



July 6, 2005

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Judy Weseman, PE, NSPE
CEO and Executive Vice-President
Professional Engineers of North Carolina
111 N. Boylan Avenue
Raleigh, NC 27603

RE: Pharmaceutical Engineering Services for Validation and Commissioning

Dear Judy:

I am writing to express the support of the North Carolina Biosciences Organization (NCBIO) for the comments and recommendations included your letter to the North Carolina North Carolina Board of Examiners for Engineers and Land Surveyors concerning Pharmaceutical Engineering Services for Validation and Commissioning Processes, a copy of which is attached hereto.

NCBIO is the trade association for the pharmaceutical life science industry in North Carolina. Our membership of more than 125 companies includes corporations such as Biogen Idec, Diosynth, GlaxoSmithKline, Novo Nordisk, Novozymes, Talecris, and Wyeth. NCBIO also represents a large number of smaller pharmaceutical and life science development companies that are or will be conducting commissioning and validation activities as part of their business operations.

NCBIO is grateful for your diligent work in this project as well as the assistance of PENC in clarifying these complex issues. We look forward to working with you and the Board in months and years ahead in assuring the availability of safe and effective pharmaceutical products and strong life science industry in North Carolina.

Sincerely,

A handwritten signature in black ink that reads 'Samuel M. Taylor'.

Samuel M. Taylor

SMT/st

cc: J. D. Solomon, PE, PENC President
Andrew Ritter, Executive Director, NCBELS
Hal Price, Project Coordinator, Biotech Manufacturer's Forum



DRAFT

June 28, 2005

Mr. Andrew Ritter
Executive Director
North Carolina Board of Examiners for Engineers and Surveyors
4601 Six Forks Road, Ste. 310
Raleigh, NC 27609

RE: Board Action Request: Pharmaceutical Engineering Services for Validation
and Commissioning Processes

Dear Andrew:

Following a detailed study discussed in the body of this letter, PENC requests that NCBELS favorably consider our conclusions and recommendations for the requirement for North Carolina professional engineers in the pharmaceutical validation and commissioning process. Although the conclusions and discussion set out below address the manufacture of pharmaceuticals, it is believed the same or similar principles will apply to the manufacture of other similar products, such as biologics, food and food additives, wine and beer.

CONCLUSIONS AND RECOMMENDATIONS

We conclude that responsibility for product safety and quality rests with technical personnel trained in chemistry, biochemistry and other sciences. We conclude that responsibility for verification that the system design meets the original engineering design scope, system start-up and turnover to the owner, and verification of system operation safety and start-up functionality (collectively, commissioning) rest with a professional engineer. "Professional engineer" is meant to refer to an engineer as defined in North Carolina G.S. 89C.

The professional engineer's responsibility in G.S. 89C-2 to safeguard life, health, and property and to promote the public welfare should be interpreted to include the design and safe operation of the pharmaceutical manufacturing equipment but should not include responsibility for the safety and quality of the pharmaceutical product as engineering education does not offer the requisite level of training in the synthesis, fermentation or other chemical, biological, and/or other combinational molecular synthesis methodologies.

We make the following recommendations:

1. Commissioning work must be done under the responsible charge of a professional engineer.
2. Validation of pharmaceutical manufacturing systems does not require the responsible charge of an engineer.
3. Corrective action undertaken as a result of the validation process may require the responsible charge of a professional engineer if design changes or re-commissioning are required.

Referring to paragraph #3 in letters sent on December 15, 2004 to pharmaceutical validation firms found in violation of G.S. 89C-24 (exemplar in Attachment 1), we would recommend modifying two sentences contained therein to say (changes shown in italics):

Activities including, but not limited to, design validation that certifies that the installation conforms to the initial engineering design; the start-up and turnover of facilities, systems, and equipment to the owner in a manner that ensures a safe and functional environment that meets established design requirements (commissioning); and corrective actions taken during validation that require design changes and/or re-commissioning that require the education, training or experience of an engineer to successfully perform must all be done under the responsible charge of a North Carolina professional engineer and, as applicable, by a North Carolina licensed engineering company. (Recommend deleting the next two sentences as they are incorporated above: Engineering analysis and recommendations are particularly required when deviations occur during protocol execution. Engineering judgment is required to determine if failure are due to problems in the design or operation, or if it is a failure in the testing procedures, including human error, malfunctioning test equipment, etc.)

