validation plan is a subset of the quality assurance program for the facility. It is a living document that defines validation activities and usually relates to the facility, systems and equipment.

The validation master plan however is prepared to cover the complete validation initiative including the cleaning of product contact surfaces, facility cleaning and process validation. The master plan also refers to other quality subsets such as change control programs, corrective and preventative actions, monitoring and a re-validation schedule. The modules of a validation master plan are depicted in Figure 2.

The master plan is typically prepared during the detailed engineering stage when the equipment and systems are identified and specified. It is not uncommon to prepare separate sub plans for cleaning and process validations since they are executed after the trial batches are started. Both the cleaning and process validation requires data from the development laboratories and cross functional teamwork with manufacturing and quality groups.

### Validation Life Cycle

The facility validation for the system equipment and controls should proceed in logical steps with engineering documentation, field test data, construction and commissioning. A typical validation flow chart (Figure 3) shows the life cycle approach, which is necessary to maintain a facility in a continuous validated stage.



If planned in the early stage of the project and carried out with proper focus for the earliest availability of the facility, the interactive effort between engineering and validation generates sufficient synergy to significantly reduce the validation schedule and cost.

### Conclusion

Proactive validation, when planned, organized and executed in a team function with engineering and commissioning can significantly accelerate validation schedules and availability of the facility for beneficial use. A validation team leader should be a part of the project team and participate from the project inception stage. Synergies generated by the cross functional team improve the quality of the facility design and shorten the validation timeline following mechanical completion. The incremental steps for facility validation should be planned and executed with interfaces between engineering and commissioning activities.

A proactive approach to validation in a facility project identifies compliance issues during

project design and accelerates execution of the qualification protocols during and after commissioning of the facility. Figure 4 illustrates the simple incremental validation steps in a successful project.

This article was previously published in ISPE Pharma Bulletin.