DISCUSSION OF FINDINGS

In a Board letter dated March 19, 2003 and addressed to William J. Heron, PE, the Board's Engineering Review Committee concluded that "the validation engineering process was determined to constitute the practice of engineering" and further determined that "...portions of engineering that are included within the documentation cannot be separated from the documentation as a whole". After further study, we feel that engineering can be separated from validation and the resultant report incorporated as an attachment in validation documentation.

These determinations were discussed by David Tuttle, Esquire, Board Counsel, at a meeting of the International Society for Pharmaceutical Engineering (ISPE) held May 25, 2005 in Research Triangle Park, and attended by the author. Subsequent discussions have led to PENC's decision to take a leadership position in more clearly defining various steps of the validation process which may represent engineering work product.

Validation Definition

The term “validation” has several meanings in both engineering and pharmaceutical applications. “Validation engineers” are employed both by pharmaceutical companies for use in starting up new pharmaceutical processes and also in other manufacturing industries for specialized expertise in computer, automotive, and other systems. The term “validation engineering” will not be used because of the lack of a clear definition in the pharmaceutical industry and because use of the term, in our opinion, invites misinterpretation of the role of an engineer in the start up of a new pharmaceutical process.

The Food and Drug Administration (FDA) requires a number of steps to be taken to assure product safety and quality. This procedure to comply with FDA regulations is called “validation”. At this time, there is no one standard reference which defines validation. However, 21CFR Part 211 Current Good Manufacturing for the Manufacture, Processing, Packing, or Holding of Drugs section 211.110 states “...control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.”

Validation is referenced in 21CFR Part 601 Biological Products section 601.12(a) which states that “...Before distributing a product made using a change, an applicant shall demonstrate through appropriate validation and/or other clinical and/or non-clinical laboratory studies, the lack of adverse effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product...”

Absent a clear validation definition in a publicly available reference, we suggest use of a validation definition found in a Talecris Standard Operating Procedure (SOP):

Validation: “The active process of providing documented evidence through testing, that a process, *using qualified equipment*, consistently and reproducibly produces a product or output meeting its predetermined specifications and quality attributes as shown by conformance to acceptance criteria.” (Reference Talecris Site Validation Master Program – SOP # CS-000-AD-161). (Attachment 2)

Talecris Biotherapeutics, formerly Bayer, manufactures pharmaceutical products in Clayton, NC and other US locations. “*Using qualified equipment*” (author’s italics) is a direct reference to the separate commissioning process.

Commissioning Definition

Although there is not presently a standard reference for pharmaceutical validation and commissioning, a generally accepted reference is the ISPE Pharmaceutical Engineering Guidelines for New and Renovated Facilities, Vol. 5, Commissioning and Qualification, March 2001. ISPE defines commissioning as

Commissioning: “A well planned, documented, and managed engineering approach to the start-up and turnover of facilities, systems, and equipment to the End-User that results in a safe and functional environment that meets established design requirements and stakeholder expectations.”
(p.19)

The Interrelationship of Pharmaceutical Commissioning and Validation

Pharmaceutical companies are responsible for written procedures for commissioning and validation of new or changed processes. Although commissioning may be completed prior to the start of validation, more typically there is overlap between the two processes. Attached is a Gant chart provided by Talecris which shows the timelines for validation and commissioning of a new system. (Attachment 3)

Pharmaceutical companies may choose to perform both functions in-house or may contract out one or both of these processes. If both processes are contracted out, they may be either sole sourced or given to two different contractors. It is common practice for competitors to be on-site at the same time with one doing commissioning and the other validation. There are steps required in commissioning which also satisfy specific validation steps. It is commonly practiced to use commissioning results to also meet certain validation requirements. It is not commonly practiced to do the reverse, i.e., use validation to meet commissioning requirements.

System Design and Control Systems

Individual unit operations and control system design are normally outsourced to companies which are highly specialized in the design of reactors, chromatography skids, control systems, and other equipment for the pharmaceutical industry. Performance of the individual components is usually factory verified with a pharmaceutical engineering representative present and again tested on-site with a pharmaceutical engineering representative (usually the same individual) present. This is part of the commissioning process. The control systems are constructed by an entity such as ABB per engineering design specifications and installed on-site. Corrections and changes to control system programming, once delivered, are typically done by a computer science major, mathematician, or other non-engineer.

Validation and the Role of the Scientist

In the pharmaceutical industry, engineers work side-by-side with scientists including chemists, biochemists, and microbiologists. In the long process to bring a drug to market, engineers work closely with the scientists to take their laboratory processes and scale them up for commercial manufacture. The role each profession plays in the scale-up provides insight into those tasks considered the domain of engineers and scientists during validation.

Scientists have the education and experience to first produce a new chemical or biological product with pharmaceutical efficacy and it is these same scientists who are responsible for maintaining product quality and safety during start-up and manufacture. It can be argued that engineers play a supporting role to the scientists in the pharmaceutical industry, serving to reduce to common practice through commercial scale equipment those laboratory efforts. Hence, validation is driven more by the scientists who synthesize and isolate the purified drug and who also test the drug quality using analytical methods.

Validation and Corrective Action (Exceptions and Discrepancies)

Validation is broken down into three steps, IQ (installation qualification), OQ (operational qualification), and PQ (performance qualification), and is focused solely on product safety and quality. Separately, commissioning is focused on equipment safety and functionality. Any exception or discrepancy found during the validation process must be listed separately in the validation report along with the corrective action for review by the FDA during inspection prior to approval of start-up.

These exceptions may result in changes to the design of the equipment or may require changes in the chemical or biological production protocol. Equipment design changes require re-commissioning. Process changes to meet product safety and quality requirements are usually accomplished by professionals with technical training in chemistry, biochemistry, and other sciences. Many of the exceptions and discrepancies are minor or of limited scope and are often easily corrected by maintenance and non-technical employees.

Absence of Generally Accepted Standard Procedure

At present, there is not a standard reference manual of protocols for pharmaceutical commissioning and validation. However, it is generally agreed in the trade that the ISPE Pharmaceutical Engineering Guides for New and Renovated Facilities, Volume 5, Commissioning and Qualification, March 2001 most clearly documents generally accepted practice for commissioning and validation. ISPE has now formed a committee to more clearly delineate requirements of commissioning and validation to be issued as ASTM procedures. I spoke with Bob Chew, PE, Commissioning Agents, Inc., who serves on the

committee. Mr. Chew stated that the ASTM procedures are approximately two years from implementation. It is anticipated that these procedures will more clearly delineate responsibility for engineering and technical professions and will provide some relief to the Board with future issues involving engineering work done in the pharmaceutical industry.

Examination of Talecris Validation Report

Talecris, Clayton, permitted me to personally examine a complete validation report and provided personnel to answer questions as I examined it without restriction. The three loose bound documents contained hundreds of pages, totaling around 8" when stacked. The validation report included all aspects of the process as directed by their internal SOPs including original design drawings, commissioning, and all three sections of validation including IQ, OQ, and PQ. Talecris performs all functions in-house except the equipment design and manufacture. This external engineering package was included in its entirety in separate sections. From this, I concluded several things. First, since validation focuses on product safety and quality, the bulk of the reporting was not engineering in nature. Second, those portions that are engineering, including other validation reports that might include consultant reports for validation and commissioning, can be included as separate sections. Hence, a commissioning report would contain an engineering seal and signature and would be an included section in the validation reporting.