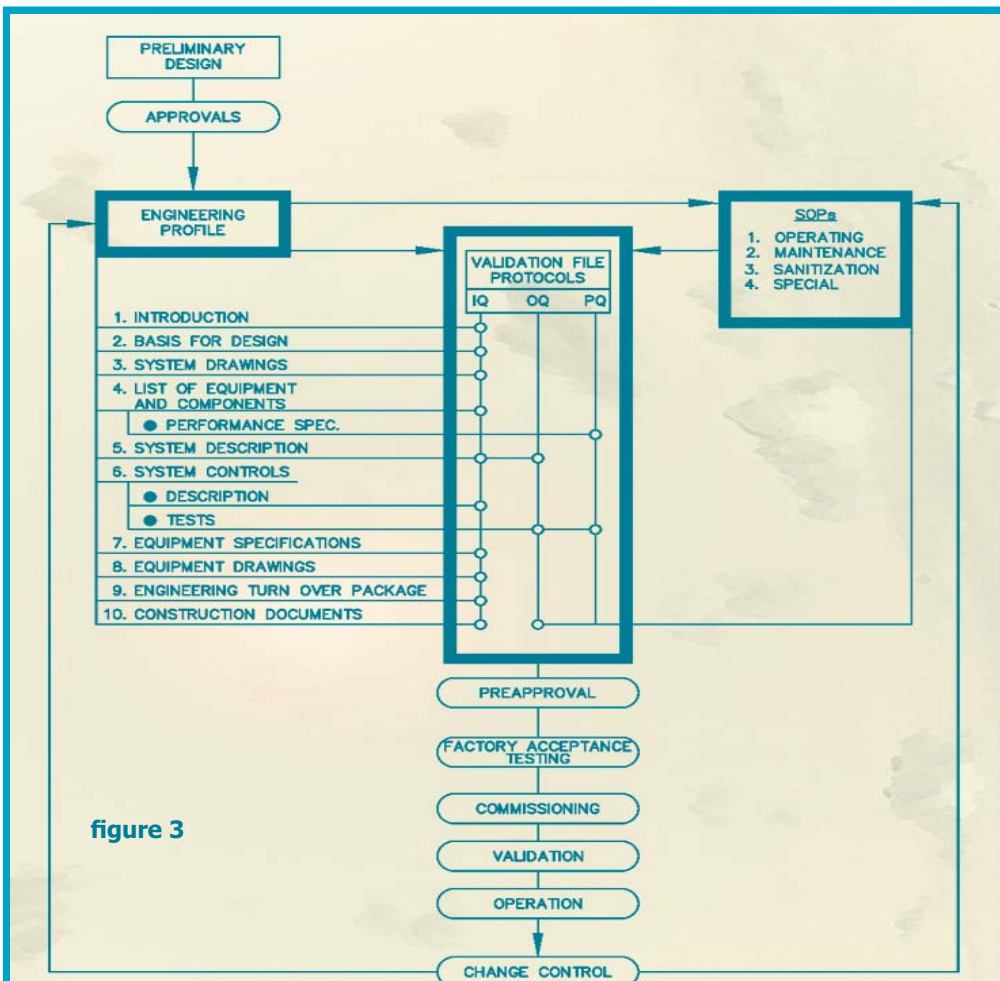


figure 3

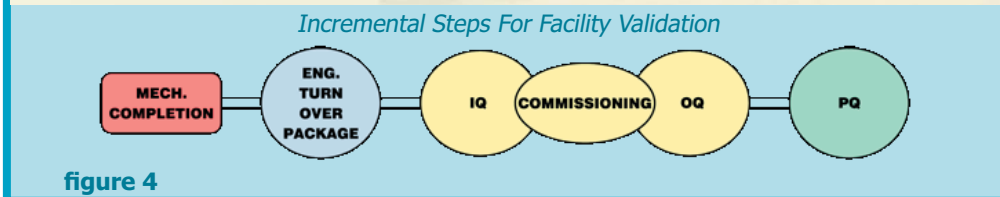
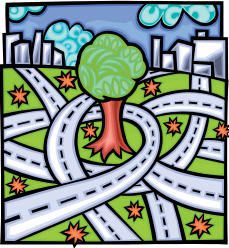


figure 4

## We wouldn't start a trip without a road map...



So how can we start a project without a plan? But if we're really honest with ourselves, we do it all the time! And we see the results in the unmet

expectations that all too often follow as a consequence. It doesn't take a career-ending catastrophe for a project to be unsuccessful. Sometimes, it's just a wistful "if only I had it to do over again".

Here are a few simple tips to keep your projects on track:

### Be sure that everybody is playing from the same sheet of music

There are a lot of different ways to structure a project: There is the traditional AIA approach of Conceptual Design, Schematic Design, Design Development, etc. On the other hand, many organizations have adopted the Basis of Design model, some with varying levels of detail. Or a Core and Shell approach may be the best choice.

The point here is that it is essential, on Day One, to define the phase structure and to define the work packages resulting from each phase (how else will you know when you're done?).

All of the participants (Owner, design professionals, Construction Manager, Vendors, etc.) need to schedule their work to be "in synch" with this overall plan.

### Determine the procurement strategy up front

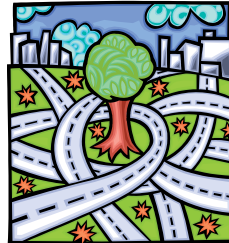
The way that the job is going to be bid and built directly impacts the structure of the Construction Documents. Will it be core and shell, will the Owner prepurchase long-lead equipment items, will it be General Contractor or CM with multiple prime contracts or will it be built "fast track" with portions of the building under construction, while others have yet to be designed? The answers to these questions (and others) will determine what information is required on which

drawings and specifications, how they are divided up and what budget contingencies need to be provided for. This can't be done after the fact – it needs to be decided before pen goes to paper.

### Communicate, communicate, communicate!

We all know that a problem, if ignored, will inevitably go from bad to worse. Timely and effective communication between owner, designer, construction manager, and sub-contractor is essential for successful project implementation. This means regular meetings, with comprehensive minutes and action items, monthly reports with meaningful financial and schedule updates (there's a lot of "smoke and mirrors" in this area – review these reports carefully and critically!), and an "early warning" system to alert key project personnel of potential problems on the horizon (nobody likes surprises!).

These are just a few thoughts on some simple but important steps you can take to get your projects off on the right foot and keep them on track. If you are planning a project, give PS&S a call for a no-cost consultation. We'd be happy to provide recommendations and suggestions, at no obligation, from one of our many experienced project managers.



## Latest News from PS&S

By growing over 50% in 2003, PS&S was one of the fastest growing design firms in the Nation. We now have a staff of nearly 500 and offices in NJ, NY, MA, IL, PA, and CA, as well as a strong presence in Puerto Rico. We continue to be ranked in the top 15 design firms in "pharmaceutical plants" by Engineering News Record.

Okay, enough statistics.

What are we really doing these days depends on whom you ask:

**Steve DeRochi** is working on the latest ISPE Lab Design Guide, a toxicology lab, and running his Architectural Group;

**Luke DeMayo** and **Elaine Gaeta** are busy providing the A/E services for a pharmaceutical facility with level 4 containment requirements;

**Bhawani Mukherjee** is busy with a number of biotech and vaccine projects, as well as running his process and validation group;

**Nihal Jay** is getting ready to move to Puerto Rico to oversee the construction phase of a solid dose facility upgrade PS&S designed and engineered;

**Mike Belikoff** is working on ways to streamline the design process through the integration of tools to review work product in a more formalized way to improve the quality and efficiency of our design efforts.

And the list goes on.

What I am doing these days is informing our clients that we can support them now not only in the New Jersey Metropolitan area and Puerto Rico, but in the Mid-West, New England and California as well.

Let us know what we can do for you.

**-Emad Youssef, P.E.**  
Senior Vice President  
732.584.0217

## Paulus, Sokolowski & Sartor, LLC



Paulus, Sokolowski and Sartor, LLC (PS&S) is an integrated design/engineering firm with all technical disciplines in-house.

#### Services:

- Planning (strategic, facilities, site and utilities)
- Bio-Processing
- Oral Solid Dose
- Active Processing ingredients
- Containment
- Parentrals
- Sterile fill/pack
- R&D Facilities
- Energy/Utilities/Infrastructure

#### Markets:

- Corporate
- Biotech/Pharma
- Educational
- Water/Waste Water
- Real Estate Development
- Environmental