Future Steps

In a meeting with pharmaceutical industry representatives held June 27, 2005, I communicated to them the conclusions and recommendations PENC planned to present to the Board. The pharmaceutical industry is in general agreement with PENC's recommendations of what constitutes the practice of engineering in the pharmaceutical validation process. The North Carolina pharmaceutical industry plans to submit a letter of support to NCBELS authored by Sam Taylor, Executive Director, North Carolina Biosciences Organization.

NCBIO future steps will include an educational outreach to all their pharmaceutical company members to encourage a review of North Carolina G.S. 89C and G.S. 55B. NCBIO also will encourage its members to verify appropriate North Carolina licensure of individuals and of companies providing engineering services.

Also agreed in the meeting on June 27 was that NCBIO's pharmaceutical manufacturing members should be encouraged to include in their Requests for Proposals (RFPs) a requirement that vendors identify a licensed North Carolina professional engineer when commissioning or engineering corrective actions are included in the job scope.

Attachment 4 summarizes activities taken in support of the conclusions and recommendations presented above. Thank you for your consideration of PENC's recommendations.

Regards,

Judith K. Weseman, PE, NSPE
CEO and Executive Vice-President

Cc: J.D. Solomon, PE, PENC President
Samuel M. Taylor, NC Biosciences Organization Executive Vice
President

Attachments (4)

ATTACHMENT 4

SUMMARY OF ACTIVITIES AND RESOURCES USED

1. Three meetings were held with North Carolina pharmaceutical industry representatives and PENC on June 7, June 22, and June 27. The list of attendees include those who attended all or part of the meetings.

PENC was represented by:

- Judy Weseman*, PE, PENC CEO and Executive Vice-President
- Mike Kessler, PE, Griffin Engineering and Technical Services, Inc., Durham

The pharmaceutical industry was represented by:

- Samuel M. Taylor*, the North Carolina Biosciences Organization (NCBIO), Executive Vice President, RTP
- Hal Price*, Biotechnology Consulting Service and consultant to NCBIO, Cary
- Glen Williams, PE, Biogen Idec, Vice President – Manufacturing & General Manager – RTP
- Frank Highsmith*, Talecris, Qualification and Validation Engineering Manager, Clayton
- Paul E. Rehder, PE, Novozymes, Director of Environmental & Engineering Services, Franklinton
- Tim Hamm, Talecris, Director, Compliance, Audits & System Quality Operations
- Connie Pilkington, Talecris, QO Compliance Manager, Clayton
- Mike Hayes, Talecris, Manager, QO Systems, Clayton

*attended all meetings

2. After the June 22 meeting at Talecris, Clayton, by request I was permitted to examine a complete validation documentation for the purpose of examining engineering and non-engineering work efforts and to determine that no significant engineering activities were omitted in the study of pharmaceutical validation and commissioning.

3. Consultants who offer validation and commissioning consulting services were made aware of our meetings although they were not invited to attend. Griffin Engineering's principal, Jim Griffin, PE, provided feedback to the ISPE members (consultants). Hal Price also communicated our process and outcomes to ISPE members.

4. Bob Chew, Commissioning Agents, Inc., provided useful insight to me regarding the development of ASTM procedures in a telephone call on June 24, 2005.
5. Sam Taylor, NC BIO, and I had numerous telephone calls and meetings starting May 31, 2005.
6. ISPE Pharmaceutical Engineering Guidelines for New and Renovated Facilities, Vol, 5, Commissioning and Qualification, March 2001 served as my principal technical reference.
7. Talecris (Frank Highsmith) presented a Powerpoint presentation at our June 22 meeting. Attachment 1 to this letter is taken from this presentation with permission.
8. Talecris (Frank Highsmith) provided the Gant diagram showing a validation time line. This diagram is included in this letter as Attachment 2 with permission.
9. A Google search was done for the term “validation engineer”. The search showed that the term is used for a large number of unrelated jobs, some of which do not require engineering training or experience as detailed in their on-line job postings.